R. A. Sheldon, H. van Bekkum

Fine Chemicals through Heterogeneous Catalysis

WILEY-VCH

Other Titles of Interest

B. Cornils / W. A. Herrmann
Applied Homogeneous Catalysis with Organometallic Compounds
2 Volumes
1996. XXXVI, 1246 pages with 1000 figures and 100 tables.
Hardcover. ISBN 3-527-29286-1
Softcover. ISBN 3-527-29594-1

B. Cornils / W. A. Herrmann / R. Schlögl / C.-H. Wong
Catalysis from A to Z
2000. XVIII, 640 pages with more than 300 figures and 14 tables.
Hardcover. ISBN 3-537-29855-X

B. Cornils / W. A. Herrmann
Aqueous Phase Organometallic Catalysis
1998. XVI, 631 pages with 180 figures and 76 tables.
Hardcover. ISBN 3-527-29478-3

M. Beller / C. Bolm
Transition Metals for Organic Synthesis
2 Volumes
1998. LVIII, 1062 pages with 733 figures and 75 tables.
Hardcover. ISBN 3-527-29501-1

Roger Arthur Sheldon, Herman van Bekkum

Fine Chemicals through Heterogeneous Catalysis

WILEY-VCH

Weinheim · New York · Chichester
Brisbane · Singapore · Toronto

Prof. Dr. R. A. Sheldon
Delft University of Technology
Organic Chemistry and Catalysis
Julianalaan 136
2628 BL DELFT
The Netherlands

Prof. Dr. H. van Bekkum
Delft University of Technology
Organic Chemistry and Catalysis
Julianalaan 136
2628 BL DELFT
The Netherlands

This book was carefully produced. Nevertheless, authors and publisher do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

First edition 2001
First reprint, 2002, of the first edition 2001

Library of Congress Card No. applied for.

British Library Cataloguing-in-Publication Data: A catalogue record for this book is available from the British Library.

Die Deutsche Bibliothek – CIP Cataloguing-in-Publication-Data

ISBN 3-527-29951-3

© WILEY-VCH Verlag GmbH. D-69469 Weinheim (Federal Republic of Germany), 2001
Printed on acid-free and chlorine-free paper.
All rights reserved (including those of translation in other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Composition: Hagedorn Kommunikation, D-68519 Viernheim.
Printing: Strauss Offsetdruck GmbH, D-69503 Mörlenbach
Bookbinding: Wilhelm Osswald & Co, D-67433 Neustadt
Printed in the Federal Republic of Germany.

Preface

The subject of this book is the application of heterogeneous catalysis in organic synthesis with emphasis on transformations of relevance to fine chemicals manufacture. Both gas and liquid phase reactions are included although the latter are more numerous, analogous to fine chemicals manufacture where substrates and products often have low volatility and/or thermal stability, necessitating operation in the liquid phase. The subject is divided on the basis of the major types of catalytic conversions employed in organic synthesis: acid and base catalysis, hydrogenation and dehydrogenation, oxidation and C-C bond formation.

Heterogeneous catalysis has a long history, dating back to the early studies of alcohol dehydration over alumina and alcohol oxidation over platinum metal in the nineteenth century. Another milestone was the discovery, by the organic chemists Sabatier and Senderens, of catalytic hydrogenations at the beginning of the twentieth century. The high potential of catalysts as „molecular marriage brokers and divorce lawyers“ gradually became apparent and, following the advent of petrochemicals in the nineteen twenties, heterogeneous catalysis by solid acids and supported metals was widely applied in oil refining and petrochemicals. In contrast, fine chemicals manufacture was dominated by synthetic organic chemists who adhered to „stoichiometric“ methodologies. But „times are a changing“. The pressure of environmental legislation has, in the last decade, provided an important stimulus for the development of clean, catalytic methodologies. And heterogeneous catalysts have the added benefit of ease of separation and reuse.

This book is directed towards chemists engaged in organic synthesis, and catalysis, both in industrial and academic laboratories, who are concerned with research and development as well as education. Our primary aim is to cultivate a deeper understanding and, hence, promote a greater utilization of heterogeneous catalysis in organic synthesis. To this end, an international group of recognized authorities in the field of heterogeneous catalysis has been gathered together.

A general introduction to the subject is followed by a discussion of basic principles regarding types of catalyst and their preparation and characterization and types of catalytic reactors. Chapter 3 deals with the different types of solid acids. In the following chapters (4-6) various (solid) acid-catalyzed transformations are reviewed, *e. g.* aromatic substitutions and rearrangements and isomerizations. Solid base-catalyzed processes, *e. g.* aldol and related condensations are discussed in Chapter 7. Subsequent chapters deal with catalytic hydrogenation and dehydrogenation (Chapter 8), catalytic oxidation (Chapter 9) and catalytic C-C bond formation (Chapter 10), culminating in a future outlook (Chapter 11).

Each chapter contains an extensive bibliography covering the principal literature through the end of 1999.

Finally, the editors would like to express their sincere thanks to their friends and colleagues who have contributed such fine chapters to this book. We gratefully acknowledge the invaluable assistance of Mrs. Mieke van der Kooij in coordinating the traffic of manuscripts between contributors, editors and publisher. We also thank Wim Jongeleen for the cover illustration. Finally, we thank Dr. Anette Eckerle and Dr. Roland Kessinger of Wiley-VCH for their help in preparing this book.

Summer 2000

Roger Sheldon
Herman van Bekkum

Contents

List of Contributors

A. Abbadi
AraChem Contract Research & Custom Synthesis
P. O. Box 2021
6020 AA Budel
The Netherlands

D. J. Ager
Richmond Chemical Corporation
4285 Mumford Drive
Hoffman Estates, IL 60195
USA

A. Baiker
Laboratory of Technical Chemistry
ETH-Zentrum
Universitätstrasse 6
8092 Zürich
Switzerland

S. Bailey
Synetix
P. O. Box 1
Belasis Avenue
Billingham
Cleveland TS23 1LB
UK

U. Barsnick
Technische Chemie und Heterogene Katalyse
Technische Hochschule Aachen
Worringerweg 1
52056 Aachen
Germany

M. Bartók
University of Szeged
Department of Organic Chemistry
Dóm tér 8
6720 Szeged
Hungary

J.-M. Basset
Laboratoire COMS CPE Lyon
UMR CNRS 9986
43 bd du 11 novembre 1918
69616 Villeurbanne Cedex
France

A. E. W. Beers
Section Industrial Catalysis
Delft ChemTech
Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

H. van Bekkum
Delft University of Technology
Organic Chemistry and Catalysis
Julianalaan 136
2628 BL Delft
The Netherlands

M. Besson
Institut de Recherche sur la Catalyse-CNRS
2 Avenue Albert Einstein
69626 Villeurbanne Cédex
France

H. U. Blaser
Solvias AG
WRO-1055.6.28
Klybeckstrasse 191
Postfach
4002 Basel
Switzerland

D. Brunel
Laboratoire de Matériaux Catalytiques et Catalyse en Chimie Organique
UMR-CNRS-5618
Ecole Nationale Supérieure de Chimie
8, rue de l'Ecole Normale
34296 Montpellier Cedex 05
France

M. Campanati
University of Bologna
Department of Industrial Chemistry
Catalysis Section
Viale Risorgimento 4
40136 Bologna
Italy

M. G. Clerici
EniTecnologie SpA
Via F. Maritano 26
20097 San Donato Milanese (MI)
Italy

C. Copéret
Laboratoire COMS CPE Lyon
UMR CNRS 9986
43, Bd du 11 novembre 1918
69616 Villeurbanne Cedex
France

A. Corma
Instituto de Tecnología Química – UPV-CSIC
Universidad Polytécnica de Valencia
Avenida de los Naranjos s/n
46022 Valencia
Spain

E. J. Creyghton
Shell International Chemicals B. V.
CTCAT/3
Badhuisweg 3
1031 CM Amsterdam
The Netherlands

A. E. van Diepen
Delft University of Technology
Section Industrial Catalysis
Julianalaan 136
2628 BL Delft
The Netherlands

A. J. van Dillen
U-Cat. b.v.
Utrecht University
Room East 807
Hugo R. Kruytbuilding
Padualaan 8
3584 CH Utrecht
The Netherlands

J. G. Donkervoort
Engelhard de Meern B. V.
Chemical Catalyst Group
Strijkviertel 67
3454 PK de Meern
The Netherlands

R. S. Downing
Boekenroodeweg 7
2111 HJ Aerdenhout
The Netherlands

A. Eisenstadt
IMI (TAMI) Institute for R&D Ltd.
P. O. Box 10140
Haifa Bay 26111
Israel

F. Fache
Institut de Recherches sur la Catalyse
Laboratoire de Catalyse et Synthèse Organique
Université Claude Bernard Lyon I, CPE
43, Bd du 11 novembre 1918
69622 Villeurbanne Cedex
France

F. Figueras
Institut de Recherches sur la Catalyse du CNRS
2 Avenue Albert Einstein
69626 Villeurbanne Cedex
France

P. Gallezot
Institut de Recherches sur la Catalyse-CNRS
2 Avenue Albert Einstein
69626 Villeurbanne Cedex
France

J. M. Garces
The Dow Chemical Company
Corporate R & D, Catalysis.
Bldg. 1776
Midland, MI 48674
USA

J. W. Geus
U-Cat. b.v.
Utrecht University
Room East 807
Hugo R. Kruytbuilding
Padualaan 8
3583 CH Utrecht
The Netherlands

K. Griffin
Johnson Matthey Plc
Process Catalyst
Orchard Road
Royston, Herts SG8 5HE
UK

M. Guisnet
Université de Poitiers
Catalyse en Chimie Organique – CNRS – DO350 – UMR 6503
40, Avenue du Recteur Pineau
86022 Poitiers Cedex
France

W. F. Hölderich
Technische Chemie und Heterogene Katalyse
Technische Hochschule Aachen
Worringerweg 1
52056 Aachen
Germany

S. Iborra
Instituto de Tecnología Química – UPV-CSIC
Universidad Polytécnica de Valencia
Avenida de los Naranjos s/n
46022 Valencia
Spain

Y. Izumi
Sugiyama Jogakuen University
Department of Human Environment
17-3, Hoshigaoka, Motomachi, Chikusa-ku
Nagoya 464-8662
Japan

P. A. Jacobs
Centrum voor Oppervlaktechemie en Katalyse
Katholieke Universiteit Leuven
Kardinaal Mercierlaan 92
3001 Heverlee
Belgium

F. Kapteijn
Section Industrial Catalysis
Delft ChemTech
Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

F. King
Synetix
P. O. Box 1
Belasis Avenue
Billingham
Cleveland TS23 1LB
UK

A. Kogelbauer
Department of Chemical Engineering and Chemical Technology
Imperial College of Science, Technology and Medicine
London SW7 2AZ
UK

H. W. Kouwenhoven
Laboratorium für Technische Chemie
ETH-Zentrum
8092 Zürich
Switzerland

E. G. M. Kuijpers
Engelhard de Meern B. V.
Chemical Catalyst Group
Strijkviertel 67
3454 PK De Meern
The Netherlands

P. J. Kunkeler
Akzo PQ Silica
Ankerkade 111
6222 NL Maastricht
The Netherlands

G. S. Lee
The Dow Chemical Company
Corporate R&D, Catalysis.
Bldg. 1776
Midland, MI 48674
USA

M. Lemaire
CPE/UCBL/CNRS
Bat. 308
43, Bd du 11 novembre 1918
69622 Villeurbanne Cedex
France

J. Lopez
Institut de Recherches sur la Catalyse du CNRS
2 Avenue Albert Einstein
69626 Villeurbanne Cedex
France

B. Lücke
Institut für Angewandte Chemie
Berlin-Adlershof e. V.
Richard-Wilstätter-Str. 12
12489 Berlin
Germany

D. J. Macquarrie
Centre for Clean Technology
Department of Chemistry
University of York
Heslington, York YO10 5DD
UK

T. Mallat
Laboratory of Technical Chemistry
ETH-Zentrum
Universitätstrasse 6
8092 Zürich
Switzerland

A. Martin
Institut für Angewandte Chemie
Berlin-Adlershof e. V.
Richard-Wilstätter-Str. 12
12489 Berlin
Germany

C. H. McAteer
Reilly Industries, Inc.
1500 South Tibbs Avenue
P. O. Box 42912
Indianapolis, Indiana 46242-0912
USA

G. R. Meima
Corporate R&D
Dow Benelux N. V.
P. O. Box 48
4530 AA Terneuzen
The Netherlands

P. Métivier
Rhodia
Centre de Recherches de Lyon
85, Ave. des Frères Perret – B. P. 62
69192 Saint Fons Cedex
France

G. J. Meuzelaar
Stockholm University
Department of Organic Chemistry
Arrhenius Laboratory
10691 Stockholm
Sweden

J. C. Mol
University of Amsterdam
Faculteit of Chemistry
Institute of Molecular Chemistry
Nieuwe Achtergracht 166
1018 WV Amsterdam
The Netherlands

A. Molnár
University of Szeged
Department of Organic Chemistry
Dóm tér 8
6720 Szeged
Hungary

J. A. Moulijn
Section Industrial Catalysis
DelftChemTech
Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

T. A. Nijhuis
Section Industrial Catalysis
Delft ChemTech
Delft University of Technology
Julianalaan 136
2628 BL Delft
The Netherlands

F. Notheisz
University of Szeged
Department of Organic Chemistry
Dóm tér 8
6720 Szeged
Hungary

Dr. Peter Panster
Degussa-Huels AG
Sivento Division – R&D and Applied
Technology Chemical Catalysts
Rodenbacher Chaussee 4
P. O. Box 1345
63403 Hanau
Germany

G. Pérot
Université de Poitiers
Catalyse en Chimie Organique – CNRS
DO350 – UMR 6503
40, Avenue du Recteur Pineau
86022 Poitiers Cedex
France

R. Prins
ETH Zürich
Laboratorium für Technische Chemie
8092 Zürich
Switzerland

P. Ratnasamy
National Chemical Laboratory
Pune 411008
India

W. Van Rhijn
Centrum voor Oppervlaktechemie en Katalyse
Katholieke Universiteit Leuven
Kardinaal Mercierlaan 92
3001 Heverlee
Belgium

D. Roberge
Technische Chemie und Heterogene Katalyse
Technische Hochschule Aachen
Worrigerweg 1
52056 Aachen
Germany

E. F. V. Scriven
Reilly Industries, Inc.
1500 South Tibbs Avenue
P. O. Box 42912
Indianapolis, Indiana 46242-0912
USA

T. Setoyama
Mitsubishi Chemical Corporation
Yokohama Research Center
1000, Kamoshida, Aoba-ku
Yokohama 227
Japan

R. A. Sheldon
Delft University of Technology
Organic Chemistry and Catalysis
Julianalaan 136
2628 BL Delft
The Netherlands

U. Siegrist
Solvias AG
WRO-1055.6.28
Klybeckstrasse 191
Postfach
4002 Basel
Switzerland

K. E. Simons
Johnson Matthey Plc
Process Catalyst
Orchard Road
Royston, Herts SG8 5HE
UK

A. P. Singh
National Chemical Laboratory
Pune 411008
India

H. Steiner
Solvias AG
WRO-1055.6.28
Klybeckstrasse 191
Postfach
4002 Basel
Switzerland

M. Studer
Solvias AG
WRO-1055.6.28
Klybeckstrasse 191
Postfach
4002 Basel
Switzerland

K. Swift
Quest International Ltd.
Willesborough Road
Ashford, Kent TN24 0LT
UK

T. Tatsumi
Yokohama National University
Catalysis Laboratory – Faculty of
Engineering
Division of Materials Science &
Chemical Engineering
79-5 Tokiwadai, Hodogaya-ku
Yokohama 240-8501
Japan

J. Thivolle-Cazat
Laboratoire COMS CPE Lyon
UMR CNRS 9986
43, Bd du 11 novembre 1918
69616 Villeurbanne Cedex
France

A. Vaccari
University of Bologna
Department of Industrial Chemistry
Catalysis Section
Viale Risorgimento 4
40136 Bologna
Italy

F. Valot
Institut de Recherches sur la Catalyse
Laboratoire de Catalyse et Synthèse
Organique
Université Claude Bernard Lyon I, CPE
43, Bd du 11 novembre 1918
69622 Villeurbanne
France

M. C. A. van Vliet
Delft University of Technology
Organic Chemistry and Catalysis
Julianalaan 136
2628 BL Delft
The Netherlands

D. E. De Vos
Centrum voor Oppervlaktechemie en
Katalyse
Katholieke Universiteit Leuven
Kardinaal Mercierlaan 92
3001 Heverlee
Belgium

J. C. van der Waal
Avantium
Julianalaan 136
2628 BL Delft
The Netherlands

Dr. Stefan Wieland
dmc (superscript: 2) – Degussa Metals
Catalysts Cerdec AG
Fuel Cell Division – Research and
Applied Technology
Rodenbacher Chaussee 4
P. O. Box 1351
63403 Hanau
Germany

T. Yokoyama
Mitsubishi Chemical Corporation
Yokohama Research Center
100, Kamoshida, Aoba-ku
Yokohama 227
Japan

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

1 Introduction

Roger Sheldon, H. van Bekkum

1.1 What are Fine Chemicals?

There are no universally accepted definitions of bulk, fine, and specialty chemicals, nor are these classifications based on any intrinsic properties. A substance that is currently viewed as a bulk chemical might well have been classified as a fine chemical at an earlier stage in its development. A useful working definition of a fine chemical is one with a price of more than 10 US dollars kg^{-1} and a volume of less than 10 000 tons per annum on a worldwide basis. We make no distinction between fine chemicals, that are often intermediates, and specialty chemicals such as pharmaceuticals, pesticides, and flavors and fragrances. The type of technology used to manufacture these products is dictated more by volume than by product application.

From a chemical viewpoint fine chemicals are generally complex, multifunctional molecules and, consequently, are often of low volatility and limited thermal stability. This means that processes are generally performed in the liquid phase. Fine chemicals manufacture often involves multistep syntheses and is generally performed in a multipurpose equipment. This contrasts with the manufacture of bulk chemicals which usually involves continuous processing in dedicated plants. Hence, the emphasis in fine chemicals manufacture is on the development of processes that have broad scope and can be implemented in standard multipurpose equipment.

1.2 The Environmental Factor

It is now widely accepted that there is an urgent need for more environmentally acceptable processes in the chemical industry [1]. This trend towards what has become known as green chemistry [2,3] or sustainable technology necessitates a paradigm shift from traditional concepts of process efficiency, that focus exclusively on chemical yield, to one that assigns economic value to eliminating waste and avoiding the use of toxic and/or hazardous substances. Green chemistry eliminates waste at the source, i. e. it is primary pollution prevention rather than waste remediation (end-of-pipe solutions).

The sheer magnitude of the waste problem in the manufacture of chemicals is readily apparent from a consideration of the amount of waste produced per kg product, the so-called '*E* factor' [4,5], in different segments of the chemical industry (Table 1).

These enormous quantities of waste consist primarily of inorganic salts, such as sodium chloride, sodium sulfate, and ammonium sulfate, formed in the reaction or in subsequent neutralization steps. The *E* factor increases dramatically on going downstream from bulk to fine chemicals and pharmaceuticals, partly because the production of the latter involves multistep syntheses and partly because of the use of stoichiometric (inorganic) reagents rather than catalytic methodologies. Although the absolute quantities are much smaller than in the synthesis of bulk chemicals, the need for greener, low-salt technologies is clearly more urgent in fine chemicals manufacture.

Comparisons of alternative processes solely on the basis of the amount of waste is obviously a gross oversimplification. An assessment of the environmental impact of a process should take both the amount and the nature of the waste into account. To this end the environmental quotient (*EQ*) was introduced [4]. It is obtained by multiplying the *E* factor by an arbitrarily assigned unfriendliness quotient, *Q*. For example, if an innocuous salt such as NaCl is assigned a *Q* value of 1 then heavy metal salts could be given a factor of, say, 100–1000 depending on their toxicity, ease of recycling, etc. The magnitude of *Q* is obviously debatable but it is clear that a quantitative assessment of the environmental impact of waste streams is, in principle, possible.

Table 1. E factors in the chemical industry.

Industry segment	Product tonnage[a]	*E* (kg waste/kg product)
Bulk chemicals	$< 10^4$–10^6	$< 1 \rightarrow 5$
Fine chemicals	10^2–10^4	$5 \rightarrow > 50$
Pharmaceuticals	10–10^3	$25 \rightarrow > 100$

[a] Depending on the product this could be the capacity of a single plant or the world-wide production.

1.3 The Development of Organic Synthesis and Catalysis

As noted above, a primary cause of waste production in the fine chemicals industry is the widespread use of stoichiometric reagents. Classical 'stoichiometric' technologies that generate copious quantities of inorganic salts are rampant in fine chemicals manufacture, primarily the domain of the synthetic organic chemist. Examples which readily come to mind are stoichiometric oxidations with permanganate, manganese dioxide, and chromium(VI) reagents, stoichiometric reductions with metal hydrides ($NaBH_4$, $LiAlH_4$, and variants thereof) and reducing metals (Zn, Fe, Mg, Na) and a wide variety of reactions that employ stoichiometric quantities of Lewis acids ($AlCl_3$, BF_3, $ZnCl_2$) or mineral acids (H_2SO_4, H_3PO_4, HF). An example of the latter, which is widely applied in fine chemicals manufacture, is Friedel–Crafts acylation, generally employing more than one equivalent of $AlCl_3$.

The solution to this waste problem is evident: the widespread substitution of antiquated stoichiometric technologies with cleaner catalytic alternatives. But if the solution is so obvious why has it not been widely applied in the past? We suggest several reasons. Firstly, because of the smaller quantities compared with bulk chemicals, the need for a reduction in waste in fine chemicals production was not fully appreciated in the past.

A second, underlying, reason is the more or less separate evolution of organic chemistry and catalysis (see Figure 1) since the time of Berzelius, who coined both terms, in 1807 and 1835, respectively [6]. Catalysis subsequently developed largely as a subdiscipline of physical chemistry. With the advent of the petrochemicals industry in the 1930s, catalysis was widely applied in oil refining and bulk chemicals manufacture. This largely involved the application of heterogeneous catalysts in the gas phase. Organic synthesis, in contrast, followed a different line of evolution. It can be traced back to Perkin's serendipitous synthesis of aniline purple in 1856 which marked the advent of the synthetic dyestuffs industry based on coal tar as the raw material. The present day fine chemicals and pharmaceuticals industries evolved largely as spin-offs of this activity. Coincidentally, Perkin was attempting to synthesize a drug, quinine, by oxidation of a coal tar-based raw material, allyl toluidine, using stoichiometric quantities of potassium dichromate.

A third reason is the pressure of time. Generally speaking, fine chemicals have a much shorter lifecycle than bulk chemicals and 'time to market' is of the utmost importance. An advantage of many time-honored classical technologies is that they are broadly applicable and can be implemented relatively quickly. In contrast, the development of an alternative catalytic technology might be more time-consuming (and expensive). Consequently, environmentally inferior technologies are used to meet market deadlines. In pharmaceuticals manufacture subsequent process changes are prohibitive because of the problems associated with FDA approval.

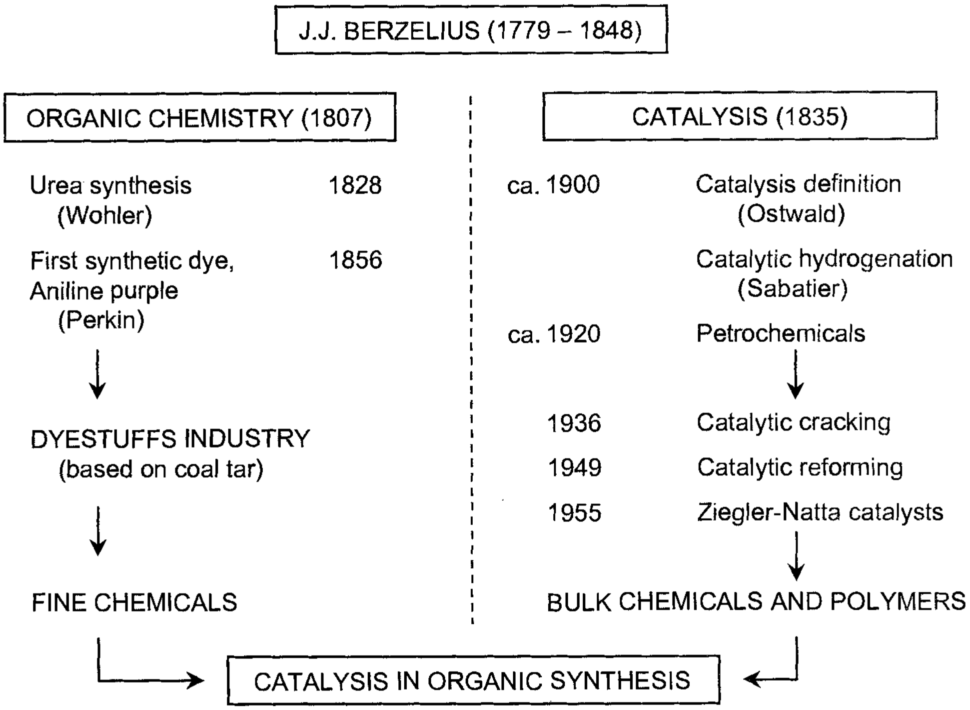


Figure 1. Evolution of organic synthesis and catalysis.

But times are changing. Under the mounting pressure of environmental legislation the fine chemicals industry is forced to focus more attention on waste minimization and avoiding the use of hazardous and/or toxic reagents. Hence, the time is ripe for the widespread application of catalytic methodologies.

1.4 Why Heterogeneous Catalysis?

In the drive towards cleaner methodologies the entire arsenal of catalytic methodologies–homogeneous, heterogeneous and enzymatic catalysis–will be brought to bear on organic synthesis. All three approaches have their advantages and limitations. Homogeneous catalysis by organometallic complexes [7] is finding wide application in both bulk and fine chemicals and is the method of choice in e.g. carbonylations and hydroformylations. Similarly, biocatalysis [8], which has the advantage of mild reaction conditions and high chemo-, regio-, and enantioselectivity, will be increasingly used in fine chemicals manufacture.

Solid, heterogeneous catalysts have the advantages of ease of recovery and recycling and are readily amenable to continuous processing. Heterogeneous catalysis has, moreover, already been widely applied in oil refining and bulk chemicals manufacture [9,10]. The experience and understanding gleaned from these applications form a sound foundation for their use in organic synthesis [11]. Sometimes, e.g. catalytic hydrogenation, bulk chemical methodologies can be readily down-scaled to fine chemical synthesis.

The use of microporous solid catalysts such as zeolites and related molecular sieves has an additional benefit in organic synthesis. The highly precise organization and discrimination between molecules by molecular sieves endows them with shape-selective properties [12] reminiscent of enzyme catalysis. The scope of molecular sieve catalysis has been considerably extended by the discovery of ordered mesoporous materials of the M41S type by Mobil scientists [13,14]. Furthermore, the incorporation of transition metal ions and complexes into molecular sieves extends their catalytic scope to redox reactions and a variety of other transition metal-catalyzed processes [15,16].

1.5 Types of Catalysts and Reactions

The catalytic reactions of interest in organic synthesis can conveniently be divided into five categories: solid-acid catalysis, solid-base catalysis, catalytic hydrogenation and dehydrogenation, catalytic oxidation, and catalytic C–C bond formation.

1.5.1 Solid-Acid Catalysis

As mentioned earlier a major source of waste derives from the use of mineral and Lewis acids which cannot be readily recovered and recycled. Widespread replacement by recyclable solids would obviate the need for hydrolytic work-up and afford a dramatic reduction in waste. Moreover, solid acids are less corrosive and easier (safer) to handle than mineral acids such as H_2SO_4 and HF.

A wide variety of solid-acid catalysts is available [17]: acidic clays, zeolites, silica-occluded heteropoly acids, sulfonated polysiloxanes, Nafion (a sulfonated perfluoroalkyl resin) and Nafion–silica composites, and a variety of hybrid sulfonated mesoporous systems (see Chapter 3).

These solid-acid catalysts are, in principle, applicable to a plethora of acid-catalyzed processes in organic synthesis [18]. These include various electrophilic aromatic substitutions, e.g. nitrations, halogenations, and Friedel–Crafts alkylations and acylations, and numerous rearrangement reactions such as the Beckmann and Fries rearrangements. Other examples include a variety of cyclization reactions such as Diels–Alder reactions and the synthesis of pyridines and other heterocycles.

1.5.2 Solid-Base Catalysis

The use of solid bases as catalysts in organic synthesis is less well-developed than solid-acid catalysis but is becoming increasingly popular [18]. For example, hydrotalcite anionic clays [19] and mesoporous silicas modified by surface attachment of organic bases [20] are effective and recyclable catalysts for aldol, Knoevenagel, and related condensations that are widely used in fine chemical synthesis.

1.5.3 Catalytic Hydrogenation

Catalytic hydrogenation over supported noble metal catalysts has a longstanding tradition, dating back to its discovery by Sabatier, of application in organic synthesis [21,22]. A wide variety of functional groups are efficiently hydrogenated, often with high chemo-, regio-, and stereoselectivity. Occasionally surface modification of supported noble metal catalysts with chiral additives can also afford high enantioselectivity [23]. Alternatively, a variety of methods is available for immobilization of chiral metal complexes on organic or inorganic supports to produce solid catalysts for enantioselective hydrogenation [24]. New developments continue to appear, e. g. the direct hydrogenation of carboxylic acids to the corresponding aldehydes [25].

1.5.4 Catalytic Oxidations

Selective oxidations, e.g. alcohol oxidations and olefin epoxidations, are pivotal transformations in organic synthesis [26]. Many of these transformations are currently performed, both on laboratory and industrial scale, by use of stoichiometric inorganic oxidants, e.g. chromium(VI) reagents. There is an urgent need, therefore, for catalytic methods that employ O_2 or H_2O_2 as the primary oxidant and are effective with a broad range of substrates. Here again, heterogeneous catalysts have the added benefits, compared with their homogeneous counterparts, of ease of recovery and recycling and amenability to continuous processing. Site-isolation of transition metal centers in a solid (inorganic) matrix can, furthermore, afford catalysts with unique activity because oligomerization of active monomeric oxometal (M=O) or related species to inactive μ-oxo complexes is precluded [27].

Various strategies can be envisaged for the immobilization of redox-active elements in a solid matrix [27,28]. Mixed oxides, e.g. the TiO_2–SiO_2 epoxidation catalyst, can be prepared by impregnation techniques or by the sol–gel method [29]. The latter is analogous to the hydrothermal synthesis of zeolites and related molecular sieves (see later). Redox metal ions can be incorporated into acidic clays or zeolites by ion exchange, and oxoanions can be similarly exchanged into hydrotalcite-like anionic clays [30].

Alternatively, redox metal ions can be incorporated into framework positions of zeolites and related molecular sieves by hydrothermal synthesis or post-synthesis modifications [15]. A suitable choice of molecular sieve, with an appropriate pore size and hydrophobicity, enables one to influence which molecules can readily access the active site on the basis of their dimensions and/or their hydrophobic or hydrophilic properties [15]. Such materials bear a resemblance to redox enzymes in which the protein mantle plays an analogous role and, for this reason, these redox molecular sieves have been referred to as mineral enzymes [31]. The prototype, titanium(IV) silicalite (TS-1), discovered by Enichem scientists in the mid-eighties, is a benchmark in heterogeneous catalysis of liquid phase oxidations [32]. TS-1 catalyzes a variety of synthetically useful oxidations with 30 % aqueous hydrogen peroxide. The success of TS-1 led to a flourish of activity world-wide, which still continues today, on the development of redox molecular sieve catalysts for selective oxidations in the liquid phase.

Redox metal centers can also be grafted on to the surface of silica, or on to the internal surface of a molecular sieve, by ligand displacement with pendant silanol groups [33]. Alternatively metal complexes can be tethered to silica or the internal surface of a molecular sieve via a spacer that is attached to the surface. This approach is analogous to the tethering of organic bases to solid surfaces referred to earlier. Metal complexes can also be attached to oxidatively stable organic polymers such as polybenzimidazole [34].

In yet another approach metal complexes are encapsulated in zeolite cages to give so-called 'ship-in-a-bottle' complexes [35] or, alternatively, in polydimethylsiloxane membranes [36].

Finally, supported noble metals widely used as hydrogenation catalysts can be used to catalyze the reverse reaction–oxidative dehydrogenation–in the presence of oxygen. This is applied, for example, in the oxidative dehydrogenation of alcohols and carbohydrates (see Sections 9.2 and 9.3).

1.5.5 Catalytic C–C Bond Formation

The generation of new C–C bonds also occupies a prominent position in organic synthesis. This often involves condensation of carbonyl compounds referred to earlier in the context of solid-base catalysis (Section 1.5.2). There are, however, also many C–C bond-forming reactions that involve transition metal catalysis and some of these can be conveniently performed with heterogeneous catalysts, e. g. olefin metathesis (Section 10.2) and Heck and related couplings (Section 10.3). Moreover, tethering of organometallic complexes to a silica surface or to the internal surface of a mesoporous host can, in principle, be used to design heterogeneous catalysts for a variety of C–C bond-forming reactions [16].

1.6 Alternative Approaches

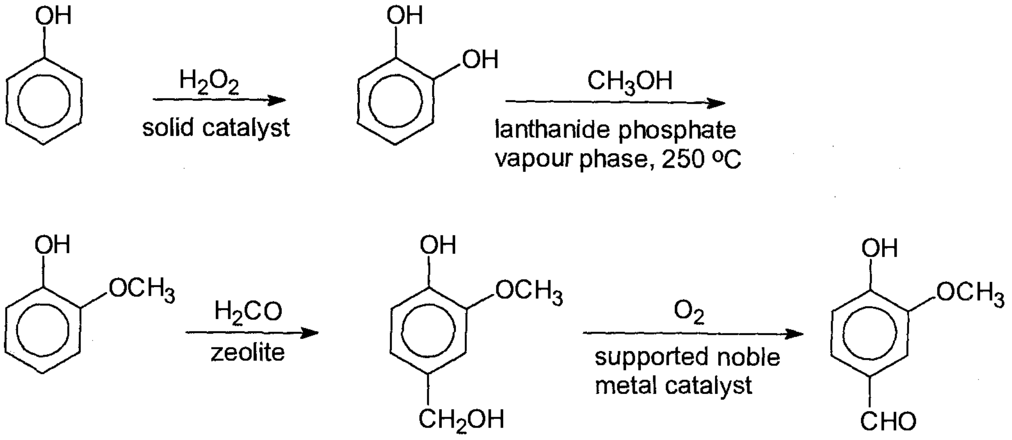
This book is concerned with the classical concept of heterogeneous catalysis–a solid catalyst with the reactants in a liquid or gas phase. As noted earlier, in the context of fine chemicals the reactants will usually be in the liquid phase and separation of the catalyst from the reactants and products involves simple filtration or centrifugation. For the sake of completeness, however, it is worth drawing attention to alternative approaches to achieving the goal of facile catalyst separation and recycling. For example, instead of the classical solid–liquid combination liquid–liquid biphasic systems can be employed. In this concept the catalyst resides in one phase, e.g. water, and the reactants and products in a separate, e.g. organic, phase. This concept is widely used in organometallic catalysis but has been reviewed elsewhere [37,38] and falls outside the scope of this book. A variation on this theme is fluorous biphasic catalysis in which the water is replaced by an immiscible fluorous phase which contains the catalyst [39]. In supported-liquid-phase catalysis (SLPC) a metal complex is dissolved in a thin film of polar solvent (usually water) adsorbed on a high-surface-area hydrophilic support such as silica or controlled-pore glasses [40]. The resulting catalyst is placed in contact with a water-immiscible liquid phase containing the reactants and the reaction occurs at the aqueous–organic interface. The catalyst can be recovered by filtration.

Another approach involves the covalent attachment of a metal complex to a (water-) soluble polymer [41]. By using thermoresponsive, 'smart', polymers the reaction can be performed in a homogeneous liquid phase and, after completion, the polymer-enlarged catalyst can be precipitated by adjusting the temperature [42].

Alternatively, membrane filtration can be used to separate soluble metal complexes, containing polymer-attached ligands, from reactants and products [43]. A major advantage of using soluble polymer-enlarged catalysts in conjunction with membrane separation is that it is readily amenable to continuous operation. A novel example of this concept is the use of dendritic ligands [44] in combination with membrane filtration.

1.7 Heterogeneous Catalysis in Multi-step Synthesis: Vanillin

An elegant example of what can be achieved by the application of heterogeneous catalysis to fine chemicals production is provided by the new process for the flavor ingredient vanillin (10 000 tons per annum worldwide production), developed by Rhodia [25]. The process (Figure 2) involves four catalytic steps, all involving a solid, heterogeneous catalyst, starting from phenol. Aromatic ring hydroxylation with H_2O_2 over a solid catalyst (see Section 9.6) is followed by gas phase O-methylation with methanol, zeolite-catalyzed hydroxymethylation (see Section



overall: $PhOH + CH_3OH + H_2CO + H_2O_2 + 1/2\ O_2 \longrightarrow \text{vanillin} + 3\ H_2O$

Figure 2. The Rhodia process for vanillin.

4.5), and, finally, oxidation of a benzylic alcohol over a supported noble metal catalyst (see Section 9.2). The only coproduct is water, three moles of which are formed per mole of vanillin.

This process is evidently superior to existing processes for vanillin, from both economic and environmental viewpoints. It is truly an example of elegance and precision in organic synthesis.

Finally it may be mentioned that catechol can also be prepared starting from glucose [45] which classifies the new vanillin process as green in two respects.

References

[1] C. Christ, Ed. *Production–Integrated Environmental Protection and Waste Management in the Chemical Industry*, Wiley–VCH, Weinheim, 1999.
[2] P. T. Anastas and J. C. Warner, Eds., *Green Chemistry: Theory and Practice*, Oxford Univ. Press, Oxford, 1998.
[3] P. T. Anastas and T. C. Williamson, Eds., *Green Chemistry: Frontiers in Chemical Synthesis and Processes*, Oxford Univ. Press, Oxford, 1998.
[4] R. A. Sheldon, *Chemtech*, March 1994, pp. 38–47.
[5] R. A. Sheldon, *Chem. Ind. (London)* **1992**, 903 and **1997**, 12; R. A. Sheldon, *J. Chem. Tech. Biotechnol.* **1997**, *68*, 381.
[6] R. Larsson, Ed., *Perspectives in Catalysis, in commemoration of Jöns Jacob Berzelius*, Liber Läromedel, Lund, 1981.
[7] B. Cornils and W. A. Herrmann, Eds., *Applied Homogeneous Catalysis with Organometallic Compounds*, VCH, Weinheim, 1996.
[8] K. Drauz and H. Waldmann, Eds., *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim, 1995.

[9] G. Ertl, H. Knözinger and J. Weitkamp, Eds., *Handbook of Heterogeneous Catalysis*, Wiley–VCH, Weinheim, 1997.

[10] J.M. Thomas and W.J. Thomas, *Principles and Applications of Heterogeneous Catalysis*, VCH, Weinheim, 1997.

[11] R.L. Augustine, *Heterogeneous Catalysis for the Synthetic Organic Chemist*, Marcel Dekker, New York, 1996.

[12] S.M. Csicsery, *Pure Appl. Chem.* **1986**, *58*, 841; S.M. Csicsery, *Zeolites* **1984**, *4*, 202; P.B. Weisz and V.J. Frilette, *J. Phys. Chem.* **1960**, *64*, 382.

[13] C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli and J.S. Beck, *Nature* **1992**, *35*, 710.

[14] J.C. Vartuli and J.S. Beck, *Curr. Opin. Solid. State Mater. Sci.* **1997**, *2*, 98.

[15] I.W.C.E. Arends, R.A. Sheldon, M. Wallau and U. Schuchardt, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1144.

[16] J.M. Thomas, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3588.

[17] Y. Izumi, K. Urabe and M. Onaka, *Zeolites, Clays and Heteropoly Acids in Organic Reactions*, VCH, Weinheim, 1992; A. Corma, *Chem. Rev.* **1995**, *95*, 559.

[18] For a recent review of industrial applications of solid acid–base catalysts see: K. Tanabe and W. Hölderich, *Appl. Catal. A: General* **1999**, *181*, 399.

[19] A. Vaccari, *Catal. Today* **1998**, *41*, 53; A. Vaccari, *Appl. Clay Sci.* **1999**, *14*, 161.

[20] D. Brunel, *Microporous Mesoporous Mater.* **1999**, *27*, 329; D.J. Macquarrie, *Green Chemistry* **1999**, *1*, 195.

[21] R.L. Augustine, *Catalytic Hydrogenation, Techniques and Applications in Organic Synthesis*, Marcel Dekker, New York, 1965.

[22] P.N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, 1979; P.N. Rylander, *Hydrogenation Methods*, Academic Press, New York, 1985.

[23] A. Baiker, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 86; A. Baiker and H.U. Blaser, in *Handbook of Heterogeneous Catalysis*, Vol. 5, G. Ertl, H. Knözinger and J. Weitkamp, Eds., Wiley–VCH, Weinheim, 1997, p. 2422.

[24] K. Fodor, S.G.A. Kolmschot and R.A. Sheldon, *Enantiomer* **1999**, *4*, 497 and references cited therein.

[25] S. Ratton, *Chem. Today*, March/April 1997, 33.

[26] S.V. Ley and A. Modin, in *Comprehensive Organic Synthesis*, B.M. Trost, I. Fleming and S.V. Ley, Eds., Pergamon, Oxford, 1992, Vol. 7, p. 251.

[27] R.A. Sheldon, I.W.C.E. Arends and H.E.B. Lempers, *Catal. Today* **1998**, *41*, 387.

[28] G. Langhendries, D.E. De Vos, B.F. Sels, I. Vancelecom, P.A. Jacobs and G.V. Baron, *Clean Prod. Proc.* **1998**, *1*, 21.

[29] M. Schneider and A. Baiker, *Catal. Rev. Sci. Eng.* **1995**, *37*, 515.

[30] B. Sels, D.E. De Vos, M. Buntinx, F. Pierard, A. Kirsch-De Mesmaeker and P.A. Jacobs, *Nature* **1999**, *400*, 855.

[31] R.F. Parton, D.E. De Vos and P.A. Jacobs, in *Zeolite Microporous Solids: Synthesis, Structure and Reactivity*, E.G. Derouane, F. Lemos, C. Naccache and F. Ramôa Ribeiro, Eds., Kluwer, Dordrecht, 1992, p. 531.

[32] B. Notari, *Advan. Catal.* **1996**, *41*, 253.

[33] For an example see: T. Maschmeyer, F. Rey, G. Sankar and J.M. Thomas, *Nature* **1995**, *378*, 159.

[34] D.C. Sherrington, In *Supported Reagents and Catalysts in Chemistry*, B.K. Hodnett, A.P. Kybett, J.H. Clark and K. Smith, Eds., Roy. Soc. Chem., Cambridge, 1998, p. 220.

[35] D.E. De Vos, R.F. Parton, B.M. Weckhuysen, P.A. Jacobs and R.A. Schoonheydt, *J. Incl. Phen. Mol. Recogn. Chem.* **1995**, *21*, 185.

[36] I.F.J. Vancelecom, K. Vercruysse, P. Neys, D. Tas, K.B.M. Janssen, P.P. Knops-Gerrits and P.A. Jacobs, *Top. Catal.* **1998**, *5*, 125.

[37] B. Cornils and W. Herrmann, Eds., *Aqueous Phase Organometallic Catalysis*, Wiley–VCH, Weinheim, 1998.

[38] G. Papadogianakis and R.A. Sheldon, in *Catalysis, Specialist Periodical Report*, Vol. 13, J.J. Spivey, Ed., Roy. Soc. Chem., Cambridge, 1997, p. 114.

[39] I.T. Horvath, *Acc. Chem. Res.* **1998**, *31*, 641.

[40] K. T. Wan and M. E. Davis, *Nature* **1994**, *370*, 449; *J. Catal.* **1995**, *152*, 25.
[41] T. Malmström and C. Andersson, *J. Chem. Soc., Chem. Commun.* **1996**, 1135.
[42] D. E. Bergbreiter, *Catal. Today* **1998**, *42*, 389.
[43] U. Kragl, C. Dreisbach and C. Wandrey, in *Applied Homogeneous Catalysis with Organometallic Compounds*, B. Cornils and W. A. Herrmann, Eds., VCH, Weinheim, 1996, p. 832.
[44] J. W. J. Knapen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. J. Wijkens, D. M. Grove and G. van Koten, *Nature* **1994**, *372*, 569.
[45] K. M. Draths and J. W. Frost in *Green Chemistry*, P. T. Anastas and T. C. Williamson, Eds., Oxford University Press **1998**, p. 150.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

2 Basic Principles/General

2.1 General Considerations and Types of Catalyst

John W. Geus, A. J. van Dillen

2.1.1 Introduction

Many different solid catalysts are employed in the production of fine chemicals. The amount of catalyst used is, however, often relatively small, viz., less than one ton per year. As a result expenditure on an individual catalyst seldom justifies much research on its optimization for the production of fine chemicals. Research aimed at improving the catalyst is worthwhile only when the selectivity is low and the cost of purifying the desired product from the by-products is high. An example is the development of enantioselective solid catalysts, where selectivity is dominating.

The small amounts of solid catalysts purchased by the fine-chemical industry means that contact between the catalyst producers and the fine-chemical industry is usually very limited. Often the fine-chemical industry does not wish to inform the catalyst producer about the specific reaction that is to be performed with the catalyst. Although there is much room for the development of better catalysts, there is no commercial incentive to improve the situation. Elucidation of the fundamental principles underlying the activity and selectivity of solid catalysts in the liquid-phase reactions characteristic of many fine-chemical processes might lead to the development of solid catalysts better adapted to specific processes.

2.1.2 Catalytically Active Surface Area

The acceleration of a chemical reaction by solid catalysts proceeds at the surface of the catalyst. The catalytic activity of solids is therefore generally proportional to the surface area of the catalytically active component of the catalyst per unit weight or per unit volume. The surface area per unit volume depends on the size of the solid particles and the bulk density. Assuming a bulk density of 1.5 g cm^{-3} and a (X-ray) density of 4.0 g cm^{-3}, which is relevant for, e. g., γ-Al_2O_3, the surface area is 2.25×10^4 m^2 m^{-3} for 0.1-mm particles and 2.25×10^6 m^2 m^{-3} for 1-μm particles. For 50-nm particles the surface area is very much larger, viz. 4.5×10^7 m^2 m^{-3}.

When it is possible to fill a reactor with catalyst up to the bulk density, these surface areas per unit volume can be achieved. We now will calculate the rate of production per unit volume of catalyst that can be obtained provided transport limitations do not interfere. We assume a product having a molecular weight of 80. Usually the number of catalytically active atoms at the surface of a solid catalyst is smaller than the total number of surface atoms, which in metal surfaces is of the order of 10^{19} m^{-1}. Here we will assume that 2×10^{18} atoms m^{-2} are catalytically active. The turnover number indicates the number of molecules reacting s^{-1} per active site. The turnover number usually ranges between 10^{-2} and 10^2 s^{-1} [1]. For this calculation we will take a turnover number of 1 s^{-1}. Finally we use a working day of 8 h–the fine-chemical industry does not usually work continuously.

For 1-cm catalyst particles with an active surface area of 225 m^2 m^{-3} production is 1.8 kg day^{-1}, whereas 10-μm catalyst particles with a surface area of 2.25×10^5 per m^3 produce 1.8 ton day^{-1} or 540 ton m^{-3} $year^{-1}$.

A reactor completely filled with catalyst to the level of the bulk density is not, however, often employed in the fine-chemical industry. Usually a weight fraction of catalyst varying from 0.07 % (*w/w*) to about 2.5 % (*w/w*) is utilized. Assuming a catalyst loading of 1 % (*w/w*), a density of reactants of 1 g cm^{-3}, and the above density of the catalyst of 4 g cm^{-3}, the volume fraction of the catalyst is 2.5×10^{-3} m^3 m^{-3}. With 1-cm catalyst particles the surface area is now only 0.56 m^2 m^{-3} . The resulting production is a mere 4.3 g day^{-1}, which is evidently not acceptable. With 10- and 1-μm catalyst particles the production is 4.3 and 43 kg day^{-1}, which is still fairly low. Production of 860 kg day^{-1} is obtained with very tiny (50-nm) catalyst particles.

2.1.3 Reactors Employed in the Fine-chemical Industry

The above discussion indicates the importance of the size of the catalyst particles–a very small size is required if a technically useful rate of production is to be achieved. The range of sizes of the catalyst particles that can be employed is, however, dominated by the reactor in which the catalyst must operate. Most of the reactions performed in the fine-chemical industry involve liquid-phase processes, normally reactions between two different dissolved compounds. Often one of the reactants is a gaseous compound, which dissolves in the liquid and migrates to the surface of the catalyst. Hydrogenation with gaseous hydrogen is an example of a reaction involving the dissolution of a gaseous reactant in a liquid before reaction.

As covered in Section 2.4 by Van Diepen and Moulijn, multipurpose reactors are usually used in the fine-chemical industry–the relatively small quantities of products of the fine-chemical industry do not justify setting up a separate reactor for each chemical conversion, as is customary in the bulk chemical industry. A range of products is therefore produced in the same reactor (Figure 1), which is consecutively loaded with a number of different catalysts. Solid catalysts are usually suspended in liquid in the multipurpose reactor. Slurry-phase catalysts are, therefore, mostly employed in the fine-chemical industry.

When chemical compounds are continuously consumed in fine-chemical plants or the market requires certain chemical compounds at a constant fairly elevated level, it is often more attractive to produce these compounds in a dedicated reactor. Now a fixed-bed reactor (Figure 2) can be more attractive than a reactor in which the catalyst is suspended in the liquid.

Integration of the reactor and the catalyst can be very advantageous. In the fine-chemical industry this integration usually entails application of catalysts as relatively thin layers on non-porous solid surfaces [2–4]. Although such reactors are currently almost exclusively used for treatment of exhaust gas, application in the fine-chemical industry provides interesting possibilities.

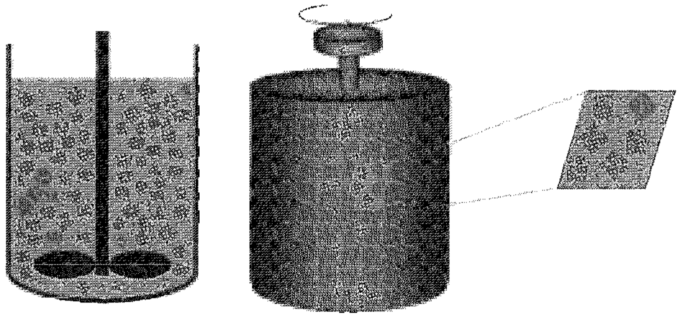


Figure 1.
Slurry-phase reactor.

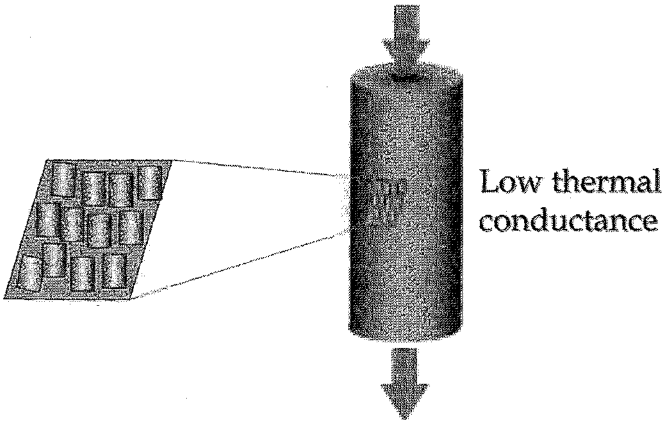


Figure 2.
Reactor with a fixed catalyst bed.

2.1.4 Slurry-phase Catalysts

As mentioned above, the catalysts employed in multipurpose reactors are usually suspended as small solid particles in the liquid containing the compounds to be processed. The above-mentioned weight fractions of catalyst from 0.07 to about 2.5 % (*w*/*w*) are common in slurry reactors. Together with the reaction products most of the catalyst is removed from the reactor and the catalyst is subsequently separated from the reaction products by filtration or centrifugation in a special unit. Heavy catalyst particles are often attractive, because the catalyst can be separated from the reaction products merely by settling and decanting the liquid.

The minimum size of the catalyst particles employed in slurry phase reactors is ca 3 μm, the size required for separation of the catalyst from the liquid reaction product(s) by filtration or centrifugation. As covered above, the surface area of catalyst particles of at least 3 μm is too small to lead to economically acceptable rates of production. Because the size of the catalyst particles cannot be reduced, employment of (highly) porous catalyst particles is required. Because of the presence of pores within catalyst particles of at least 3 μm, the total surface area is much larger than the external surface area. Employment of porous catalyst particles, however, has two drawbacks–the rate of transport through the generally narrow pores in the catalyst particles can determine the rate of the reaction [5,6], and the mechanical strength of porous catalyst particles is often difficult to maintain at the level required to avoid attrition.

The size of the porous catalyst particles does not, therefore, determine the catalytically active surface area. Transport through the bulk of the liquid to the catalyst particles, however, can also significantly affect the apparent rate of the reaction. The number of catalyst particles per unit weight increases when the size of the catalyst particles drops. The average path length reactants must cover in the bulk of the liquid therefore decreases when more catalyst particles are dispersed in the liquid, that is, when the size of the catalyst particles is smaller, because a smaller size leads to more catalyst particles per unit weight. Although the activity per unit weight of catalyst is thus often determined by the number of catalyst particles per unit weight that can be separately dispersed in the liquid, the size of the particles in technical catalysts is generally not well controlled. Usually a broad distribution of sizes between 10 and 100 μm is present in commercial catalysts employed in liquid-phase suspensions. Clustering of small catalyst particles suspended in a liquid can also strongly influence the apparent activity of a catalyst. The average path length to be covered by reactants in the bulk of the liquid to reach a catalytically active site rises as a result of clustering of small particles in the same way as it does when the size of the catalyst particles is increased.

The lengths of the pores in the catalyst particles can severely affect the selectivity of catalytic reactions. For a fairly rapid reaction leading to a product that is liable to further reaction to undesirable products, equally rapid removal of the desired initial reaction product from the pore system of a catalyst particle is necessary. Extensive research (Unilever) has been performed on the properties of nickel catalysts for the hardening (partial hydrogenation) of edible oils [7]. Catalyst present as ca 80-µm particles furnished a product much inferior to that obtained when the same catalyst was present as 3–10 µm particles.

With the batch reactors used in the fine-chemical industry, the rate of the catalytic reaction is generally not decisively important. The number of catalyst particles per unit volume of the liquid to be treated is one of the experimental factors determining the apparent activity of the catalyst. Because the size of the catalyst particles usually affects the apparent activity of the catalyst only, the size is not critical, provided the particles are no smaller than ca 3 µm. When the size of the particles is below this, separation of the catalyst from the reaction product(s) is difficult, and with still smaller sizes even impossible. The requirement to avoid particles smaller than ca 3 µm imposes fairly severe requirements on the mechanical strength of catalyst particles employed in slurry-phase reactors. When the catalyst particles are liable to attrition, which leads to particles smaller than 3 µm, it is difficult to purify the reaction product(s) completely from the catalyst. Especially with fine-chemicals to be used in the food or pharmaceutical industry, contamination of the reaction product with the catalyst is usually not acceptable. Either mechanically strong catalyst particles must therefore be employed with slurry-phase catalysts or the reactor must be adapted to minimize attrition. With a bubble-column reactor the attrition of suspended catalyst particles is much smaller than with a reactor equipped with a stirrer that vigorously agitates the suspension.

Many catalysts must be thermally treated in a gas flow to convert the catalyst precursor into the actual catalytically active component. For 3–100-µm catalyst particles treatment in a gas flow is problematic. With small particles the pressure drop is high; the catalyst is either easily blown out of the reactor or channeling, in which the gas flow passes only through some sections of the catalyst bed in which the catalyst particles are vigorously moving, cannot be avoided. When the catalyst can be exposed to atmospheric air after thermal pretreatment, the treatment can be conducted on larger particles, which are subsequently ground to the desired size range.

Catalysts in which a metal is the active component are, however, pyrophoric after thermal treatment of the metal precursor in a reducing gas flow. Grinding of a reduced catalyst in an inert atmosphere without intermediate exposure to atmospheric air has been performed with nickel fat-hardening catalysts. After the grinding procedure the small catalyst particles are taken up in hardened fat, which protects the nickel against oxidation. The procedure is, however, tedious and cannot be readily executed with the small batches of catalyst usually used in the fine-chemical industry.

2.1.5 Fixed-bed Catalysts

The catalyst particle sizes required in fixed bed reactors are analogous to the size of catalyst particles to be thermally treated in a gas flow. A minimum size of several mm is needed to avoid a large pressure drop. Because the size is significantly larger than that of slurry-phase catalysts, the need to employ porous catalyst particles is even more serious. However, the length of the pores also increases with increasing size of the catalyst particles. Consequently, transport limitations in the pores of the catalyst particles might arise readily. Because the diffusion coefficient in the gas phase (about 10^{-5} m^2 s^{-1}) is much higher than in the liquid phase (about 10^{-9} m^2 s^{-1}), transport limitations will be particularly apparent within fixed catalyst beds employed with liquid reactants [8].

When the selectivity of a catalytic reaction is liable to be bad because of transport limitations, fixed-bed catalysts cannot be used with liquid-phase reactants. When selectivity is less important, fixed-bed catalysts have some advantages. Firstly, the catalyst need not be separated from the reaction products–a flow of reactants can simply be passed through the reactor. Furthermore, the catalyst can be readily thermally pretreated in a gas flow. Hence, deactivated catalysts can be regenerated in situ in the reactor. Exchange of the catalyst of a fixed-catalyst bed by another catalyst is, however, usually a tedious procedure. Fixed-catalyst beds are therefore used only within dedicated reactors in which only one or a limited number of products is produced. Also the lifetime of catalysts employed in fixed-bed reactors must usually be long, viz., two to five years.

The particles for fixed-bed catalysts are produced by extrusion, tabletting, or by using a spherudizer. The strength of the catalyst particles should be sufficient to survive loading in the reactor. It is highly important that the liquids to be catalytically treated do not weaken the catalyst particles of a fixed-bed catalyst, because a high pressure drop might readily develop.

2.1.6 Integration of the Catalyst and the Reactor

Interest has recently developed in the integration of the catalyst with another technological operation. Most well known is catalytic distillation [9], in which a catalytic reaction is combined with a distillation process. It is possible to shift the thermodynamic equilibrium by removal of a specific component by establishing a liquid–gas equilibrium. Catalytic distillation employs a distillation column simultaneously as a catalytic reactor and thus saves the costs of a reactor. Conversion can, furthermore, be increased considerably because of the shift in the equilibrium which results from the change in the composition of the reaction mixture as a result of the distillation process. With catalytic distillation the catalyst is present in the distillation column. The state of the art is to mount the catalyst in bags ('teabags') of glass fiber in the distillation column. To avoid transport limitations fairly small catalyst particles are desired. In another embodiment of the catalytic distillation process, the catalyst is mounted in a gauze structured as a well established distillation column packing. Finally the catalyst is applied as a thin porous layer on the surface of conventional distillation column packings.

It is obvious that catalytic distillation requires a reactor dedicated to one specific type of catalytic reaction. It can be questioned whether the fine-chemical industry performs many reactions needing a dedicated reactor. Application of the catalyst as a thin porous layer on the surface of a metal or ceramic material, however, affords interesting possibilities in the fine-chemical industry. With liquid-phase reactions, the catalyst is still almost completely involved in the reaction when the layer in which the catalyst is present is not much thicker than ca 100 μm. Separation of the catalyst from the reaction product, removal of the catalyst from the reactor, and collection and storage of the catalyst is no longer required; this greatly facilitates operation. The catalyst can, furthermore, be treated thermally in a gas flow, because the pressure drop depends on the structure of the solid on which the catalyst has been applied. This structure can easily be selected thus that the pressure drop is low. When, finally, the catalyst is applied to a metal surface with appreciable thermal conductivity the temperature of the reaction can be maintained accurately at the value desired.

When the catalyst is applied to the walls of monolith channels or on the surface of a static mixer, high conversion can be achieved within a reasonable volume. With highly active catalysts it is consequently possible to direct the reactants from one storage vessel through the reactor to the vessel storing the product or to the distillation column which purifies the products. Instead of storing several catalysts, small reactors containing the required catalysts as a thin layer on the surface of a suitable solid structure can be employed.

2.1.7 Solid Catalysts Employed in the Fine-chemical Industry

Catalysts in which the active component is a metal, and solid-acid catalysts, are much used in the fine-chemical industry. Metal catalysts are generally used to perform hydrogenations and oxidations. Solid-acid catalysts can replace conventional liquid-acid catalysts, which avoids the production of waste acid. Solid-acid catalysts are usually ion-exchangers, though clay minerals and, especially, zeolites are also employed. With zeolites the shape selectivity can have additional advantages.

2.1.8 Metal Catalysts

The difficulty of thermal treatment of slurry-phase catalysts has resulted in the predominant use of Raney metals and precious metals in the fine-chemical industry. Raney metals are produced from an aluminum alloy of the metal to be used as a catalytically active component. Treatment with alkali leaches aluminum from the alloy and leaves a very finely divided metal [10] as ca 10 to 20 nm metal particles clustered into conglomerates of several microns. Aluminum remaining in the metal after treatment with alkali protects the metal against oxidation. The aluminum reacts very slowly with the water in which the Raney metals are stored and thus releases hydrogen; (hydrated) aluminum oxide not leached by treatment with alkali is also present. The aluminum oxide is usually present beside the clusters of metal particles.

Electron microscopy is a very appropriate means of illustrating the peculiar structure of Raney metals. Figure 3 shows a scanning electron micrograph of a conventional Raney nickel catalyst. It is apparent that the catalyst consists of fairly large particles mixed with smaller particles. The dimension of the larger particles is ca 50 µm, whereas that of the smaller particles is ca 2 µm. The particles in Figure 3 are actually highly porous, as is evident from the transmission electron

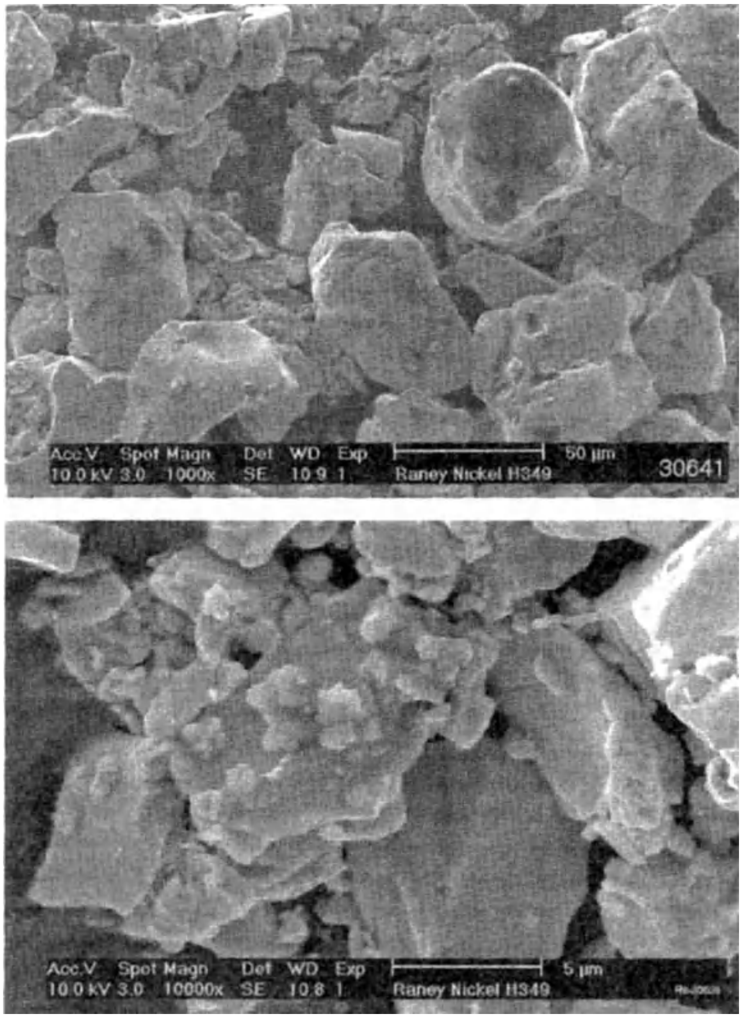


Figure 3. Scanning electron micrographs of a Raney nickel catalyst at two different magnifications (Philips XL-30 FEG scanning electron microscope).

micrograph of the same Raney nickel catalyst shown in Figure 4. To prepare specimens suitable for transmission electron microscopy, the Raney nickel catalyst was ultrasonically treated in a suspension of ethanol and a drop of the suspension was placed on a holey carbon film. The dimensions of the primary particles are apparent from the transmission electron micrograph presented in Figure 4.

Raney metals are attractive because thermal treatment in a gas flow is not required to produce the catalytically active metal. Storage of the pyrophoric catalyst is, moreover, easy, because the catalyst can be stored in water. Another important advantage is that the catalyst particles are heavy, which enables separation of the catalyst by settling and decantation. A final attractive feature of Raney metals is that they can be exposed to alkaline liquids. Many other metal catalysts are not stable in alkaline liquids. Most well known is Raney nickel, which is an attractive hydrogenation catalyst [11–20]. Raney copper and Raney cobalt are also frequently employed. Raney metals are mostly used for hydrogenations in the fine-chemical industry. Raney nickel and Raney cobalt often have different selectivity; the reason for the difference between nickel and cobalt is often obscure, though cobalt is more liable to poisoning and oxidation.

A nickel catalyst analogous to Raney nickel is Urushibara nickel [21], produced by adding zinc dust to a solution of a nickel salt, generally nickel chloride. The zinc reduces the nickel to metallic nickel, which precipitates as very small particles mostly on the metallic zinc. The precipitate contains metallic zinc, zinc

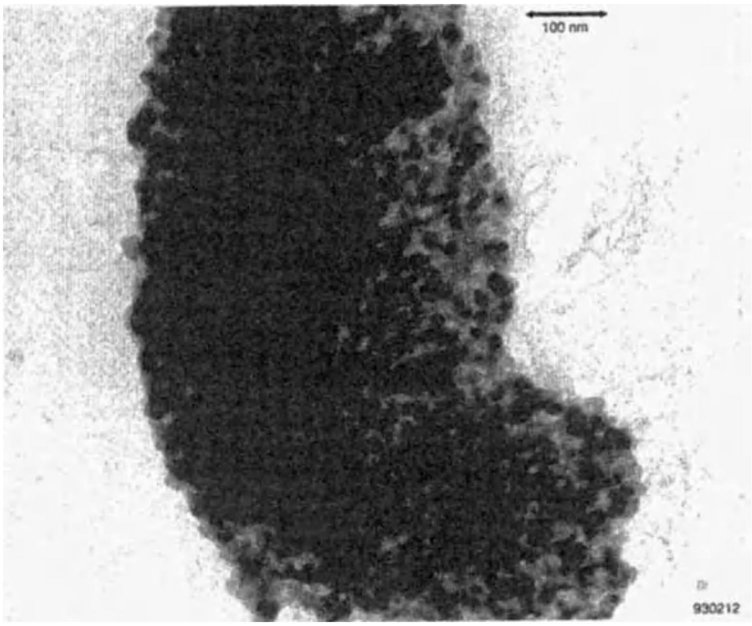


Figure 4. Transmission electron micrograph of a Raney nickel catalyst (Philips EM-420 Transmission electron microscope). For preparation of the specimen see text.

hydroxide, and zinc hydroxyhalide. An activation treatment is required before an active catalyst results. The activation procedure involves treatment with acid or alkali. The zinc hydroxide and the hydroxyhalide are removed by reaction with an alkaline solution, and the metallic zinc is partly dissolved by treatment with acetic acid solution. The remaining metallic zinc stabilizes the nickel. An advantage of Urushibara nickel is reportedly that it is not pyrophoric, in contrast to Raney nickel.

When Raney metals do not have the required selectivity or activity, precious metals are used. Precious metals can also be employed for catalytic oxidation reactions. Because of the high price of precious metals, it is important to have most of the metal atoms at the surface where the atoms can be catalytically active. Precious metal catalyst particles are, therefore, commonly as small as 1 nm, exposing more than 50 to 80 % of the metal atoms. To produce and to stabilize small catalytically active particles a catalyst support or carrier is used. A catalyst support is a highly porous material with a high surface area that is often itself not catalytically active. A support is usually employed to prevent sintering of active components during thermal treatment or during a catalytic reaction that is executed at elevated temperatures. Figure 5 shows schematically how a support prevents sintering of metal particles during thermal treatment. With active components containing relatively cheap base metals the aim is to provide a maximum active surface area per unit volume, which is achieved by relatively high loadings of the support with the active component(s). With base metals a loading of 10 % (*w/w*) or more is usual, which results usually in fairly large supported particles. As said above, however, precious metals have to be employed as very small particles with most of the metal atoms in the surface, which calls for metal particles of at most ca 2 to 3 nm. The loading of the support with precious metals is therefore usually less than ca 3 % (*w/w*) and often not more than 1 % (*w/w*).

Precious metals can be reduced by reaction with hydrogen even at room temperature. It is therefore possible to reduce supported precious metal catalysts after suspension in the liquid where the catalytic reaction is to proceed, merely by passing a flow of hydrogen through the liquid. It must, however, be considered that the water produced during the reduction of the precious metal particles must be removed from the surface of the catalyst before the reactants can approach the catalytically active sites. With liquids that are not miscible with water, it might take some time before the water is released from the metal surface. That precious metal catalysts need not be reduced at elevated temperatures in a gas flow is one reason these expensive metals are attractive for the fine-chemical industry. As

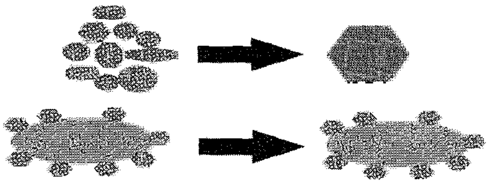


Figure 5. Schematic representation of a supported catalyst.

mentioned above, precious metals can also be employed for catalytic oxidations with dioxygen at low temperatures.

Because catalysts to be employed in the fine-chemical industry must be resistant against (weakly) acid and alkaline liquids, active carbon is the support of choice for precious metal catalysts. Activated carbon is a relatively complicated support [22]. The material contains very small clustered carbon particles and graphitic platelets. Because the small carbon particles have an oxidized surface, they are hydrophilic. The surface of the graphite platelets is hydrophobic. The precious metal particles are usually present between the finely divided carbon particles. To attach the metal precursor to the surface of the active carbon, the surface is often oxidized by treatment with nitric acid or with hypochlorite [23]. Oxidation leads to the formation of carboxylic acid groups on the surface of the carbon; these can bond positively charged precious metal complexes. Oxidation must, however, be performed cautiously. Too severe oxidation leads to disintegration of the activated carbon particles. Ammonia complexes of precious metals are usually used when very homogeneous distribution is desired. Impregnation can also be achieved with chloride complexes of precious metals. Previous oxidation of the activated carbon also raises the hydrophilicity of the carbon surface. More extensive penetration of the impregnating solution results, which leads to a more uniform distribution of complexes, such as, H_2PtCl_6. At lower pH the carboxylic acid groups at the carbon surface are not ionized.

Another support that can withstand alkaline solutions is titania. Though titania has been studied much less than alumina and silica as a catalyst support, interest in titania supports has increased. One of the problems with titania is the production of mechanically strong 10–100-μm particles.

Copper-based catalysts are often used for selective reductions in the fine-chemical industry. Although copper catalysts are highly selective and thus do not produce much methane and other saturated hydrocarbons, their activity is usually low. To achieve a reasonable activity the temperature must often be raised to a level where the equilibrium is at the side of the dehydrogenated compound. Then a very high hydrogen pressure is required, which calls for expensive reactors. The Adkins catalyst, a catalyst prepared by coprecipitation of copper and chromium oxide, is often used in the fine-chemical industry for ester hydrogenation [24–26]. The copper in the catalyst precursor can be easily reduced leaving the chromia as a support for small copper particles. The considerable density of the catalyst particles leads to a rapid settling, which enables fairly smooth separation of the catalyst. Because of environmental problems with chromia, the Adkins catalyst is currently replaced by copper–zinc oxide catalysts for some applications. The copper–zinc oxide catalyst also is produced by coprecipitation.

2.1.9 Solid-Acid Catalysts

To avoid the production of waste acid, it is attractive to perform acid-catalyzed reactions with solid acids, and sulfonic acid-type polymeric ion-exchangers are often employed in the industry. Transport through the liquid phase in the narrow pores of the beads proceeds slowly, with the result that transport limitation is often encountered. Although several technical processes are performed with ion-exchangers as solid-acid catalysts, little literature is available other than the patent literature. For hybrid materials see Sections 3.3 and 3.5.

Other solid catalysts are zeolites (cf. Section 3.2) and clay minerals (Section 3.1). Many reactions in the fine-chemical industry are performed with organic liquids or in organic solvents. When the surface of a solid-acid catalyst is hydrophilic, the presence of small amounts of water can completely block the surface of the catalyst. Carefully dried catalysts and reagents must then be employed. It may be noted that zeolites with a high silica-to-alumina ratio are hydrophobic. The (internal) surface of the zeolite is, therefore, not readily poisoned by accumulation of (traces of) water. With zeolites, moreover, use can be made of the uniform size of the pores to perform shape-selective reactions after passivation of the catalytic sites on the external surface of the zeolite crystallites. In the bulk-chemical industry several interesting reactions have been developed with zeolite catalysts [27] (cf. the review of Tanabe and Hölderich [28]).

The narrow pores within zeolite crystallites do not promote the transport of liquids. Although small zeolite crystallites are attractive for liquid phase reactions, the size of solid crystallite particles required for separation from the liquid remains ca 3 µm. Small zeolite crystallites are therefore taken up in 'binders' to provide larger particles. The binders are supposed to have wide pores through which transport is rapid.

The development of clay minerals as solid-acid catalysts has been impeded by the general use of natural clay minerals often contaminated with impurities which are difficult to remove. Clay minerals are often used as supports for homogeneous catalysts, such as zinc chloride.

References

[1] Gabor A. Somorjai 'Chemistry in Two Dimensions : Surfaces' Cornell University Press Ithaca and London (1981) p. 384.

[2] J. P. DeLuca and L. E. Campbell in 'Advanced Materials in Catalysis' (James J. Burton and Robert L. Garten eds.) Academic Press New York (1977) p. 293.

[3] Said Irandoust and Bengt Andersson *Catal. Rev. -Sci. Eng.* **30** (1988) 341.

[4] Andrzej Cybulski and Jacob A. Moulijn *Catal. Rev. -Sci. Eng.* **36** (1994) 179.

[5] J. M. Smith 'Chemical Engineering Kinetics' 2nd Edition McGraw–Hill Kogakusha Ltd. Tokyo (1970) p. 399.

[6] Octave Levenspiel 'Chemical Reaction Engineering' Second Edition John Wiley & Sons, New York (1972).

[7] J. W. E. Coenen in 'The Mechanism of Heterogeneous Catalysis' (J. H. de Boer ed.) Elsevier Amsterdam (1960) p. 126; J. W. E. Coenen *J. Oil Chem. Soc.* **53** (1976) 382.

[8] W. J. Beek and K. M. K. Muttzall 'Transport Phenomena' John Wiley & Sons London (1973) p. 24.
[9] William P. Stadig *Chemical Processing* February (1987) p. 27.
[10] M. Raney U. S. Patent 1,628,191 (1927).
[11] R. Sassoulas and Y. Trambouze *Bull. Soc. Chim. France* **5** (11964) 985.
[12] J. Freel, W. J. M. Pieters, and R. B. Anderson *J. Catal.* **16** (1970) 281.
[13] A. B. Fasman, V. F. Timofeeva, V. N. Rechkin, Yu. F. Klyuchnikov, and I. A. S. Sapukov *Kinet. Katal.* **13** (1972) 1513 Translation Kin. Catal. 1347.
[14] D. J. Young and M. S. Wainwright *J. Catal.* **64** (1980) 116.
[15] M. S. Wainwright *J. Catal.* **64** (1988) 124.
[16] P. Fouilloux *Appl. Catal.* 8 (1983) 1.
[17] S. Sane, J. M. Bonnier, J. P. Damon, and J. Masson *Appl. Catal.* **9** (1984) 69.
[18] U. Birkenstock, R. Holm, B. Reinfandt, and S. Storp *J. Catal.* **93** (1985) 55.
[19] M. L. Bakker, D. J. Young, and M. S. Wainwright *J. Mater. Sci.* **23** (1988) 3921.
[20] T. Koscielski, J. M. Bonnier, J. P. Damon, and J. Masson *Appl. Catal.* **49** (1989) 91.
[21] Y. Urushibara *Bull. Chem. Soc. Japan* **26** (1952) 280.
[22] L. R. Radovic and F. Rodriguez-Reinoso *in* 'Chemistry and Physics of Carbon' (Peter A Thrower ed.) Vol. 25 Marcel Dekker, Inc. New York (1997) p. 243.
[23] D. Richard and P. Gallezot *in* 'Preparation of Catalysts IV' (B. Delmon, P. Grange, P. A. Jacobs, and G. Poncelet, eds.) Elsevier, Amsterdam (1987) p. 71.
[24] F. M. Capece, V. diCastro, C. Furlani, G. Mattogno, C. Fragale, M. Gargano, and M. Rossi *J. Electron Spectrosc. and Related Phenomena* **27** (1982) 119.
[25] A. Imura, Y. Inoue, and I. Yasumori *Bull. Chem. Soc. Japan* **56** (1983) 2203.
[26] S. P. Tonner, M. S. Wainwright, D. L. Trimm, and N. W. Cant *Appl. Catal.* **11** (1983) 93.
[27] W. F. Hölderich and H. van Bekkum *in* 'Introduction to Zeolite Science and Practice' (H. van Bekkum, E. M. Flanigan, and J. C. Jansen eds.) Elsevier, Amsterdam (1991) p. 631.
[28] W. F. Hölderich *in* 'Proceedings of the 10th International Congress on Catalysis' (L. Guczi, F. Solymosi, and P. Tetenui, eds.) Akademiai Kiado, Budapest (1993) p. 121.
K. Tanabe and W. F. Hölderich *Appl. Cat. A* (181) (1999) 399.

2.2 Preparation of Solid Catalysts

John W. Geus, A. J. van Dillen

2.2.1 Demands on Solid Catalysts

In the preparation of solid catalysts to be employed in the fine-chemical industry the structure and chemical composition of the catalysts must meet conflicting demands which must be carefully considered. Three characteristics of solid catalysts are decisive, viz.:

- the catalytically active surface
  - a sufficiently large active surface area per unit weight or unit volume of catalyst is required;
  - the catalytically active surface must be stable at the temperatures of pretreatment and the intended catalytic reaction; and
  - the catalytically active surface must have the desired structure and chemical composition
- the transport properties
  - the transport of reactant molecules to the catalytically active surface, and of the reaction products from the surface, must proceed sufficiently rapidly; and
  - the transport of thermal energy to and from the catalyst particles must occur smoothly
- the mechanical strength
  - for technical applications the mechanical strength of catalyst particles is most important.

In the previous section we dealt with the surface area per unit weight or unit volume required to achieve technically acceptable conversions. The conclusion was that porous catalyst particles must usually meet the demands both of pressure drop (fixed bed catalysts) or of viability of separation (suspended catalyst particles) and of the extent of the catalytically active surface area. When the catalyst must be thermally pretreated, the active surface area should not severely drop as a result of sintering of the active particles. Although solid catalysts in fine-chemistry operations are usually employed in liquid phases, i. e. not at highly elevated temperatures, sintering of the active component(s) should not occur during the reaction.

Some catalytic reactions proceed only on surfaces with a specific structure. In fine chemistry, the size of metal particles can significantly affect catalytic activity and selectivity. With small metal particles, penetration of foreign atoms into the metal surface can proceed easily, because the number of neighboring metal atoms in the surface is small. As might be expected, the catalytic reactions of foreign atoms penetrating into the metal surface is often different from that of foreign atoms adsorbed on the surface. The most well known example is the activity of platinum particles in oxidation reactions. On exposure to dioxygen small platinum particles react to form platinum oxide, in contrast with large platinum particles that merely adsorb dioxygen dissociatively as oxygen atoms. Because oxygen atoms in platinum oxide are more strongly bonded than the oxygen atoms adsorbed on platinum surfaces, the activity of small platinum particles in oxidation reactions is remarkably low, despite the large platinum surface area. In monosaccharide oxidation, deactivation of supported platinum catalysts as a result of reaction with dioxygen is well known; interruption of the oxygen flow leads to reduction of the platinum oxide and restoration of the initial high activity.

As discussed above, the transport properties of porous catalyst particles of ca 3 to 100 μm are extremely important for the selectivity of catalytic reactions in which the desired initial products are liable to further reaction to undesired material. The ratio of the rate of catalytic reaction to that of transport within the pore system of catalyst particles is represented by Thiele's modulus [1], which is proportional to the pore length and to the square root of the diameter of the pores. Accordingly reducing the size of the catalyst particles is more effective than increasing the diameter of the pores.

Small catalyst particles of diameter larger than ca 3 μm, but not larger than ca 10 μm, are attractive. The number of catalyst particles per unit weight of catalyst is inversely proportional to the third power of the diameter. The surface area per catalyst particle is proportional to the second power of particle size. Consequently the surface area exposed per unit weight of catalyst is inversely proportional to the first power of the size of the catalyst particles. Both transport from the bulk of the liquid to the external surface of the catalyst particles and transport within the pores of the catalyst particles are therefore favorably affected by a drop in size. Because the mass transfer coefficient from the bulk of the liquid to the external surface of suspended catalyst particles is inversely proportional to the diameter, transport to the external surface is inversely proportional to the square of the diameter of the particles. Special procedures are involved in the technical production of 3–10-μm particles; this will be covered later.

The last of the above requirements concerns the mechanical strength of the catalyst particles. As mentioned above, both with fixed-bed catalysts and with suspended catalysts the mechanical strength of the particles is the most important property. With fixed catalyst beds fracture of the catalyst particles leads to a pressure drop which is too high; this leads to blow-out of the catalyst or channeling. Suspended catalysts cannot be separated from the reaction products when fracturing results in particles smaller than 3 μm. Subsequent separation is usually extremely expensive. Often thermal treatment of oxides considerably increases their mechanical strength. Thermal treatment is, however, expensive and can lead to large particles which must be ground to the size range desired; this also is costly.

With active components supported on activated carbon the adhesion of the active particles to the carbon is important. The interaction between precious metal particles or clusters of small particles and carbon surfaces can be low, which might lead to segregation of very small precious metal particles or slightly larger clusters of small particles into the liquid. Separation of such small particles or clusters of particles by filtration or centrifugation is not possible. the precious metal particles should, therefore, either be firmly attached to the surface of the activated carbon or occluded in the structure of the carbon.

2.2.2 Preparation Procedures [2]

It has been explained above that solid catalysts usually must have a high surface area, and that this can be achieved only with highly porous particles consisting of small elementary particles. Small particles can be produced by two essentially different procedures, both of which are extensively used for the production of solid catalysts for the fine-chemical industry, viz., selective removal of one or more specific components from large solid particles and controlled growth of solid from molecularly dispersed material.

The Raney metals discussed above are typical examples of production by selective removal. The aluminum of the alloy with the desired catalytically active metal is selectively dissolved by treatment with alkali. Because dissolution is performed at low temperatures, i. e. below ca 100 °C, sintering of the remaining metal particles does not occur. Despite the many papers on Raney nickel [3–12], less has been published on the preparation of other Raney metals. The production of the initial aluminum alloy and the thermal treatment of the alloy has not been extensively investigated. The phase diagram of the nickel–aluminum system is rather complicated.

The catalytic properties of Raney metal catalysts can be significantly modified by addition of promoting elements to the aluminum alloy or to the final Raney catalyst [12–14]. Although the reason for the promotion by foreign elements is still obscure, there are indications that Raney metals themselves have a hydrophobic surface if the surface is not locally oxidized. When the presence of an aqueous layer on the surface of the Raney metals is desired to achieve high selectivity, the presence at the metal surface of a promoter not dissolving in the alkaline solution might increase surface hydrophilicity. An interesting application is the Asahi process for production of cyclohexene by selective hydrogenation of benzene on Raney nickel coated with a thin layer of a special aqueous solution. The intermediately formed cyclohexene is rapidly removed through the aqueous layer to the organic liquid.

The second of the preparation procedures is used to produce precious metal catalysts. The (precursor of the) active component is grown from molecularly dispersed material. As mentioned above commercial precious metal catalysts are almost always supported catalysts. Whereas the loading of the support with relatively cheap catalytically active materials is determined by the desired activity per unit weight or unit volume of catalyst, which often calls for a loading of more than 10 % (*w/w*) of the active component, loading with precious metals is usually low, i. e. less than 3 % (*w/w*). When the loading is low, impregnation of the support with a solution of the active precursor and subsequent drying can be used. Preferably pore-volume impregnation or incipient wetness impregnation is used [15]. It is essential that the desired loading of the active component is present in an amount of solution not exceeding the pore-volume of the support. An obvious advantage of an impregnation and drying procedure is that no waste water is produced, and material dissolved in the solution cannot get lost. With precious metals, avoiding the risk of loss in, e. g., wash water or filtrates is especially attractive. Another attractive feature of depositing an active precursor by impregnation and drying is that the procedure can be employed with shaped support particles. Support particles of the desired mechanical strength and porous structure are generally commercially available. Shaping of a powdered support loaded with the (precursor of the) active component, which might call for tedious research, is thus not required. The properties of commercial activated carbon supports, however, are usually less well known, because it is difficult to control the properties of activated carbon supports precisely.

When a high loading of the support with less expensive catalytically active component(s) is desired, impregnation and drying is usually not effective. Precipitation of an active precursor on to a finely divided support suspended in the solution from which the precipitation will be effected is a usual preparation procedure. After separation from the liquid, washing of the loaded support and drying, the material must be shaped. With catalysts to be used suspended in a liquid the loaded support can be dried and calcined after which the usually mechanically strong material can be ground to the desired dimensions.

The activated carbon supports commonly employed are impregnated with liquids in which precious metals are molecularly dissolved [16]. Because the loading of the activated carbon with the precious metals is usually low, a pore-volume or incipient wetness impregnation can be used to apply the precious metal. After impregnation the solvent is removed by drying, which leads to deposition of the precious metal on the carbon support. Usually the dissolved species of the precious metals used for impregnation is not adsorbed extensively by the surface of the active carbon. As a result crystallization of the precious metal compound proceeds during drying at spots where the water vapor can readily escape to the gas phase. It has been shown that transport of the solution from the interior surface to the sites where the liquid evaporates takes place by migration of a liquid layer present on the pore walls within the porous solid. Consequently relatively large clusters of the species deposited upon drying of the solution are present within the porous activated carbon particles. After reduction of the deposited species large clusters of small metal particles can be seen within the porous structure of the carbon.

The transmission electron micrograph represented in Figure 1 shows a typical carbon-supported precious metal catalyst. Activated carbon contains very small clustered particles beside carbon flakes. A flake is indicated in the micrograph. Precious metal particles are usually present only at the edges of the flakes. On the small carbon particles fairly uniform distribution of small precious metal particles has been achieved. Two clusters of platinum particles can also be seen in the micrograph of Figure 1.

In Section 2.1 we discussed the adsorption of positively charged complexes of precious metals on the surface of oxidized carbon. The oxidation of activated carbon must be performed cautiously, because severe oxidation leads to complete

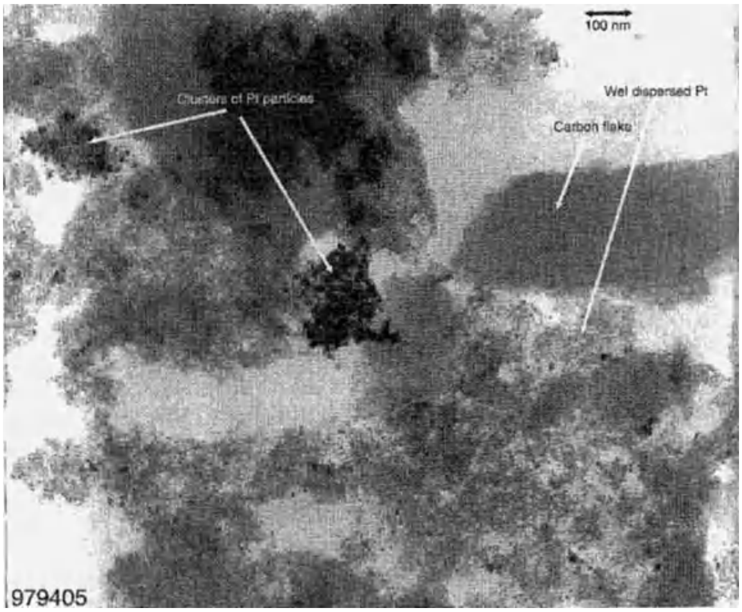


Figure 1. Transmission electron micrograph of a platinum-on-carbon catalyst (Philips EM-420 transmission electron microscope).

oxidation of the carbon. Although reduction of a species adsorbed uniformly over the surface leads to very small metal particles, adsorption of precursors of precious metals is not frequently applied. The clusters of small metal particles resulting from a conventional impregnation procedure do not sinter rapidly under the conditions of most catalytic reactions in which precious metal catalysts are employed. The activity of clusters of small metal particles with a high specific metal surface area is, therefore, still sufficient.

Reduction of the precious metal species initially deposited within the structure of activated carbon can be performed by passing a flow of hydrogen through a suspension in a liquid of the carbon loaded with the precursor. Also an organic compound, e. g. formaldehyde, can reduce the precursor of the precious metal, although a slightly elevated temperature (ca 40 to 60 °C) is usually required. It can be attractive to impregnate a support with a solution of an organometallic compound of the precious metal to be deposited. The organometallic compound is selected so that slightly raising the temperature after completion of the impregnation leads to reduction of the precious metal to the metallic state. Much patent literature is available on the complexing and reduction of silver to produce catalysts for the production of ethylene oxide [17–19]. Most of the complexing and reducing agents mentioned for silver can also be employed with precious metals.

Van Koten et al. developed a procedure for the preparation of precious metal catalysts alloyed with, e. g., copper and gold, that can be accommodated easily by the fine-chemical industry [20–22]. For selective hydrogenation such catalysts have significant advantages. The method of preparation involves reaction of an organocuprate complex containing zerovalent lithium with a precious metal complex. The reaction leads initially to an unstable complex of copper with the precious metal in which the copper is atomically mixed with the precious metal. The complex subsequently decomposes to zero-valent alloy particles. Van Gorp et al. [23] developed a procedure for applying the resulting alloy particles to fumed silica supports; this was later improved by Spee et al. [22].

It is well known that activated carbon is a difficult support material despite its many favorable properties. Because activated carbon is made from natural materials, such as, peat or wood, it is difficult to prepare highly reproducible materials. A carbon support the properties of which can be controlled more closely, therefore would be very attractive. It has long been known that mechanically strong carbon fibers can grow out of metal particles able to react to metal carbides when such supported metal catalysts are exposed to carbon-containing gaseous molecules under conditions where the gaseous molecules can react thermodynamically to produce graphite. Growth of such carbon nanofibers within a catalytic reactor is disastrous, because the mechanically strong carbon fibers cause disintegration of the catalyst particles, which leads to a very high pressure drop. The carbon fibers are so strong that even the metallic reactor can be severely damaged; they do, however, seem to be an excellent carbon support [24].

The structural properties of the clusters of carbon nanofibers resulting from the growth of fibers from metal particles, such as iron or nickel, can be controlled within wide ranges. The surface area per unit weight and the pore volume can be controlled. A large pore volume as a result of very wide pores can be readily achieved; this is highly attractive for liquid-phase reactions. One result of the high mechanical strength is that substantial attrition of the skeins of nanofibers does not occur. The growth of clusters of carbon fibers to highly porous mechanically strong particles of millimeter dimensions has also been achieved.

In contrast with activated carbon these carbon nanofibers are hydrophobic, which is often highly attractive when apolar liquids are being employed as solvents. The fibers can be made hydrophilic by oxidation with, e. g., nitric acid. Hoogenraad established that adsorption of positively charged palladium ammine complexes proceeds readily on the carboxylic acid groups generated by mild oxidation of the fibers. After reduction he arrived at a loading of about 2 % (*w/w*) palladium as particles of about 1 nm. After loading with precious metal clusters the fibers can be made hydrophobic again by treatment at 300 °C. At this temperature the carboxylic acid groups are removed as carbon monoxide and carbon dioxide without substantial sintering of the palladium particles. Hoogenraad et al. demonstrated that the dispersion of small (diameter < 10 μm) clusters of carbon nanofibers strongly affects catalytic activity in the hydrogenation of nitrobenzene [25]. The nature of the carbon surface alone (hydrophilic or hydrophobic) determines the dispersion of the clusters of carbon nanofibers in different liquids. Van Gorp and Spee used the decomposition of organometallic compounds to deposit very finely divided alloys of precious metals and copper, or of gold, on nanofibers.

Teunissen et al. observed that carbon nanofibers can absorb large amounts of alkali metals, for example up to 30 % (*w/w*) of metallic potassium. In carbon fibers thus loaded the alkali metals are much more reactive because of the much larger surface area exposed compared with liquid or solid alkali metals. Carbon fibers loaded with alkali metals can, furthermore, be used to deposit transition metals on the surface of the fibers by reduction of suitable compounds, such as water-free acetates, in suitable non-aqueous solvents. Consequently supported transition metals difficult to reduce at low temperatures can be readily prepared.

Separation of solid catalysts from liquids by filtration, centrifugation, or settling and decanting is limited to catalyst particles of ca 3 µm. The separation calls, furthermore, for additional equipment. Small ferromagnetic particles are interesting as a catalyst support, because they can readily be separated from a liquid by an inhomogeneous magnetic field. Thermal treatment in a gas flow can also be achieved fairly easily with ferromagnetic particles, because they can be kept fixed in a gas flow. The ferromagnetic particles cannot, however, have a high permanent magnetic moment, because redispersion of the particles is then not readily possible, and so ferromagnetic particles of a low magnetic hardness that can easily be demagnetized are required. Small ferromagnetic metal particles are pyrophoric and thus highly reactive. Magnetic oxides, such as magnetite (Fe_3O_4) or chromium dioxide (CrO_2), have a lower magnetic moment and are also reactive. Teunissen et al. have found that small ferromagnetic particles can be encapsulated by graphite layers by keeping the alumina- or silica-supported metal particles within a gas flow containing molecules liable to decomposition to graphite. Subsequent dissolution of the alumina or silica support in acid or alkaline solutions, respectively, sets free the small encapsulated ferromagnetic particles.

Graphite surfaces are extremely inert; they can withstand both alkaline and (strongly) acid solutions as has been established for the encapsulated ferromagnetic particles. Precious metal particles, such as palladium particles, can be deposited on to the graphite surfaces. The catalytically active ferromagnetic particles thus prepared have high activity in the hydrogenation of nitrobenzene. Removal of the ferromagnetic particles from a multipurpose reactor is easily possible by immersion of the pole of an electromagnet into the liquid and switching the magnet on.

Supported copper particles usually sinter severely during thermal treatment that leads to extensive reduction. Copper catalysts to be employed in non-oxidizing acid solutions must therefore be prepared according to special procedures leading to highly thermostable copper catalysts. Deposition–precipitation [2] of copper precursors on to suspended powdered supports can lead to highly thermostable copper catalysts. For lower copper loadings, impregnation with a copper complex of citric acid also leads to a copper catalyst that can be reduced almost completely without severe sintering of the supported copper particles.

We mentioned above two copper catalysts produced by coprecipitation, viz., the Adkins catalyst (copper–chromia) and the copper–zinc oxide catalyst. The precursor of the two catalysts is produced by coprecipitation. The preparation of the catalysts involves selective removal of carbonate ions, water, and the oxygen atoms bonded to copper. The intimate mixing of the copper ions with the precursor of the supports and the strong interaction of copper with both zinc oxide and chromia furnish copper particles that are still small even after virtually complete reduction of the copper.

Van Gorp [23] improved a procedure published by Blanchard et al. [26,27] for application, at low temperatures, of particles of metals difficult to reduce on supports such as silica, alumina or titania. Blanchard et al. applied an aluminum alkyl to the surface of an oxidizing support. Subsequent addition of a suitable compound of a transition metal leads to the generation of very small metal particles on the support. Because the amount of aluminum alkyl that can be grafted on the surface of the support is limited, the loading of the support is bound to remain low. Nevertheless highly active catalyst can be prepared according to the procedure of Blanchard et al., which might not deviate much from conventional procedures in fine-chemical plants. Van Gorp established that the amount of water on the support must be carefully controlled.

2.2.3 Conclusions

Raney metals and supported precious metal catalysts are very easy to employ in the fine-chemical industry. The application of promoters with Raney metals and stabilization by metallic aluminum remaining in the catalyst call for more fundamental investigations. Research on the initial aluminum alloy calls for experience in metallurgy, which is usually not available in laboratories dealing with solid catalysts.

The procedure of choice for the preparation of supported precious metal catalysts is impregnation of the support and drying. Loss of the metal in the filtrate cannot proceed with this procedure. Although the properties of activated carbon supports are difficult to control, this support is usually preferred. Carbon is relatively inert to acid and basic liquids, and the precious metal can be readily recovered by combustion of the carbon.

References

[1] Octave Levenspiel ‘Chemical Reaction Engineering’ Second Edition John Wiley & Sons, New York (1972) p. 472.
[2] J.W. Geus in ‘Preparation of Catalysts III’ (G. Poncelet, P. Grange, and P.A. Jacobs eds.) Elsevier, Amsterdam (1983) p. 1.
[3] R. Sassoulas and Y. Trambouze *Bull. Soc. Chim. France* **5** (11964) 985.
[4] J. Freel, W.J.M. Pieters, and R.B. Anderson *J. Catal.* **16** (1970) 281.
[5] A.B. Fasman, V.F. Timofeeva, V.N. Rechkin, Yu. F. Klyuchnikov, and I.A.S. Sapukov *Kinet. Katal.* **13** (1972) 1513 Translation Kin. Catal. 1347.
[6] D.J. Young and M.S. Wainwright *J. Catal.* **64** (1980) 116.
[7] M.S. Wainwright *J. Catal.* **64** (1988) 124.
[8] P. Fouilloux *Appl. Catal.* 8 (1983) 1.
[9] S. Sane, J.M. Bonnier, J.P. Damon, and J. Masson *Appl. Catal.* **9** (1984) 69.
[10] U. Birkenstock, R. Holm, B. Reinfandt, and S. Storp *J. Catal.* **93** (1985) 55.
[11] M.L. Bakker, D.J. Young, and M.S. Wainwright *J. Mater. Sci.* **23** (1988) 3921.
[12] T. Koscielski, J.M. Bonnier, J.P. Damon, and J. Masson *Appl. Catal.* **49** (1989) 91.
[13] J.M. Bonnier, J.P. Damen, B. Delmon, B. Doumain, and J. Masson *J. Chim. Phys. (France)* **84** (1987) 889.
[14] J.M. Bonnier, J. Court, and P.T. Wierzchowski *Appl. Catal.* **53** (1989) 217.
[15] For an almost exhaustive set of references see ref. [22] p. 249.

[16] F. Rodriguez-Reinoso in 'Porosity in Carbons' (J. W. Patrick ed.) Edward Arnold London (1995) p. 261.
[17] R. P. Nielsen U. S. Patent 3 702 259.
[18] G. de Krijger and F. Wattimena U. S. Patent 3 563 913.
[19] G. K. Boreskov et al. U. S. Patent 4 130 570.
[20] M. S. Cohen, J. G. Noltes and G. van Koten U. S. Patent 4 152 303 (1979).
[21] M. S. Cohen, J. G. Noltes and G. van Koten U. S. Patent 4 222 898 (1980).
[22] M. P. R. Spee, M. D. Meijer, M. Q. Slagt, G. van Koten, and J. W. Geus *Stud. Surf. Sci. Catal.* **108** (1996) 313.
[23] K. van Gorp 'Preparation of Heterogeneous Catalysts from Organometallic Precursors' Thesis Utrecht University (1996).
[24] J. W. Geus, A. J. van Dillen, and M. S. Hoogenraad in 'Synthesis and Properties of Advanced Catalytic Materials' (Enrique Iglesia, Peter W. Lednor, Dick A. Nagaki, and Levi T. Thompson eds.) Materials Research Society Pittsburgh (1995) p. 87.
[25] M. S. Hoogenraad, M. F. Onwezen, A. J. van Dillen, and J. W. Geus in 'Proceedings of the 11th International Congress on Catalysis' Elsevier Science b. v. Amsterdam (1966) p. 1331.
[26] M. Blanchard, J. Barrault, and A. Derouault in 'Preparation of Catalysts V' (G. Poncelet, P. A. Jacobs, P. Grange, and B. Delmon eds.) Elsevier, Amsterdam (1991) p. 187.
[27] J. Barrault, M. Blanchard, A. Derouault, M. Ksiki, and M. I. Zaki *J. Mol. Catal.* **93** (1994) 289.

2.3 Characterization of Solid Catalysts

John W. Geus, A. J. van Dillen

Important data about industrial catalysts include the size, shape, and mechanical strength of the catalyst particles and the (weight) loss on ignition.

The shape and size of fixed-bed catalyst particles can be determined visually. Catalyst particles intended for use as suspensions in liquids are usually much smaller, and their shape must be assessed by means of a light microscope or, preferably, a scanning electron microscope. The greater depth of focus of a scanning electron microscope enables the production of photographs of the images; these can be studied more intensively. Several automatic techniques are available for determination of the size-distribution of the catalyst particles. Commercial light-scattering equipment is widely available. Down to a particle size of ca 1 μm static light-scattering can be used. Much smaller particles can be measured by dynamic light-scattering, which calls for more expensive apparatus. Another well-established procedure is the Coulter counter technique. A flow of a suspension of the catalyst particles is passed through a circular aperture that contains a thin insulating strip along a line passing through the center of the aperture. Because catalyst particles usually have a fairly low electrical conductance, the electric current passing through the conducting water drops abruptly when a catalyst particle passes through the aperture. The number of drops in the electrical current is a measure of the number of particles passing through the aperture, and the magnitude of the decrease reflects the size of the particle. To measure particle size distributions centered around different sizes, apertures of a different diameter are available. Calibration of decreases in the current arising from particles of known size and known electrical conductivity is usually required. One problem with activated carbon is that the material is usually a better electrical conductor than water. A suspension in a non-aqueous liquid can, therefore, be used, and peaks of increasing current are measured. Finally scattering of α-radiation from a small radioactive source can be employed to assess particle-size distributions. With all the techniques mentioned one of the most important steps is to prepare a suspension of the catalyst particles that is representative of the suspension in the liquid to be catalytically treated. Ultrasonic treatment is usually employed, but such treatment can cause fracture of the catalyst particles. With careful research, samples of the fresh catalyst particles and of the ultrasonically treated catalyst should be studied by scanning electron microscopy.

The mechanical strength of catalyst particles is technically one of the most important characteristics. With suspended catalysts attrition leads to fines that cannot be readily separated from the reaction products. Attrition can be determined by subjecting a weighed amount of catalyst sample in a laboratory reactor to intensive stirring and determining the weight of the catalyst separated from the liquid. Ultrasonic treatment or passage of the suspension through a small centrifugal pump can also be employed. The mechanical strength of the larger particles of fixed-bed catalysts is expressed as the side-crushing strength, which results from the pressure required to crush 50 % of the catalyst particles investigated. It is important that the catalyst particles have previously been carefully dried, because the mechanical strength of porous catalyst particles that have taken up moisture is much lower. Another means of determination of the mechanical strength is to put a weighed amount of the catalyst particles in a cylinder which is rotated for a fixed period of time. Subsequently the number of catalyst particles fractured is measured.

The loss on ignition is usually determined, because catalysts are purchased per unit weight. The weight of water taken up is not involved in the actual weight of the catalyst. Although the loss on ignition can be simply measured by determining the weight of a catalyst sample before and after calcination, catalyst supported on activated carbon cannot be kept at elevated temperatures in air, because oxidation will rapidly oxidize the carbon. Air-oxidation of activated carbon usually begins at ca 500 °C, but the presence of catalytically active materials reduces the temperature of onset of oxidation to ca 300 °C. Activated carbon-supported catalysts are, furthermore, often delivered with a water content as high as 50 % (*w/w*). The reason for the high water content of carbon-supported precious metals has not been clearly elucidated. It has been observed that exposure to atmospheric air significantly raises the hydrophilicity of activated carbon. Keeping the pores of the activated carbon filled with water might prevent oxidation of the surface of the activated carbon thus maintaining its properties.

Other data required to classify industrial catalysts are total surface area per unit volume or per unit weight; pore volume and pore-size distribution; and catalytically active surface area per unit volume or per unit weight.

With supported catalysts in particular the catalytically active surface is much smaller than the total surface area, because the surface area of the support is usually much larger than the active surface area. With non-supported catalysts, such as Raney metals, it is, however, also highly important to compare the total surface area with the active surface area to assess whether residual alumina covers a significant fraction of the metal surface. Therefore separate measurements of total surface area and catalytically active surface area are required.

2.3.1 Total Surface Area and Pore-size Distribution

The total surface area is calculated from the amount of physical adsorption of nitrogen at 77 K. During the thirties Brunauer, Emmett, and Teller [1,2] presented a theory dealing with the multilayer adsorption of gases on solids. They assumed that the first layer of gas molecules is adsorbed more strongly than subsequent layers, and that the heat of adsorption of subsequent layers is constant. They also assumed the absence of lateral interaction between adsorbed molecules. On the basis of these much criticized assumptions they derived an adsorption isotherm, which describes the experimentally determined adsorption isotherms excellently. From the adsorption isotherm a value corresponding to the volume of the adsorbed monolayer is calculated. With physical adsorption the amount of gas adsorbed is usually plotted as a function of the relative pressure, that is the pressure divided by the saturation pressure at the same temperature. From the surface area of one molecule adsorbed in the monolayer the total surface area can be calculated; this has become known as the BET surface area after Brunauer, Emmett and Teller. Nitrogen is usually employed as adsorbate, but measurements have also been obtained with argon and xenon. Although the BET theory has provided very good results with oxides such as, alumina, silica, and titania, graphite surfaces do not follow the BET adsorption isotherm neither do other materials, such as Teflon.

Brunauer, Deming, Deming, and Teller [3] later distinguished five different physical adsorption isotherms. The Type I adsorption isotherm is characteristic of chemisorption, for which the first layer is adsorbed much more strongly than subsequent layers. The type II isotherm is characteristic of the multilayer adsorption exhibited with physical adsorption near the boiling point of the adsorbate. Type III isotherms are obtained for multilayer physical adsorption with condensation of the adsorbate in narrow pores whereas Type IV isotherms are obtained when the first layer is adsorbed with a lower heat than the heat of condensation of the adsorbate. Finally, Type V isotherms are characteristic of adsorption according to Type IV on an adsorbent with narrow pores.

The volume of (liquid) nitrogen taken up at saturation measures the pore volume of the catalyst, v_{por}. A mean pore diameter can be calculated from the pore volume and the BET surface area, S_{BET}. If the presence of cylindrical pores is assumed, the mean pore diameter, d_{m}, is $d_{\mathrm{m}} = 4(v_{\mathrm{por}}/S_{\mathrm{BET}})$.

At the Technical University of Delft De Boer and coworkers Lippens, Broekhoff, and Linssen [4–7] significantly extended calculations from the physical adsorption isotherms. These authors calculated the thickness of the adsorbed layer of nitrogen as a function of the relative pressure at 77 K by dividing the (liquid) volume of adsorbed nitrogen by the BET surface area. For agreement with the BET theory the authors used the denomination statistical thickness of the adsorbed nitrogen layer. Plotting the thickness of the adsorbed layer as a function of the relative pressure for a wide range of porous materials in which no capillary condensation of nitrogen could proceed they obtained a single curve. Plotting the volume of the adsorbate as a function of the thickness of the adsorbed layer leads to a straight line, the *t*-plot. The slope of the *t*-plot represents the surface area of the material.

Gregg and Sing [8] developed a slightly different procedure which leads to results analogous with those from the *t*-plot. Instead of the (statistical) thickness of the adsorbed layer these authors employ the adsorbed volume normalized for the volume adsorbed at $P/P_0 = 0.4$. When the gas volume adsorbed at $P/P_0 = 0.4$ is V_{ads} (0.4), Gregg and Sing use $V_{\mathrm{ads}}/V_{\mathrm{ads}}$ (0.4) $= \alpha_{\mathrm{s}}$. Plotting V_{ads} as a function of α_{s} provides a graph analogous to the *t*-plot.

When capillary condensation of nitrogen in pores present in the catalyst proceeds, there is a positive deviation from the *t*-plot because at a given relative pressure more nitrogen is taken up than is adsorbed on a flat surface. Because the curvature of the meniscus of the capillary condensed nitrogen is different during adsorption and desorption, the sorption isotherm usually exhibits hysteresis, unless only open slit-shaped pores are present. The shape of the hysteresis loop indicates the shape of the pores, viz., cylindrical, open or closed slit-shaped, and ink bottle. De Boer distinguished five different hysteresis loops and related the different loops to more detailed pore shapes. Broekhoff [7] developed a thermodynamically rigorous procedure for calculation of the pore-size distribution from the hysteresis loop.

A problem with active carbon is that the usual *t*-plot is not obtained for adsorption isotherms measured on carbon. At 77 K adsorption is often limited because migration of adsorbed molecules over the surface is required to enter narrow pores. At 77 K the mobility of adsorbed species is often not sufficient. Carbon dioxide adsorption is therefore employed to assess the surface area of activated carbon supports.

Experimental determination of physical adsorption was initially a very difficult procedure requiring the use of manometers with liquid mercury. Also, the temperature of the liquid nitrogen used to keep the adsorbent at a low temperature could vary because of condensation of oxygen in the nitrogen. Nowadays impressive commercial automatic equipment is available that measures a complete adsorption isotherm within a night. For assessment of surface area only, apparatus is available that measures a single point of the BET isotherm. Though the accuracy is obviously less, measurement is very rapid and therefore very appropriate for measurement of the surface area of a large number of analogous samples.

Another technique for measurement of pore-size distributions is mercury porosimetry [9]. Because mercury does not wet the surface of oxides (the contact angle varies from 135 to 143 °), pressure is required to force mercury into the pores. The pressure at which mercury is taken up indicates the diameter of the pores, and the volume of mercury intruding gives the volume of the pores. Modern equipment enables the use of very high pressures, and thus measurement of pore diameters of ca 4 nm. It can therefore be concluded that mercury porosimetry and nitrogen adsorption can both be used to measure pores down to a diameter of about 4 nm; mercury porosimetry can, however, be used to determine pore of diameters as large as 200 µm. Modern equipment employs computer programs that enable ready calculation of the pore-size distribution from experimental data.

Thermoporimetry [10,11] can reliably be used to obtain the pore-size distribution of porous particles suspended in water. The basis of the technique is that the surface area of the ice–liquid water interface increases when the ice penetrates narrow pores. As the diameter of a pore is smaller, the increase in interfacial area is larger. To freeze the water in narrower pores thus requires lower temperatures. The temperature at which the heat of solidification of water is set free thus indicates the width of the pores, and the amount of heat released indicates the pore volume. Measurement by DSC (differential scanning calorimetry) can provide the data for determination of the pore-size distribution of porous particles suspended in pure water. It has been observed that the first layer of water molecules present on the surface of oxides cannot be frozen; apparently the interaction with the surface of the oxides is so high that the layer is already 'frozen' without attaining the structure of ice. Thermoporimetry can, therefore, also provide data about the interaction of water with the surfaces of solids. Thermoporimetry with other liquids, e. g. benzene, can provide information about the interaction of surfaces with, e. g., apolar liquids.

2.3.2 Catalytically Active Surface Area Per Unit Weight of Catalyst

The catalytically active surface area per unit weight of catalyst is the most important characteristic of a solid catalyst. To measure the active surface area selective adsorption on the active surface is required. Chemisorption, adsorption with an energy characteristic of chemical bonds, is usually sufficiently specific to provide a reliable measure of the active surface area of metals. In contrast with physical adsorption, chemisorption is usually confined to a monolayer or less. With chemisorption dissociation of the adsorbate often occurs. Hydrogen and oxygen generally dissociate upon adsorption on metal surfaces. At higher coverages of oxygen, some non-dissociated oxygen species might be adsorbed.

Hydrogen adsorption at relatively low temperatures is often specific for metal surfaces. Because of the very low boiling point of hydrogen, physical adsorption is negligible unless the temperature is low, viz. ca 77 K, and the pressure is high, e. g. 200 mm Hg. At more elevated temperatures hydrogen can react with the surface of reducible oxides to form water. The temperature at which hydrogen adsorption is performed therefore cannot be too high when the catalyst contains metals and reducible oxides. Adsorption of hydrogen is usually performed at room temperature, and it is usually assumed that one hydrogen atom is adsorbed per metal surface atom.

Nickel surfaces and surfaces of supported precious metal particles can fairly reliably be calculated from the extent of hydrogen adsorption. The metal surface must first be reduced and the adsorbed hydrogen must subsequently be removed by evacuation at elevated temperatures. It is important that a sufficiently high pumping speed is maintained in the vessel containing the metal catalyst, because complete removal of hydrogen requires a low pressure and a relatively long time.

Evacuation for a long period of time can lead to desorption of water, which can oxidize the nickel surface. Although a low pressure of hydrogen can prevent oxidation of nickel surfaces by water, hydrogen is more rapidly removed during evacuation than water vapor, which is slowly released by oxidic supports. With precious metals there is no risk of oxidation of the metal surface by water. Nevertheless evacuation at elevated temperatures may lead to sintering of clusters of the small metal particles often present in supported precious metal catalysts. An alternative procedure has therefore been developed. It has been observed that admission of carbon monoxide leads to desorption of hydrogen adsorbed on the surface of precious metals. A supported precious metal catalyst reduced by hydrogen can therefore be cooled to room temperature and exposed to pulses of carbon monoxide in a flow of nitrogen. A thermal conductivity cell can determine the amounts of hydrogen released by the action of each pulse of carbon monoxide. Summation of the amounts of hydrogen set free by the pulses of carbon monoxide provides the total amount of hydrogen adsorbed. Unfortunately admission of carbon monoxide does not lead to desorption of hydrogen adsorbed on nickel surfaces. On adsorption of carbon monoxide adsorbed hydrogen penetrates further into the nickel surface, as was apparent from the effect on the ferromagnetism of nickel.

As mentioned above, Raney nickel is often employed as a catalyst in the fine-chemical industry. Because alumina and aluminum remain within the Raney nickel, and the possibility that nickel oxide is present in the Raney nickel, the BET surface area can be much larger than the free nickel surface area. It is therefore important to be able to determine the free metal surface area in Raney nickel. The free nickel surface area of Raney metal catalysts is, however, difficult to measure. During evacuation of Raney nickel at elevated temperatures huge amounts of hydrogen are released. After some debate it was demonstrated that there was little hydrogen present within the nickel crystallites, but that the hydrogen originated from the reaction of residual aluminum with the water in which the Raney nickel is stored. Removal of hydrogen and of metallic aluminum and water, the source of hydrogen, at temperatures at which there is no significant sintering of the Raney nickel is, however, almost impossible. It might be possible to assess the nickel surface area of Raney nickel by thorough removal of the water and subsequent measurement of the number of adsorbed (protium) hydrogen atoms by exchange with deuterium. It has, however, to be determined whether water can be removed at temperatures at which Raney nickel does not sinter.

Although adsorption of oxygen can also be used to measure the free metal surface area, interaction of metal surfaces with oxygen is usually not confined to the surface, but several monolayers are taken up. It has been found that admission of oxygen to small particles of well-evacuated catalysts can increase the rate of transport appreciably, compared with adsorption of oxygen beyond a monolayer. Completion of a monolayer of oxygen can be assessed by plotting the time involved in virtually complete uptake of an oxygen dose as a function of the dose number. The time to take up a dose of oxygen increases abruptly when a monolayer of oxygen has been adsorbed.

Interaction of metal surfaces with nitrous oxide (N_2O) leads to adsorption of oxygen and release of dinitrogen. The pressure, therefore, does not change. Although nitrous oxide reacts less extensively with metal surfaces than does nitrogen dioxide, it may be noted that nitrous oxide and iron–MFI zeolite is a powerful oxidizing system capable of converting benzene selectively into phenol. Interaction of nitrous oxide with metallic copper surfaces results in adsorption of ca a monolayer, as was observed with silver surfaces. Adsorption of oxygen from nitrous oxide does not lead to a pressure drop, since the amount of dinitrogen released is equal to the nitrous oxide decomposed. The reaction of nitrous oxide can be measured by cooling a cold trap attached to the adsorption vessel. Nitrous oxide has a much higher boiling point than nitrogen; the remaining nitrous oxide therefore will condense in the cold trap.

Another interesting procedure is measurement of hydrogen consumption during temperature-programmed reduction as a means of accurate assessment of the amount of oxygen deposited from nitrous oxide on metal surfaces. A relatively simple apparatus suffices to provide accurate results. Performing a subsequent complete oxidation of the metal particles by reaction with dioxygen at high temperatures, and then measurement of hydrogen consumption, enables determination of the amount of reducible metal present in the catalyst.

2.3.3 Extent of Reduction of Metal Catalysts

With supported metal catalysts that have to be treated in a reducing gas flow at elevated temperatures to convert the catalytic precursor into the desired metal, it is important to assess the extent of reduction. Often the oxidic phase of the catalytically active precursor is stabilized by interaction with the support. It is even possible for a finely divided precursor to react with the support to a compound much more stable than the corresponding metal oxide. An example is cobalt oxide, which can react with alumina to form cobalt aluminate, which is very difficult to reduce to metallic cobalt and alumina. Another example is silica-supported iron oxide. Usually the reduction of iron(III) to iron(II) proceeds readily, because the reduction to iron(II) is hardly thermodynamically limited by the presence of water vapor. Iron(II), however, reacts rapidly with silica to iron(II) silicate, which is almost impossible to reduce.

The extent of reduction of the precursors of catalytically active metals is usually assessed by (i) temperature-programmed reduction; (ii) thermogravimetry; (iii) release of hydrogen upon treatment with acid; (iv) reaction with iodine; and (v) determination of the saturation magnetization with ferromagnetic metals (iron, nickel, and cobalt).

Temperature-programmed reduction is most commonly employed. Hydrogen is passed through the catalyst the temperature of which is raised linearly with time and the consumption of hydrogen is measured as a function of the temperature. Knowledge of the loading of the support and integration of the hydrogen consumption provides the extent of reduction. One must take into account that at the same temperature level the reduction at a stationary temperature is commonly higher than that at increasing temperature. Thermogravimetry provides the same information, although weight loss during reduction results not only from loss of oxygen from the metal oxide, but also from desorption of water present on the catalyst precursor. The increase in weight upon exposure to oxygen subsequent to the reduction can indicate accurately the extent of reduction, because now only oxidation of the reduced metal particles proceeds. To avoid formation of explosive mixtures, the balance must be purged with inert gas after the reduction and before admitting oxygen. Unless the metal particles are very large, the small metal particles present in most catalysts are readily completely oxidized by reaction with oxygen. Thermogravimetry has also demonstrated that desorption of water vapor from the surface of the support can lead to oxidation of the metal. Measurements on nickel-on-silica catalysts have provided the experimental evidence.

Reaction of a non-noble metal with an acid leads to a salt of the metal and hydrogen. The determination has been especially employed with nickel, which was dissolved in sulfuric acid. It is important to remove adsorbed hydrogen, by careful evacuation, before performing the reaction with sulfuric acid. Reaction with excess iodine and back titration of the iodine also enables calculation of the extent of reduction. The measurement of the saturation magnetization of reduced iron, nickel, or cobalt catalysts calls for a strong magnetic field and a low temperature. Small ferromagnetic particles are superparamagnetic, which implies that the saturation magnetization can only be approached at high magnetic field strengths and low temperatures.

2.3.4 Solid-acid Catalysts

The adsorption of gaseous ammonia can therefore be used to measure the number of acid sites. Because adsorption of ammonia is more difficult to measure than desorption, temperature-programmed desorption of ammonia is often employed to measure the number of active sites of solid-acid catalysts. Integration of the thermal desorption plots gives the total number of acid sites and the desorption temperature indicates their strength. Ion-exchangers cannot, however, readily be heated to the temperatures required for complete desorption of ammonia without being decomposed.

As well as ammonia, adsorption and desorption of several other basic gas molecules, e. g. pyridine, are employed to measure the number and the strength of acid sites. Infrared absorption spectroscopy of adsorbed pyridine can indicate the nature of the acid sites (Brønsted or Lewis acid).

2.3.5 Dispersion of Active Component(s) Over the Support

From the extent of reduction and the surface area of the metal, as calculated from the extent of chemisorption, the mean size of the metal can be calculated. The broadening of the maxima in the X-ray diffraction pattern also measures a mean particle size. Usually the mean particle size calculated from the X-ray line-broadening is larger than that calculated from the extent of reduction and the surface area of the metal particles. The difference is because X-ray line-broadening provides a weight-mean particle size, $\Sigma n_i d_i^4/\Sigma n_i d_i^3$, whereas the extent of chemisorption and the extent of reduction result in a volume–surface mean diameter, $\Sigma n_i d_i^3/\Sigma n_i d_i^2$.

It is important to be able to determine the dispersion of the (precursor of the) active particles over the support. When clusters of small particles are present, the catalyst is much more liable to sintering of the active component to large particles of a low surface area than when the active component is present as small particles well distributed over the surface of the support and not in contact with each other. The line-broadening of the X-ray diffraction profile indicates only the presence of small particles, but not the extent of clustering. Only after thermal treatment does clustering becomes apparent from the sharpening of the X-ray diffraction pattern. Electron microscopy can show the presence of clusters, but often the concentration of clusters on the support is low. Because at high magnification the volume analyzed in the electron microscope is small, it can be difficult to observe the clusters. Therefore application of XPS (X-ray photoelectron spectroscopy) to assess the distribution of the active species over the support can be very informative.

XPS is fairly surface-sensitive, which implies that only a thin layer at the surface of the specimen is analyzed. The thickness of the layer analyzed depends upon the energy of the emitted photoelectrons. When clusters of the active component are present on the support, the amount of the active component measured with XPS is much smaller than with a uniform dispersion of the active component over the support. The ratio of the intensities of the XPS signals of the active component and the support is consequently much lower when clusters of the active component are present. Kuijpers [12] has developed a calculation procedure to derive the size of the (clusters of) supported particles from the ratio of the XPS data [13, 14]. Later on Gijzeman has refined the calculation.

Electron microscopy is in principle ideal for characterization of solid catalysts containing elementary particles of the support of ca 50 nm or larger and particles of the active components of sizes down to 1 nm. The ability to assess the elemental composition on a very small scale by analysis of the emission of X-rays or the electron-loss spectrum has added substantially to the power of the technique. The volume analyzed in transmission electron microscopy is, however, usually very small; it is therefore difficult to ensure that the volume studied in the electron microscope is representative for the catalyst. Furthermore the preparation of suitable specimens, that must be thinner than ca 0.1 μm, can also introduce artifacts. It is therefore advisable to combine electron microscopy with results from macroscopic techniques, such as, X-ray line broadening and surface area measurements. If the specimens investigated in the electron microscope are representative for the catalyst, electron microscopy can provide direct information about the build-up of the catalyst even with the fairly complicated catalyst compositions that are sometimes employed to obtain the selectivity required.

The adherence of small particles of precious metals to the surface of the support can be assessed by transmission electron microscopy. It has been observed that mild ultrasonic treatment of the catalyst in a liquid, such as ethanol, can remove precious metal particles from the surface of the support. After applying a drop of the suspension resulting from the ultrasonic treatment on the carbon films used as specimen support the precious metal particles released from the support show up on the carbon support film. Especially dark-field techniques are useful to indicate the presence of precious metal particles on the carbon support film.

With modern scanning electron microscopes many of the restrictions of the transmission electron microscope have been alleviated. Firstly, thin samples are no longer required. With instruments equipped with a field-emission gun, magnifications as low as 50× and as high as 100 000× can be achieved routinely. Imaging the back-scattered electrons gives the distribution of the heavy elements at a high resolution, whereas the secondary electrons are indicative of the shape and the size of the solid particles present in the specimen. Analysis of the emitted X-rays can indicate the elemental composition.

2.3.6 Conclusions

The characterization of solid catalysts calls for expensive equipment and specialized personnel. In the fine-chemical industry it is, therefore, not useful to perform the characterization of a solid catalyst within its own laboratory. It might, however, be worth obtaining the results of characterization from the catalyst producer, if they are available. The properties of solid catalysts can often be used for reasonably accurate prediction or rationalization of catalyst performance.

References

[1] S. Brunauer, P.H. Emmett, and E. Teller *J. Am. Chem. Soc.* **60** (1938) 309.

[2] J.H. de Boer 'The Dynamical Character of Adsorption' Clarendon Press Oxford (1953) p. 61.

[3] S. Brunauer, L.S. Deming, W.S. Deming, and E. Teller *J. Am. Chem. Soc.* **62** (1940) 1723.

[4] B.C. Lippens, B.G. Linsen, and J.H. de Boer *J. Catal.* **3** (1964) 32.

[5] B.C. Lippens and J.H. de Boer *J. Catal.* **4** (1963) 319.

[6] J.H. de Boer, B.G. Linsen, and Th. J. Osinga *J. Catal.* **4** (1965) 643.

[7] J.C.P. Broekhoff and B.G. Linsen *in* 'Physical and Chemical Aspects of Adsorbents and Catalysts' (B.G. Linsen ed.) Academic Press London and New York (1970) p. 1.

[8] S.J. Gregg and K.S.W. Sing 'Adsorption, Surface Area and Porosity' 2nd Edition Academic Press New York (1982).

[9] S. Lowell and Joan E. Shields 'Powder Surface Area and Porosity' Third Edition Chapman and Hall London (1991) Chapter 10 and 11.

[10] M. Brun, A. Lallemand, J.F. Quinson, and C. Eyraud J. Chim. Phys. (France) 70 (1973) 973, 979, 990.

[11] C.J.G. van der Grift, H. Barten, C.J. van Miltenburg et al. in 'Characterization of Porous Solids' (K.K. Unger et al. eds.) Elsevier Amsterdam (1988) p. 619.

[12] H.P.C.E. Kuijpers *Solid State Ionics* **16** (1985) 15.

[13] H.P.C.E. Kuipers, H.C.E. van Leuven, and W.M. Visser *SIA, Surf. Interface Anal.* **8** (1986) 235.

[14] H.P.C.E. Kuipers and D.P. de Bruijn *Ned. Tijdschr. Natuurk.* A **55** (1989) 85.

2.4 Reactors

A. E. van Diepen, J. A. Moulijn

Mechanically stirred batch reactors are often used for the production of fine chemicals and pharmaceuticals. One might wonder why this is so. One important reason for the choice of this type of reactor is its widespread use in laboratory and pilot-scale research and development programs–the mechanically stirred batch reactor is, therefore, often the first reactor that comes to mind. Frequently, however, other types of reactor are preferable for reasons such as better reactant conversion, product selectivity, ease of catalyst separation, etc.

Rational reactor selection and design requires information on thermodynamics, chemical kinetics, heat and mass transport, and reactor hydrodynamics. In practice, a quantitative analysis is based on reactor models and engineering correlations. In this chapter we limit ourselves to a qualitative discussion, emphasizing principles rather than quantitative calculations.

2.4.1 Introduction

In the production of fine chemicals and pharmaceuticals, catalyzed reactions are becoming more important. While many of these reactions are catalyzed by soluble, homogeneous catalysts, the possibilities and advantages of heterogeneous catalysis must not be overlooked.

Solid-catalyzed reactions can occur in either the liquid or gas phase. Gas-phase reactions are not very common in the production of fine chemicals, because complex molecules with limited volatility and thermal stability are usually involved, which makes operation at the high temperatures required for their vaporization impossible. Gas–liquid reactions with a solid catalyst probably encompass the largest number of applications in fine-chemical and pharmaceutical processes [1]. Two other classes of solid-catalyzed reaction taking place in the liquid phase are liquid–solid reactions and liquid–liquid–solid reactions, but these are much less common. We shall, therefore, focus on gas–liquid–solid reactions, in which the solid is a heterogeneous catalyst.

Catalytic reactions can be run in *batch* mode or as a *continuous* process. In a batch process the reactants, catalyst, and other reaction components are loaded in an appropriate vessel, the reaction is run, and the products are removed from the vessel after some time and separated from the catalyst. In a continuous system the reactants are passed over the catalyst and the products removed at the same rate as the reactants are added. Another, intermediate, option is semibatch operation; one of the reactants is added, gradually or step-wise, to the reactor, which has been loaded with catalyst and the other reactant(s).

In the production of fine chemicals batch or semibatch operation is most popular, because often the quantity of material produced does not economically justify continuous operation. Furthermore, many fine chemical plants are so-called multipurpose or multi-product plants (MPPs), in which many different compounds are produced using the same equipment. This is fully analogous to the kitchen at home, designed to prepare food in small quantities and with highly different compositions. Still, in fine-chemicals production continuous operation is sometimes justified and even required, for instance for fast exothermic reactions.

Apart from the classifications mentioned above, solid-catalyzed reactions can also be differentiated on he basis of whether the catalyst is suspended in the liquid phase (slurry reactors) or present in the form of a packed bed of particles (fixed-bed reactors).

2.4.2 Three-phase Catalytic Reactions (G–L–S)

In fine-chemicals production three-phase reaction systems are common for the hydrogenation and hydrogenolysis of different organic functional groups. Other reactions, such as heterogeneously catalyzed catalytic oxidations, hydrodesulfurizations, and reductive aminations are encountered less frequently.

The three phases present in this kind of reaction are a *gas* phase, containing, e. g., hydrogen or oxygen, a *liquid* phase, often consisting of a solvent, containing the dissolved reactants, and the *solid catalyst.* Besides dissolving the reactants, the solvent also provides a liquid layer around the catalyst particles, which might help to:

- avoid deactivating deposits and thus ensure higher catalyst effectiveness;
- achieve better temperature control because of the higher heat capacity of liquids; and
- modify the active catalyst sites to promote or inhibit certain reactions.

Besides these positive effects there is, however, a disadvantage–an extra barrier is introduced between the gaseous reactants (e. g., hydrogen) and the catalyst (see Figure 1). Mass transfer of the gaseous reactant to the liquid phase is often, but not always, the limiting step.

The organic substrate is usually present at much higher concentrations than the hydrogen dissolved in the liquid; hydrogen is the 'limiting' reactant. Therefore, the rate of mass transfer of hydrogen is of predominant significance. As shown in Figure 1, a number of steps must occur before hydrogen can be converted to products. The major steps are: (i) mass transfer from the gas bubble to the liquid, (ii) mass transfer from the liquid to the external surface of the catalyst particle, and (iii) diffusion inside the pores of the catalyst particle, accompanied by chemical reaction.

Therefore, in the choice and design of three-phase reactors, not only must the intrinsic kinetics be considered, but also the mass-transfer characteristics. For example, it is useless to try and improve the reaction rate by using a more active catalyst or increasing the catalyst load, when the overall rate of reaction is determined by mass transfer from the gas bubbles to the liquid phase, i. e. when the latter is slow compared with the intrinsic rate of reaction. Instead, one should

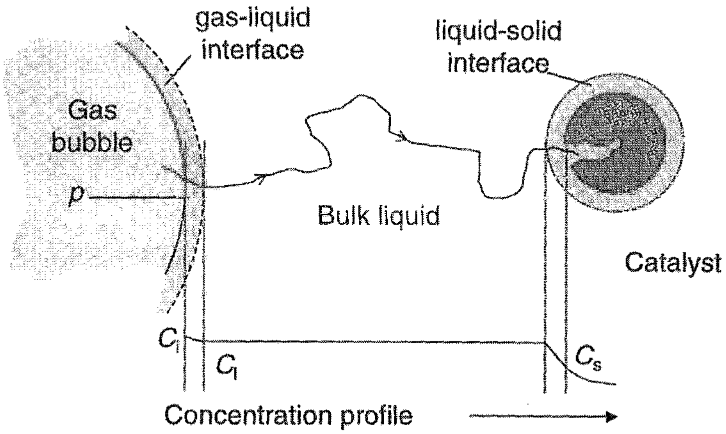


Figure 1. Mass transfer of hydrogen in gas/liquid/solid catalyst system; transport of H_2 limiting; $p = H_2$ pressure; $C = H_2$ concentration, C_i at interface, C_l in bulk liquid, C_s at catalyst surface.

try to increase the gas-to-liquid mass transfer rate, for example by improving mixing conditions. When the diffusion in the interior of the catalyst particles is rate determining, not only are the rates often reduced but selectivities are also affected. In this circumstance one should consider using smaller catalyst particles to improve liquid-to-solid mass transfer. Egg-shell catalysts, in which the active catalyst species is located in the outer shell of the catalyst particle, might also be used to improve selectivity.

Heat-transfer limitations can also occur, because many catalyzed gas–liquid reactions are exothermic. This might lead to the formation of local hot spots. This occurs readily for oxidation and hydrogenation reactions in particular.

2.4.3 Characteristics of Three-phase Catalytic Reactors for Fine-chemicals Production

In fine-chemicals production with heterogeneous catalysis two main types of cylindrical reactor are in common use–stirred tank reactors with a small so-called aspect ratio (length-to-diameter ratio), and column reactors (e. g., jet-loop reactor, bubble-column reactor, trickle-bed reactor) with a relatively large aspect ratio.

As discussed above, in the production of fine chemicals the mechanically stirred batch reactor is most popular. This is not surprising. In the laboratory reactions are usually conducted in mechanically stirred tank reactors, a natural (but not always correct) choice is to use a larger mechanically stirred tank reactor on the industrial scale. This illustrates the traditional method of scale-up. Furthermore, a tendency to duplicate known equipment usually wins when considering the choice of the reactor type for a particular process.

2.4.3.1 Reactors with Moving Catalyst

The stirred-tank, bubble-column, and jet-loop reactors (Figure 2) are all suspension reactors in which very fine catalyst particles (1–200 μm) are distributed throughout the volume of the liquid. There are many variations of each reactor type–for instance, stirred tanks can have different types of agitator, cooling jacket, or cooling coils. Bubble columns can be empty, packed, or fitted with trays.

In all reactor types presented in Figure 2 good mixing is important to aid in the transport of hydrogen (or oxygen, etc.) from the gas phase to the catalyst. Depending on equipment design and operation, the liquid phase approaches perfect mixing to a greater or lesser extent.

The mechanically stirred tank reactor is most commonly used in batch processes. It is the workhorse of the fine-chemicals industry. The catalyst particles are suspended in the liquid, which is almost perfectly mixed by a mechanical agitator. It is also possible to apply a hollow stirrer that encompasses two functions, i. e. mixing and addition of the gaseous reactant. Cooling is usually accomplished by coils within the reactor or by use of a cooling jacket. Another option is circulation of the liquid/solid slurry over external cooling elements.

In bubble columns, agitation of the liquid phase, and hence suspension of the catalyst is effected by the gas flow. The gas is often recycled to cause more turbulence and thus better mixing. Circulation of the liquid is often required to obtain a more uniform suspension. This can either be induced by the gas flow (airlift loop reactor) or by use of an external pump. In the latter instance it is possible to return the slurry to the reactor at a high flow rate through an ejector (Venturi tube). The local under-pressure causes the gas to be drawn into the passing stream, thus affording very efficient mixing. This type of reactor is called a jet-loop or Venturi reactor.

Jet-loop reactors tend to replace stirred-tank reactors in recently built equipment for fine-chemical hydrogenation. The external heat exchanger on the liquid circu-

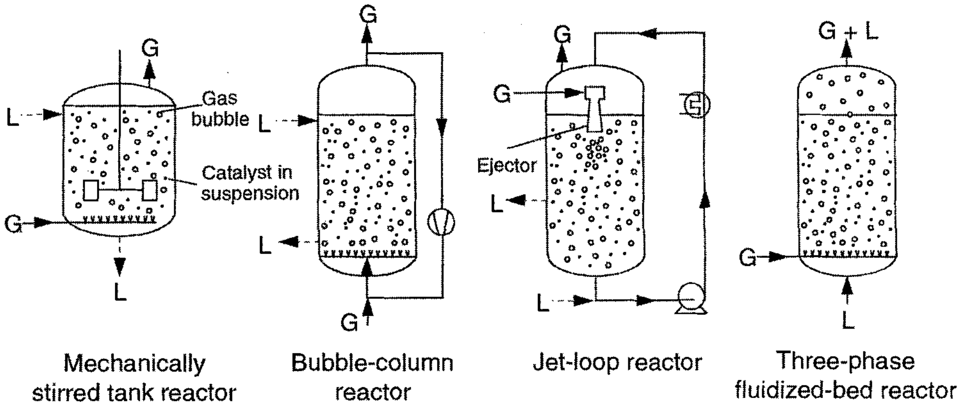


Figure 2. Reactors with moving catalyst particles (G = gas, L = liquid, dashed arrows indicate optional liquid flow for reactors operating in continuous mode).

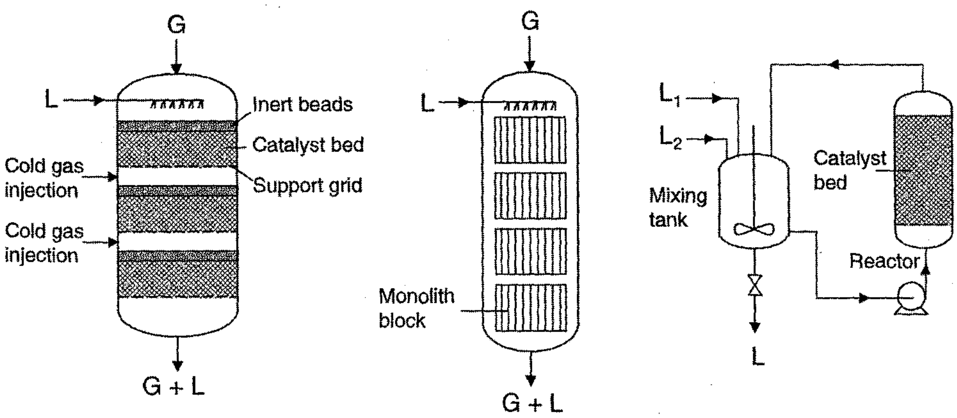
lation loop enables high heat removal capacity, which is a great advantage in highly exothermic reactions. A limitation on the use of jet-loop reactors is that the catalyst must be compatible with the pump, i. e. has low hardness and high attrition resistance. It is self-evident that these requirements are conflicting and, as a consequence, a compromise is needed.

The three-phase fluidized-bed reactor (ebulliated-bed reactor) differs from suspension reactors in the use of larger catalyst particles (0.1 to 5 mm) and the formation of a well-defined agitated catalyst bed. Whereas suspension reactors can operate in both batch and continuous mode with regard to the liquid phase (and catalyst), the ebulliated-bed reactor only operates in continuous mode, and hence is generally not the appropriate choice for the production of fine chemicals.

2.4.3.2 Reactors with a Fixed Bed of Catalyst

Figure 3 shows two examples of reactors with a fixed catalyst for gas–liquid reactions, viz. the trickle-bed reactor and the three-phase monolith reactor. In these reactors the flow of liquid phase usually approaches plug flow. The figure also shows an example of a batch reactor system for a liquid–liquid reaction consisting of a mixing tank and a fixed-bed reactor with upward flow. This set-up is applied in aromatic acylation.

Trickle-bed reactors, i. e. fixed-bed reactors with cocurrent downflow of gas and liquid, have large-scale applications in oil refining processes such as hydrotreating and catalytic hydrogenation of residues. Trickle-bed reactors also have significant potential in fine chemicals production, among other reasons because they are well suited for high-pressure operations. Despite their continuous operation, small size trickle-bed reactors can be adapted to batch-wise operation by multiple recycling



Trickle-bed reactor

Three-phase monolith reactor

Batch reactor system for liquid-liquid reaction

Figure 3. Three-phase reactors with fixed catalyst (G = gas, L = liquid).

of the liquid product [2], similar to the depicted batch reactor system for a liquid–liquid reaction.

An important aspect of trickle-bed reactors is the wetting of the catalyst particles; because of uneven distribution of the liquid phase 'dry spots' can occur; these might lead to relatively high local mass-transfer rates. At first sight this might be seen as an advantage, but it can lead to catalyst deactivation or, even more important, temperature runaway. Temperature control is relatively difficult, and often several beds are used with intermediate cooling, e. g., by injection of cold gas, as shown, or by use of heat exchangers. The relatively large particle size (1.5–5 mm) required to prevent excessively large pressure drops is a disadvantage for fast reactions, because transport limitations inside the catalyst particle become important. This often reduces the rate of reaction and the selectivity.

An alternative to the trickle-bed reactor, developed only recently, is the three-phase monolith reactor [3,4].The monolith catalyst has the shape of a block with straight narrow channels with the catalytic species deposited on the walls of these channels. Advantages of the monolith reactor compared with the trickle-bed reactor are its low pressure drop and the much smaller diffusion distance, because of the thin catalyst layer. They also are claimed to be intrinsically safe.

Although the monolith reactor has already found a number of applications in gas-phase reactions (e. g., the catalytic purification of exhaust gases from automobiles), it is not currently applied in commercial gas–liquid reactions in fine chemicals production.

2.4.3.3 Comparison–Reactor Choice

A rational choice from the variety of reactor types available requires knowledge of reaction kinetics, thermodynamics, and the properties of the reaction mixture throughout the reaction. Table 1 lists characteristic properties of the reactors discussed above, which can serve as guidelines for preliminary reactor selection. Experimental techniques and correlations for evaluation of the various parameters can be found in, for instance Refs 1, and 4–6, and references cited therein.

The more catalyst present per unit volume of reactor, the higher the rate of reaction can become (expressed as amount converted per unit reactor volume). Therefore, intrinsically slow reactions (reactions that are determined by the kinetic regime, and not by mass transfer) are usually best conducted in a reactor with a large volume fraction of catalyst, such as the trickle-bed reactor. With very active catalysts, on the other hand, where mass transfer dictates the rate of the overall process, slurry reactors are more suitable.

The rate of mass transfer between gas and liquid, determined by the product of the gas–liquid interfacial area, a_l, and the mass transfer coefficient, k_l, is an important parameter; many heterogeneously catalyzed gas–liquid reactions are limited by mass transfer of the gaseous reactant. The greater the product a_lk_l, the faster is mass transfer, and therefore, the observed rate of reaction for reactions in which mass transfer is the controlling step, i. e. for intrinsically fast reactions. The largest a_lk_l can be achieved in stirred-tank reactors and jet-loop reactors, so

Table 1. Characteristics of three-phase reactor types. Typical values are given [1,2,4,5,7].

Characteristics	Catalyst in suspension				Fixed bed	
Reactor	Stirred tank	Bubble column	Jet-loop	3-Phase fluid bed	Trickle-bed	3-Phase Monolith
Catalyst	Mobile small particles 1–200 µm			Mobile particles 0.1–5 mm	Spheres, extrudates, etc. 1.5–6 mm	Blocks with channels covered with catalyst layer 10–150 µm
Mode of operation	(Semi)batch or continuous			Continuous	Continuous (+ quasi batch), cocurrent downward	
Liquid hold-up ($m_l^3\ m_r^{-3}$)	0.8–0.9	0.8–0.9	0.8–0.9	0.2–0.8	0.05–0.25	0.1–0.5
Fraction of catalyst ($m_{cat}^3\ m_r^{-3}$)	0.01–0.1	0.01–0.1	0.01–0.1	0.1–0.5	0.55–0.6	0.07–0.15
a_l ($m_i^2\ m_l^{-3}$)	1000–2000	600–1000	2000–3000	500–1000	100–1000	500–1000
$k_l\ a_l$ (s^{-1})	0.15–0.5	0.05–0.25	0.2–1.5	0.05–0.3	0.01–0.3	0.05–0.7
$k_s\ a_s$ (s^{-1})	0.1–0.5	≈ 0.25			0.06	0.03–0.09
$\eta \approx$	1	1	1	< 1	< 1	< 1

a_l = gas–liquid interfacial area per unit volume of liquid; a_s = liquid–solid interfacial area per unit volume of liquid; k_l = mass-transfer coefficient from gas–liquid interface to bulk liquid $\approx 10^{-4} - 4 \times 10^{-4}\ m_l^3\ m_i^{-2}\ s^{-1}$ for all systems; k_s = mass transfer coefficient from liquid–solid interface to solid surface ($m_l^3\ m_s^{-1}\ s^{-1}$).

for this kind of reaction these will probably be a better choice than, for instance, a bubble-column reactor. If besides the desired reaction a fast reaction producing an undesirable by-product also occurs, the bubble column would be preferred.

For exothermic reactions, heat transfer is usually also an important factor, for reasons of temperature control and energy costs. In this respect, slurry reactors are superior to fixed-bed reactors. In particular, the jet-loop reactor with its external heat exchanger provides excellent temperature control.

Table 2 summarizes the main advantages and disadvantages of the reactors discussed.

Table 2. Advantages and disadvantages of three-phase catalytic reactors.

Reactor type	Advantages	Disadvantages
Slurry	Highly active catalysts can be used. Small particles with catalyst effectiveness approaching unity. Good temperature control. Higher liquid–solid mass transfer rates. Low pressure drop. Ease of design and scale-up.	Close to perfect mixing, so high liquid conversion not possible. Catalyst/product separation difficult. Operation at high pressure (> 30 bar) can be costly. Homogeneous side reactions can become important.
Trickle-bed	Flow approaches plug flow, so high conversion is possible. No catalyst/product separation required. Operation at high pressure possible. Lesser importance of homogeneous side reactions. High reaction rate per unit volume of reactor.	Larger particles with catalyst effectiveness smaller than unity. Poor heat transfer. Strong, crush resistant and non-deactivating catalyst required. Pressure drop can become excessive for small particles. Reactor design and scale-up difficult.
3-Phase monolith	Flow approaches plug flow. Good mass transfer properties (intermediate between slurry and trickle-bed reactors). Short diffusion distances, catalyst effectiveness larger than in trickle-bed reactor. Very low pressure drop. Ease of design and scale-up.	Short residence time. Poor heat transfer. Higher catalyst manufacturing cost. Uniform fluid distribution over channels difficult. Technology not yet proven.

2.4.4 Design Aspects of Stirred Tank Batch Reactor

Because the stirred-tank batch reactor is still the most commonly used reactor in the production of fine chemicals, some design and scale-up aspects of this type of reactor will be discussed in more detail.

The most important choices in the design of batch reactors are: reactor volume; selection of the agitator; speed of the agitator; power consumption; geometry of the tank, including baffles; and heat exchange area (internal and external).

A stirred-tank reactor is a cylindrical vessel with an elliptical or torospherical bottom and cover (1 → 100 m^3). It is equipped with an axially mounted stirrer rotating at a speed ranging from 25 (large-scale reactor) to 1400 rpm (laboratory reactor).

Proper agitator selection is very important to provide good contact between the phases. Firstly, the catalyst particles must be kept uniformly suspended in the reaction medium. When a gaseous reactant is used, agitation is of primary importance in facilitating the gas-to-liquid mass transfer. In addition, good agitation is needed for optimum temperature control.

A distinction is usually made between close clearance/large diameter and small diameter/high speed impellers. The first class is used for viscous reaction mixtures. It includes anchor stirrers and helical ribbons. The diameter of these agitators typically is between 70 and 100 % of the tank diameter.

Turbine impellers are generally used for low to moderate viscosity mixtures. Their diameters are between 0.25 and 0.5 times the tank diameter and they run at higher speeds. Mixers are generally categorized by the flow pattern they produce relative to the shaft centerline or the impeller axis (axial or radial or combined, see Figure 4). Further, breakdown is based on whether mixing mainly oc-

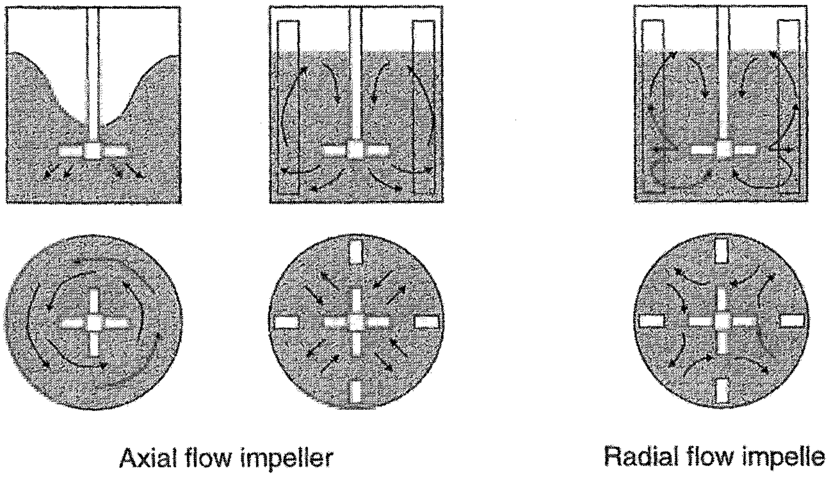


Figure 4. Time-averaged picture of flow pattern for axial flow impeller in tank without (left) and with baffles (middle) and radial flow impeller in baffled tank. Top: vertical plane; bottom: horizontal plane.

curs through bulk liquid flow (blending of miscible liquids and solids suspension) or through turbulent motion on a microscopic scale, i. e. shear (mass and heat transfer).

Stirred-tank reactors equipped with high-speed impellers are normally equipped with two or four baffles designed to prevent the formation of a vortex and rotation of the reaction mixture with the stirrer, as illustrated in Figure 4. Each baffle has a width of between 0.08 and 0.12 times the tank diameter. In normal practice, there is a space between the tank wall and the baffle equal to about one-third the baffle width. It is also desirable to keep the baffles off the bottom of the tank to keep solids from depositing.

Figure 5 shows some impellers typically used for low-viscosity mixtures. The six-blade Rushton turbine [8] is commonly used for gas dispersion and to promote gas–liquid mass transfer and heat transfer. It is, however, not often used for the suspension of solids. This stirrer provides mainly radial fluid flow within the reactor.

An alternative stirrer, the pitched-blade turbine is especially suited for high-speed liquid–solid applications, where the use of baffles might be impractical. The fluid can be directed up or down, depending on the direction of the pitch of the blades. The pitched-blade turbine is more flow-efficient than radial style impellers. Designs incorporate three and four blades at 45 ° or 30 ° pitch. The pitched blade is used when a balance of flow and shear (turbulence) is required.

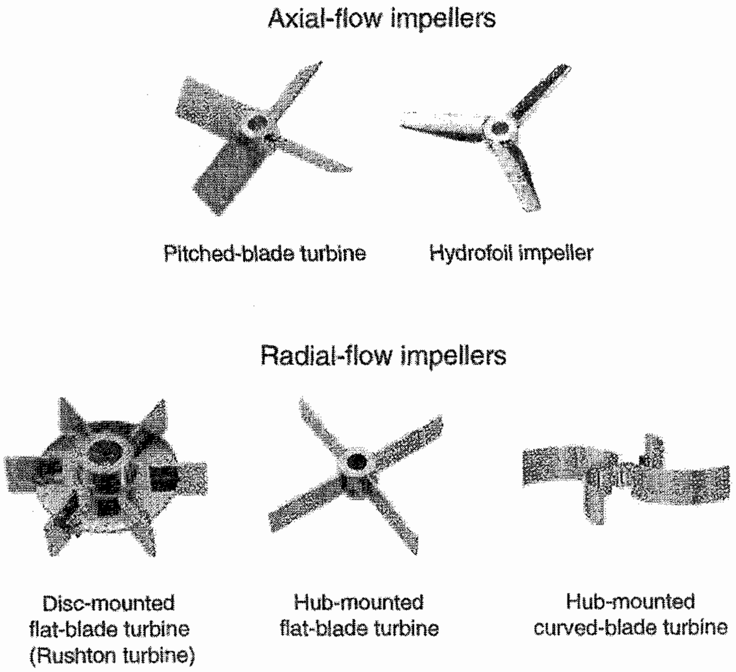


Figure 5. Typical impeller types.

Another type of axial flow impeller is of the hydrofoil design. The hydrofoil offers the best high-flow design. It affords one of the most efficient flow patterns with low power consumption and shear.

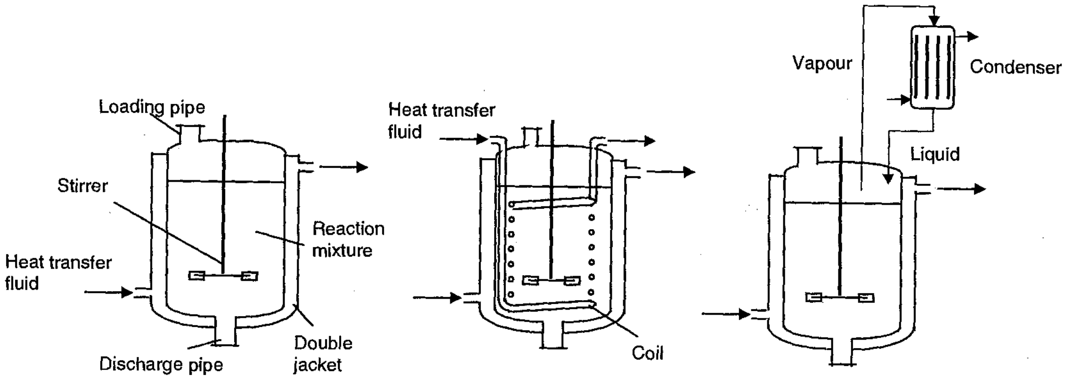
Hollow-shaft agitators are being used increasingly. Instead of churning the liquid reaction mass, the hollow agitator pumps gases from the headspace above the liquid to the lowest part of the reactor vessel. A specially designed impeller vigorously disperses these gases into the reactor bottom. This enables injection of the gas flow in the region where turbulence is most intense, i. e. at the tip of the stirrer blades.

Gas bubbles react with the liquid/slurry as they rise. Unreacted gases are reintroduced into the liquid through the hollow shaft. Advantages of hollow-shaft agitators are vigorous gas–liquid mixing, thorough suspension of solid catalysts, large gas–liquid interfacial areas (typically exceeding 2500 m^2 m^{-3} of reactor volume), enhanced gas–liquid and liquid–solid mass transfer rates, and very high heat transfer coefficients.

To keep all the catalyst particles suspended and to achieve a uniform dispersion of bubbles, a minimum amount of agitation is required. The minimum agitation speed for complete catalyst suspension depends, among other conditions, on catalyst loading and particle size [1,9,10]. Minimum agitation speed for uniform bubble dispersion depends mainly on the gas flow rate [11].

Power consumption for agitation is another important design parameter. It increases with increased agitation speed and tank diameter. Power consumption decreases with increased gas velocity. Correlations have been summarized by Baldi [12]. The presence of solid catalyst particles influences power consumption only slightly [6].

Section 2.4.5 will discuss the reason why heat transfer is fundamental in the design and operation of stirred-tank batch reactors. Figure 6 shows some of the batch reactor systems most often encountered in practice.



Double jacket

Double jacket and internal coil

Vapour phase condensation

Figure 6. Heat-exchange solutions in stirred batch reactor systems. Adapted from Ref. 5.

Double-jacket reactors are most easily built, but the heat exchange area is limited. Exchange area can also be installed inside the reactor but its presence will hinder stirring and cleaning. No glass-lined reactors equipped with internal cooling systems are available commercially. Therefore, when a large heat exchange area is needed, an external heat exchanger is required. A reflux condenser can be used when a reaction is conducted at the boiling point of the reaction mixture. Alternatively, part of the liquid can be recirculated through an external heat exchanger (similar to the jet-loop reactor, Figure 2). In this instance the reactor is not mechanically agitated (obviously) but mixing is provided by liquid circulation.

2.4.5 Scale-up of Stirred-Tank Batch Reactors–Runaway Reactions

In general, the histories of temperature, concentrations and mixing conditions in a full-scale reactor differ significantly from those in a laboratory reactor. Therefore, it is not surprising that selectivities usually change upon scale-up, as a result of undesired side reactions, unless proper measures have been taken.

The influence of heat transfer on yield and selectivity in scaling up batch and semibatch reactors will be illustrated using a series reaction, taking place in an ideal jacketed stirred-tank reactor. This reaction is composed of two irreversible elementary steps, both exothermic and both with first order kinetics:

**Equation here

A is the reactant, P the desired product, and S an undesired by-product. k_1 and k_2 are the reaction rate constants (s^{-1}). An example of such a reaction is the partial hydrogenation of an alkyne (A) to an alkene (P) and further to an alkane (S). Table 3 lists the variables used in the simulations.

Table 3. Variables used in the simulation of (semi)batch reactors.

Variable	Value	Unit	Remarks
$k_{10} =$	0.5	s^{-1}	
$k_{20} =$	1.0×10^{11}	s^{-1}	
$E_1 =$	20	$kJ\ mol^{-1}$	
$E_2 =$	100	$kJ\ mol^{-1}$	
$\Delta H_1 =$	-300	$kJ\ mol^{-1}$	
$\Delta H_2 =$	-250	$kJ\ mol^{-1}$	
$c_p =$	4	$kJ\ kg^{-1}\ K^{-1}$	
$\rho =$	1000	$kg\ m^{-3}$	
$U =$	500	$W\ m^{-2}\ K^{-1}$	
C_{A0}	1000	$mol\ m^{-3}$	(batch reactor)
C_{A0}	460	$mol\ m^{-3}$	(semibatch reactor)
T_0	295	K	
T_h	345	K	($0 < t < 3600$ s)
T_h	295	K	($t > 3600$ s)

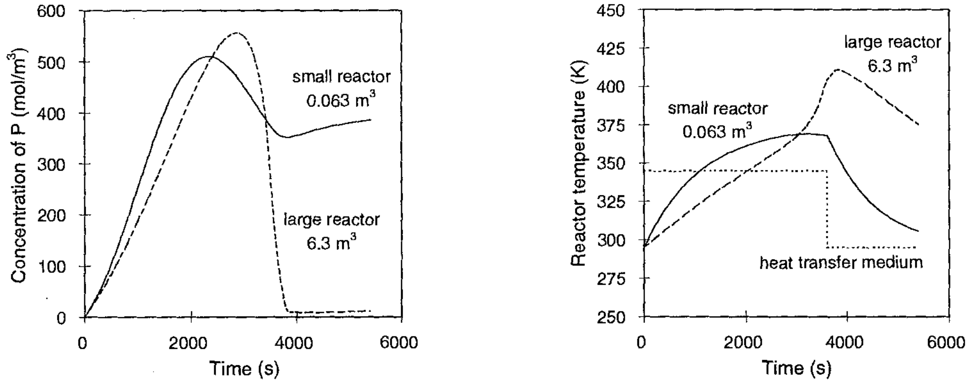


Figure 7. Ideal batch reactor; concentration of P (left) and reactor temperature (right) against time.

Figure 7 shows the results of calculations for small and a large reactors. After 5400 s the reaction is stopped. Clearly, the selectivity in a large-scale reactor is significantly less than in a pilot reactor. The yield in the latter is 38 %, whereas in the former it is 1 % only. The reason is that the cooling area-to-volume ratio of the large reactor is much smaller than that of the small reactor, which results in a temperature excursion ('runaway'). Hence, the rate of the second reaction increases, consequently resulting in reduced selectivity.

Obviously, the procedure followed in this example is far from optimum. It is not advisable to apply a step-shaped temperature profile. It is better to switch off the heat supply immediately after initiating the reaction and then start cooling intensively. After the temperature peak has passed, the temperature can be kept at the desired level by moderate cooling. Figure 8 (left) shows that a procedure in which

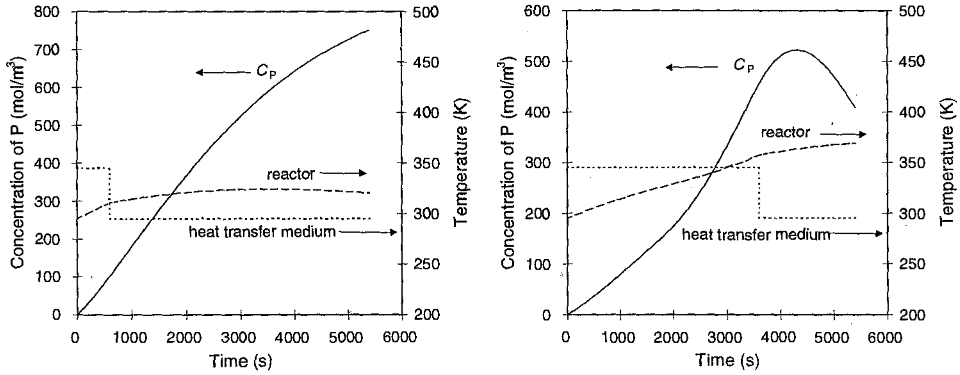


Figure 8. Concentration of P and reactor temperature against time in a large batch reactor with cooling starting after 600 s (left) and a large semibatch reactor (right).

cooling is started after 600 s, is much better: a yield of 75 % is obtained. The reason is that the temperature is kept below the value (ca 340 K) at which the consecutive reaction becomes important.

In the semibatch mode, a completely different procedure is followed: reactant A is dosed at a rate determined by the rate of heat removal. In this way it is relatively easy to obtain a high yield of P. As an example, Figure 8 (right) gives the results of a simulation based on nearly the same process conditions as were chosen for the example of the batch reactor that gave such a disastrous result (Figure 7). The difference is that only part of the amount of A is added instantaneously and the remaining amount of A is dosed continuously, starting after 1800 s, at a rate of 0.3 mol m^{-3} s^{-1}. It was assumed, for purposes of simplicity, that the volume of the reaction mixture and its physical properties did not change during dosing. Clearly, this semibatch reactor performs well–the yield is ca 40 %, better even than in the laboratory-size batch reactor. This is remarkable, because again the cooling was certainly not optimum.

Table 4 compares the results of computations for both batch and semibatch reactors, with different cooling policies. The data presented clearly show that even with inappropriate cooling the yield and selectivity in a large semibatch reactor are better than those in an even smaller batch reactor. It is also clear that optimizing the cooling affords spectacular improvements. Evidently, this type of modeling greatly helps in the design and operation of (semi-) batch processes.

Note that we have assumed ideal conditions–i. e. mixing problems, etc., in the large reactor have not been taken into account. We have, furthermore, assumed the reaction to be kinetically determined, which often is not so for three-phase reactions such as hydrogenations and oxidations.

For a more general background to this chapter, see [13].

Table 4. Batch and semibatch reactor results (after 5400 s).

Reactor	Cooling starts after (s)	V (m^3)	A_h/V (m^{-1})	Conversion (% mol)	Selectivity (% mol)	Yield on P (% mol)
Batch	3600	0.063	9.5	92.5	41.6	38.5
Batch	3600	6.3	2.6	97.8	1.2	1.2
Batch	600	6.3	2.6	76.6	98.0	75.1
Semibatch	3600	6.3	2.6	85.6	47.2	40.2

Notation

A_h	heat-exchange area	m^2
a_l	gas–liquid interfacial area	$m_i^2\ m_l^{-3}$
a_s	liquid–solid interfacial area	$m_s^2\ m_l^{-3}$
C	concentration	$mol\ m^{-3}$
c_p	heat capacity	$kJ\ kg^{-1}\ K^{-1}$
E	activation energy	$kJ\ mol^{-1}$
ΔH	reaction enthalpy	$kJ\ mol^{-1}$
k	reaction rate constant for first order reaction ($= k_0 \cdot \exp(-E/RT)$)	s^{-1}
k_0	pre-exponential factor	s^{-1}
k_l	mass transfer coefficient from gas–liquid interface to bulk liquid	$m_l^3\ m_i^{-2}\ s^{-1}$
k_s	mass transfer coefficient from liquid–solid interface to solid surface	$m_l^3\ m_s^{-2}\ s^{-1}$
p	pressure	bar
R	gas constant	$kJ\ mol^{-1} K^{-1}$
T	temperature	K
t	time	s
U	overall heat transfer coefficient	$W\ m^{-2}\ K^{-1}$
V	reactor volume	m^3

Greek

η	internal effectiveness factor, measure of catalyst utilization	–
ρ	density	$kg\ m^{-3}$

Subscripts

0	initial value
1	reaction 1
2	reaction 2
A	pertaining to reactant A
cat	catalyst
h	heat transfer medium
i	interface
l	liquid
P	pertaining to reactant P
r	reactor (part occupied by fluids (gas + liquid))
s	at catalyst surface

References

[1] P. L. Mills, P. A. Ramachandran and R. V. Chaudhari, 'Multiphase reaction engineering for fine chemicals and pharmaceuticals', Reviews in chemical engineering, vol. 8, N. R. Amundson and D. Luss (eds.), Freund Publishing House Ltd., London (1992).

[2] J. F. Jenck, in: Heterogeneous Catalysis and Fine Chemicals II M. Guisnet *et al.* (eds.), Elsevier, Amsterdam (1991) 1–19.

[3] A. Cybulski and J. A. Moulijn, Monoliths in heterogeneous catalysis, *Catal. Rev. Sci. Eng.* **36** (1994) 179.

[4] S. Irandoust, A. Cybulski and J. A. Moulijn, 'The use of monolithic catalysts for three-phase reactions', in: Structured catalysts and reactors, A. Cybulski and J. A. Moulijn (eds.), Marcel Dekker, New York (1998) 239–265.

[5] Trambouze, P., van Landeghem, H., Wauquier, J. P. 'Chemical reactors, design/engineering/operation', Technip, Paris, 1988.

[6] P. A. Ramachandran and R. V. Chaudhari, 'Three-phase catalytic reactors', Topics in chemical engineering, vol. 2, Gordon and Breach Science Publishers, New York, 1983.

[7] L. L. van Dierendonck, J. Zaharadník and V. Linek, 'Loop Venturi reactor–a feasible alternative to stirred tank reactors?', *Ind. Eng. Chem. Res.* **37** (1998) 734–738.

[8] Rushton, J. H., *Chem. Ing. Prog.* **46** (1950) 395–404.

[9] T. N. Zwietering, *Chem. Eng. Sci.* **33** (1958) 244–253.

[10] K. J. Carpenter, 'Agitation', in: Handbook of batch process design, P. N. Sharrat (ed.), Blackie Academic and Professional, London, 1997.

[11] A. W. Nienow, C. M. Wisdom and J. C. Middleton, in: 'Mixing, 2nd European Conference, Cambridge, March/Apr. 1977, proceedings, Paper F2, Cambridge, England, H. S. Stephens and J. A. Clarke (eds.), Cranfield (1978).

[12] G. Baldi, 'Multiphase chemical reactors', A. Gianetto and P. L. Silveston (eds.), Hemisphere Publishing Corporation, Washington D.C., (1986) pp. 375–395.

[13] J. A. Moulijn, M. Makkee and A. E. van Diepen, 'Chemical Process Technology' Wiley, New York to be published.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

3 Solid-acid Catalysts–General

3.1 Acidic Clays

M. Campanati, A. Vaccari

3.1.1 Introduction

Clay minerals (or clays) are very versatile materials and hundreds of millions of tons currently find applications in ceramics (including building materials) and as paper coatings and fillings, cat litter, drilling muds, foundry molds, pharmaceuticals, etc. Furthermore, clays can be used as adsorbents, ion exchangers, decolorizing agents, catalysts or catalyst supports, etc., depending on their specific properties [1–11]. For the last use, because increasingly stringent environmental issues and process optimization require the substitution of liquid acids by more friendly solid catalysts, untreated or appropriately modified clays can be regarded as very promising substitutes, because of their wide range of composition, use in catalytic amounts (unlike $AlCl_3$), easily manipulated properties, low cost, etc. These solid acids hold their acidity internally, and are thus easy and safe to handle although their acid strength can nevertheless be very strong, sometimes tenfold that of concentrated sulfuric acid. Furthermore, being mainly derived from silicon and aluminum oxides, they can be disposed of easily and safely [12–14].

Promising applications appear continually in the literature and further ones in new areas can be expected in the near future, taking into account the possibilities for technological upgrading of these materials, with the transition from 2- to 3-dimensional structures *via* the preparation of pillared clays. Exhaustive reviews and monographs have been published in recent years on the use of clays, acid treated clays, or pillared clays, dealing with their applications on both laboratory and industrial scales [2,8,10,11,15–28]. In this contribution the properties of clays more relevant in catalysis are examined as a function of recent catalytic applications, with the goal of illustrating the flexibility of these materials and the wide range of their current and possible applications.

3.1.2 Structure

Clays are mainly hydrous layer silicates of the phyllosilicate family in which the basic building blocks are $Si(O,OH)_4$ tetrahedra and $M(O,OH)_6$ octahedra ($M = Al^{3+}$, Mg^{2+}, Fe^{3+}, Fe^{2+}, etc), which polymerize to form two-dimensional sheets. Clays can be dioctahedral or trioctahedral, depending on the number of available octahedral sites in the structure occupied by cations, which in turn depends on the cation present (for example Al^{3+} or Mg^{2+}) in the octahedral sheets. The combination of a sheet of tetrahedra with a sheet of octahedra forms the layer (ca 0.7 nm thick) in 1:1 minerals, while in the 2:1 type (the most industrially interesting) a sheet of octahedra is sandwiched between two sheets of Si tetrahedra (ca 1.0 nm thick). Table 1 reports the main electroneutral structures and those obtained by isomorphous substitution of Si^{4+} in the tetrahedral sheet or Al^{3+} or Mg^{2+} in the octahedral sheets (which occur most often). When the incoming cation has a lower valence than the outgoing cation the lattice becomes negatively charged and neutrality is maintained by the exchangeable cations; the following general formulas may be used for the dioctahedral and trioctahedral clays:

Table 1. Classification of clays [5,8,29].

Group name	Layer type	Layer charge per unit cell	Octahedral occupancy	Subgroup	Species
Serpentine	1:1	$\cong 0$	tri-	Serpentines	Chrysolite
Kaolinite			di-	Kaolinites	Kaolinite, dickite
Talc	2:1	0	tri-	Talcs	Talc
Pyrophyllite			di-	Pyrophyllites	Pyrophyllite
Smectite	2:1	$0.6 < X < 1.2$[a]	tri-	Saponites	Saponite, hectorite
			di-	Montmorillonites	Montmorillonite, beidellite
Vermiculite	2:1	$1.2 < X < 1.8$[b]	tri-	Trioct. vermicul.	Trioctahedral vermiculite
			di-	Dioct. vermicul.	Dioctahedral vermiculite
Mica	2:1	$\cong 2$[c]	tri-	Trioct. micas	Phlogopite, biotite
			di-	Dioct. micas	Muscovite, paragonite
Brittle mica	2:1	$\cong 4$[d]	tri-	Trioct. britt. micas	Clintonite
			di-	Dioct. britt. micas	Margarite
Chlorite	2:1	variable[e]	tri-	Trioct. chlorites	Clinochlore
			di-	Dioct. chlorites	Donbassite
Sepiolitie	–	variable[f]	tri-	Sepiolites	Sepiolite
Palygorskite			di-	Palygorskites	Palygorskite

Interlayer type: [a]hydrated cation (might be monovalent); [b]hydrated cation (usually Mg^{2+}); [c]unhydrated cation (usually K^+); [d]unhydrated divalent cation; [e]hydroxy-octahedral layer; [f]none, these minerals have chain-like crystal structures in which water molecules and exchangeable cations are located.

$$(Si_{8-x}M_x)^T(Al_{4-y}M'_y)^o(OH)_4O_{20}M''^{n+}{}_{(x+y)}/nH_2O$$

$$(Si_{8-x}M_x)^T(Mg_{6-y}M'_y)^o(OH)_4O_{20}M''^{n+}{}_{(x+y)}/nH_2O$$

where T and O refer to the tetrahedral and octahedral sheets, respectively, M and M′ have units of charge less than the substituted cation and M″ is an exchangeable cation with valence *n*. It must be noted that charge balance can be that of entire octahedral sheets, such as in chlorites, often called 2:2 minerals because of the stability of the resulting unit (ca. 1.4 nm thick), although they should be considered as 2:1 minerals plus an hydroxy-interlayer (i. e. 2:1:1).

It is worth noting that the clay structure might have a significant effect on the catalytic properties. For example, kaolinites effectively catalyze normal electron-demand Diels–Alder cycloaddition presumably through stabilization of the dienophile by hydrogen bonding, thus reducing the HOMO (diene)–LUMO (dienophile) energy gap. The stereoselectivity, i. e. *endo* preference, is rather high, if moisture is carefully excluded from the reaction medium to avoid irreversible deactivation [24]. In contrast, by choice of a clay mineral with high layer charge, and thus narrower interlamellar space, the proportion of the kinetically less favored, but less bulky, *exo* isomer may be improved (Figure 1) [30].

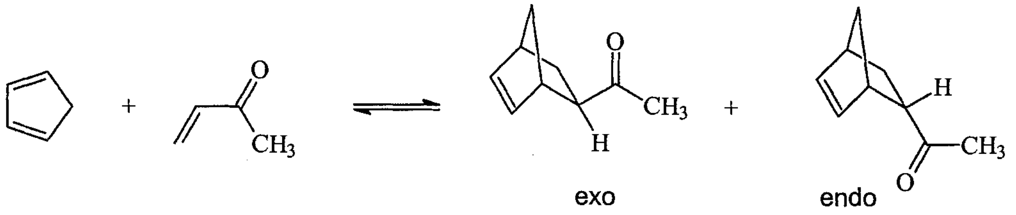


Figure 1. Synthesis of *exo* and *endo* isomers by Diels–Alder reaction between cyclopentadiene and methyl vinyl ketone [30].

3.1.3 Main Properties and Catalytic Applications

The properties of clays depend on composition and particle size [1–9,11]. For example, the BET surface area determined by N_2 adsorption decreases with increasing particle size, evidence that only the external surface area is measured. In all cases, the experimental values are significantly lower than those calculated for single-layer particles, because of the stacking of the elementary layers into aggregates. The different values determined as a function of drying procedure and, mainly, type of exchangeable cations, indicate that the number of layers per aggregate and the agglomeration of the aggregates in a powder depend on the cation and on the drying-procedure [9]. Related to the particle size is also the cation exchange capacity (CEC). The structural formulea give the amount of negative charge per unit cell as a result of isomorphous substitution (or pH-independent part). It must, moreover, be considered that at the edges of the crystals the sheet structure is broken and terminated by OH groups, which might contribute to the CEC. This contribution depends on the crystal size, pH and type of exchangeable cations and might reach, for example, ca 10% of the total CEC for 100-nm particles [9].

Clays have both Brønsted and Lewis acid sites, the amount and strength of which can be substantially modified by acid treatments and/or ion exchange [31–34]. The strength of the Brønsted sites can be determined in different ways: Hammett indicators, butylamine titration, IR spectroscopy using probe molecules, microcalorimetric or temperature programmed desorption methods [7,9,34–39]. There is a direct correlation between acid strength and composition (Table 2).

The synthesis of a superacid clay, with Hammett acidity ranging from −13.2 to −12.7 has also recently been reported [40]. The surface acidity decreases as the amount of residual water in the clay increases, with an extension related to the nature of the exchangeable cations (significant for Ca^{2+} and Mg^{2+} ions or almost negligible for K^+ and Al^{3+}) and activation conditions adopted [9,11,24,38].

Promising catalytic applications of clays or acid-treated clays are encountered in the field of organic and/or fine chemistry; these show specific features such as use in catalytic amounts (unlike $AlCl_3$), simple recovery and reuse of the catalyst, ease of set-up and work-up, gains in yield and/or selectivity, etc. which might be useful tools to move towards environmentally friendly technologies [41–43]. Moreover, acid treated clays can also be used as supports for microwave-activated organic reactions in the absence of solvent, achieving high reactivity partially because of the stability of these supports towards intense microwave fields further improvements are possible as a result of their optimization (Figure 2) [25,44].

Table 2. Acid strength and acidity (determined either by Hammett indicators in an aprotic solvent or by butylamine titration) of some clays [7,9,37].

Clay	H_0
Na^+ montmorillonite (0.04 meq g^{-1})	$-3.0 < H_0 < +1.5$
NH_4^+ montmorillonite	$-3.0 < H_0 < +1.5$
H^+ montmorillonite (0.65 meq g^{-1})	$-8.2 < H_0 < -5.6$
Acid treated clay	$H_0 < -8.2$

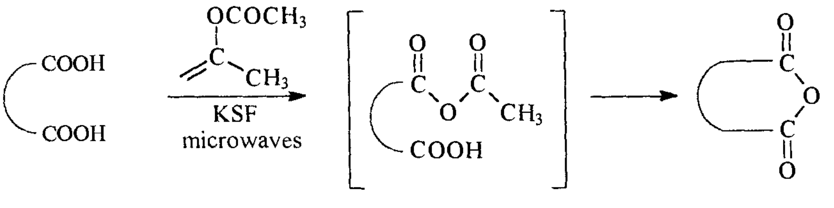


Figure 2. Synthesis of cyclic anhydride from dicarboxylic acid and isopropenyl acetate using KSF and microwaves [44].

Acid treatment of clays can be conducted in different ways: solid-state ion-exchange [46], washing with dilute mineral acid (exchanging the interlamellar cations with protons) or heating a suspension of clay in a mineral acid for different times (strongly modifying the clay structure) (Figure 3) [16,31–34,45]. When using acid-treated clays structural stability is critical; they might, for example, be converted to clays containing exchangeable ions leached from the lattice [47]. It is important to remember that the optimum acid treatment conditions vary from one clay to another, depending on chemical composition, level of hydration, nature of the exchangeable cations and, mainly, reaction conditions. For example, Sabu et al. reported that after a treatment with boiling 2 wf/M HCl some natural Indian clays with Fe^{2+} and Ti^{2+} ions in their lattice had catalytic activity in benzene alkylation significantly higher than that of the pure clay and of some reference materials (K10 or KSF and some Lewis acids supported on K10) [48].

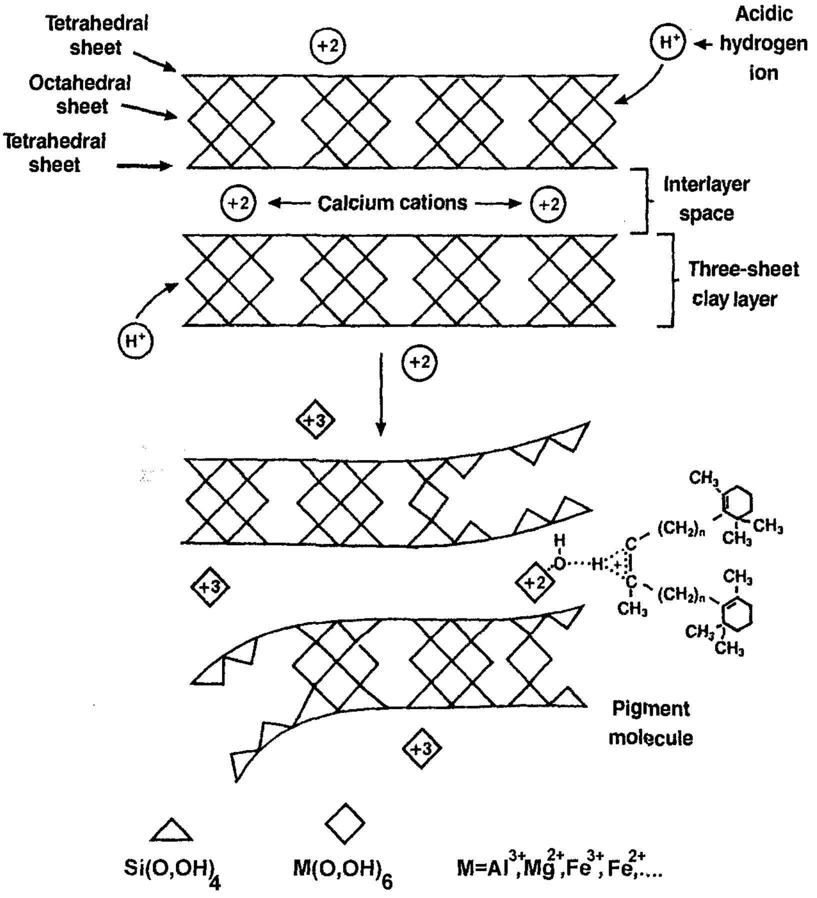


Figure 3. Schematic representation of the acid activation of clay [45].

The acid treatment conditions resulting in maximum catalytic activity depend on the reaction being catalyzed [32]. Reactions between polar molecules might require clays acid treated under mild conditions or for short times, capitalizing on the large number of acid sites available in the internal surface. In contrast, the surface accessible to apolar molecules is solely the external face and the edge areas of the clay platelets. These reactions require more severely treated clays and the catalytic activity depends on fine tuning of changes in surface area and reduced cation-exchange capacity. It must be noted that in a swelling medium, optimum catalytic activity can be achieved not by acid treatment, but simply by ion exchange with acidic cations such as Al^{3+} ions; in contrast, this last treatment has a negligible effect in a nonswelling medium [49].

Commercial acid-treated clays (e. g. K10, KSF, etc., from Aldrich or Süd-Chemie or F13, F20, F20X, etc., from Engelhard), widely used industrially as acid catalysts or adsorbents in hydrocarbon cracking [10,45] and, thus, well-defined and reliable materials, may be employed as reference materials. On the basis of current literature, K10 is by far the most intensively investigated commercially available acid-treated clay, although small differences resulting from the preparation conditions used have also been reported for the widely used K10 [50].

Some interesting reviews have appeared in recent years on the use of clays in organic synthesis and/or industrial applications [e.g. 10,15–18,21–25,27,29] and new catalytic applications of acid treated clays appear continually in the literature, for example in the synthesis of heterocyclic compounds. K10 has been used in the formation, under standard conditions, of carbon–nitrogen bonds and, more generally, in the chemistry of nitrogen derivatives; its catalytic activity is similar to that of HCl (Figure 4A) [51]. It has, furthermore, recently been reported [52] that cycloaddition reactions of furan with α,β-unsaturated carbonyl dienophiles can be performed in the complete absence of solvent by using K10 as the catalyst (Figure 4B).

Heterocyclic compounds can also be obtained in the vapor phase, with evident advantages in comparison with conventional liquid-phase reactions. For example, the synthesis of alkylquinolines has been recently reported using either zeolites [53] or K10 [54] as catalysts. With the latter 2-methyl-8-ethylquinoline was synthesized from ethylene glycol and 2-ethylaniline, the reaction being favored by increasing the temperature and amount of ethylene glycol and operating in a partially reducing atmosphere (Figure 5).

Clays or acid treated clays can also be effective supports for inorganic salt catalysts or reagents. For example, *Clayzic*, *Kaozic* or *Japzic* are acronyms for K10-, kaolinite- or Japanese acid clay-supported $ZnCl_2$, and *Clayfen* and *Claycop* are acronyms for Fe(III) or Cu(II) nitrates supported on K10 clay [16,24,31–34,55–57]. Although commercially available acid treated clays have been widely studied, the structural requirements vary considerably and maximum activity generally requires 'tuning' of the support for individual adsorbed salts [25]. For example, maximum activity in the Friedel–Crafts alkylation of benzene by benzyl chloride was obtained by using as the support a clay treated with acid for a long time (20 h). This support had almost no features of clay, with relatively low surface area and the presence of mesopores (10–14 nm range), in which the active fraction of

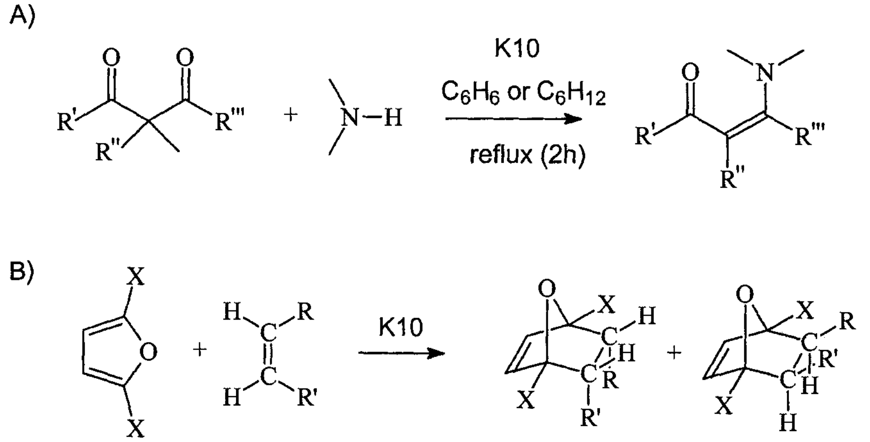


Figure 4. A. Synthesis of enamino carbonyl derivatives from 1,3-dicarbonyl compounds and amines [51]. B. Reaction of furan with *α,β*-unsaturated carbonyl compounds [52].

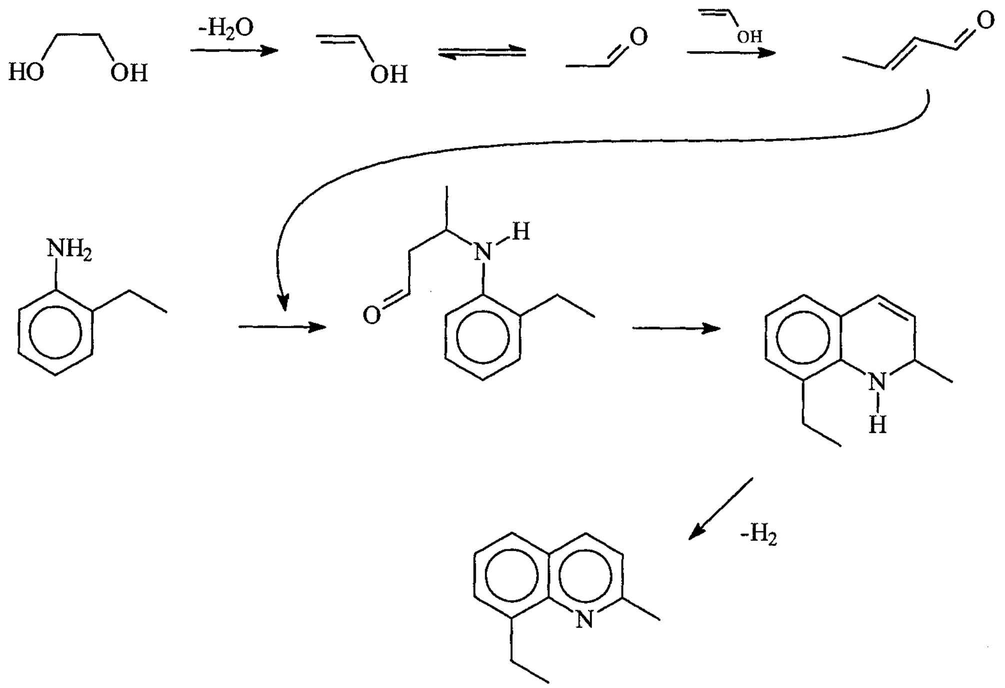


Figure 5. Reaction pathway for the vapor phase synthesis of 2-methyl-8-ethylquinoline from 2-ethylaniline and ethylene glycol, using K10 as catalyst [54].

$ZnCl_2$ was adsorbed [50]. In contrast, with anisole optimum activity was achieved by use of supports treated for short times, and there was evidence of a significant contribution by the Brønsted acid sites on the clays. This result, together with the low activity of the catalyst, suggests that $ZnCl_2$ Lewis acid sites are quite strongly coordinated by anisole, reducing their catalytic activity [50]. It must, however, be remarked that a quantitative yield for this reaction after 15 min at room temperature by use of K10 impregnated with $ZnCl_2$ (or *Clayzic*) also has been reported [58]. Finally, acid-treated commercial clays have also recently been applied to the liquid-phase alkylation of naphthalene by isopropanol, with high activity and stability, although lower selectivity for β and $\beta\beta$ isopropylated products, than dealuminated mordenite [59].

Friedel–Crafts acylations can be effectively catalyzed by clays modified by exchange of interlamellar cations or impregnation with metal chlorides [56]. Comparison of catalytic performance in the benzoylation of mesitylene (Table 3) and anisole showed the superiority of the exchanged clays compared with impregnated clays. The catalytic activity of the impregnated clays depended more on the activation procedure than on the nature of the starting clay. The authors also reported that for the exchanged clays there was strong dependence on the type of reaction and on the nature of the reaction partners, with, for example, an efficiency sequence in the acylation of *p*-xylene by benzoyl chloride ($Zr^{4+} < Ti^{4+} < Al^{3+} < Cu^{2+} < Cr^{3+} < Co^{2+} < Zn^{2+} < Fe^{3+}$) different from that for bulk metal chlorides [17,60]. Cornelis and Laszlo [24], stressing the advantages of Friedel–Crafts clay catalysts, claimed that their scientific work was the basis of the development of commercial 'Envirocats' catalysts [61].

The nature of the acylating agent must also be considered. For example, with mesitylene and different acyl chlorides, the yield in the acylation product depended on both the activity and the stability of the electrophilic species RCO^+ previously

Table 3. Acylation of mesitylene by benzoyl chloride with either supported (§) or exchanged clay catalysts (@) (*activation temperature) [56].

Catalyst	Reaction temp. (K)	Reaction time (min)	Yield (%)
§Kaozic-533*	343	1800	85
§Japzic-533*	343	1800	72
§Kaozic-533*	433	60	74
§Japzic-533*	433	60	100
§Japzic-633*	433	15	100
§Clayzic-533*	433	10	100
@K10-Al^{3+}	433	15	98
@K10-Ti^{4+}	433	15	100
@K10-Cr^{3+}	433	15	94
@K10-Fe^{3+}	433	15	98
@K10-Co^{2+}	433	15	100
@K10-Cu^{2+}	433	15	84
@K10-Zn^{2+}	433	15	85

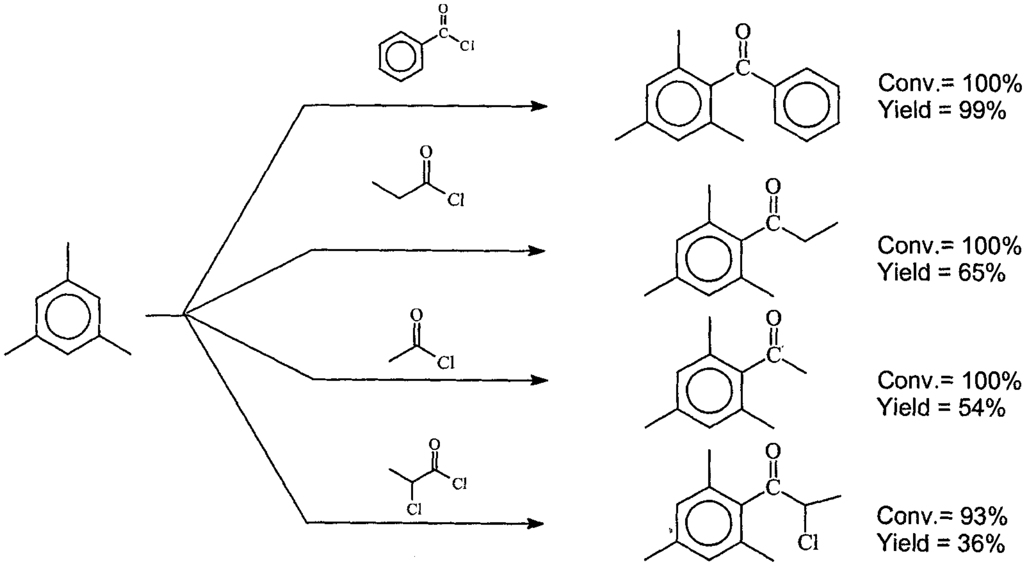


Figure 6. Effect of the nature of the acyl chloride in the reaction with mesitylene with use of K10 as catalyst (reaction temperature = 473 K; reaction time = 15 min). Conversion referred to the acyl chloride [62].

formed (Figure 6) [62]. Similar data were, however, obtained by use of acetyl chloride or anhydride, with evident advantages in comparison with the homogeneous reaction catalyzed by $AlCl_3$. There was, furthermore, a significant reduction in the amount of catalyst required, even more relevant considering that clay catalysts can be easily separated and reused (Figure 7) [62]. Finally, it is worth noting that a catalyst prepared by impregnating bentonite with $FeCl_3$ has been reported as very active in the vapor-phase chlorination of chlorobenzene, although with selectivity for dichlorobenzenes lower than that observed over zeolites, because of the absence of shape-selective effects. The active species in this reaction were shown to be like Lewis acid sites, with Hammett acidity $H_0 > -3.0$ [57].

Not only acid sites, but also electron-accepting or oxidizing sites can occur at the edges or in the structure of the clays. The former may be identified as trigonal Al^{3+} ions, acting as Lewis sites, whereas Fe^{3+} ions in the lattice are the structural oxidizing sites [63]. Redox properties can, moreover, be induced by exchangeable cations [63–65]; thus clays or acid treated clays can be useful supports, for example, for noble metals, nickel, or copper in the production of hydrogenation catalysts in which the lamellar structure of the support may confer useful size and shape selectivity [25]. These catalysts might, on the other hand, also be chemoselective, as was recently reported for the hydrogenation of cinnamaldehyde, with almost exclusive formation of cinnamyl alcohol by use of a 5 % (*w/w*) Pt/K10 catalyst. The beneficial role of the support was attributed to the Lewis acid center of the acid-treated clay, which provides suitable anchoring sites for C=O moieties (Figure 8) [49].

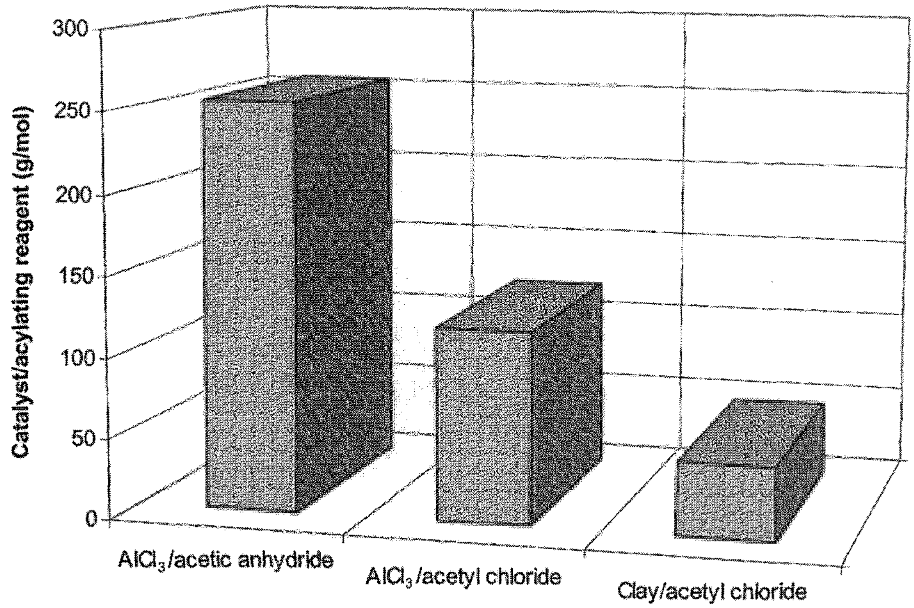


Figure 7. Ratios of the amount of catalyst (AlCl$_3$ or acid-treated clays) to the amount of acetyl chloride or acetic anhydride in the acylation of mesitylene (for the latter catalyst the same value was obtained with both acylating reagents) [62].

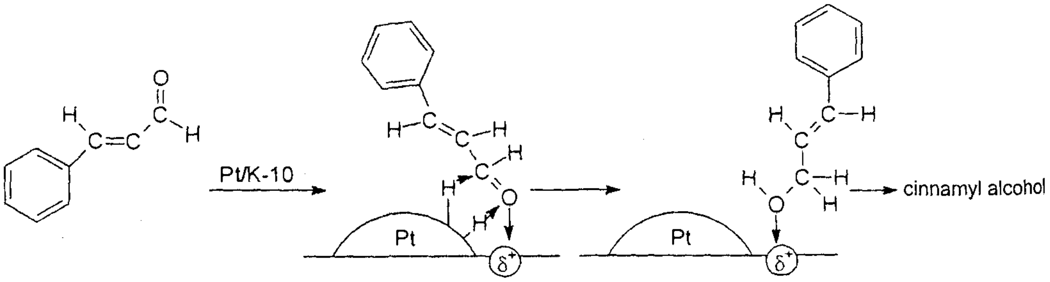


Figure 8. Formation of cinnamyl alcohol in the hydrogenation of cinnamaldehyde over 5 % (*w/w*) Pt/K10 catalyst [49].

Clays or modified clays have also been used to prepare supported reagents, although at present only on a laboratory scale [16,24,25,34,55]. For example, the nitration of phenols is normally performed with mixtures of nitric and sulfuric acids, with only modest overall yields (ca 60 %) and formation of the *meta* isomer and by-products of polynitration, together with the normal *ortho-* and *para*-substituted derivatives. The clay-supported Fe(NO$_3$)$_3$ (*Clayfen*) not only improves the overall yield in the nitration of phenol (up to ca 90 %), but is also very active

Table 4. Yield (%) in the room-temperature nitration of a variety of phenols by use of clay-supported ferric nitrate (*Clayfen*) [16,24,55].

Phenol	*ortho*	*para*	Reaction conditions
–	39	41	Diethyl ether, 20 h
4-CH_3	58	–	Diethyl ether, 20 h
3-CH_3	20	34	Diethyl ether, 20 h
4-Cl	88	–	Diethyl ether, 20 h
4-F	69	–	Toluene, 5 h
β-naphthol	63	–	Tetrahydrofuran, 2 h
4-*t*-C_4H_9	92	–	Toluene, 1.5 h
3-OH	58	–	Diethyl ether, 2 h
4-CHO	93	–	Toluene, 72 h
Estrone	55	–	Toluene, 24 h

in the nitration of many other phenols (Table 4), with a high regioselectivity, nearly ruling out both formation of the *meta* isomer and hazardous polynitration [16,24,55]. It should be noted that for the estron nitration (an important process in the pharmaceutical industry as the gateway to a variety of estrogenic drugs) the yield obtained is a significant improvement over the best value previously reported (39 %), reducing the cost per gram of the target molecule to ca 1/3 [24].

3.1.4 Pillared Interlayer Clays (PILC)

Another key point in the improvement of clays material design is the pillaring step, i. e. the synthesis of materials with 3-D network structures; this produces new and inexpensive materials with properties complementary to those of zeolites (pore size and shape, acidity and redox properties, etc.). PILC are obtained by linking robust, three-dimensional species to a layered host and the final properties can be modulated by carefully choosing the nature of the pillaring agent, type of clay and particle size, pillaring procedure, thermal treatment, etc., thus providing a powerful and flexible way of designing tailored catalysts. Control of the pillaring process is, therefore, a promising means of obtaining solids with: (i) a high surface area (up to 600 $m^2\ g^{-1}$), (ii) a broad spectrum of properties (structural, chemical, catalytic, etc.), and (iii) controlled internal structures, with reactive sites and/or species chosen to match particular applications or to provide host structures for chemical or physical processes.

PILC are so wide and important a subject that they require a full paper, thus discussion here is limited to a survey of the main aspects; for more detailed information, reference should be made to the original literature [e. g. 2,8,9,11,19,20, 26–28,66–71].

The pillaring process requires a clay with relatively low negative charge density and a chemical substance with a large positive charge. For example, if highly charged vermiculites (Table 1) are used the polyoxocations hydrolyze almost completely to give gibbsite-type interlayer structures. On the other hand, starting from a single clay, controlled calcination can be used to prepare a series of samples with CEC ranging from that of the raw material down to virtually zero [8,72]. Under the conditions that: (i) the guest species are homogeneously distributed, (ii) the clay sheets are rigid and do not bend, (iii) all the sheets are pillared, and (iv) adsorption of the pillaring molecules on the external surface is negligible, a two-dimensional channel system is generated (unlike in zeolites in which three-dimensional channel systems are often present) (Figure 9).

Many of the different pillaring agents reported in the literature (organic compounds, metal trischelates, organometallic complexes, metal cluster cations, metal oxide sols, polyoxocations, etc.) have drawbacks such as low reactivity or lack of thermal stability, and polyoxocations are by far the most widely employed. Many different polyoxocations (Al, Ni, Zr, Fe, Cr, Mg, Si, Bi, Be, B, Nb, Ta, Mo, Ti, and, more recently, Cu, Ga, and Ce) have been reported in the open and patent literature and clays with multielement or doped pillars also have been claimed [2,8,9,19,20,68–70,73–75]. However, the chemical composition, structure and charge are at present well defined only for the Al-polyoxocation, in which the Keggin ion $[Al_{13}O_4(OH)_{24}(H_2O)_{12}]^{7+}$ is identified.

PILC are prepared by controlled hydrolysis reactions which can be carried out in solution or in the interlamellar space of the clay (the former allows better control of the nature of the polyoxocations). In addition to the different parameters already mentioned, the calcination process also plays a key role. Three general cases may occur: (i) the polyoxocations exit from the clay (no pillaring), (ii) they degrade in situ giving rise to layers of aluminum hydroxide (thick ca. 1.4 nm), and (iii) in the case of true pillaring, the polyoxocations dehydrate up to 573 K and dehydroxylate between 573 and 673 K (thick ca 1.9 nm). The stability of pillared clays as a function of the calcination temperature depends on the nature of the clays and the composition of the pillars. For example, Al-pillared clays remain stable up to temperatures varying between 773 K (montmorillonites) and 1023–1073 K (saponites) or even higher for rectorite, a clay consisting of interstratified sheets of smectite and mica [70]. On the other hand, significant increases in stability may be achieved using mixed polyoxocations or doping the pillars with small amounts of another element (see above).

From the viewpoint of making catalysts at a competitive price, three important criteria need to be met: (i) use the whole clay material, after minimal refining (i. e., low cost), (ii) pillar the Ca or (Ca, Na) forms, not only the Na forms (i. e., no pre-exchange), and (iii) be able to use clay-polyoxocation concentrations (> 15 % *w/w* solids) that can be economically and effectively spray-dried to give a usable particle size distribution (40–200 μm) [8]. Non-purified clays as starting materials

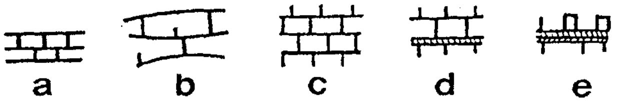


Figure 9. Schematic representation of the possible PILC: (a) ideal; (b) with bent sheets; (c) with pillars on the external surface; (d) incompletely pillared; (e) unpillared, with micropores created by the external pillars [9].

and concentrated clay slurries have been investigated and sufficiently good results were not obtained [69]. However, in recent papers [76,77], a new pillaring method has been reported where concentrated (50 % *w/w*) acetone slurries of non-purified natural calcium bentonites or of various dioctahedral and trioctahedral smectites are used which allow well crystallized and homogeneously distributed PILC to be prepared.

PILC exhibit significantly different acidity than clays or acid-treated clays. This property is of particular importance for catalytic applications and has been thoroughly studied in recent years, to establish the relationships between observed acidity and structural data and, consequently, the catalytic properties of pillared clays [8,19,70,78]. Because of their specific properties (thermal and/or hydrothermal stability, selectivity, low cost, etc.), PILC have been mainly investigated in high-temperature reactions of interest to the refining industry, [2,8,19,20,27,67–71, 74,75]. However, the progress in fluid catalytic cracking (FCC) has been rapid and dramatic, requiring a continuous increase in the maximum temperature of hydrothermal stability and, consequently, changing the target of PILC research [8].

PILC have been widely investigated in liquid-phase organic reactions conducted up to 523 K ca (alkylation, acylation, transalkylation, dehydration, isomerization, etc) [8,19,20,28,29,50,62,69–71,79–84], showing generally activities lower than those of the starting clays, although they are easier to regenerate [2,8,9,70,72]. However, pillared acid-activated clays have been reported to be very effective in Brønsted catalyzed processes, with activity greater than that of both conventional PILC and acid-treated clays (Figure 10) [83].

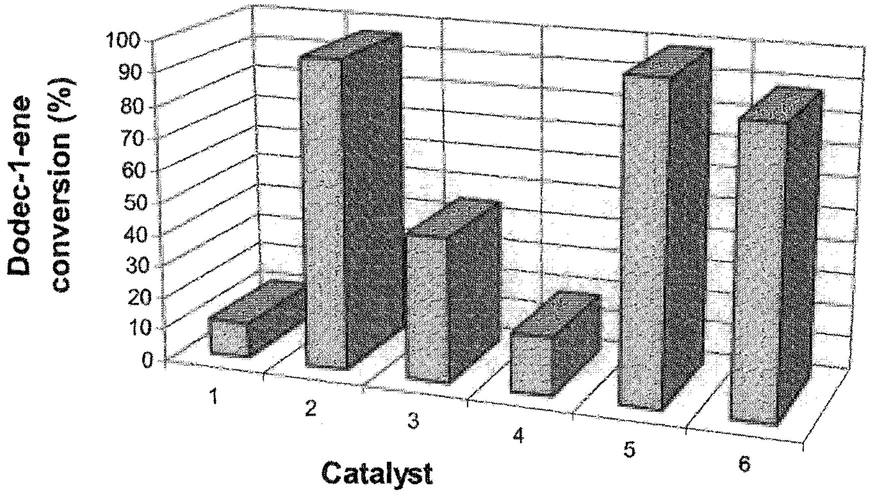


Figure 10. Activity of clay catalysts for 1-dodecene alkylation of benzene at 473 K (reaction time = 3 h; 1 = starting montmorillonite; 2 = acid treated montmorillonite; 3 = acid treated montmorillonite calcined at 773 K per 4 h; 4 = pillared montmorillonite calcined at 773 K for 4 h; 5 = acid treated pillared montmorillonite calcined at 773K for 4 h; 6 = K10) [83].

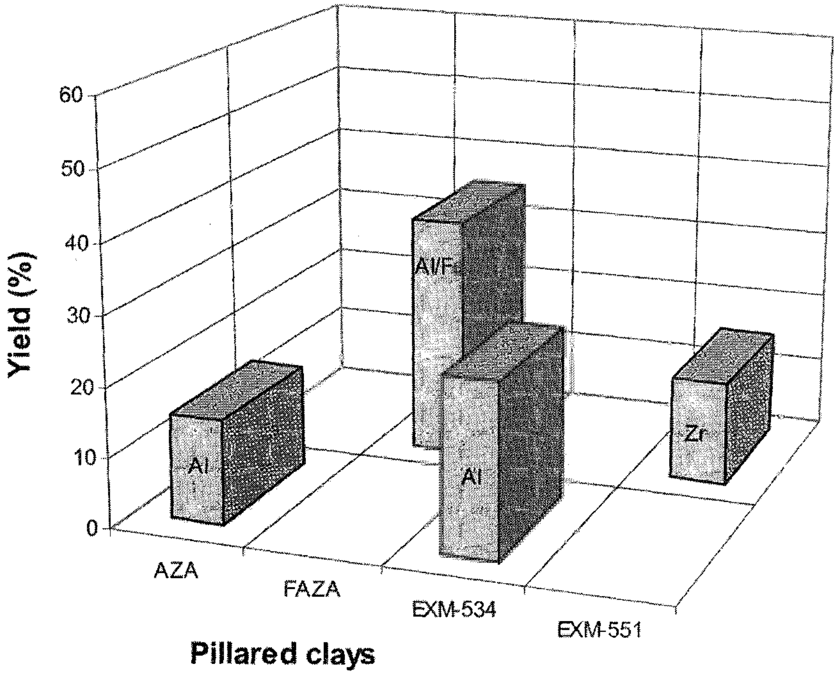


Figure 11. Catalytic activity as a function of the nature of the pillaring element for some pillared montmorillonites in the acylation of mesitylene with acetyl chloride (reaction temperature = 473 K; reaction time = 15 min; AZA and FAZA supported by Concerted European Action–Pillared Layered Structures (CEA–PLS); EXM-534 and EXM-551 provided by Süd Chemie) [62].

PILC have also been investigated in the acylation of mesitylene with acetyl chloride [62], showing in comparison with the starting clays: (i) higher activities related to the presence of additional Lewis acid sites in the pillars [8,9,19,20,28,29], regardless of the nature of the starting clays (saponite or montmorillonite) and (ii) considerable improvement related to the presence of Fe^{3+} ions inside the pillars. Moreover, by comparing PILC obtained from the same starting materials (AZA and FAZA by CEA–PLS or EXM-534 and EXM-551 by Süd-Chemie, respectively) (Figure 11) the scale of activity was found to be $Fe^{3+} > Al^{3+} > Zr^{4+}$. This scale of activity differs from the normal sequence of the bulk metal chlorides as Lewis acids [60], while it is in good agreement with that already reported for clays modified through impregnation by metal chlorides [17,56]. Furthermore, the catalytic activity increased at first as the amount of Fe^{3+} ions inside the pillars increased and then decreased at higher Fe content, because of the segregation of substantial amounts of iron oxide (Figure 12) [62].

Unlike clays, PILC have a rigid structure and no differences are observed as a function of the reaction medium. Furthermore, the pore size of a PILC, which plays an important role in shape-selective catalysis, is determined by both inter-

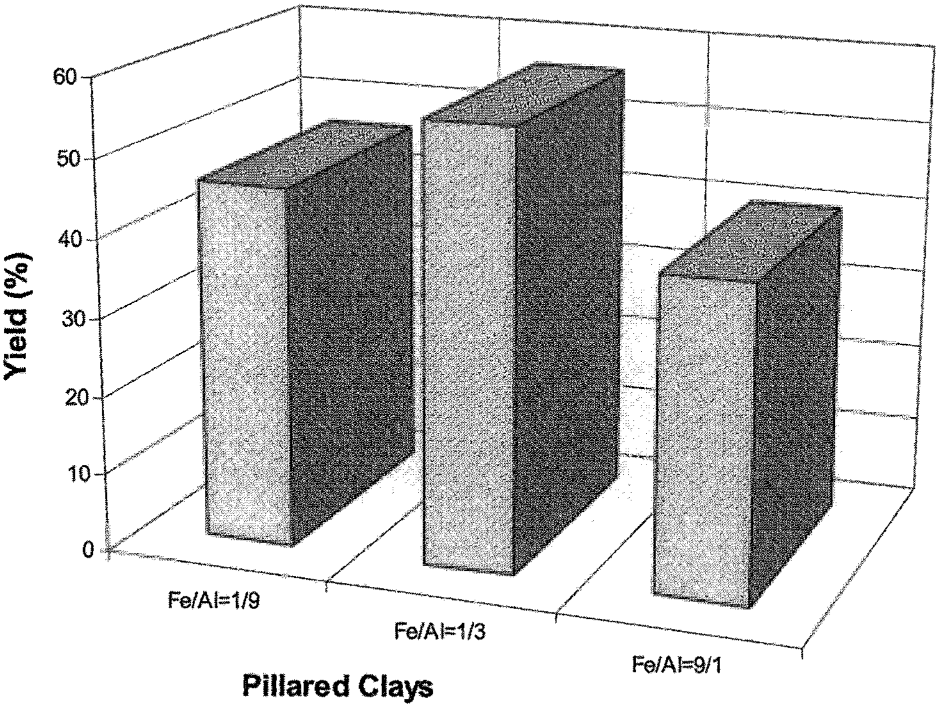


Figure 12. Catalytic activity as a function of the Fe/Al ratio in a pillared montmorillonite in the acylation of mesitylene with acetyl chloride (reaction temperature = 473 K; reaction time = 15 min) [62].

layer distance and lateral distance or pillar density. The interlayer distance depends on the size of the pillaring species, while the lateral distance is regulated by the charge density of the clay and by the extent of the pillaring process [8]. PILC exhibit broader pore size distributions than zeolites, which can be controlled and adjusted to a desirable predominant size [9,26]. Although PILC are generally defined as having at least 50 % of their surface area in pores larger than 3.0 nm [8], narrower ranges have been reported by many authors [8,9,19,26,85,86]. It is therefore possible to use PILC in the reactions of bulky organic molecules. Among these applications, of industrial relevance is the synthesis of durene (1,2,4,5-tetramethylbenzene), raw material to produce pyromellitic anhydride and, from it heat-resisting polymers, which may be obtained either by disproportion of 1,2,4-trimethylbenzene (Figure 13) [79,80] or its reaction with methanol [81]. However, it must be pointed out that there is not general agreement on the presence of shape-selectivity effects in PILC. Indeed, while Kikuchi and coworkers [8,79,80] proposed the presence of shape-selectivity effects to justify the preferential formation of durene, in agreement with to the findings of Doblin et al. [87] in the cracking of *n*-octane and 2,2,4-trimethylpentane, Butruille and Pinna-

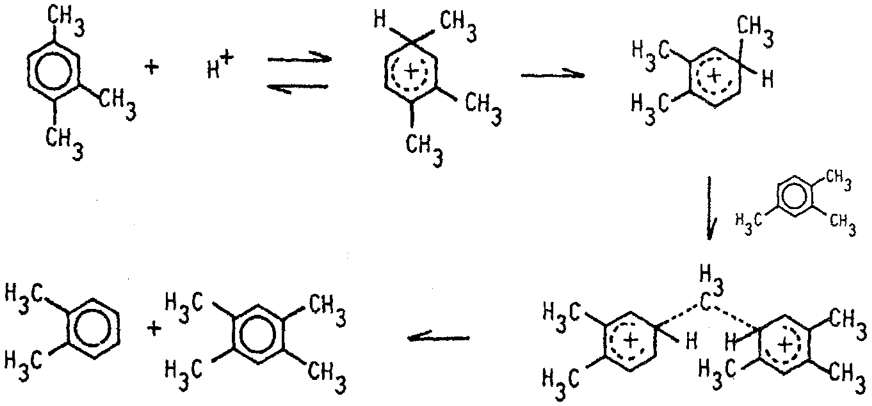


Figure 13. Reaction pathway in the disproportionation of 1,2,4-trimethylbenzene using Al-pillared clays [79].

vaia [26] reviewing the data of previous studies reported in the literature, concluded that there is no unequivocal example of a cage effect with Al-PILC, probably because of their broader pore size distribution than in zeolites.

3.1.5 Conclusions

Environmental issues as well as process optimization requires the replacement of liquid acids by more friendly and safe solid-acid catalysts. The use in organic syntheses of clays or clay-modified catalysts or reagents recommends itself by its simple implementation, the small amount of catalyst required (in comparison to standard Lewis acids, such as $AlCl_3$, or Brønsted acids, such as concentrated sulfuric or nitric acids), the presence of the acidity internally (making them safe to handle), the use of more environmentally compatible conditions and/or substances, the simple recovery and/or reuse and, finally, the harmless disposal. Furthermore, clay microreactors may display enzyme-like characteristics.

Clays or modified clays are commercially available at reasonable prices and a broad spectrum of their applications already exists, and even more applications will be found in the future in unexpected areas, due to the possibilities of designing catalysts tailored for specific reactions and/or substrates. In particular, the key role that they can play in the production of fine chemicals should be emphasized. Furthermore, montmorillonite, as such or modified, was the clay used in most of the applications reported in this paper; yet it is just one among the many smectites and there are many other, very different families of clays.

In conclusion, although much research has been done regarding the use of these catalysts, some progress was accomplished in a disorderly way, mainly for PILC, making difficult their wide application in the industrial catalysis [28,70]. On the other hand, future prospects include the development of new catalysts and/or the tuning of their properties or shape in liquid phase reactions or, even more of industrial interest, the synthesis of large amounts of products in the vapor phase, with continuous production and economic advantages.

Acknowledgments

Thanks are due to the Ministero per l' Università e la Ricerca Scientifica e Tecnologica (MURST, Roma) and National Research Council (CNR, Roma) for financial support.

References

[1] Fodwen L., Barrer R. A. and Tinker P. B. (eds), Clay Minerals: their Structure, Behaviour and Use, The Royal Society, London, 1984.

[2] Decarreau A. (ed.), Matériaux Argileux, Societé Française de Minéralogie et Cristallographie, Paris, 1990.

[3] Grim R. E., Clay Mineralogy, McGraw–Hill, New York, 1968.

[4] Van Olphen H. and Fripiat J. J., Data Handbook for Clay Minerals and Other Non-metallic Materials, Pergamon, Oxford, 1979.

[5] Bailey S. W., in Crystal Structures of Clay Minerals and their X-ray Identification (G. W. Bridley and G. Brown, eds), Monograph 5 of the Mineralogical Society, Longmans, London, 1980.

[6] Nemecz E., Clay Minerals, Akadémiai Kiado, Budapest 1981.

[7] Newman A. C. D., Chemistry of Clays and Clay Minerals, Monograph 6 of the Mineralogical Society, Longmans, London, 1987.

[8] Burch R. (ed.), *Catal. Today* **2**, 185 (1988).

[9] Schoonheydt R. A., in Introduction to Zeolite Science and Practice (H. van Bekkum, E. M. Flanigen and J. C. Jansen, eds), Elsevier, Amsterdam, 1991, p. 201.

[10] Chitnis S. R. and Sharma M. M., *Catal. Today* **32**, 93 (1997).

[11] Vaccari A., *Catal. Today* **41**, 53 (1998).

[12] Thomas J. M., *Sci. Am.* **266**, 112 (1992).

[13] Pinnavaia T. J., in Proc. 10th Int. Clay Conf. Adelaide, CSIRO, Melbourne, 1995, p. 3.

[14] Butruille J.-R. and Pinnavaia T. J., in Proc. 10th Int. Clay Conf. Adelaide, CSIRO, Melbourne, 1995, p. 92.

[15] Adams J. M., Clapp T. V. and Clement D. E., *Clay Miner.* **18**, 411 (1983).

[16] Laszlo P., *Acc. Chem. Res.* **19**, 121 (1986).

[17] Laszlo P. and Mathy A., *Helv. Chim. Acta* **70**, 557 (1987).

[18] Adams J. M., *Appl. Clay Sci.* **2**, 309 (1987).

[19] Figueras F., *Catal. Rev. -Sci, Eng.* **30**, 457 (1988).

[20] Mitchell V. (ed.), Pillared Layered Structures. Current trends and Applications, Elsevier Applied Science, London, 1990.

[21] Ballantine J. A., in Solid Supports and Catalysts in Organic Synthesis (K. Smith, ed.), Harwood, U. K., 1992, p. 100.

[22] Izumi Y. and Onaka M., *Adv. Catal.* **38**, 245 (1992).

[23] Laszlo P., *Chem. Ind. (Dekker)* **53**, 429 (1994).

[24] Cornelis A. and Laszlo P., *Synlett.* **3**, 155 (1994).

[25] Brown D. R., *Geol. Carpathica–Clays* **45**, 45 (1994)

[26] Butruille J.-R. and Pinnavaia T. J., in Comprehensive Supramolecular Chemistry (J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle and J.-M. Lehn, eds), Vol. 7, Pergamon, Oxford, 1996, p. 219.

[27] Corma A., *Chem. Rev.* **97**, 2373 (1997).

[28] Vaccari A., *Appl. Clay Sci.* **14**, 161 (1999).

[29] Vaccari A., in Actas XV Symp. Iberoamer. Catalisis (E. Herrero, O. Annunziata and C. Perez, eds), Vol. 1, Univ. Nac. Cordoba, Cordoba Arg., 1996, p. 37.
[30] Adams J. M., Dyer S., Martin, K., Matear W. A. and McCabe R. W., *J. Chem. Soc., Perkin Trans. 1* **6**, 761 (1994).
[31] Rhodes C. N. and Brown D. R., *J. Chem. Soc., Faraday Trans. I* **89**, 1387 (1993).
[32] Rhodes C. N. and Brown D. R., *Catal. Letters* **24**, 288 (1994).
[33] Rhodes C. N., Massam J. and Brown D. R., *Acta Univ. Carolinae Geologica* **38**, 367 (1994).
[34] Cornelis A. and Laszlo P., *Janssen Chimica Acta* **8**, 3 (1990).
[35] Knozinger H., in Elementary Reaction Steps in Heterogeneous Catalysis (R. W. Joyner and R. A. van Santen, eds), Kluwer, The Netherlands, 1993, p. 267.
[36] Flessner U., Jones D., Roziere J., Storaro L., Talon A., Jiménez-Lòpez A., Rodriguez-Castellòn E., Trombetta M. and Busca G., Abstracts EuropaCat IV, Rimini (I), 1999, p. 470.
[37] Benesi H. A. and Winquist B. H. C., *Adv. Catal.* **27**, 170 (1978).
[38] Brown D. R. and Rhodes C. N., *Catal. Letters* **45**, 35 (1997).
[39] Arena F., Dario R. and Parmaliana A., *Appl. Catal.* **A170**, 127 (1998).
[40] Li L., Ma S., Zhang Y. and Bao Y., *Jilin Daxuae Ziran Kexue Xuebao* **2**, 87 (1995); *Chem. Abstract.* **123**, 117381z (1995).
[41] Sheldon R. A., *J. Mol. Catal.* **A107**, 75 (1996).
[42] Sheldon R. A., *Chem. Ind. (London)*, 15 (1997).
[43] Sheldon R. A., in Catalysis of Organic Reactions (F. Herkes, ed.), Dekker, New York, 1998, p. 273.
[44] Villemin D., Labiad B. and Loupy A., *Synth. Commun.* **23**, 419 (1993)
[45] Engelhard (USA), Separation Products, *Tech. Bull.* (1996).
[46] Crocker M., Herold R. H. M., Emeis C. A. and Krijger M., *Catal. Letters* **15**, 339 (1992).
[47] Ovcharenko F. D., *Dev. Sedimentol.* **35**, 239 (1982).
[48] Sabu K. R., Sukumar R. and Lalithambika M., *Bull. Chem. Soc. Jpn.* **66**, 3535 (1993).
[49] Szöllösi G., Török B., Baranyi L. and Bartók M., *J. Catal.* **179**, 619 (1998).
[50] Elsen A., Grobet P., Keung M., Leeman H., Schoonheydt R. A. and Toufar H.(eds), Proc. Euroclay '95, Leuven (B), 1995.
[51] Vanden Eynde J. J., Mayence A., Lor P. and Van Haverbeke Y., *Bull. Soc. Chim. Belg.* **104**, 387 (1995).
[52] Avalos M., Babiano R., Bravo J. L., Cintas P., Jiménez J. L. and Palacios J. C., *Tetrahedron Letters* **39**, 9301 (1998).
[53] Mcateer C. H., Davies R., Calvin J. R., *World Patent* 03,051 (1997) to Reilly Industries Ltd.
[54] Campanati M., Savini P., Tagliani A., Vaccari A. and Piccolo O., *Catal. Letters* **47**, 247 (1997).
[55] Cornelis A. and Laszlo P., *Synthesis*, 909 (1985).
[56] Cornelis A., Gerstmans A., Laszlo P., Mathy A. and Zieba I., *Catal. Letters* **6**, 103 (1990).
[57] Jang H. J., Choi P. H. and Park S.-E., *Bull. Korean Chem. Soc.* **16**, 507 (1995).
[58] Clark J. A., Kybett A. P., Macquarrie D. J., Barlow S. J. and London P., *J. Chem. Soc. Chem. Commun.*, 1353 (1989).
[59] Ferini I., Rombi E., Monaci R., Solinas V. and Vaccari A., in Proc. TCC-97 (G. Centi, S. Galvagno and I. Milone, eds), Giardini Naxos CT (I), 1997, p. 95.
[60] Olah G. A., Friedel–Crafts Chemistry, Wiley, New York, 1992.
[61] Contract Catalysts (UK), Envirocats Supported Reagents, *Tech. Bull.* (1991).
[62] Campanati M., Fazzini F., Fornasari G., Piccolo O., Tagliani A. and Vaccari A., in Catalysis of Organic Reactions (F. Herkes, ed.), Dekker, New York, 1998, p. 307.
[63] Theng B. K. G., The Chemistry of Clay–Organic Reactions, Hilger, London, 1974.
[64] Soma Y., Soma M. and Harada I., *J. Phys. Chem.* **88**, 3034 (1986).
[65] Soma Y., Soma M. and Harada I., *J. Contaminant Hydrology* **1**, 95 (1986).
[66] Pinnavaia T. J., *Science* **220**, 4595 (1983).
[67] Occelli M. L., Lynch J. and Senders J. V., *J. Catal.* **107**, 557 (1997).
[68] Vaughan D. E. W., in Perspective in Molecular Sieve Science (W. H. Flank and T. E. Whyte, eds), American Chemical Society, Washington D. C., 1988, p. 308.
[69] Benito I., Pesquera C., Blanco C. and González, *Trends in Inorganic Chemistry* **4**, 93 (1996).

[70] Lambert J.-F. and Poncelet G., *Topics in Catalysis* **4**, 43 (1997).
[71] Cheng S., *Catal. Today* **49**, 303 (1999).
[72] Purnell J. H., *Catal. Letters* **14**, 11 (1992).
[73] Corrado K. A., Kostapapas A.,. Suib S.L and Coughlin R. W., *Solid State Ionics* **22**, 117 (1986).
[74] Occelli M. L., *J. Mol. Catal.* **35**, 377 (1986).
[75] Vaughan D. E. W., *US Patent* 4,666,877 (1987).
[76] Storaro L., Lenarda M., Ganzerla R. and Rinaldi A., *Microporous Mater.* **6**, 55 (1996).
[77] Storaro L., Lenarda M., Perissinoto M., Lucchini V. and Ganzerla R., *Microporous Mater.* **20**, 317 (1998).
[78] Min E. Z., in Zeolites and Microporous Crystals (T. Hattori and T. Yashima, eds), Elsevier, Amsterdam, 1994, p. 443.
[79] Kikuchi E., Matsuda T., Fujiki H and Morita Y, *Appl. Catal.* **11**, 331 (1984).
[80] Kikuki E., Matsuda T., Ueda J. and Morita Y., *Appl. Catal.* **16**, 401(1985).
[81] Matsuda T., Matsukata M., Kikuki E. and Morita Y., *Appl. Catal.* **21**, 297 (1986).
[82] Molina R., Schutz A. and Poncelet G., J. Catal. 145, 79 (1994).
[83] Mokaya R. and Jones W., *J. Chem. Soc., Chem. Commun.*, 929 (1994).
[84] Geatti A., Lenarda M., Storaro L., Ganzerla R. and Perissinoto M., *J. Mol. Catal.* **A121**, 111 (1997).
[85] Safdar Baksh M., Kikkinides E. S. and Yang R. T., Ind. Eng. Chem. 31, 2181 (1992).
[86] Tanev P. T., Butruille J.-R. and Pinnavaia T. J., in Chemistry of Advanced Materials. An Overview (L. V. Interrante and M. J. Hampden-Smith, eds), Wiley, New York, 1998, p. 329.
[87] Doblin, C., Mathews J. F. and Turney T. W., *Catal. Letters* **23**, 151 (1994).

3.2 Zeolites as Catalysts

A. Corma

3.2.1 Introduction

In an ideal solid catalyst all the active sites should be identical and isolated one from each other. It is, furthermore, highly desirable that the location of the active site has the appropriate geometry and electronic environment to stabilize the transition state of the reaction to be catalyzed. It is apparent that these requirements are not too far from those of an enzyme, except for the higher thermal and mechanical stability of the solid catalyst. Unfortunately, real solid catalysts are far from ideal because their active sites are heterogeneous, and consequently they catalyze, besides the desired reaction, other parallel and consecutive undesired reactions. There is, however, one type of solid catalyst–the zeolites–that approaches ideality more than any other.

Zeolites and zeotypes can be defined as microporous crystalline structures (Figure 1 and Table 1) in which the framework is formed by tetrahedral of silica, in which there is isomorphic substitution with trivalent or tetravalent elements such as for instance Al, Ge, B, Fe, Cr, Ge, Ti, etc. [1]. Similar types of structure can also be achieved with the framework formed by Al and P, with or without other transition metal elements [2]. These types of structure are denoted as AlPOs, SAPOs, and MEAPOs, depending on the composition of the framework [3].

The main characteristics of microporous molecular sieves is that they contain micropores with dimensions between 0.4 and 1.4 nm–similar to those of many reactant molecules of interest. Closer analysis of the characteristics of the materials reveals properties highly desired in most catalysts:

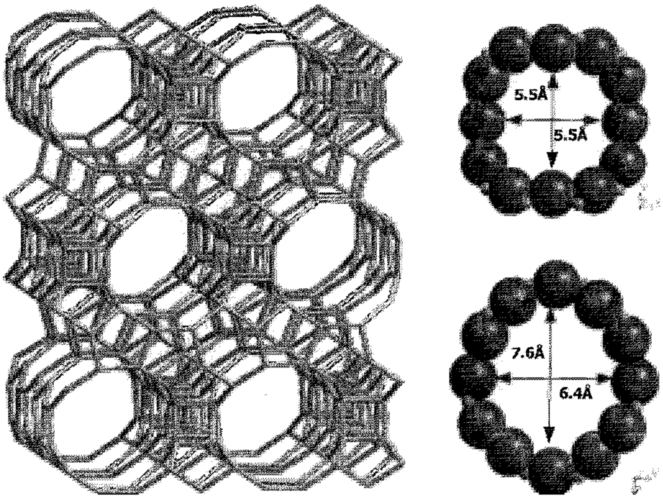


Figure 1. Structure and pore sizes of beta zeolite.

Table 1. Zeolites and zeotypes and their major channel ring size.

Molecular sieve type	Framework structure type (IUPAC CODE)	Type species	Window size
Ultralarge pore	CLO	Cloverite	20
		JDF-20	20
	UFI	VPI-5, MCM-9, AlPO$_4$-54	18
	AET	AlPO$_4$-8, MCM-37	14
	CFI	CIT-5	14
	DON	UTD-1	14
Large pore	FAU, EMZ	Cubic and hexagonal Faujasite, SAPO-37	12
	BEA	Beta	12
	MOR	Mordenite	12
	OFF	Offretite	12
	MAZ	Mazzite, Omega, ZSM-4	12
	LTL	Linde Tpe L	12
	MTW	ZSM-12	12
	CON$_a$	SSZ-26, SSZ-23	12
	AFI	AlPO$_4$-5, SAPO$_4$-5, SSZ-24	12
	ATO	AlPO$_4$-31, SAPO-31	12
	AFR	SAPO-40	12
	AFS	MAPSO-46	12
	AFY	COAPO-50	12
	ATS	MAPO-36	12
	ISV	ITQ-7	12
	IFR	ITQ-4, SSZ-42, MCM-48	12
	SAO	STA-1	12
	CON	CIT-1	12
Medium pore	MFI	ZSM-5, Silicate	10
	MEL	ZSM-11	10
	FER	Ferrierite	10
		ZSM-48	10
	MTT	ZSM-23	10
	TON	ZSM-22, Theta 1	10
	HEU	Clinoptilolite	10
	AEL	AlPO$_4$-11, SAPO-11	10
	AFO	AlPO$_4$-41	10
	STF	SSZ-35	10
	SFF	SSZ-34	10
	MWW	MCM-22, ITQ-1, SSZ-25	10
	NES	NU-87	10
	STT	SSZ-23	
Small pore	LTA	A	8
	ERI	Erionite, AlPO$_4$-17	8
	CHA	Chabazite	8
	KFI	ZK-5	8
	RHO	RhO, BeAsPO-RHO	8
	AEI	AlPO$_4$-18	8
	AFT	AlPO$_4$-52	8

Table 1. Cont.

Molecular sieve type	Framework structure type (IUPAC CODE)	Type species	Window size
Small pore	ANA	$AlPO_4$-24	8
	APC	$AlPO_4$-C, $AlPO_4$-H_3, MCM-1	8
	APD	$AlPO_4$-D	8
	ATT	$AlPO_4$-33, $AlPO_4$-12-TAMU	8
	ATV	$AlPO_4$-25	8
	AWW	$AlPO_4$-22	8
		$AlPO_4$-12	8
		$AlPO_4$-14	8
		$AlPO_4$-14A	8
		$AlPO_4$-15	8
		$AlPO_4$-21	8
	ATN	MAPO-39	8
	CHA	SAPO-34, COAPO-44, COAPO-47, ZYT-6	8
	ITE	ITQ-3	8
	RTH	RUB-13	8
	MTF	MCM-35	8
	AFX	SAPO-56, SSZ-16	8
	GIS	MAPSO-43	
	LTA	SAPO-42	

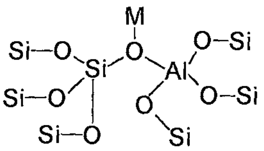
- the presence of a strong electric field within the channels [4] that can preactivate the molecules;
- high surface areas in the order of 700 $m^2\ g^{-1}$;
- high adsorption capacity, presenting not only a concentration effect that will enhance the rate of bimolecular reactions, but also the possibility of tuning the hydrophobicity–hydrophilicity; and
- the possibility of shape selectivity towards reactants, transition state, or products [5].

All these properties are important; no less important is the possibility of introducing isolated, well defined active sites in accessible framework positions. More specifically, one can introduce acid, base, and/or redox active sites directly during the synthesis or by post-synthesis treatment [6]. Zeolites and zeotypes are prepared under hydrothermal conditions in basic or acid media, at a range of temperatures normally from 80 to 180 °C, and from a few hours to several days or even weeks.

3.2.2 Acid Zeolites

3.2.2.1 Framework Composition

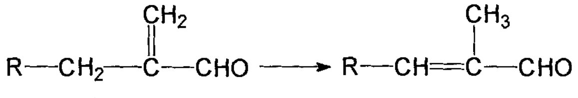
When acid zeolite catalysts must be prepared, trivalent elements which can be in tetrahedral coordination are introduced to the synthesis media with silica. Then a structure with framework groups of the type:



can be formed in which the negative charge associated with the tetrahedrally coordinated trivalent atom (in this example Al) is compensated by an inorganic and/or organic cation (M) that acts as structure directing agent [7]. In a subsequent step the cations, most commonly alkali or alkaline earth or quaternary ammonium, are either exchanged directly with H^+ or replaced with protons after previous exchange with $NH_4{}^+$ followed by calcination at temperatures above 400 °C. When the compensating cations are quaternary ammonium these can be directly decomposed upon calcination leaving protons as the compensating cations. This procedure gives solid-acid catalysts in which the number of potential Brønsted acid sites is equal to the number of trivalent atoms present in the silica frame; the acid strength of the catalyst can be directly related to the average Sanderson electronegativity (ASE) of the structure [8]–the higher the ASE the higher the average acid strength of the Brønsted acid sites. Thus aluminosilicates should furnish stronger acid sites than gallosilicates; those in gallosilicates are stronger than in borosilicates. However, one should take into account that this refers to the average acid strength and this will only correspond closely to each individual active site when the local composition is identical.

This can only occur when there is high dilution of acid sites in the framework, i. e. for samples with high Si/T^{III} ratios; even then different topological positions have different acidities owing to different T–O–T′ angles. However, for high T^{III} content, and more specifically high Al-containing samples, the local acidity of a given bridging hydroxyl group can be modified by varying the number of Al atoms in the next nearest neighbor position (NNN) of the Al which supports the acid site. A completely isolated Al^{IV} will have zero NNN and supports the strongest type of framework Brønsted acid site [9]. Thus, by changing the framework Si/Al ratio, either during synthesis or post-synthesis, it is possible to change not only the total number but also the acid strength of the Brønsted acid sites. Thus, if reactions such as olefin double-bond isomerization, alcohol dehydration, or a large number of isomerization reactions requiring weak to mild acidity are to be catalyzed, then zeolites with rather low Si/Al ratios (Si/Al ~ 2.5) should be prepared. When greater acid strength is required, e. g. for aromatic alkylation and alkylaromatic isomerization, zeolites with Si/Al ratios above 4 could be better catalysts. However, for reactions, e. g. paraffin cracking or aromatic acylations with organic anhydrides or organic acids, which require strong acid sites, isolated Al atoms in the zeolite framework will result in the strongest acidity, and therefore, samples with a Si/Al ratio $\gtrsim 10$ will be preferred.

Another way of controlling the acid strength of the Brønsted acid sites is by changing the nature of the T^{III} atoms. For instance, a low acidity Boron ZSM-5 zeolite containing Ce is active and selective for isomerization of 2-alkylacroleins into 2-methyl-2-alkenals without skeleton isomerization (Eq. 1) [10].



$$R{-}CH_2{-}\overset{\overset{CH_2}{\|}}{C}{-}CHO \longrightarrow R{-}CH{=}\overset{\overset{CH_3}{|}}{C}{-}CHO \qquad (1)$$

where R = alkyl, aryl, arylalkyl.

The control of zeolite acidity is of special importance when catalyzing reactions involving strong bases such as NH_3 or pyridines. For such reactions a zeolite catalyst with excessive acidity will be rapidly poisoned by adsorption of the reactant or the basic products. For instance, in the aldol condensation of aldehydes and ketones with ammonia for the production of pyridine and 3-methylpyridine, an important intermediate in the synthesis of vitamin B3, milder acidities are preferred [11].

There is no doubt that zeolite electronegativity plays a predominant role in determining the final acidity of the zeolite Brønsted sites. When, however, different structures with similar framework compositions were compared, different acidity, as measured by use of probe molecules, was found. For example, the binding energy of NH_3 on H-Mordenite and H-ZSM-5 is 160 and 145 kJ mol^{-1}, respectively [12]. It has, therefore, been proposed that the distances and bond angles in the Al–OH–Si group can affect the acidity of the hydroxyl groups [13]. The deprotonation energy decreases when the T–O–T angle is increased, and consequently the acidity increases [14].

Today we tend to see the influence of zeolite structure on reactivity for acid-catalyzed reactions, not only because of different intrinsic acidity, but because of the effect of the structure and the local surroundings on adsorption, and on the stabilization of the activated complex. It seems logical that the structure will determine both spatial conformation and the number of hydrogen-bonds that the 'protonated' transition complex can form with the framework anion. This hydrogen-bond-acceptor ability is an important component of the zeolites as microcatalytic reactors [15,16].

3.2.2.2 Extra-framework Composition

Partial exchange of Brønsted acid sites by alkaline, alkaline earth, transition or rare earth cations can modify the acidity of the final zeolite. The local geometry of the Brønsted acid site is affected by the nature of the cation and this consequently causes a change in the value of the proton affinity of the site [17,18].

When zeolites are dealuminated by steam-calcination part of the framework Al is extracted and generates extra-framework species (EFAL) that can be cationic, anionic or neutral. Some of these EFAL species can act as Lewis acid sites [19] or can influence the Brønsted acidity, by either neutralizing Brønsted acid sites by cation exchange, or by increasing the acidity by a polarization effect and/or by withdrawing electron density from lattice oxygens [20–22]. However, under mild steaming the Al can also become partially, and reversibly, disconnected from the lattice [23]. This opens the way to Lewis acid catalysis by the Al [24].

3.2.3 Basicity in Zeolites

3.2.3.1 Basic Zeolites–Framework Composition

The basic sites of zeolites are of the Lewis type and correspond to framework oxygens; the basicity of a given oxygen will be related to the density of negative charge. Then, in just the opposite way as occurred with acidity, the lower the average electronegativity of the framework, the higher the average basic strength [24,25] (Figure 2).

The basicity associated with the oxygen bonded to a T^{III} element will depend on the local composition. By changing the framework Si/Al ratio and/or the electronegativity of the T^{IV} or T^{III} atoms, the basic strength of the zeolite can be changed. In accordance with these principles there is good correlation between the average basicities calculated by use of average Sanderson Electronegativity (ASE) [24,26,27] and the catalytic activity of basic zeolites for side-chain alkylation of toluene by methanol and for Knoevenagel condensations of benzaldehyde with different alkaline compensating cations and different framework compositions.

Taking into account the electronegativity of the framework one could increase the basicity of a zeolite by substituting framework oxygens by nitrogens. Then, two different types of strong basic sites could be developed [28]

$$\equiv\text{Si-NH-Si}\equiv \qquad \equiv\text{Si-O-Si}\equiv\text{NH}_2$$

By high-temperature treatment in the presence of NH_3, Kerr and Shipman [29] were able to form an amido zeolite Y, by forming $SiO_3(NH_2)$ groups. Others [30] have synthesized a sodalite structure with phosphorus and nitrogen in the framework. To balance the P–N–P bond a Cl^- ion surrounded by tetrahedrally arranged Zn^{2+} ion was entrapped at the center of each β-cage. A similar type of oxygen–nitrogen substitution has been tried in AlPO-5 without success [31]. None of these materials has been tested as base catalysts.

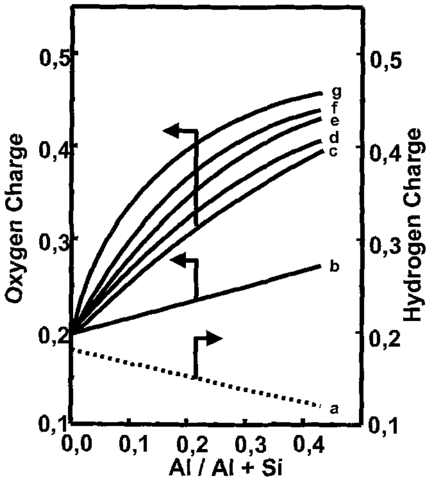


Figure 2. Influence of zeolite composition on basicity.

Alkali-exchanged zeolites can be used for selective condensation reactions [32–37], double bond isomerization, alkylation of toluene by methanol, monomethylation of phenylacetonitrile with methanol and dimethyl carbonate (DMC) [38], and selective N-alkylation with methanol, ethanol, and 2-propanol as alkylating agents [39–44]. However, the basicity of alkaline exchanged zeolites is rather low.

3.2.3.2 Basic Zeolites–Extra-framework Composition

It is possible to produce strongly basic zeolites by over-exchange with alkali [45–47] or alkaline earth [48] metals and producing, after thermal decomposition, the corresponding highly dispersed basic oxides within the pores. In these zeolites the basic active sites are associated with the very small particles of alkaline oxides and, more specifically, to Cs_2O. To avoid destruction of the zeolite during the activation procedure, the presence of water should be avoided during calcination. Such destruction occurs by hydrolysis of the Si–O–Si bonds rather than by the hydrolysis of Al–O–Si bonds, and in this sense X zeolite is preferred to more Si-rich zeolites.

With both alkaline and alkaline earth oxides the order of basicity increases when the size of the cation is increased: $Na_XO/NaX < K_XO/KX \approx Rb_XO/RbX < Cs_XO/CsX$. However, it seems (at least for MgO) that the entrapped oxides are less basic than the corresponding bulk oxides [49–51].

The basicity of zeolite catalysts can be increased even further by occluding alkali metal clusters. In this way $Na_4{}^{3+}$, $K_3{}^{2+}$, $Rb_6{}^{4+}$, $Rb_3{}^{2+}$, $Cs_3{}^{2+}$, $Cs_4{}^{3+}$ and continuum Cs cations and superlattice structures arising from the presence of Na or K clusters arrays have been reported in zeolite Y [52–58].

The samples can be prepared by alkali metal vapor treatment of the zeolite, treatment of the molecular sieve with a solution of the alkali metal in liquid ammonia or in primary amines, treatment of the zeolite with organolithium compounds, or decomposing sodium azide previously impregnated on sodium zeolites [59–62].

It should be remarked that for very strong zeolite basic catalysts the presence of CO_2 and H_2O should be avoided in any stage of preparation and reaction, because these lead to rapid catalyst deactivation.

3.2.4 Redox Molecular Sieves

3.2.4.1 Oxidation Sites in Framework Positions

The most relevant heterogeneous catalysts used in liquid phase oxidations are [63]:

- *supported metals*, in which the most important limitation is its fast decay;
- *metallic ions* or *supported metal complexes*, for which regeneration and problems associated with ligand degradation are important limitations; and
- *supported metal oxides*, the major limitation of which is that they dissolve giving homogeneous catalytic species, although a partial exception to this is

the Ti/SiO_2 catalyst developed by Shell which is active only in the presence of organic hydroperoxides.

Another option that sometimes enables immobilization of isolated metal ions stable to leaching, and avoidance of the formation of oligomers, is the synthesis of zeolites or zeotypes containing isolated metal ions in framework positions. In these the oxidation properties of the metal atoms are associated with the main characteristics of zeolites which involve shape-selective effects and unique adsorption properties which can be tuned in terms of their hydrophobicity–hydrophilicity, enabling selection of the proportions of reactants with different polarities that will be adsorbed in the pores. Researchers at ENI succeeded in introducing Ti into silicalite producing the TS-1 redox molecular sieve oxidation catalyst [64]. TS-1 has an MFI structure formed by a bidimensional system of channels with 0.53 nm × 0.56 nm and 0.51 nm × 0.51 nm pore dimensions. The incorporation of Ti into the framework has been demonstrated by use of several techniques–XRD, UV–visible spectrophotometry, EXAFS–XANES; a good review has been published by Vayssilov [65].

The presence of a silica framework with few defects makes TS-1 a highly hydrophobic material suitable for oxidations in the liquid phase with H_2O_2 as oxidant. Thus, TS-1 has proven to be successful in the oxidation of alcohols, epoxidation of linear olefins, hydroxylation of aromatics, ammoximation of cyclohexanone, oxidation of alkanes to alcohols and ketones, oxidation of amines, oxidation of sulfur-containing compounds, and oxidation of ethers [66–75].

Since then other zeolite structures have been synthesized including TS-2 [76], Ti-Beta [77,78], Ti-ZSM-48 [79], Ti-ZSM-12 [80], Ti-mordenite [81], Ti-UTD-1 [82], and Ti-ferrierite [83,84]. Ti has also been incorporated in mordenite, Beta, SSZ-33, Y, L, MAZ, UTD-1 and NU-1 structures by post-synthetic treatment [74,85–87]; although they have some activity, the activity and selectivity of samples produced by post-synthetic procedures are lower than those obtained by direct synthesis [88].

Because of the diameter of the pores, TS-1 is limited to the oxidation of larger molecules and the use of organic hydroperoxides [89]. Taking this into account, Ti-Beta zeolite with 12-member ring tridirectional pores with dimensions close to 0.70 nm could, in principle, enlarge the catalytic possibilities of TS-1. Indeed, Ti-Beta can use H_2O_2 as oxidant but its activity and selectivity are lower than for TS-1 [78]. For instance, during the epoxidation of olefins, the selectivity to epoxide is lower for Ti-Beta and glycols are formed as a result of opening of the epoxide by H_2O. This unwanted reaction can be partially avoided by introducing alkali metal cations to the reaction media; these neutralize residual acidity present in the zeolite [90]. Much improved epoxide selectivity was found when T^{III}-free Ti-Beta samples were synthesized, and even more so when defect-free hydrophobic Al-free Ti-Beta samples were prepared [91], as is apparent from Table 2.

Table 2. Influence of Al content and the presence of defects on the activity and selectivity of Ti-Beta in the epoxidation of 1-hexene with H_2O_2, using methanol as solvent.

Method of synthesis	Chemical composition Si/Al	TiO_2 (%, *w/w*)	Defects	Turnover frequency (mol (mol Ti)$^{-1}$ h^{-1})	Epoxide selectivity
Cogel	300	4.7	Yes	20.8	25.9
Dealuminated seeds	∞	2.5	Yes	28.6	75.4
F^- media	∞	2.5	No	32.2	96.4

Besides Ti, other transition metals such as V, Cr, Fe ..., have been introduced in zeolite framework positions but most are leached strongly in the presence of H_2O_2 [88].

3.2.4.2 Oxidation Sites in Extra-framework Positions

Redox-type zeolite catalysts can also be prepared in which the active sites occupy extra-framework positions and are obtained by different post-synthesis procedures, including anchoring the transition metal complexes (TMC) [92–94], CVD deposition, trapping the TMC within the pores during zeolite synthesis [95,96], or encapsulation of the TMC by the ship-in-a-bottle technique.

The ship-in-a-bottle technique is perhaps the most common method for encapsulation of transition metal complexes. In this way the tetradentate Schiff base ligand SALEN (bis-salicylidene) ethylenediamine can diffuse through the 12 MR windows of faujasite. Then, when complexed with a previously exchanged metal ion, nearly square planar coordination geometry is formed inside the α-cages [97–100]. Mn complexes with a chiral ligand, prepared by the ship-in-a-bottle technique inside Y and EMT zeolites, have enantioselectively carried at the epoxidation of olefins [101,102].

Other complexes including phthalocyanines and metal clusters have also been encapsulated in several zeolites such as Y, EMT, VPI-5 and mesoporous materials [103–110].

3.2.5 Conclusions

Zeolites can be used as microreactors in which the size of the reactor, i. e. the size of pores and cavities can be varied. The adsorption properties of zeolites can be modified and this, with their molecular sieve properties either for reactants, products, or transition states can be very useful for directing the reaction towards the desired products.

Acidic, basic, and redox active sites can be introduced either in framework or in extra-framework positions. A good understanding of the nature of the active sites and their interaction with the substrates is being achieved by combining theoretical calculations, characterization, and reactivity studies. It seems that the interactions between active sites and reactants are more complex than previously supposed and that the reactant adsorbed and the transition state will interact not only with the particular acidic or basic site, but also with neighboring framework atoms. This probably occurs via Van der Waals interactions which stabilize the adsorbed reactant and the transition state, thus increasing the activity of zeolite catalysts.

We have seen that it is possible to design active sites with acidic or basic strength better adapted to the needs of a particular reaction. In comparison with progress made in acidic or basic catalysis with zeolites, redox catalysis with zeolites is in its infancy. We are just now understanding that properties such as zeolite hydrophobicity, pore dimensions, and active site location are determinant factors for this type of catalyst. Several reviews are recommended for those interested in organic chemistry [111–113].

Zeolites have also transformed the field of chiral catalysis, because of the possibility of introducing extra-framework active sites in the pores of these materials. There is, however, one subject yet to be investigated–the synthesis of chiral zeolite structures and/or chiral framework sites.

References

[1] Sheldon, R. A., Dakka, J., *Catal. Today* **19**, 215 (1994).

[2] Wilson, S. T., Lok, B. M., Messina, C. A., Cannan, T. R., Flanigen, E. M., *J. Am. Chem. Soc.* **104**, 1146 (1982).

[3] Flanigen, E. M., *Stud. Surf. Sci. Catal.* **58**, 1 (1991).

[4] Barrer, R. M., *J. Colloid. Sci.* **21**, 416 (1966).

[5] Csicsery, S. M., *ACS Monograph* **171**, 680 (1976); and *Zeolites* **4**, 202 (1984).

[6] Gontier, S., Tuel, A., *Appl. Catal. A* **118**, 173 (1994).

[7] Barrer, R. M., Denny, P. J., *J. Chem. Soc.*, 971 (1961).

[8] Mortier, W. J., *J. Catal.* **55**, 138 (1978).

[9] Pine, L. A., Maher, P. J., Wachter, W. A., *J. Catal.* **85**, 466 (1984).

[10] Fisher, R., Hölderich, W., Mrosz, W. D., Strohmeyer, M., Eur. Patent 0167021 (1986).

[11] Feitler, D., Wetstein, H., US Patent 5013843 (1991).

[12] Herron, N., Farneth, W. E., *Adv. Mater.* **8**, 959 (1996).

[13] Datka, J., Boczen, M., Rymarowicz, P., *J. Catal.* **114**, 368 (1988).

[14] Carson, R., Cooke, E. M., Dwyer, J., O'Malley, P. J. in 'Zeolites as Catalysts, Sorbents, and Detergent Builders', (H. G. Karge and J. Weitkamp, Eds.), Elsevier, Amsterdam, p. 39 (1989).

[15] A. Corma, *Chem. Rev.* **95**, 559 (1995).

[16] Brändle, M., Sauer, J., *J. Am. Chem. Soc.* **120**, 1556 (1998).

[17] Gonzales, N. O., Chakraborty, A. K., Bell, A. T., *Catal. Lett.* **50**, 135 (1998).

[18] Koningsberger, D. C., Miller, J. T., in 'Zeolites: A Refined Tool for Designing Sites', (L. Bonneviot and S. Kaliaguine, Eds.) Elsevier, Amsterdam, p. 125 (1995).

[19] Corma, A., Fornés, V., Herrero, E., Martínez, A., Prieto, J., *Prep. Am. Chem. Soc. Div. Petrol. Chem.* **32**, 369 (1987).

[20] Mirodatos, C., Barthomeuf, D., *J. Chem. Soc., Chem. Commun.*, 39 (1981).

[21] Garralón, G., Corma, A., Fornés, V., *Zeolites* **9**, 84 (1988).

[22] Koningsberger, D. C., Miller, J. T., *Stud. Surf. Sci. Catal.* **101**, 841 (1996).

[23] Bourgeat-Lami, E., Massiani, P., Di Renzo, F., Espiau, P., Fajula, F., Des Courières, T., *Appl. Catal.* **72**, 139 (1991); Wouters, B. H., Chen, T. H., Grobet, P. J., *J. Am. Chem. Soc.* **120**, 11419 (1998).

[24] Kunkeler, P. J., Zuurdeeg, B. J., van der Waal, J. C., van Bokhoven, J. A., Koningsberger, D. C., van Bekkum, H., *J. Catal.* **180**, 234 (1998).

[25] Barthomeuf, D., *Stud. Surf. Sci. Catal.* **65**, 157 (1991).

[26] Barthomeuf, D., *NATO Asi Series C* **444**, 375 (1993).

[27] Mortier, W. J., *Stud. Surf. Sci. Catal.* **37**, 253 (1988); Uytterhoeven, L., Dompas, D., Mortier, W. J., *J. Chem. Soc., Faraday Trans.* **88**, 2753 (1992).
[28] Corma, A., Viruela, P., Fernández, L., *J. Mol. Catal. A* **133**, 241 (1998).
[29] Terr, G. T., Shipman, G. F., *J. Phys. Chem.* **72**, 3071 (1968).
[30] Shickd, W., Lucke, J., *Angew. Chem. Int. Ed. Engl.* **2**, 213 (1992).
[31] Stein, A., Wehrle, B., Jansen, H., *Zeolites* **13**, 291 (1993).
[32] Corma, A., Martín-Aranda, R. M., *J. Catal.* **130**, 130 (1991).
[33] Corma, A., Martín-Aranda, R. M., Sánchez, F., *J. Catal.* **126**, 192 (1990).
[34] Corma, A., Martín-Aranda, R. M., Sánchez, F., *Stud. Surf. Sci. Catal.* **59**, 503 (1991).
[35] Corma, A., Martín-Aranda, R. M., *Appl. Catal. A* **105**, 271 (1993).
[36] Rode, E. J., Gee, P. E., Marquez, L. N., Uemura, T., Bazargami, M., *Catal. Lett.* **9**, 103 (1991).
[37] Posner, L. S., Augustine, R. L., *Chem. Ind.* **62**, 531 (1995).
[38] Ono, Y., *CatTech* **1**, 31 (1997).
[39] Prasad Rao, P. R. H., Massiani, P., Barthomeuf, D., *Catal. Lett.* **31**, 115 (1995).
[40] Prasad Rao, P. R. H., Massiani, P., Barthomeuf, D., *Stud. Surf. Sci. Catal.* **84**, 1449 (1994).
[41] Su, B. L., Barthomeuf, D., *Appl. Catal. A*, **124**, 73 (1995).
[42] Yuvaraj, S., Palanichamy, M., *React. Kinet. Catal. Lett.* **57**, 159 (1996).
[43] Singh, P. S., Bandyopadhyay, R., Rao, B. S., *Appl. Catal. A* **136**, 177 (1996).
[44] Selva, M., Bomben, A., Tundo, P., *J. Chem. Soc. Perkin Trans. 1* **7**, 1041 (1997).
[45] Hathaway, P. A., Davis, M. E., *J. Catal.* **116**, 263 and 279 (1989).
[46] Lasperas, M., Cambon, H., Brunel, D., Rodriguez, I., Geneste, P., *Microp. Mater.* **1**, 343 (1993).
[47] Yagi, F., Tsuji, H., Hattori, H., *Microp. Mater.* **9**, 237 (1997).
[48] Brownscombe, T. F., US Patent 5053372 (1991).
[49] Yagi, F., Tsuji, H., Hattori, H., *Microp. Mater.* **9**, 237 (1997).
[50] Kim, J. C., Li, H. X., Chen, C. Y., Davis, M. E., *Microp. Mater.* **2**, 413 (1994).
[51] Brownscombe, T. F., Slaugh, L. F., Eur. Patent 370553 (1989).
[52] Anderson, P. A., Singer, R. J., Edwards, P. P., *J. Chem. Soc., Chem. Commun.* 914 (1991).
[53] Anderson, P. A., Armstrong, A. R., Edwards, P. P., *Angew. Chem. Int. Ed. Engl.* **33**, 641 (1994).
[54] Sun, T., Seff, K., Heo, N. H., Petranovski, V. P., *J. Phys. Chem.* **98**, 5678 (1994).
[55] Liu, X. S., Thomas, J. K., *J. Chem. Soc., Faraday Trans.* **91**, 759 (1995).
[56] Martens, L. R. M., Vermeiren, W. J. M., Huybrechts, D. R., Grobet, P. J., Jacobs, P. A., *Proc. 9th Int. Congress Catal.*, Calgary 420 (1988).
[57] Sun, T., Seff, K., *J. Phys. Chem.* **48**, 10156 (1994).
[58] Woodall, L. J., Anderson, P. A., Armstrong, A. R., Edwards, P. P., *J. Chem. Soc., Dalton Trans.*, 719 (1996).
[59] Bordiga, S., Ferrero, A., Giamello, E., Spoto, G., Zecchina, A., *Catal. Lett.* **8**, 375 (1991).
[60] Yoon, D. B., Kochi, J. K., *J. Chem. Soc., Chem. Commun.*, 510 (1998).
[61] Kiricsi, I., Hannus, I., Kiss, A., Fejes, P., *Zeolites* **2**, 247 (1982).
[62] Martens, L. R. M., Grobet, P. J., Jacobs, P. A., *Nature* **315**, 568 (1985).
[63] Sheldon, R. A., Wallau, M., Schuchardt, U., *Angew. Chem. Int. Ed.* **36**, 1144 (1997).
[64] Taramasso, M., Manara, G., Fattore, V., Notari, B., US Patent 4666692 (1987); US Patent 4410501 (1993).
[65] Vayssilov, G. N., *Catal. Rev. Sci. Eng.* **39**, 209 (1997).
[66] Esposito, A., Neri, C., Buonomo, F., US Patent 4480135 (1984).
[67] Clerici, M. G., Romano, U., Eur. Patent 230949 (1987).
[68] Esposito, A., Taramasso, M., Neri, C., Buonomo, F., US Patent 2116974 (1985).
[69] Roffia, P., Pandovan, M., Moretti, E., de Alberti, G., Eur. Patent 208311 (1987).
[70] Huybrechts, D. R. C., WO Patent 90105126 (1990).
[71] Clerici, M., Anfossi, B., Bellussi, G., Eur. Patent 412596 (1990).
[72] Gontier, S., Tuel, A., *Appl. Catal. A* **118**, 173 (1994).
[73] Reddy, R. S., Reddy, J. S., Kumar, R., Kumar, P., *J. Chem. Soc., Chem. Commun.*, 84 (1992).
[74] Notari, B., *Adv. Catal.* **41**, 253 (1996).

[75] Taramasso, M., Perego, C., Notari, B., US Patent 4410501 (1983).
[76] Reddy, J. S., Kumar, R., Ratnasamy, P., *Appl. Catal.* **23**, 69 (1986).
[77] Camblor, M. A., Corma, A., Pérez-Pariente, J., *J. Chem. Soc., Chem. Commun.*, 589 (1992).
[78] Corma, A., Camblor, M. A., Esteve, P., Martínez, A., Pérez-Pariente, J., *J. Catal.* **145**, 151 (1994).
[79] Serrano, D. P., Li, X. X., Davis, M. E., *J. Chem. Soc., Chem. Commun.*, 745 (1992).
[80] Tuel, A., *Zeolites* **15**, 236 (1995).
[81] Kim, G. J., Cho, B. R., Kim, J. H., *Catal. Lett.* **22**, 259 (1992).
[82] Balkus, K. J., Gabrielov, N. S., *Mater. Res. Soc. Symp. Proc.*, 368 (1995).
[83] Schreyeck, L., Caullet, P. H., Mongenel, J.Ch., Guth, J. L., Marler, B., *Chem. Commun.*, 2187 (1995); and *Microp. Mater.* **6**, 259 (1996).
[84] Corma, A., Díaz, U., Domine, M. E., Fornés, V., *Chemical Commun.*, in press (2000).
[85] Rigutto, M. S., De Ruiter, R., Niederer, J. P. M., van Bekkum, H., *Stud. Surf. Sci. Catal.* **84**, 2245 (1994).
[86] Dartt, C. B., Davis, M. E., *Appl. Catal. A* **143**, 56 (1996).
[87] Ahedi, R. K., Shevade, S. S., Kotasthane, A. N., *Zeolites* **18**, 361 (1997).
[88] Arends, I. W. C. E., Sheldon, R. A., Wallau, M., Schuchardt, J., *Angew. Chem. Int. Ed. Engl.* **36**, 1144 (1997).
[89] Tatsumi, T., Negishi, S., Timinaga, H., *J. Chem. Soc., Chem. Commun.*, 476 (1990).
[90] Sato, T., Dakka, J., Sheldon, R. A., *J. Chem. Soc., Chem. Commun.*, 1887 (1994).
[91] Blasco, T., Camblor, M. A., Corma, A., Esteve, P., Martínez, A., Prieto, C., Valencia, S., *Chem. Commun.* **23**, 67 (1996).
[92] Corma, A., Iglesias, M., del Pino, C., Sánchez, F., *Stud. Surf. Sci. Catal.* **75**, 2293 (1993).
[93] Maschmeyer, T., Rey, F., Sankar, G., Thomas, J. M., *Nature* **378**, 159 (1995).
[94] Sutra, P., Brunel, D., *Chem. Commun.*, 2485 (1996).
[95] Balkus Jr., K. J., Eissa, M., Lavado, R., *Stud. Surf. Sci. Catal.* **94**, 713 (1995).
[96] Balkus Jr., K. J., Nowinska, K., *Microp. Mater.* **3**, 665 (1995).
[97] Chatterjee, D., Bjaj, H. C., Das, A., Blatt, K., *J. Mol. Catal.* **92**, 1235 (1994).
[98] De Vos, D. E., Thibault-Starzyk, F., Jacobs, P. A., *Angew. Chem. Int. Ed. Engl.* **33**, 431 (1994).
[99] Ernst, S., Batreau, O., *Stud. Surf. Sci. Catal.* **94**, 479 (1995).
[100] Zsigmond, A., Notheisz, F., Szegletes, Z. S., Backvall, J. E., *Stud. Surf. Sci. Catal.* **94**, 728 (1995).
[101] Sabater, M. J., Corma, A., Domenech, A., Fornés, V., García, H., *Chem. Commun.*, 1285 (1997).
[102] Ogunwumi, S. B., Bein, T., *Chem. Commun.*, 901 (1997).
[103] Romanovsky, B. V., Gabrielov, A. G., *J. Mol. Catal.* **74**, 293 (1992).
[104] Paez-Mozo, E., Gabriunas, N., Lucaccioni, F., Acosta, D., Patrono, P., La Ginesta, A., Ruiz, P., Delmon, B., *J. Phys. Chem.* **97**, 1281 (1993).
[105] Parton, R. F., Grobet, P. J., Jacobs, P. A., *Stud. Surf. Sci. Catal.* **83**, 371 (1994).
[106] Ernst, S., Traa, Y., Deeg, W., *Stud. Surf. Sci. Catal.* **84**, 925 (1994).
[107] Balkus, K. J., Eissa, M., Lavado, R., *J. Am. Chem. Soc.* **117**, 10753 (1995).
[108] De Vos, D., Bein, Th., *Chem. Commun.*, 917 (1996).
[109] Bremard, C., Ginestet, G., Le Maire, M., *J. Am. Chem. Soc.* **118**, 12724 (1996).
[110] Liu, Ch. J., Li, S. G., Pang, W. G., Che, Ch. M., *Chem. Commun.*, 65 (1997).
[111] Venuto, P. B., *Microp. Mater.* **2**, 297 (1994).
[112] Hölderich, W. F., van Bekkum, H., *Stud. Surf. Sci. Catal.* **58**, 613 (1991).
[113] Espeel, P., Parton, R., Toufar, H., Martens, J., Hölderich, W., Jacobs, P., in *'Catalysis and Zeolites'* (J. Weitkamp and L. Puppe, Eds.), Springer Verlag, p. 377 (1999).

3.3 Sulfonated Polysiloxanes

S. Wieland, P. Panster

3.3.1 Motivation and Expected Advantages

The previous two sections dealt with inorganic materials–acidic clays and zeolites–and their use as solid-acid catalysts. Other oxides, e. g. TiO_2, Al_2O_3, ZrO_2, sulfated oxides, and oxides impregnated with liquid acids, for example H_3PO_4 on SiO_2 (solid phosphoric acid), are also catalytically active, the activity arising from either Lewis- or Brønsted- acid sites or both.

Purely organic ion-exchange resins, e. g. polystyrene-based sulfonated resins can also be used as solid-acid catalysts. They have a high capacity–up to 5 mmol H^+ (g dry resin)$^{-1}$. Chemically these resins with attached $-SO_3H$ groups very much resemble homogeneous acids such as H_2SO_4 or *p*-toluenesulfonic acid, with which the organic chemist is more familiar. Disadvantages of these resins are their limited thermal stability (desulfonation at temperatures $> 90-130$ °C) and swelling in organic solvents. These problems can be partly overcome by use of extensively crosslinked divinylbenzene matrixes.

Advantages of inorganic, oxidic supports or catalysts are their rigid structure, well-defined pore structure irrespective of solvent, temperature and pressure, and their thermal and chemical stability. These advantages combined with the high Brønsted acidity of the sulfonic acid group motivated the exploration of sulfo groups attached to polysiloxanes, i. e. the combination of a rigid silica matrix to which $-SO_3H$ groups are attached via organic spacer units. The polysiloxanes reported in the literature predominantly bear sulfophenyl-, sulfobenzyl-, 2-(sulfophenyl)ethyl-, and 3-sulfopropyl-groups.

3.3.2 Synthetic Approaches

The different approaches used to synthesize sulfonated polysiloxanes can be distinguished according to synthesis/modification of the solid siliceous network, to the organosilane precursor used, and to the generation of the active sulfonic acid group, as given in Figure 1.

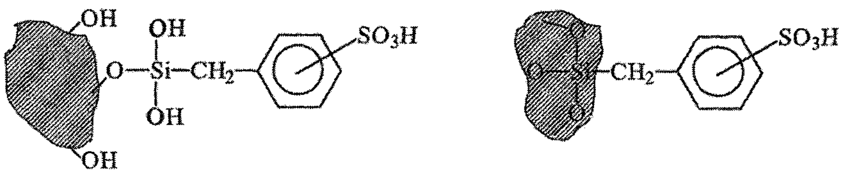
Aryl- and alkylsulfonated polysiloxanes are available. Aryl sulfonated polysiloxanes are generally synthesized by sulfonation of solid aryl polysiloxanes whereas alkyl sulfonated polysiloxanes are synthesized by starting either with an aqueous solution of the sulfonic acid-functionalized silane or with a highly crosslinked mercapto or polysulfan functionalized polysiloxane. Figure 3 gives an overview of the predominantly synthesized sulfonated siloxane units.

Method of building-up the siliceous matrix	**organosilane precursors used**	**generation of sulfonic acid group by post-reacting the solid polysiloxanes**
reaction of organosilanes with silica gel surface	non-sulfur containing trialkoxy aryl silanes like - phenyl silanes, e.g. $PhSi(OEt)_2$ - benzyl silanes, e.g. $PhCH_2Si(OMe)_3$ - 2-ethylphenyl silanes, e.g. $PhCH_2CH_2SiCl_3$	sulfonation of the aromatic ring using chlorosulfuric acid
precipitation or preparation of silica-gel type materials via polycondensation	sulfur group containing silanes like - mercapto alkyl silanes, e.g. $(OMe)_3SiCH_2CH_2CH_2SH$ - polysulfan dialkyl silanes, e.g. $(OMe)_3Si(CH_2)_3\text{-S-S-}(CH_2)_3Si(OMe)_3$	oxidative cleavage of the S-S bond or oxidation of -SH group using $KMnO_4$ or H_2O_2
	sulfonated organosilanes, especially $(OH)_3Si\text{-}CH_2\,CH_2\,CH_2\text{-}SO_3H$	n.a.

Figure 1. Approaches to the synthesis of sulfonated polysiloxanes. Any combination of the first and second rows of the table is possible. The second row gives the organosilane precursors required and whether post-reaction of the solid formed is necessary.

3.3.2.1 Grafting of Silanes to Silica

These functionalized siloxane units can be incorporated in silica matrices by different methods. One obvious way is surface modification of silica gels by reacting the hydroxyl groups with the silane precursors given in Figure 1, e. g. trimethoxy-(benzyl)silane, then sulfonation of the benzyl groups [1,2]. A disadvantage of this approach is the low H^+ capacity achieved–only 0.1–0.6 mmol g^{-1}–and the danger of hydrolytic cleavage of the organosilane moiety bound to the silica, because surface-grafted siloxanes are not as tightly bound as siloxanes derived from polycondensation from a homogeneous phase (Figure 2). The same applies if the formed porous silica particles are reacted with organosilanes.



surface grafted siloxane sol-gel derived polysiloxane

Figure 2. Schematic difference between surface grafted siloxanes and polysiloxanes embedded in sol–gel-derived matrices

3.3.2.2 Copolycondensation and Sol–Gel Processing

In contrast with the simple surface attachment of these functionalized organosilanes by grafting to silicas, copolycondensation of functionalized and non-functionalized network-forming silanes, e. g. tetramethoxysilane, yields a crosslinked matrix (see also Figure 4). Generally, this approach gives products with higher functional-group densities and increased stability against hydrolytic degradation. Typically this is achieved by acid-catalyzed hydrolysis of a mixture of tetraalkoxysilanes and arylalkoxysilanes in aqueous ethanol. The resulting solid is isolated by filtration, washed, sulfonated, washed again, and dried [3]. Alternatively, an aqueous solution of 3-(tris-hydroxysilyl)propyl sulfonic acid can be reacted with tetraethoxysilane. Use of the sol–gel process in the synthesis of the latter acidic polysiloxanes enables the isolation of products of consistently controllable size with a relatively narrow particle-size distribution, e. g. from 100 to 400 μm, for use in suspension or as spheres with diameters up to 1.4 mm for fixed-bed applications [4]. Furthermore, these catalysts have high porosity, large mesopores (diameters > 20 nm) and high BET surface areas ($300-600\ m^2\ g^{-1}$).

3.3.2.3 Sulfonation of Arylsiloxanes

As in the synthesis of polystyrene-based cation exchange resins, sulfonation of the aryl group containing siloxane, prepared by either of the routes mentioned above, can be achieved with chlorosulfonic acid. In principle, each aryl group can be sulfonated and high capacities of $2.4-3.2$ mmol $H^+\ g^{-1}$ are reported [3]. This requires good accessibility of the aryl group for sulfonation. Drawbacks are lack of specificity and the presence of homogeneous acids that must be removed by thorough washing. Oversulfonation can result in a partial or complete solubility of the products in water. It also cannot be excluded that directly Si-bound sulfur species are formed. Another reported [6] synthetic approach is nucleophilic substitution of a chloro group in (chloroaryl)siloxanes by use of Na_2SO_3.

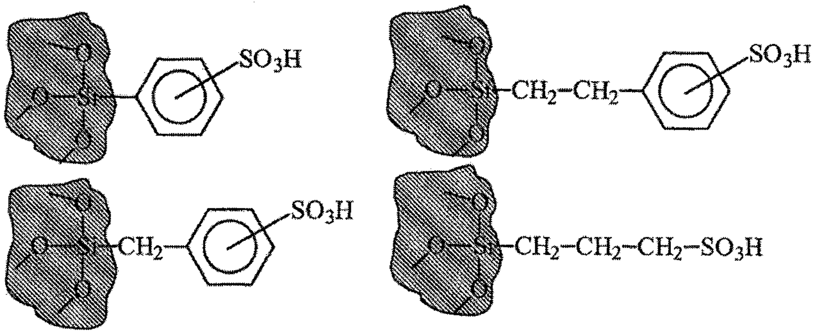


Figure 3. Functional subunits of sulfonated polysiloxanes as attached to the solid phase.

3.3.2.4 Oxidation of Sulfur-functionalized Siloxanes

Mercapto- or sulfane-functionalized polysiloxanes can be converted by oxidation into the corresponding sulfonic acid polysiloxanes [3,5]; different methods have been described. Care must be taken not to dissolve the polysiloxane matrix as the resulting sulfonic acid functional siloxanes are more water-soluble than the starting siloxanes. Thus enough network-forming SiO_2 units must be present to retain the functionalized siloxanes in the matrix. On the other hand, as 3-(tris-hydroxysilyl)propyl sulfonic acid, for example, is completely water-soluble it can be easily synthesized. Its two-step synthesis starts from a sulfur-bridged alkoxysilane which is hydrolyzed in acidic medium to form a solid (Eq. 1). The solid is washed to remove alcohol that would consume oxidizing agent in the subsequent oxidative cleavage of the sulfur bridge by hydrogen peroxide (Eq. 2) [7].

$$S_4[(CH_2)_3Si(OC_2H_5)_3]_2 + 3H_2O \rightarrow S_4[(CH_2)_3SiO_{3/2}]_2 + 6C_2H_5OH \qquad (1)$$

$$S_4[(CH_2)_3SiO_{3/2}]_2 + 11H_2O_2 \rightarrow 2HO_3S(CH_2)_3Si(OH)_3 + 2H_2SO_4 + 5H_2O \qquad (2)$$

The resulting aqueous solution of $HO_3S(CH_2)_3Si(OH)_3$ is further concentrated and then used as a precursor in the synthesis of acidic polysiloxanes via copolycondensation with tetraalkoxysilane. To obtain a solid, water-stable product, a large excess of network-forming alkoxysilane is necessary. Hydrolytic cleavage of siloxane bonds, forming water soluble siloxane oligomers or monomers, is a general feature of polysiloxanes, it is especially important when ionic, hydrophilic groups are attached to the siloxane unit.

3.3.3 Characterization of the Polysiloxanes

3.3.3.1 General

The general characteristics of polysiloxanes are given by the properties of the siliceous matrix and by its organic substituents. The siloxane matrix is inherently susceptible to degradation via hydrolytic cleavage of the siloxane bonds. This leads to restrictions on the use of these materials in aqueous media. On the other hand, silanol groups, always present on these materials, add to the overall acidity of these materials, an aspect which is important in high temperature gas-phase applications. To avoid leaching of the organo-substituted siloxane units, it is important to have them very well embedded in the siloxane matrix, as can be seen from Figure 3. By copolycondensation it is not only possible to incorporate siloxanes bearing the sulfonic acid group but also additional functionalized or unfunctionalized siloxanes. These can be used to modify, increase, or tune the catalytic activity, as in the synthesis of bisphenol-A. Introduction of alkyl- or aryl-substituted siloxanes changes the adsorption properties, the hydrophobicity, and the

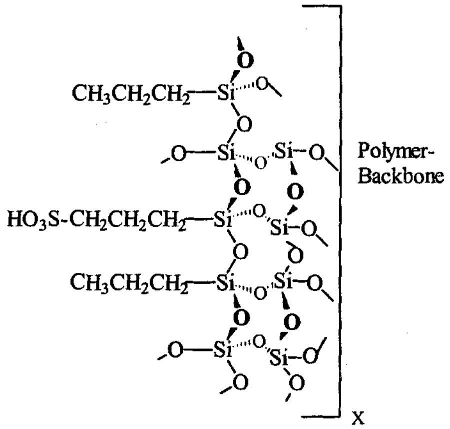


Figure 4. Schematic representation of a cross-linked polysiloxane structure formed by copolycondensation of tetraalkoxysilane, propyltrialkoxysilane and 3-(tris-hydroxysilyl)propyl sulfonic acid. Note the embedding of the functionalized siloxanes into the matrix in contrast with simple attachment to the surface of a preformed solid.

stability against hydrolytic degradation, the latter by shielding the siloxane bonds against hydrolytic attack of oxo bases.

The advantages of these catalysts are, especially, their high structural stability, i. e. no swelling and no shrinking in organic media, in contrast to polystyrene-based cation-exchanges resins, and their high-temperature stability and high catalytic activity, which is comparable with that of soluble acids such as H_2SO_4 or *p*-toluene sulfonic acid, on the basis of high Brønsted acid strength.

3.3.3.2 Analytical Determination of Capacity

Determination of sulfur in the polysiloxane by elemental analysis is used to calculate the capacity of acidic groups in the polysiloxanes. Simple acid–base titration is often misleading if strong bases, e. g. NaOH, are used, because they react not only with the sulfonic acid but also with silanols and even with siloxane bonds, as shown in Eqs (3) and (4).

$$HO - SiO_{3/2} + NaOH \rightarrow Na^{+-}O - SiO_{3/2} + H_2O \tag{3}$$

$$O_{3/2}Si - O - SiO_{3/2} + NaOH \rightarrow O_{3/2}Si - OH + Na^{+-}O - SiO_{3/2} \tag{4}$$

To avoid these errors one determines the acid groups by back-titrating a small excess of base added to the stirred polysiloxane.

3.3.3.3 NMR Spectroscopy

Solid-state MAS ^{29}Si NMR spectroscopy gives information about the connectivity of the Si atoms. Resonance frequencies for Si atoms attached to one organic side chain ($R-SiO_3$-type) are in the range −60 to −80 ppm and unsubstituted Si atoms (SiO_4-type) are in the range −90 to −110 ppm. Within each region, the Si atoms bearing more –OH groups are at lower frequencies, e. g. $(HO)_2Si^*(OSi...)_2$, −90 ppm; $(HO)Si^*(OSi...)_3$, −101 ppm; $Si^*(OSi...)_4$, −109 to −110 ppm, as was found in studies on silica gels [8–12] and on methyl(phenyl)siloxane resins [13]. An MAS ^{29}Si NMR spectrum typical of these types of polysiloxane is given in Figure 5.

To check purity and composition with regard to incorporated organosiloxane units (Figure 6) standard ^{1}H NMR spectra can be taken from these polysiloxanes after dissolving in $NaOD/D_2O$.

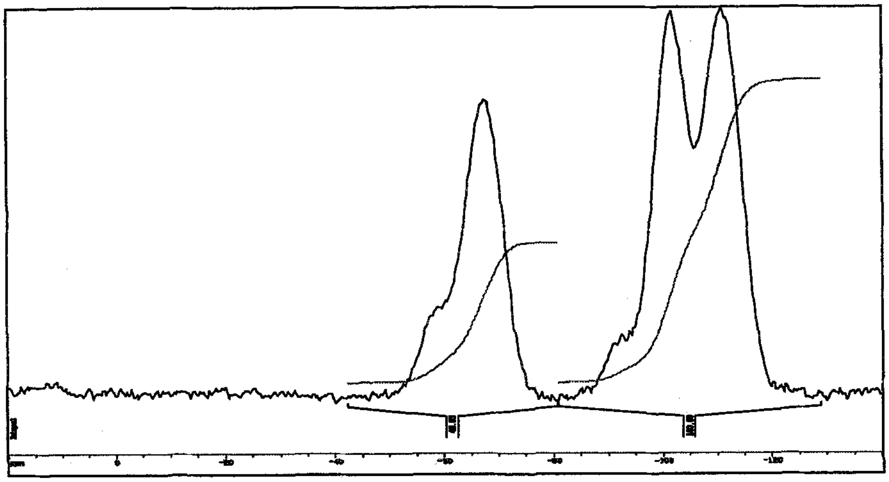


Figure 5. MAS ^{29}Si NMR spectrum of a polysiloxane with the formula $7\ SiO_2 \cdot O_{3/2}SiCH_2CH_2CH_2SO_3H$

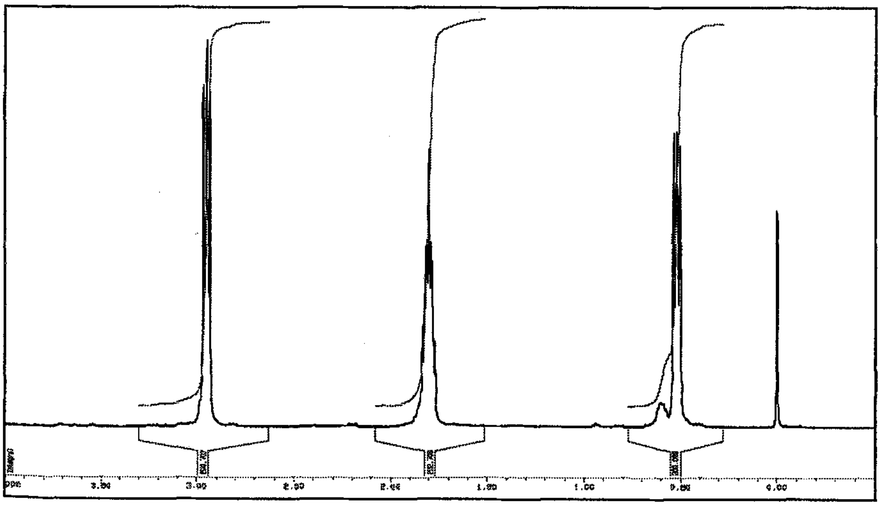


Figure 6. ^{1}H NMR spectrum of $(DO)_3SiCH_2CH_2CH_2SO_3D$, obtained after dissolving $O_{3/2}SiCH_2CH_2CH_2SO_3H$ containing polysiloxane in $NaOD/D_2O$.

3.3.3.4 Thermal Stability

Sulfonated polysiloxanes are extremely stable in gas-phase reactions. No degradation of catalytic activity has been found from study of catalysts thermally pretreated under nitrogen up to 300 °C and also after hydrothermal pretreatment, i. e. steaming up to 190 °C [3]. In this study it was further concluded, that the stability is limited by the cleavage of Si–C bonds rather than C–S bonds. In gas-phase reactions, however, no hydrolytic degradation of the siloxane matrix can occur. The picture changes when treating the materials under hydrothermal conditions in liquid aqueous phase or protic solvents. Loss of capacity is observed as a result of rupture of the siloxane bonds connecting the functional groups to the matrix.

3.3.4 Applications and Reactions

Sulfonated polysiloxanes have been tested in a variety of reactions. A typical reaction used to compare the acid strength of these catalysts with that of other solid acids is dehydration of isopropanol to yield propene [3]. The splitting of ethers, especially MTBE, at temperatures up to 200 °C has also been successfully demonstrated [14].

A variety of reactions have been studied [15] including alkylation of phenols and phenol derivatives with olefins, and alkylation of methylstyrene with 2,3-dimethyl-1-butene. The latter reaction, which is a probe reaction for the synthesis of fragrances [16], proceeded with better yields than with other solid-acid catalysts. The rate of reaction was found to be highly dependent on method of drying of the catalyst and on the amount of residual water. Another illustrative example of the use of these solid-acid catalysts is the esterification of free tallow fatty acid with high boiling alcohols, e. g. 2-ethylhexanol. In the initial stages of the esterification reaction, the rate of reaction is determined by the effectiveness of water removal. The reaction readily goes to completion and the acid number in the crude product is found to drop to < 0.2 mg KOH g^{-1}.

The high thermal stability also has a significant influence on conversion rates in the esterification of phthalic anhydride with alcohols, e. g. 1-octanol or 2-ethylhexanol, to yield dioctyl phthalates. Product yields $> 99\%$ for the diester are reported for residence times between 30 and 50 min and temperatures between 150 and 180 °C [15,17,18].

Sulfonic acid-functionalized polysiloxanes are also used in catalytic aminations, e. g. in ammonia [21]. The use of mercapto- and sulfonic acid groups bearing polysiloxanes was also studied in the industrially very important condensation reaction of acetone with phenol to give bisphenol-A [19,20].

Alkyl sulfonic acid-bearing polysiloxanes are also used as a support for powder-type precious metal catalysts (particle size < 200 μm) that can be used in hydrogenolysis reactions. The conversion of 1-phenylethanol to ethylbenzene proceeds quantitatively ($> 99\%$) at the same rate as achieved with the combination of H_2SO_4 and a Pd/C catalyst [15].

3.3.5 Summary

Sulfonated polysiloxanes might overcome the disadvantages of polystyrene-based cation-exchange resins but they have other intrinsic disadvantages arising from the siloxane matrix. Although their chemical and thermal stability is excellent and despite successful demonstration of their use in a variety of chemical reactions, no industrial use has yet been reported, mainly because production is more complicated and expensive and so cannot compete with much cheaper polystyrene-based materials produced on a large scale.

References

[1] A. Saus, B. L. Limbacker, R. Brulls, R. Kunkel in B. Imelik, C. Naccache, G. Coudurier, Y. Ben Taarit, J. C. Vedrine (eds.), Catalysis by Acid and Bases, Elsevier, Amsterdam, Oxford, New York, Tokyo, 1985, p. 383.

[2] A. Saus, E. Schmidl, J. Catal., 1985, **94**, 187.

[3] Y. Ono, S. Suzuki in Acid–Base Catal., Proc. Int. Symp., Sapporo 1988, 379–396 (Edited by K. Tanabe).

[4] P. Kleinschmit, P. Panster, European Patent EP 582811 to Degussa AG.

[5] P. Panster, H. Grethe, P. Kleinschmit, German Patent DE 3226093 to Degussa AG.

[6] K. Nakajima, H. Yasuda, Japanese Patent JP 06100695 and JP 92-274801 to Tonen Kagaku Kk.

[7] T. Goebel, A. Jänes, P. Panster, European Patent EP 548821 to Degussa AG.

[8] D. W. Sindorf, G. E. Maciel, J. Am. Chem. Soc., 1983, **105**, 1487.

[9] E. Lippmaa, M. Magi, A. Samoson, G. Engelhardt, A. -R. J. Grimmer, J. Am. Chem. Soc., 1980,**102**, 4889.

[10] A. Pines, M. G. Gibby, J. S. Waugh, J. Chem. Phys., 1973, **59**, 569.

[11] G. E. Maciel, D. W. Sindorf, J. Am. Chem. Soc., 1980, **102**, 7606.

[12] A. M. Zaper, J. L. Koehig, Adv. Colloid Interface Sci., 1985, **22**, 113.

[13] G. Engelhardt, H. Jancke, E. Lippmann, A. Samoson, J. Organomet. Chem. 1981, **210**, 295.

[14] U. Schwenk, A. Saus, O. Gürtler, W. Laarz, Dechema Monographien Band 122, 1991, 171–188.

[15] S. Wieland, P. Panster, Studies in Surface Science and Catalysis, 1997, **108**, 67–74.

[16] T. F. Wood, W. M. Easter, M. S. Carpenter, J. Angiolini: J. Org. Chem. 1963, **28**, 2248–55.

[17] K. Scharmer, European Patent EP 310843.

[18] P. Panster, S. Wieland, European Patent EP 827947 to Degussa AG.

[19] E. Auer, R. Gradl, H. Jacobsen, H. Lansink Rotgerink, S. Wieland European Patent EP 765897, E. Auer, H. Jacobsen, H. Lansink Rotgerink, H. Riedemann, S. Wieland European Patent EP 765851 to Degussa AG.

[20] K. Inoue, T. Ohkubo, T. Terajima, European Patent EP 693470, EP 95-111437 to Mitsui Toatsu Chemicals.

[21] D. Arntz, T. Haas, T. Hofen, W. Weber, S. Wieland, European Patent EP 816323 to Degussa AG.

3.4 Silica-occluded Heteropolyacids

Yusuke Izumi

3.4.1 Introduction

The Keggin-type heteropolyacid (hereafter abbreviated HPA) is a unique catalyst material because it has the dual catalytic functions of strong acidity and high oxidizing capacity [1–5]. HPA has been applied commercially as an efficient catalyst in several petrochemical processes, including the direct hydration of propene (1972) [6,7], isobutene (1984) [8] and *n*-butenes (1989) [9], the oxidation of methacrolein to methacrylic acid (1982) [10], the oligomerization of tetrahydrofuran to polymeric diols (1985) [11], and the oxidation of ethene to acetic acid (1997) [12].

HPA is very soluble in oxygen-containing polar solvents such as water, alcohol, ether, and ketone. In these polar solvents, HPA works as an efficient acid catalyst for alkene hydration, the Prins reaction, nucleophilic cleavage of alicyclic and cyclic ethers, esterification, hydrolysis, transesterification, and acetalization. The catalytic activity of HPA in these reactions is much higher than that of ordinary protonic acids such as sulfuric acid and *p*-toluenesulfonic acid, and the activation energies of the HPA-catalyzed reactions are remarkably reduced, owing to stabilization of the cationic reaction intermediates by the heteropoly anion [1,4].

Immobilization of such catalytically highly efficient HPA into an insoluble, readily recoverable solid acid is, therefore, an interesting and significant research target because environmentally benign solid-acid catalysts should replace problematic sulfuric acid and aluminum chloride. Several efforts have been made to immobilize HPA. Active carbon tightly entraps HPA inside its pores to form an insoluble solid acid that catalyzes liquid-phase organic reactions in polar media

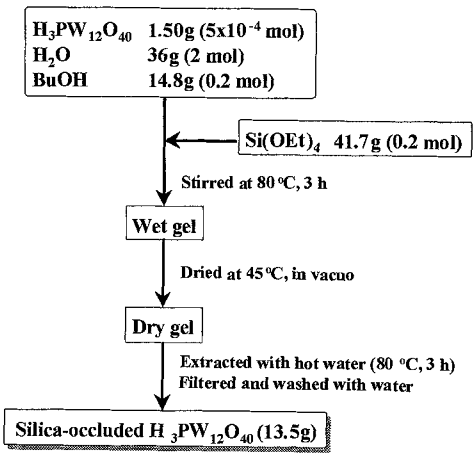


Figure 1. Standard method for preparation of silica-included $H_3PW_{12}O_{40}$.

[13], but the carbon-entrapped HPA suffers from the problems of leaching of the HPA in highly polar solvents and reduced acid strength. HPA is also immobilized by salt formation. A cesium acid salt of HPA $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, which is insoluble in water and has a large surface area (136 m^2 g^{-1}) resulted in good acid catalysis in the liquid phase [14]. The author first pointed out that HPA could be effectively immobilized in a silica matrix by means of the sol–gel technique to form 'silica-occluded' HPA [15]. This silica-occluded HPA has recently been studied and characterized in detail by Molnár et al. as a catalyst in ester hydrolysis, Friedel–Crafts adamantylation, and transalkylation, and in the synthesis of *tert*-butyl methyl ether [16]. Another attempt includes the encapsulation of HPA in a zeolite matrix by a ship-in-a-bottle technique [17,18]. Amongst these attempts, the immobilization of HPA in a silica matrix seems to be most convenient and reliable in practical application.

3.4.2 Preparation of Silica-occluded Heteropolyacid

A standard preparative method for silica-occluded 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) with good reproducibility is shown in Figure 1 [15c]. High silica contents (> 80% *w/w*) are required to make the silica network dense, because the heteropoly anions with a molecular size of 1 nm must be effectively caged. Using this method, $H_3PW_{12}O_{40}$ is completely immobilized in the silica matrix, and no leakage of $H_3PW_{12}O_{40}$ is observed during extraction with hot water, as is shown in Figure 1. In addition, because tetraethyl orthosilicate charged for inclusion is totally hydrolyzed, silica-occluded $H_3PW_{12}O_{40}$ composite is obtained quantitatively. In the formulation of Figure 1 the occluded $H_3PW_{12}O_{40}$ content of the silica matrix is 11 % (*w/w*). A Langmuir-type nitrogen adsorption isotherm is observed for this composite. The silica-occluded $H_3PW_{12}O_{40}$ is a microporous material with a surface area of 554 m^2 g^{-1} and a pore volume of 0.2 mL g^{-1} (Figure 2).

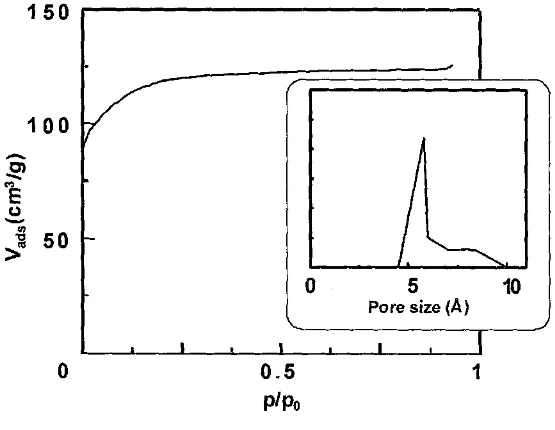


Figure 2. Nitrogen adsorption isotherm and pore-size distribution of silica-occluded $H_3PW_{12}O_{40}$.

3.4.3 Liquid-phase Organic Reactions over Silica-occluded $H_3PW_{12}O_{40}$

Silica-occluded $H_3PW_{12}O_{40}$ can be used as an insoluble solid-acid catalyst in several liquid-phase reactions such as ester hydrolysis [15c], esterification [15d], hydration [15d], alkylation of phenol [15d] in polar media, and Friedel–Crafts type alkylation and transalkylation [16] in non-polar media.

3.4.3.1 Hydrolysis of Ethyl Acetate

Table 1 summarizes the catalytic activity of silica-occluded $H_3PW_{12}O_{40}$ in the hydrolysis of ethyl acetate with excess water, in comparison with the activity of an ion-exchange resin, Amberlyst 15, and H-ZSM-5 [15d]. In terms of the activity per unit weight of solid acid, Amberlyst-15 is the most active catalyst because the amount of acid is very large. H-ZSM-5 is quite inactive under the reaction conditions shown in Table 1. With regard to turnover frequency based on the total amount of acid, i.e. the activity per unit acid site, silica-occluded $H_3PW_{12}O_{40}$ has much higher activity than the resin catalyst. This suggests that silica-occluded $H_3PW_{12}O_{40}$ acts as a very strong solid acid in water. The silica-occluded $H_3PW_{12}O_{40}$ can be easily recovered from the reaction medium by simple filtration, and can also be used repeatedly without deactivation.

Interestingly, the silica-occluded $H_3PW_{12}O_{40}$ is much more active in the hydrolysis reaction than homogeneous aqueous $H_3PW_{12}O_{40}$, when the $H_3PW_{12}O_{40}$ content is the same for both catalyst systems. In this hydrolysis reaction the $H_3PW_{12}O_{40}$ caged in the silica network possibly exists as highly concentrated aqueous droplets in silica matrix, and its effective concentration might be much higher than in the homogeneous system. In reactions catalyzed by HPA the reaction rate generally depends not only on the proton concentration but also on the concentration of heteropoly anion. The order of the reaction is, therefore, more than unity with regard to the concentration of HPA [1,4]. Consequently, $H_3PW_{12}O_{40}$ present as highly concentrated aqueous droplets in a silica matrix is more active than aqueous $H_3PW_{12}O_{40}$.

Table 1. Hydrolysis of ethyl acetate over solid acids[a].

Solid acid	Activity[b]	TOF[c]	Amount of acid (meq g^{-1})
$H_3PW_{12}O_{40}$ (as solution)	1.7	1.7	1.0
$H_3PW_{12}O_{40}$ in SiO_2[d]	0.49	4.9	0.1
Amberlyst-15	4.7	1.0	4.9
H-ZSM-5[e]	–	–	0.23

[a] H_2O, 9.5 g; AcOEt, 0.5 g; catalyst, 0.1 g; 60 °C.
[b] Specific rate (10^{-2} min^{-1} g^{-1}).
[c] Turnover frequency/10^{-2} mmol meq^{-1} min^{-1} (based on the total amount of acid).
[d] Silica-occluded $H_3PW_{12}O_{40}$ (1.0 g, $H_3PW_{12}O_{40}$ content 11 % *w/w*).
[e] Si/Al ratio 70.

$H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, and $H_3PW_6Mo_6O_{40}$ cannot effectively be occluded in a silica matrix because these acids are leached from the silica network in the course of the occlusion process. Titania and zirconia were both unsuitable as matrices for occlusion of HPA.

3.4.3.2 Hydration of Isobutene

Liquid-phase hydration of alkenes has an advantage over vapor-phase hydration because equilibrium conversion of alkene is much higher. Indeed, several homogeneous liquid-phase hydration processes have been commercialized since 1972. These include the manufacture of 2-propanol [7], *t*-butyl alcohol [8], and 2-butanol [9] by use of heteropolyacid catalysts. A high-silica ZSM-type zeolite has recently been introduced as an industrial catalyst for the heterogeneous liquid-phase hydration of cyclohexene [19]. A sulfonated resin catalyst is applied for the hydration of propene and isobutene.

The hydration activity of silica-occluded $H_3PW_{12}O_{40}$ is shown in Table 2, and compared with that for homogeneous $H_3PW_{12}O_{40}$ and Amberlyst-15 [15d]. Because the kinetic data were approximately arranged by a zero-order reaction equation, the hydration activity is expressed in terms of the specific rate per unit acid amount of catalyst. Silica-occluded $H_3PW_{12}O_{40}$ is more active for the hydration than Amberlyst-15. The higher catalytic activity of silica-occluded $H_3PW_{12}O_{40}$ than homogeneous $H_3PW_{12}O_{40}$ has also been observed for the above described hydrolysis of ethyl acetate.

Table 2. Liquid-phase hydration of isobutene[a].

Catalyst (g)	*t*-BuOH yield (%)	Specific rate[b]
$H_3PW_{12}O_{40}$ in SiO_2 (1.0)[c]	0.21	1.1
$H_3PW_{12}O_{40}$ (0.5) (as solution)	0.20	0.21
Amberlyst-15 (1.0)	2.53	0.27

[a] 80 °C, 1 atm, 5 h, i-C_4H_8 flow rate 20 mL min^{-1}; H_2O, 9.0 g; 1,4-dioxane, 9.0 g.
[b] Specific rate per unit acid amount of catalyst (mol L^{-1} h^{-1} $(meqH^+)^{-1}$).
[c] Silica-occluded $H_3PW_{12}O_{40}$.

3.4.3.3 Alkylation of Phenol

Silica-occluded $H_3PW_{12}O_{40}$ is a microporous material with a relatively sharp pore-size distribution with a peak at 0.55 nm (Figure 2). This microporous property seems to be favorable for molecular shape-selective reactions. Indeed, silica-occluded $H_3PW_{12}O_{40}$ acts as a shape-selective solid-acid catalyst in the solvent-free alkylation of phenol with formaldehyde (Scheme 1).

Table 3. Alkylation of phenol with trioxane catalyzed by solid acids.

Catalyst	PhOH conversion (%)	Dihydroxydiphenylmethane selectivity (%)		
		4,4′-	2,4′-	2,2′-
$H_3PW_{12}O_{40}$–SiO_2[a]	26	48	39	13
HY (2.8)[b]	18	27	47	26
HUSY (7.0)[c]	38.6	34	45	21
H-Mor (10.1)	10.5	47	39	14
H-ZSM-5 (70)	11.7	50	38	12
SiO_2–Al_2O_3 (4.6)	8.9	11	58	31

[a] Silica-included $H_3PW_{12}O_{40}$.
[b] Numerical in the parenthesis denotes the molecular ratio of Si/Al.
[c] Dealuminated Y zeolite.

Table 3 lists the catalytic activity of silica-occluded $H_3PW_{12}O_{40}$ and of various types of acidic zeolites in the liquid-phase alkylation of phenol with trioxane. Proton-type Y zeolite (HY) and ultra stable Y zeolite (HUSY) with large pore sizes, and amorphous silica–alumina, gave relatively large amounts of the thermodynamically most stable 2,4′- and 2,2′-dihydroxydiphenylmethane isomers. On the other hand, proton-type mordenite (H-Mor) and H-ZSM-5 with smaller pore-sizes yielded larger amounts of the slimmest 4,4′-dihydroxydiphenylmethane isomer. Silica-occluded $H_3PW_{12}O_{40}$ afforded selectivity comparable with that of the 4,4′ isomer, but conversion of phenol was higher than for the shape-selective zeolite catalysts.

References

[1] Y. Izumi and M. Otake, *Kagaku Sosetsu* (Japanese), No. 34, **1982**, p. 116.
[2] I. V. Kozhevnikov, K. I. Matveev, *Appl. Catal.*, **1983**, *5*, 135.
[3] M. Misono, *Catal. Rev.*, **1987**, *29*, 269.
[4] Y. Izumi, K. Urabe, M. Onaka, 'Zeolite, Clay, and Heteropoly Acid in Organic Reactions', Kodansha–VCH, **1992**.
[5] T. Okuhara, N. Mizuno, M. Misono, *Adv. Catal.*, **1996**, *41*, 113.
[6] Y. Mizutani and Y. Izumi, *Yuki Gosei Kagaku Kyokai Shi* (Japanese), **1977**, *35*, 761.
[7] Tokuyama Soda, Japanese Patent 49-739405 (1974), US 3,758,615 (1973).
[8] A. Aoshima, S. Yamamatsu, and T. Yamaguchi, *Nippon Kagaku Kaishi* (Japanese), **1987**, 976.
[9] T. Yamada, *Petrotech* (Japanese), **1990**, *13*, 627.
[10] N. Shimizu, M. Ueshima, and M. Wada, *Shokubai* (Japanese), **1988**, *3*, 555.
[11] A. Aoshima, S. Tonomura, and S. Yamamatsu, *Polymers for Advanced Technologies*, **1990**, *2*, 127.
[12] K. Sano, T. Suzuki, H. Uchida, *Shokubai* (in Japanese), **1999**, *41*, 86.
[13] Y. Izumi, K. Urabe, *Chem. Lett.*, **1981**, 663.
[14] T. Okuhara, T. Nishimura, K. Ohashi, M. Misono, *Chem. Lett.*, **1990**, 1201.
[15] (a) Y. Izumi, M. Ono, M. Ogawa, K. Urabe, *Chem. Lett.*, **1993**, 825; (b) Y. Izumi, M. Ono, M. Kitagawa, M. Yoshida, and K. Urabe, *Microporous Mater.*, **1995**, *5*, 255; (c) Y. Izumi, *Res. Chem. Intermed.*, **1998**, *24*, 461; (d) Y. Izumi, K. Hisano, T. Hida, *Appl. Catal. A: General*, **1999**, *181*, 277.

[16] Á. Molnár, C. Keresszegi, B. Török, *Appl. Catal. A: General*, **1999**, in press.
[17] B. Sulikowski, J. Haber, A. Kubacka, K. Pamin, Z. Olejniczak, J. Ptaszynski, *Catal. Lett.*, **1996**, *39*, 27.
[18] S. Mukai, T. Masuda, I. Ogino, K. Hashimoto, *Appl. Catal.*, *A*, **1997**, *165*, 219.
[19] H. Ishida, *Catal. Surveys of Japan*, **1997**, *1*, 241.

3.5 Hybrid Sulfonated Mesoporous Systems

W. Van Rhijn, D. De Vos, P. A. Jacobs

Application of a solid material in a specific acid-catalyzed reaction entails well-defined requirements of mechanical and thermal stability, and, in view of strict environmental legislation, of catalyst recovery and re-use. This section discusses modification of the surface of inorganic solids with organic sulfonic acid groups. Combining properties of organic and inorganic compounds into hybrid materials is a well-considered approach to optimization of the number, dispersion, accessibility, and strength of acid sites in solid catalysts [1,2]. To prevent leaching of weakly bound physisorbed active sites, covalent attachment of sulfonic acids to the matrix is the preferred option [3].

3.5.1 Amorphous Solid Sulfonic Acids

3.5.1.1 Organic Resin–Silica Composites

Although sulfonated macroreticular styrene–divinylbenzene copolymers, e. g. Amberlyst®, Dowex® or Lewatit®, are widely used in acid-catalyzed continuous liquid-phase reactions (e. g. MTBE, TAME, bisphenol A synthesis), only a fraction of the active sites participates in the reaction and above 130 °C, these materials lose sulfonic acid groups. The mechanical stability of the matrix is, moreover, often insufficient [4].

To overcome such limitations, Imura et al. covered the surface of a silica gel with sulfonated cross-linked polystyrene [5]. After adsorption of styrene, divinylbenzene, and *t*-butyl peroxide and subsequent free-radical polymerization, the acid groups are introduced via classical sulfonation. Control of the thickness of the crosslinked polymer layer on the surface is essential to prevent pore clogging. This sulfonated polystyrene–SiO_2 hybrid material preserves a large specific surface area, with a typical ion-exchange capacity of 1.8 meq g^{-1}. Alternatively, a sulfonated layer can be deposited on silica by copolymerization of silica-supported methacrylate and potassium *p*-styrene sulfonate [6].

In an analogous approach, a supported polyphenyl ketone is formed by adsorption and acid-catalyzed condensation of a mixture of phthalic acid and phthalic anhydride on an amorphous aluminosilicate. Via sulfonation up to 0.8 meq SO_3H groups can be introduced per g. Although polysulfophenyl ketone as such has a very limited surface area (1–3 m^2 g^{-1}), the SiO_2–Al_2O_3 supported version has a much larger specific surface, coupled with high thermal and chemical stability. These supported sulfophenyl ketones can be used for isobutene oligomerization, MTBE synthesis, butene isomerization, and esterifications [7].

In a recent approach, poly(styrene-*co*-styrylethyltrimethoxysilane) [P(ST-STMS)] and TEOS were processed into an organopolymer–polysiloxane (Figure 1a). P(ST–STMS) was obtained in a radical polymerization of styrylethyltrimethoxysilane and styrene. After sulfonation, the composite material has an ion exchange capacity of 0.3–1.3 meq g^{-1} [8].

In contrast with conventional acid resins, sulfonated perfluorocarbon-based Nafion® polymers can withstand temperatures up to 200 °C and have superacid sites. Nafion beads, however, have an extremely low surface area (< 0.02 m^2 g^{-1}) [9]. To increase the accessibility of the sites, Nafion was encapsulated in a highly porous silica network by use of a sol–gel process [9,10]. Starting from a Nafion solution and soluble silicon sources, a 13 % (*w*/*w*) Nafion porous composite was prepared with a 344 m^2 g^{-1} BET surface area, a 0.85 cm^3 g^{-1} pore volume, a 9.8 nm mean pore diameter, and a CEC of 0.14 meq g^{-1} [9]. The composite has significantly better activity than Nafion NR 50 for reactions in the gas phase or in apolar, non-swelling solvents. Reported examples include the dimerization of α-methylstyrene, the isomerization of 1-butene and the propylation, acylation, or nitration of aromatic compounds [9–11].

3.5.1.2 Modification of Silica via Si–C Bonds

A widespread technique for anchoring functional entities to a hydroxyl-covered surface is grafting with an organosilane such as $RSiCl_3$ or $RSi(OR')_3$ [2,12,13]. The covalent bond with the support is formed by condensation of the chloro or alkoxy groups with the surface silanols. A broad range of organosilanes is commercially available, e. g. with R = 3-mercaptopropyl or 2-phenylethyl. Generally, grafting on silica results in relatively low loadings (ca. 0.5 meq g^{-1}). After silylation, physisorbed material must be removed thoroughly by washing [12].

Aromatic trichlorosilanes such as phenyl- or benzyltrichlorosilane have been used by Unger for grafting on silica and subsequent sulfonation with chlorosulfonic acid (Figure 1b) [14]. The Si–C(benzyl) bonds are stable toward the sulfonation, whereas Si–C(phenyl) bonds are much more prone to heterolytic cleavage. Alternative aromatic Si compounds are (4-phenylbutyl)chlorodimethylsilane and 2-phenylethyltrichlorosilane [14].

Aliphatic sulfonic acids can be prepared from immobilized thiols. Suitable starting compounds are alkylchlorosilanes [15], haloalkylsilanes [16], 3-mercaptopropylmethyldimethoxysilane [17], dimethoxymethylsilyl-3-propylisothiouronium chloride, or 3-mercaptopropyltriethoxysilane [18]. The intermediate $SiO_2–(CH_2)_n–SH$ materials ($n \geq 3$) are further oxidized with H_2O_2/CH_3COOH or 20 % HNO_3. This oxidation step can result in some splitting of the Si–C bond, limiting the maximum loading to 0.5 meq g^{-1}. Sulfonic acid groups can also be bound to a siliceous support by reacting γ-glycidoxypropyl silica with Na_2SO_3 [19].

A unique approach for attaching acids to an inorganic matrix is the synthesis of a linear ladder polyphenylsilsesquioxane with subsequent grafting to an inorganic matrix and sulfonation (Figure 1c). In the esterification of acetic acid with isopropanol, the apparent rate constant is higher for the grafted sulfonated polyphenylsilsesquioxane than for Amberlyst-15 [6].

Perfluorosulfonic acids were covalently attached to a silica matrix by use of $(EtO)_3Si(CH_2)_3(CF_2)_2O(CF_2)_2SO_3H$ (Figure 1d). Alternatively, the same perfluorosulfonatotriethoxysilane was employed in a sol–gel process. Despite the low acid site density (0.2 meq g^{-1}), the activity of $SiO_2–(CH_2)_3(CF_2)_2O(CF_2)_2SO_3H$

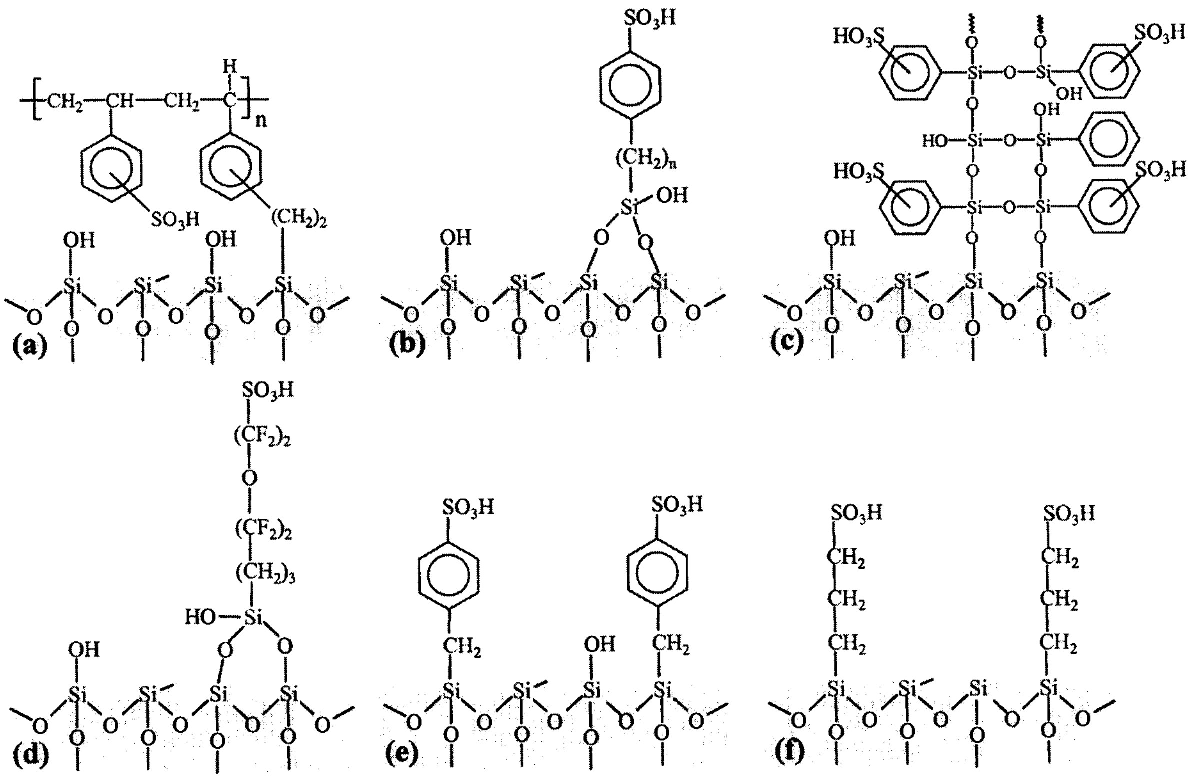


Figure 1. Sulfonated amorphous solids: (a) sulfonated polystyrene–silica hybrid prepared via the sol–gel technique. SiO_2-grafted groups: (b) alkylphenylsulfonic acid; (c) sulfonated polyphenylsilsesquioxane; (d) perfluorosulfonic acid; (e) benzylsulfonic acids attached to a chlorinated silica; (f) sulfonated polysiloxane.

in the isomerization of 1-butene and in the alkylation of toluene with 1-heptene is orders of magnitude higher than that of classical resins [20].

In a less frequently used technique, a silica surface is first chlorinated with, for instance, thionyl chloride. Next the Cl is displaced by a strong nucleophile such as benzyl- [21] or phenyllithium [22] (Figure 1e). Thus a new Si–C bond is formed containing an Si atom that initially was part of the silica support. This approach precludes the formation of surface-bound Si oligomers [12]. Eventual sulfonation of the aromatic rings leads to a useful catalyst.

3.5.1.3 Sol–Gel Preparation

Because the grafting techniques described in Section 3.5.1.2 lead to rather low loading, it is of interest to incorporate functional groups directly and in large amounts into a material via a sol–gel process. Open and patent literature report colloidal silicas [23], aerogels [24] and xerogels [14] with 3-mercaptopropyl, 2-phenylethyl, or benzyl functional groups. These materials are valuable precursors to sulfonated polysiloxanes (Section 3.3).

Poly(sulfophenyl)siloxane (2.0 meq g^{-1}), poly(sulfobenzyl)siloxane, poly(sulfophenylethyl)siloxane, and poly(sulfopropyl)siloxane (0.8 meq g^{-1}) were prepared by Ono et al [25]. Documented applications of these sulfonated polyorganosiloxanes include the dehydration of alcohols, the esterification of isobutanol with acetic acid and the vapor-phase nitration of benzene.

Polysiloxanes with alkylsulfonic acid groups have been marketed under the trade name Deloxan® (Figure 1f). The commercial Deloxan ASP catalyst is a macroporous polysiloxane with 0.7–1.1 meq g^{-1} active groups, with a pore size between 30 and 200 nm, a specific surface area of ca 400–600 m^2 g^{-1} and 1.5–2.0 mL g^{-1} pore volume. The catalyst has been tested, e. g. in the esterification of free tallow fatty acids, in the synthesis of dioctyl phthalates, and in the propylation of mesitylene and anisole [26]. In the patent literature Panster and Kleinschmit also describe the synthesis of a phenylenesulfonate containing organopolysiloxane (2.2–3.2 meq g^{-1}) [27].

3.5.2 Ordered Sulfonic Acid Catalysts

The M41S group of mesoporous materials comprises lamellar MCM-50, cubic MCM-48 and the familiar hexagonal MCM-41 structures [28,29]. MCM-41 has a honeycomb-like structure of hexagonally packed cylindrical pores (1.5–10 nm diameter). H-Al-MCM-41 has been prepared by hydrothermal synthesis and H^+ exchange but, because of the amorphous atomic ordering, the catalytic properties are rather reminiscent of a mildly acid amorphous SiO_2–Al_2O_3 than of a strongly acid zeolite [29]. Preparation of sulfonated ordered mesoporous silicas leads to materials with a high surface area, a narrow pore size distribution, excellent site accessibility, high loading, and high acid strength [30,31].

3.5.2.1 Immobilization of Sulfonic Acids via Grafting and Coating

By analogy with the amorphous supports, preformed MCM-41 can be functionalized by reaction of surface silanols or siloxanes with silylating agents such as 3-mercaptopropyltrimethoxysilane. After oxidation of the thiols with H_2O_2, a solid sulfonic acid is obtained [30,32]. Because of the high surface area (up to 1000 m^2 g^{-1}) and the ordered pore structure, organosiloxane loadings tend to be significantly higher for MCM-41 materials than for amorphous silicas [12].

Starting from a vacuum-dried support, individual functional groups can be grafted' onto the support in water-free conditions, for instance in toluene under reflux (Figure 2) [30]. Grafting leads to moderate loadings (0.8–1.5 meq g^{-1}) [12,30,32]. Solid-state ^{29}Si NMR shows the material to contain functional groups attached to the surface by a single bond only (Figure 3a; T^1 = $[HS(CH_2)_3Si(OSi)(OH)_2]$). Hence leaching of active groups must be carefully monitored.

If a well-controlled amount of water is present on the material, its surface can be 'coated' with a crosslinked monolayer of mercaptopropyl-Si groups (Figure 2). This coating technique uses a Dean–Stark trap to distil part of the water from a hydrated MCM-41, dispersed in toluene. NMR indicates that the surface layer consists of well-embedded T^2 and T^3 species (Figure 3b). The –SH site density can be controlled by the degree of hydration of the surface. Depending on the pore size, the maximum coverage with thiol groups increases from 2.4 meq g^{-1}

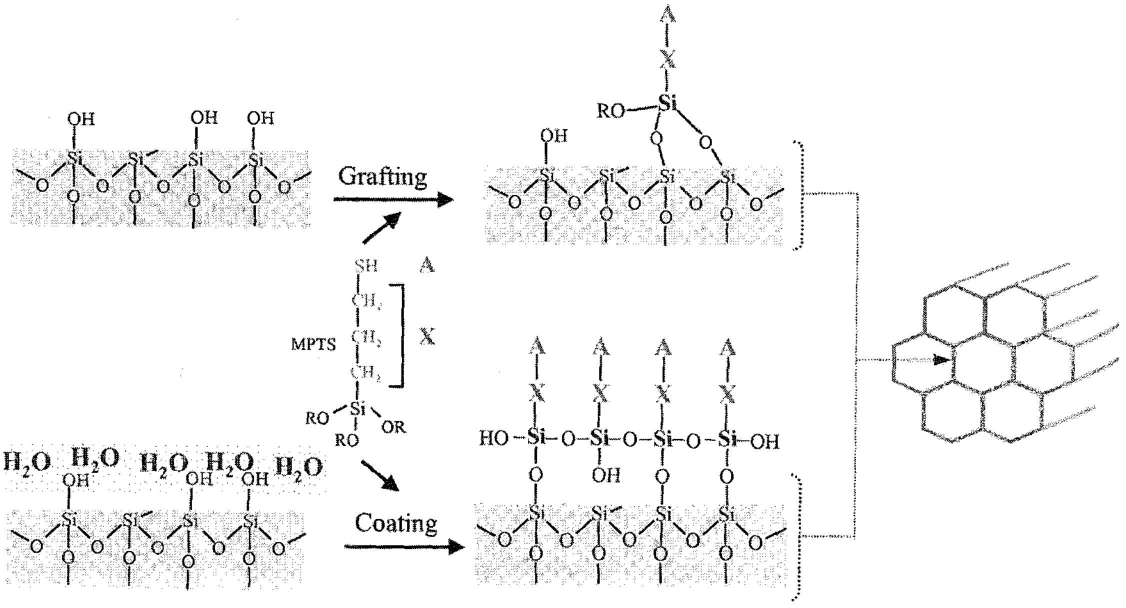


Figure 2. Grafting and coating of a mesoporous ordered SiO_2 with mercaptopropyl groups (R = Me, Et).

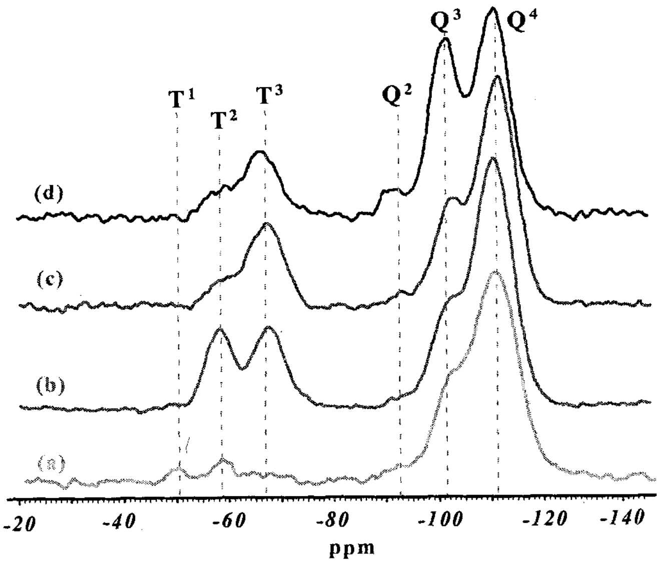


Figure 3. ^{29}Si MAS NMR of (a) grafted MCM–$(CH_2)_3$–SH, (b) coated MCM–$(CH_2)_3$–SH, (c) co-condensed HMS–$(CH_2)_3$–SH, and (d) co-condensed MCM–$(CH_2)_3$–SH.

for a medium pore size MCM-41 (2.9 nm pore diameter) through 3.6 meq g^{-1} for a 4 nm MCM-41, up to 5.2 meq g^{-1} for an average pore diameter of 5.5 nm [30,33]. Coating shifts the MCM-41 N_2 adsorption isotherm downward and to the left, implying a reduced pore volume, average pore diameter, and BET surface (Figure 4) [34].

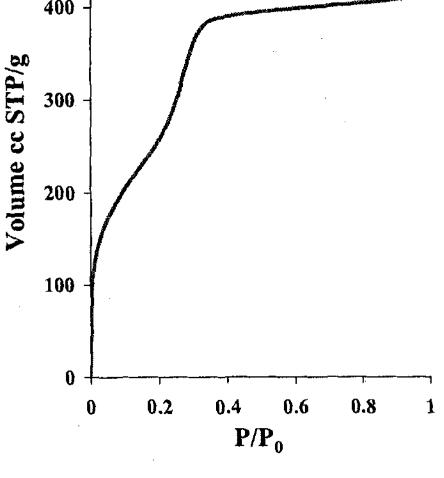


Figure 4. N_2 adsorption isotherm of co-condensed MCM–$(CH_2)_3$SH.

3.5.2.2 Sol–Gel Synthesis with Structure-directing Agents

If a sol containing $RSi(OR')_3$ and TEOS or TMOS is processed in the presence of a self-assembling surfactant, hybrid ordered mesoporous silicas can be obtained (Figure 5). For instance, hybrid MCM type materials with covalently linked phenyl or alkyl groups were prepared in a micellar cetyltrimethylammonium bromide solution [35]. Instead of the oligomeric or polymeric Si precursors of a typical MCM-41 synthesis, this preparation employs monomeric Si sources such as TEOS. In a similar approach, dodecylamine was used as the structure-directing agent to obtain HMS type materials with incorporated organic groups (HMS = hexagonal mesoporous silica) [36]. The synthesis of MCM- and HMS-type materials with incorporated mercaptopropyl groups was achieved by use of 3-mercaptopropyltriethoxysilane (MPTS) or its methoxy analog [30,31,37]. Even typical non-ionic surfactants such as Tergitol or Triton-X have been used to prepare such hybrid structures [38].

For such 'co-condensed' mercaptopropyl materials, the type of siloxane, the (co)solvent, the catalyst, and the molar composition of the gel affect the amount of thiol incorporation, the particle morphology, the pore size, and the long range order, as reflected in the X-ray pattern. The molar ratio of the Si precursors (TE(M)OS–MPTS) can be varied anywhere between 0/100 and 30/70, enabling loadings up to 3.2 meq g^{-1}. When the fraction of MPTS in the total Si surpasses 30 %, an ordered material is no longer obtained. Figure 3 shows that in materials resulting from co-condensation the R–Si groups ($T^2 < T^3$) are better incorporated in the walls than for silylated (T^1, T^2) or coated materials ($T^2 \leq T^3$). The type IV N_2 isotherm of a co-condensed thiol silicate is typical of an ordered mesoporous silica. However, microporous ordered thiol silicates with a pore diameter of 1.4 nm have been prepared via similar procedures [31], and these materials have a type I isotherm (Figure 4). In the sulfonic acid form, typical co-condensed materials have a high surface area (> 500 m^2 g^{-1}), a considerable pore volume (> 0.40 mL g^{-1}) and a narrow pore size distribution with pore diameters between 1.4 and 3 nm.

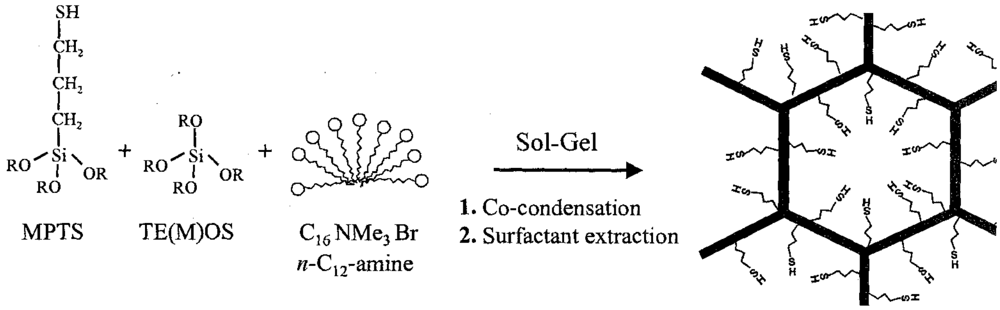


Figure 5. Co-condensation of mercaptopropylsiloxane and TEOS or TMOS in an ionic or non-ionic surfactant solution.

Finally, Davis and co-workers introduced 2-phenylethyl groups during the synthesis of zeolites Beta and Y to obtain a shape-selective strong acid catalyst. Organic groups on the external surface and intracrystalline templates were eliminated before sulfonation of the intrazeolitic phenyl groups. The physicochemical stability of such sulfonic zeolites is a major asset. However, the very low loading with ethylphenylsulfonic acid groups (0.13 meq g^{-1}) is a major drawback [39].

3.5.2.3 Organic Catalysis with Ordered Solid Sulfonic Acids

Mesoporous sulfonic acids are of particular interest for reactions involving molecules that are too large to access the smaller pores of conventional molecular sieves or for the preparation of bulky reaction products. In the hydroxyalkylation of methylfuran with acetone, the ordered mesoporous sulfonic acids surpass large pore zeolites such as H-Beta, with an excellent yield of 82 % for 2,2-bis(5-methylfuryl)propane instead of 45 % for H-Beta [30]. The activity of the sulfonic MCMs is also clearly superior to that of zeolites Beta and Y in the D-sorbitol dehydration–esterification forming isosorbide dilaurate, or in the liquid biphasic preparation of monoesters starting from various polyols and fatty acids [30]. The catalyst of Stein and co-workers was highly active and selective in the tetrahydropyranylation of ethanol with 2,3-dihydropyran [31]. In this type of reaction also the non-modified H-MCM-41 material is an excellent catalyst [40].

References

[1] (a) Judenstein, P; Sanchez, C Hybrid organic–inorganic materials: a land of multidisciplinarity. *J. Mater. Chem.* **1996**, 6, 511–525 (b) Schubert, U; Hüsing, N; Lorenz, A Hybrid inorganic–organic materials by sol–gel processing of organofunctional metal alkoxides. *Chem. Mater.* **1995**, 7, 2010–2027.

[2] Moller, K; Bein, T Inclusion chemistry in periodic mesoporous hosts. *Chem. Mater.* **1998**, 10, 2950–2963.

[3] Clark, JH; Macquarrie, D Environmentally friendly catalytic methods. *Chem. Soc. Rev.* **1996**, 303–310.

[4] Chakrabarti, A; Sharma, M Cationic ion exchange resins as catalysts. *React. Polym.* **1993**, 20, 1–45.

[5] Imura, S; Fukano, K Solid support for liquid chromatography. US 4 140 653, **1979**; JP 0 117 276, **1975**.

[6] Carlier, E; Revillon, A; Guyot, A; Baumgartner, P Functional silica supported polymers IV. Synthesis and catalytic activity of silica-grafted sulfonated polyphenylsilsesquioxane. *React. Polym.* **1993**, 21, 15–25.

[7] Jarecka, T; Datka, J Acid and catalytic properties of new thermostable sulfocationic exchangers supported on aluminosilicates. *Appl. Catal. A* **1999**, 184, 203–209.

[8] Wei, Y; Wang, W; Jin, D; Tartakovskaya, L Synthesis of sulfonated polystyrene–silica hybrids and their applications as ion-exchange material. *J. Appl. Polym. Sci.* **1997**, 64, 10, 1893–1902.

[9] Harmer, MA; Farneth, WE; Sun, Q High surface area Nafion resin/silica nanocomposites: a new class of solid-acid catalysts. *J. Am. Chem. Soc.* **1996**, 118, 7708–7715.

[10] Harmer, MA; Farneth, WE; Sun, Q Towards the sulfuric acid of solids. *Adv. Mater.* **1998**, 10, 1255–1257.

[11] (a) Sun, Q; Farneth, WE; Harmer, MA Dimerization of α-methylstyrene (AMS) catalyzed by sulfonic acid resins: a quantitative kinetic study. *J. Catal.* **1996**, 164, 62–69. (b) Sun, Q; Harmer, MA, Farneth, WE But-1-ene isomerization over NafionR resin/silica composite catalyst. *Chem. Commun.* **1996**, 1201–1202.

[12] Clark, JH; Macquarrie, D Catalysis of liquid phase organic reactions using chemically modified mesoporous inorganic solids. *Chem. Commun.* **1998**, 853–860.

[13] Van der Voort, P; Vansant, EF Silylation of the silica surface: a review. *J. Liq. Chrom. Rel. Techn.* **1996**, 19, 2723–2752.

[14] Unger, KK Porous silica: its properties and use as support in column liquid chromatography. *Journal of Chromatography library*, 16, Amsterdam: Elsevier, **1979** and references therein.

[15] Sebastian, I; Istvan, H Process for the chemical modification of surfaces of inorganic solids. US3956179, **1976**; GB1460315, **1975**; DE2313073, **1973**.

[16] Weigard, N; Sebastian, I; Halasz, I Neuartige Kationenaustauscher auf Kieselgelbasis I. Darstellung und Eigenschaften. *J. Chromatogr.* **1974**, 102, 325–332.

[17] Sebastian, I Method of chemically modifying the surface of solids. GB1506226, **1978**.

[18] Carlier, E; Guyot, A; Revillon, A; Llauro, Darricades, MF; Petiaud, R Functional polymers supported on porous silica 1. Grafting active precursors onto porous silica. *React. Polym.* **1991/1992**, 16, 41–49.

[19] (a) Chang, SH; Gooding, KM; Regnier, FE Use of oxiranes in the preparation of bonded phase supports. *J. Chromatogr.* **1976**, 120, 321–333. (b) Roy, AK; Burgum, A; Sujata, R Preparation of ion-exchange resin and effect of pH on protein binding of ion-exchange silica. *J. Chromatogr. Sci.* **1984**, 22, 84–86.

[20] Harmer, MA; Sun, Q; Michalczyk, MJ; Yang, Z Unique silane modified perfluorosulfonic acids as versatile reagents for new solid-acid catalysts. *Chem. Commun.* **1997**, 1803–1804.

[21] (a) Locke, DC; Schermund, JT; Banner, B Bonded stationary phases for chromatography. *Anal. Chem.* **1972**, 44, 90–92. (b) Saunders, DH; Barford, RA; Magidman, P; Olszewski, LT; Rothbart, HL Preparation and properties of a sulfobenzylsilica cation exchanger for liquid chromatography. *Anal. Chem.* **1974**, 46, 834–838. (c) Saunders, DH, Barford, RA; Magidman, P; Rothbart, HI Preparation and use of stable, bound stationary phases US 3,987,058, **1976**.

[22] Unger, K; Thomas, W; Adrian, P Herstellung oberflächenmodifizierter Adsorbentien III. Arylierung von Siliciumdioxidoberflächen durch Reaktion mit Organolithiumverbindungen. *Kolloid-Z. u. Z. Polymere* **1973**, 251, 45–52.

[23] Espiard, P; Guyot, A; Mark, J Surface functionalized colloidal silica particles from an inverse microemulsion sol gel process. *J. inorganic and organometallic polymers* **1995**, 5, 391–407.

[24] (a) Hüsing, N; Schubert, U Organofunctional silica aerogels. *Journal of the Sol–Gel Sciences and Technologies* **1997**, 8, 807–812. (b) Hüsing, N; Schubert, U Aerogels–airy materials: chemistry, structure, and properties. *Angew. Chem. Int. Ed.* **1998**, 37, 22–45.

[25] (a) Suzuki, S; Ono, Y; Nataka, S; Asaoka, S Structures and thermal and hydrothermal stabilities of sulfonated poly(organosiloxanes) by ^{29}Si and ^{13}C CP MAS NMR. *J. Phys. Chem.* **1987**, 91, 1659–1663. (b) Ono, Y; Suzuki, S in Acid–base Catalysis, Proceedings of the Int. Symp. on Acid–Base Catalysis **1988**, 379–396. (c) Suzuki, S; Tohmori, K; Ono, Y Vapor-phase nitration of benzene over polyorganosiloxanes bearing sulfo groups. *Chem. Lett.* **1986**, 747–750.

[26] (a) Wieland, S; Panster, P Replacing liquid acids in fine chemicals synthesis by sulfonated polysiloxanes as solid acids and as a support for precious metal catalysts. *Stud. Surf. Sci. Catal.* **1997**, 108, 67–74. (b) Deschler, U; Kleinschmit, P; Panster, P 3-chlorpropyltrialkoxysilane-Schlüsselbausteine für die industrielle Herstellung organofunktionalisierter Silane und Polysiloxane sowie moderner Verbundmaterialien. *Angew. Chem.* **1986**, 98, 237–253. (c) Wieland, S; Panster, P Process for the preparation of esters of carboxylic acids and therefore useful catalysts. EP 0113719, **1997**. (d) Hitzler, MG; Smail, FR; Ross, S; Poliakoff, M Friedel–Crafts alkylation in supercritical fluids: continuous, selective and clean. *Chem. Commun.* **1998,** 359–360.

[27] Panster, P; Kleinschmit, P Phenylenesulfonate group-containing organopolysiloxanes, method for their preparation and use. US 4 647 644, **1987**.

[28] (a) Kresge, CT; Leonowicz, ME; Roth, WJ; Vartuli, JC; Beck, JS Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature* **1992**, 359, 710–712. (b) Beck, JS; Vartuli, JC; Roth, WJ; Leonowicz, ME; Kresge, CT; Schmitt, KD; Chu, CT; Olson, DH; Sheppard, EW; McCullen, SB; Higgins, JB; Schlenker, JL A new family of mesoporous molecular sieves prepared with liquid crystal templates. *J. Am. Chem. Soc.* **1992**, 114, 10834–10843.

[29] (a) Corma, A From microporous to mesoporous molecular sieve materials and their use in catalysis. *Chem. Rev.* **1997**, 97, 2373–2419. (b) Corma, A Preparation and catalytic properties of new mesoporous materials. *Top. Catal.* **1997**, 4, 249–260. (c) Beck, JS; Vartuli, JC Recent advances in the synthesis, characterization and applications of mesoporous molecular sieves. *Current opinion in solid state & Material Science* **1996**, 1, 79–87. (d) Raman, NK; Anderson, MT; Brinker, CJ Template-based approaches to the preparation of amorphous, nanoporous silicas. *Chem. Mater.* **1996**, 8, 1682–1701. (e) Ciesla, U; Schüth, F Ordered mesoporous materials *Microporous mesoporous materials* **1999**, 27, 131–149.

[30] (a) Van Rhijn, WM; DeVos, DE; Sels, BF; Bossaert, WD; Jacobs, PA Sulfonic acid functionalized ordered mesoporous materials as catalysts for condensation and esterification reactions. *Chem. Commun.* **1998**, 317–318. (b) Van Rhijn, W; De Vos, D; Bossaert, W; Bullen, J; Wouters, B; Grobet, P; Jacobs, PA Sulfonic acid bearing mesoporous materials as catalysts in furan and polyol derivatization. *Stud. Surf. Sci. Catal.* **1998**, 117, 183–190.

[31] Lim, MH; Blanford, CF; Stein, A Synthesis of ordered microporous silicates with organosulfur surface groups and their applications as solid-acid catalysts. *Chem. Mater.* **1998**, 10, 467–470.

[32] (a) Mercier, L; Pinnavaia, TJ Access in mesoporous materials: Advantages of a uniform pore structure in the design of a heavy metal ion adsorbent for environmental remediation *Adv. Mater.* **1997**, 9, 500–503. (b) Mercier, L; Pinnavaia, TJ Heavy metal ion adsorbents formed by the grafting of a thiol functionality to mesoporous silica molecular sieves: Factors affecting Hg(II) uptake. *Environ. Sci. Technol.* **1998**, 32, 2749–2754.

[33] (a) Feng, X; Fryxell, GE; Wang, LQ; Kim, AY; Liu, J; Kemner, KM Functionalized monolayers on ordered mesoporous supports. *Science* **1997**, 276, 923–926. (b) Wei, Y; Jin, DL; Ding, TZ; Shih, WH; Liu, XH; Cheng, SZD; Fu, Q *Adv. Mater.* **1998**, 10, 161–165. (c) Liu, J; Feng, XD; Fryxell, GE; Wang, LQ; Kim, AY; Gong, M, Hybrid mesoporous materials with functionalized monolayers. *Chem. Eng. Tech.* **1998**, 21, 97–100.

[34] Bossaert, WD; De Vos, DE; Van Rhijn, WM; Bullen, J; Grobet, PJ; Jacobs, PA Mesoporous sulfonic acids as selective heterogeneous catalysts for the synthesis of monoglycerides. *J. Catal.* **1999**, 182, 156–164.

[35] Burkett, SL; Sims, SD; Mann, S Synthesis of hybrid inorganic–organic mesoporous silica by co-condensation of siloxane and organosiloxane precursors. *Chem. Commun.* **1996**, 1367–1368.

[36] Macquarrie, D Direct preparation of organically modified MCM-type materials. Preparation and characterization of aminopropyl-MCM and 2-cyanoethyl-MCM. *Chem. Commun.* **1996**, 1961–1962.

[37] Fowler, CE; Burkett, SL; Mann, S Synthesis and characterization of ordered organosilica–surfactant mesophases with functionalized MCM-41-type architecture. *Chem. Commun.* **1997**, 1769–1770.

[38] Richer, R; Mercier, L Direct synthesis of functionalized mesoporous silica by non-ionic alkylpolyethyleneoxide surfactant assembly. *Chem. Commun.* **1998**, 1775–1776.

[39] Jones, CW; Katsuyuki, T; Davis, ME Organo-functionalized molecular sieves as shape-selective catalysts. *Nature* **1998**, 393, 52–54.

[40] Kloetstra, R; van Bekkum, H Catalysis of the tetrahydropyranylation of alcohols and phenols by the H-MCM-41 mesoporous molecular sieve. *J. Chem. Research (S)* **1995**, 26–27.

3.6 The Use of Nafion and Nafion–Silica Composites in Solid Acid Catalysis

A. E. W. Beers, T. A. Nijhuis, F. Kapteijn

3.6.1 Introduction

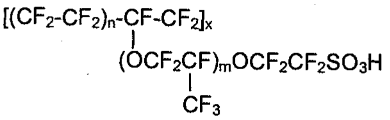
In acid catalysis there is much interest in replacing conventional, homogeneous catalysts, e. g. corrosive metal chlorides and mineral acids, by solid catalysts. This results in an easy separation from the reaction mixture and after regeneration the solids can be reused. In this way the corrosive and environmentally unfriendly waste streams will be drastically reduced. For this application many solid acids are under investigation, especially the ion-exchange polymer resins, of which Nafion is the material with the highest Brønsted acidity [1–5].

Nafion and related polymers were initially developed by DuPont for commercial application as membranes in electrochemical processes. This is mainly because these materials are relatively inert towards corrosive environments and have high permselectivity, which allows cations to diffuse faster through the membranes than anions [1].

3.6.2 The Ion-exchange Resin Nafion

The Nafion resin is a perfluorinated ion-exchange polymer. The backbone structure is similar to Teflon, with pendant sulfonic acid groups [6]. The structure of Nafion is shown in Figure 1, in which $m = 1, 2,$ or 3 and n has a value of ca 6–7 with x ca 1000 [7,8]; this results in an equivalent mass of 1200 g mol^{-1} (0.8 meq H^+ g^{-1}).

The ionic groups ($-SO_3H$) form clusters in the chemically stable Teflon-like matrix ($-CF_2CF_2-$) [6]. These hydrophilic domains form micelles, surrounded by the hydrophobic fluorocarbon backbone and connected by small channels. The Nafion resin is prepared as a copolymer of tetrafluoroethylene and perfluoro-2-(fluorosulfonylethoxy)propyl vinyl ether [1,7]. Unlike other resinsulfonic acids, e. g. sulfonated polystyrenes (Dowex-50, Amberlyst-15, Amberlite IR-112, etc.), Nafion and related perfluoroalkanesulfonic acids are stable in corrosive environments and the maximum operating temperature is up to 473K [8].



$$\begin{array}{l} [(CF_2\text{-}CF_2)_n\text{-}CF\text{-}CF_2]_x \\ \qquad\qquad\quad | \\ \qquad\quad (OCF_2CF)_mOCF_2CF_2SO_3H \\ \qquad\qquad\qquad | \\ \qquad\qquad\quad CF_3 \end{array}$$

Figure 1. The general structure of Nafion.

Nafion is commercially available as Nafion NR50 (DuPont) in the form of relatively large (2–3 mm) beads. A disadvantage of these beads is the low surface area (typically $\leq$ 0.02 m^2 g^{-1}) [8]. Water-selective Perma Pure membranes also consist of the polymer Nafion and were especially developed for removal of water from gas-phase streams [9]. Nafion is also available as a 5 % solution in a mixture of lower aliphatic alcohols and water [10].

3.6.3 Nafion in Catalysis

What makes Nafion so useful for catalytic purposes is the superacidity of the acidic form of the polymers. Because the sulfonic acid group is attached to a highly electron-withdrawing perfluoroalkyl backbone, a relatively high polarization of the –OH bond results. Because methods for measuring solution acidity cannot be directly applied to heterogeneous solid materials, determination of the acidity of Nafion-H is difficult. Nevertheless, studies indicate that the acidic character of Nafion-H resin is comparable with that of 100 % sulfuric acid, because the estimated Hammett H_0 acidity function value of Nafion-H, approximately -12, is comparable with that of 100 % sulfuric acid [1].

The properties of Nafion-H have led to an extensive development of different acid catalyzed reactions, especially by Olah and co-workers. Sharma et al. [3,11] describe the use of a variety of ion-exchange resins in catalysis and extensive information about the use of Nafion can be found in the reviews of Olah et al. [1] and of Waller [4].

Examples of these Nafion-catalyzed reactions are:

- alkylation of aromatic compounds with alkyl halides [12], with ethene and propene [13], and with methyl alcohol [14];
- acylation of (substituted) aromatic compounds with benzoyl chlorides, anhydrides [15], or carboxylic acids [5];
- isomerization reactions, e. g. the isomerization of epoxides to carbonyl compounds [16];
- the Fries rearrangement of phenyl acetate [17];
- preparation of 1,1-diacetates from aldehydes [18];
- esterification of carboxylic acids with alcohols [19];
- oligomerization of *iso*-butene [20].

3.6.4 Nafion–Silica Composites

To overcome the disadvantage of the low surface area (< 0.02 m^2 g^{-1}) of pure Nafion NR50 beads, researchers at DuPont developed Nafion–silica composites, in which small (20–60 nm) Nafion resin particles are embedded in a porous silica matrix [7]. The composites, available under the trade name SAC13 (containing 13 % (*w*/*w*) Nafion) are prepared by a sol–gel technique. Because of the higher surface area and accessibility of the active sites the application of this material as a solid-acid catalyst has become attractive.

This method of preparing the Nafion–silica composites is highly analogous to the sol–gel synthesis of pure silica (Brinker et al. [21]). Firstly, a silicon alkoxide, e. g. tetramethyl orthosilicate (TMOS), is prehydrolyzed by addition of hydrochloric acid. This silicate solution is added to an alkaline solution containing Nafion. Condensation of the solution is accelerated by the presence of the base leading to gelation within a few seconds. The resulting composite material is highly porous, with a surface area of ca 350 $m^2\ g^{-1}$. It is also possible to 'tune' the microstructure by varying the processing conditions, e. g. pH [7].

Botella et al. [22] found that increasing the surface area of the composites results in greater interaction between the active phase and the silica support, because of the greater number of silanol groups. This strong interaction results in reduced acidity of the sulfonic acid groups. This was also shown by Pálinkó et al. [23] using FTIR techniques, and enabled measurement of an interaction between the $-SO_3H$ groups of the Nafion backbone and the hydroxyl clusters of the silica, resulting in a decrease in acidity.

In our study of the acylation of anisole with carboxylic acids [24], and the Nafion–silica composite as the catalyst, no leaching was detected during reaction conditions. This was also not observed in the study of Botella et al. [22] in the alkylation of 2-butene by isobutane.

3.6.5 Nafion–Silica Composites in Catalysis

The activity of Nafion composites of greater surface area was investigated in different organic reactions, e. g. Friedel–Crafts alkylation and acylation, the Fries rearrangement, the dimerization of α-methylstyrene, esterification reactions, and isobutane alkylation.

3.6.5.1 Friedel–Crafts Alkylation

Different alkylation reactions have been investigated with Nafion as a catalyst. An example is the propylation of benzene to cumene. Large rate enhancements were observed on use of Nafion–silica composites, compared with bulk polymeric catalysts such as pure Nafion NR50 and Amberlyst-15. The activity of the composite was ca 6–7 times higher than that of pure Nafion beads on the basis of the total amount of catalyst. If this correlation were made on the basis of the total number of acid sites on Nafion, the activity would be ca 50 times higher. Amberlyst-15 was about twice as active as the Nafion NR50 particles (on the basis of the total amount of catalyst) [7].

In the alkylation of 2-butene by isobutane the activity of Nafion–silica composite was very high compared with pure Nafion and similar to that of zeolite H-BEA [22].

3.6.5.2 Friedel–Crafts Acylation

The Friedel–Crafts acylation is an important reaction in the synthesis of many fine chemicals (e. g. pharmaceuticals, fragrances, and agrochemicals). In syntheses of these products the acylation reaction often is a basic step in which an aromatic ketone is formed. The activity of pure Nafion NR50 and that of the Nafion–silica composite with 13 % Nafion have been studied in the acylation of anisole, toluene, and xylene with two reactive carboxylic acid chlorides, namely phenylacetic acid chloride and phenylpropionic acid chloride [25]; a much higher yield was always obtained with the composite. The activity of the composites was also very high in a study of the acylation of anisole with carboxylic acids. Thus, the Nafion–silica composite containing 25 % (*w*/*w*) Nafion resulted in a 28-fold increase in reaction rate (normalized for the amount of Nafion) compared with pure Nafion. The composite containing 13 % (*w*/*w*) of Nafion resulted in a tenfold higher activity. Selectivity towards the aromatic ketone were also higher for the composites than for pure Nafion. This greater selectivity is ascribed to reduced acidity–interaction with the silica matrix leads to a greater selectivity [5].

3.6.5.3 Fries Rearrangement

The Fries rearrangement of phenyl acetate to *o*- and *p*-hydroxyacetophenone is also a very valuable reaction in the pharmaceutical industry. Nafion–silica composites containing 13 and 40 % (*w*/*w*) Nafion were also studied in this reaction and compared with pure Nafion and with zeolites such as HBEA, HUSY, HZSM5, and HY. The Nafion–silica composites resulted in better conversion than the pure analog, but in this study the BEA zeolite resulted in the highest conversion and a relatively high selectivity. Unfortunately, no reactions rates were given so no conclusions can be drawn about the intrinsic activity of the different catalysts [17].

3.6.5.4 Dimerization of α-Methylstyrene

The unsaturated dimers produced in the acid-catalyzed dimerization of α-methylstyrene are used as molecular weight-controlling agents in the production of copolymers such as acrylonitrile–butadiene–styrene resins or styrene–butadiene rubber. When the activity of pure Nafion NR50 and that of a Nafion–silica composite were compared it was found that the rate of dimerization of α-methylstyrene in cumene was very low when Nafion NR50 was used. An activity of more than two orders of magnitude higher was found for the composite compared with the bulk Nafion. On a weight basis Amberlyst-15 was ca one-seventh as active as the composite [26].

3.6.5.5 Esterification Reactions

Another solid-acid catalyzed reaction in which the Nafion–silica composites are much more active than the non-supported pure resin and Amberlyst-15 is the addition–esterification of carboxylic acids to cyclic olefins. For example, the addition of saturated carboxylic acids to dicyclopentadiene, leading to starting esters for the flavor and fragrance industry [27].

3.6.6 Conclusions

Nafion–silica composite has proved to be a promising catalyst in acid catalysis. Different studies with this catalyst revealed very high activities per weight of catalyst compared with the pure Nafion and with other solid-acid catalysts, e. g. zeolites. If these activities were to be normalized (g Nafion)$^{-1}$ the activity values are even higher. Leaching tests showed no decomposition of the catalyst during reaction. By fixing this catalyst on the walls of a structured reactor, e. g. a monolith, solid-acid catalyzed reactions in the liquid phase can be performed with easy catalyst separation. In diffusion limitation the catalyst is used more efficiently, because of the thin catalytic layer [5].

The Nafion–silica composite is rather expensive, thus the commercially available catalyst, SAC13 (containing 13 % Nafion) costs approximately \$1000 kg^{-1} [28] compared with, e. g., \$50 kg^{-1} for BEA zeolite [29]. Perhaps the costs of the composite will decrease in the future when these materials have been fully developed.

For continuous processing it is necessary that the catalyst does not deactivate and that it is possible to regenerate the catalyst for reuse. If not, catalyst disposal will lead to waste production and other solid-acid catalysts, e. g. zeolites, might be more attractive. This aspect must still be investigated in detail, as must the reproducibility of the production of the composites. Finally, it should be mentioned that the selectivity of the reactions can be affected by reducing the acidity of the acid sites, because of an interaction between the silica matrix and the polymer backbone.

References

[1] G. A. Olah, P. S. Iyer and G. K. Surya Prakash, Synthesis (1986) 513.
[2] S. J. Sondheimer, N. J. Bunce and C. A. Fyfe, J. Macromol. Sci.– Rev. Macromol. Chem. Phys. C26 (1986) 353.
[3] M. M. Sharma, React. Funct. Polym. 26 (1995) 3.
[4] F. J. Waller, 308 (1985) 42. ACS Symposium Series.
[5] A. E. W. Beers, I. Hoek, T. A. Nijhuis, R. S. Downing, F. Kapteijn and J. A. Moulijn, Top. Catal., accepted for publication.
[6] R. A. Zoppi, I. V. P. Yoshida and S. P. Nunes, Polymer 39 (1997) 1309.
[7] M. A. Harmer, W. E. Farneth and Q. Sun, J. Am. Chem. Soc. 118 (1996) 7708.
[8] F. J. Waller and R. Warren van Scoyoc, Chemtech (1987) 438.
[9] Perma Pure Inc., New Jersey, USA.
[10] Technical Bulletin DuPont, Philadelphia.
[11] A. Chakrabarti and M. M. Sharma, React. Polym. 20 (1993) 1.
[12] G. A. Olah and D. Meidar, Nouv. J. Chim. 3 (1979) 269.
[13] G. A. Olah, J. Kaspi and J. Bukala, J. Org. Chem. 42 (1977) 4187.
[14] J. Kaspi, D. D. Montgomery and G. A. Olah, J. Org. Chem. 43 (1978) 3147.
[15] G. A. Olah, R. Malhotra, S. C. Narang and J. A. Olah, Synthesis (1978) 672.
[16] G. K. Surya Prakash, A. Mathy, G. A. Olah and E. R. Marinez, Appl. Catal. A: Gen. 181 (1999) 283.
[17] A. Heidekum, M. A. Harmer and W. F. Hoelderich, J. Catal. 176 (1998) 260.
[18] G. A. Olah and A. K. Mehrotra, Synthesis (1982) 962.
[19] G. A. Olah, A. P. Fung and D. Meidar, Synthesis (1981) 280.

[20] I. Bucsi and G. A. Olah, J. Catal. 137 (1992) 12.

[21] C. J. Brinker, K. D. Keefer, D. W. Schaefer and C. S. Ashley, J. Non-Cryst. Solids 48 (1982) 47.

[22] P. Botella, A. Corma and J. M. López-Nieto, J. Catal. 185 (1999) 371.

[23] I. Pálinko, B. Török, G. K. Surya Prakash and G. A. Olah, Appl. Catal. A: Gen. 174 (1998) 147.

[24] A. E. W. Beers, In press (2000).

[25] A. Heidekum, M. A. Harmer and W. F. Hölderich, J. Catal. 188 (1999) 230.

[26] Q. Sun, W. E. Farneth and M. A. Harmer, J. Catal. 164 (1996) 62.

[27] A. Heidekum, M. A. Harmer and W. F. Hölderich, J. Catal. 181 (1999) 217.

[28] Engelhard De Meern B. V., The Netherlands.

[29] Zeolyst International, Great Britain.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

4 Solid-acid Catalysts–Aromatic Substitution

4.1 Nitration of Aromatic Compounds

A. Kogelbauer, H. W. Kouwenhoven

4.1.1 Introduction

Nitration of organic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature. Extensive and well documented reviews have been published by Ingold [1], Olah [2,3,6], Schofield [4,5], and Ione [7], among others. The last review covers specifically the use of zeolitic catalysts in the nitration of aromatic compounds with nitrogen oxides and the relevant reaction mechanisms. Development of heterogeneous catalysts to replace sulfuric acid, the catalyst of the traditional liquid phase nitration process, is a goal in several studies. It seems that compared with other solid-acid materials some zeolites are superior catalysts, because of selectivity, chemical stability, and regenerability. Results of recent research on the application of heterogeneous catalysts in the nitration of aromatic compounds are discussed in this chapter.

4.1.2 Reaction Mechanism

The mechanism of electrophilic aromatic nitration has been clarified over the last 50 years. The foundation of the present understanding was laid by Ingold and Hughes [1]. In the course of their studies Ingold and Hughes developed the concept of activating and deactivating groups in aromatic molecules. The accepted reaction mechanism consists of the steps:

$$H^+ + HNO_3 \rightleftharpoons H_2ONO_2^+ \tag{1}$$

$$H_2ONO_2^+ \rightleftharpoons NO_2^+ + H_2O \tag{2}$$

$$NO_2^+ + ArH \rightleftharpoons HArNO_2^+ \tag{3}$$

$$HArNO_2^+ \rightarrow ArNO_2 + H^+ \tag{4}$$

First the nitric acid is protonated by the stronger sulfuric acid. Protonated nitric acid forms water and the NO_2^+ ion, the nitronium ion is the active agent in acid-catalyzed aromatic nitration. Its solvation in different media affects its reactivity and the selectivity of the reaction. With reactive aromatics an additional kinetic step must be added to the above mechanism between steps (2) and (3):

$$NO_2^+ + ArH \rightleftharpoons \text{first intermediate} \tag{2a}$$

$$\text{first intermediate} \rightleftharpoons HArNO_2^+ \tag{2b}$$

Although the nature of the 'first intermediate' is still disputed, in gas-phase studies of electrophilic aromatic substitution the existence of π-complex first intermediates has been proven experimentally. The reaction mechanisms have been reviewed by Olah et al. [6].

4.1.3 Commercial Manufacture of Nitroaromatic Compounds

The nitration of benzene for commercial production of nitrobenzene (NB) is a well established process which has been used since about 1860 [8]. In the basic process a mixture of nitric acid and sulfuric acid is used as nitrating agent and the strongly exothermic reaction is conducted in batch- or in continuous reactors. Typically the nitrating acid consists of 56–60% (*w/w*) H_2SO_4, 27–32% (*w/w*) HNO_3, and 8–17% (*w/w*) H_2O at a reaction temperature of 50–90 °C. The reaction mixture forms two phases in which the reactants are dissolved, the rate of reaction is accordingly dependent on the kinetics and on the mixing efficiency. The yield relative to benzene is ca 95–98% (*w/w*); the main by-products are nitrophenols and picric acid. Sulfuric acid is gradually deactivated by water generated during the reaction and has to be replaced after deactivation. Chemical feedstock represents ca 85% of the variable costs in benzene nitration. Chemical engineering research into nitration processes has yielded many valuable improvements and results related to improved mixing of the reactants, better energy management and reduced production of waste materials have been implemented in the design of modern nitration plants. In current commercial practice continuous adiabatic nitration is preferred to batch processing; its main advantages are lower capital and labor costs. Increasingly stringent environmental regulations have led to the development of improved methods for product recovery and regeneration of spent sulfuric acid. The latter is now commonly performed off-site by specialized firms.

Several variations of the conventional process have been proposed:

Single-phase nitration with a 2–4-fold excess of 98+ % nitric acid at a reaction temperature of 20–60 °C and ambient pressure, which may be used for the nitration of benzene and mixtures of benzene and toluene. In the latter case NB and dinitrotoluene (DNT) are co-produced and total conversion is claimed to be high and very selective.

Azeotropic nitration of benzene is conducted at 120–160 °C with excess benzene. Water generated during the reaction is removed as a water–benzene azeotrope and may be separated from the benzene, which is recycled to the reactor. The sulfuric acid remains dry and can be used for longer periods between regeneration.

Nitration of toluene for production of mononitrotoluenes (MNT) is conducted either batch-wise or in continuous operation under somewhat milder conditions than those used for benzene nitration because of the activating effect of the methyl group. The nitrating acid usually has the composition: 52–56 % (*w/w*) H_2SO_4, 28–32 % (*w/w*) HNO_3 and 12–20 % (*w/w*) H_2O, and the reaction temperature is ca 25–40 °C. The yield of MNT is typically ca 96 %, the product contains 55–60 % (*w/w*) *o*-, 3–4 % (*w/w*) *m*- and 35–40 % (*w/w*) *p*-nitrotoluene (*p*-NT). Because the greatest demand is for *p*-NT, research has been directed to the development of methods for increasing the *p/o* ratio of the product. An increased *p/o* ratio was, e. g., obtained by replacing sulfuric acid with other acids such as phosphoric acid or aromatic sulfonic acids.

Nitration of mononitrotoluene for production of DNT is conducted as described for toluene under somewhat more severe conditions. The nitrating acid has the composition: 65 % (*w/w*) H_2SO_4, 25 % (*w/w*) HNO_3 and 10 % (*w/w*) H_2O, and the reaction temperature is 65–70 °C. When using the product of the mononitration as a feedstock for the dinitration, the yield of DNT is typically ca 96 %, the product contains 20 % (*w/w*) 2,6-DNT, 76 % (*w/w*) 2,4-DNT and 0.6 % (*w/w*) 3,5-DNT. The commercial value of 2,4-DNT is considerably higher than that of 2,6-DNT, it may be obtained by nitration of *p*-NT.

4.1.4 Solid-acid-based Nitration

Most solid-acid-based nitration systems use special nitrating agents that are either expensive, difficult to handle, or regarded as safety hazards. For large-scale industrial production of intermediates, however, liquid-phase nitration with nitric acid of azeotropic composition is still the most desirable route, owing to economic considerations. Because none of the solid acids yet reported has an acid site concentration even close to that of sulfuric acid by weight or volume, all of those systems are less active. This is mainly because of rapid poisoning of solid-acid catalysts by water present in the reaction mixture or formed during the nitration with nitric acid. Effective removal of the water is, therefore, of paramount importance in the implementation of a viable large-scale nitration process. Few catalyst systems have been described that effect nitration of deactivated substrates or, in particular nitration of toluene to DNT. Generally, the trend in the development of new nitration catalysts is aimed at minimizing by-product formation and improving regiocontrol of the desired isomer product (increasing *para* selectivity) by use of catalysts. Most of the procedures, however, lend themselves only to small-scale preparative purposes.

4.1.5 Liquid-phase Reactions

Nitronium ion-containing solutions are readily obtained by mixing nitric acid or other NO_2–X compounds with strong acids, which can be either Brønsted or Lewis acids. Earlier attempts to use solid-acid catalysts in the liquid phase for nitration date back to the work of Wright et al. [9] who performed the nitration of toluene with 90% nitric acid and dehydrated sulfonic ion-exchange resins (Rohm & Haas Amberlite IR-120). Approximately 30% phenylnitromethane was formed as a by-product by side-chain nitration. Despite higher *p*-NT selectivity after proper adjustment of the reaction conditions, resulting presumably in the formation of tight ion-pairs of the form SO_3^-–NO_2^+ on the resin surface, the low thermal stability of such resins and their tendency to degrade slowly at elevated temperatures limits their practical use. The reaction occurred stoichiometrically rather than catalytically, as was shown by determination of the dependence of fractional toluene conversion on the amount of resin used, which yielded a turn-over number of unity.

As further examples of heterogeneous systems we mention in Table 1 the use of Nafion-H [10] and polyphosphoric acid (PPA) [11]. Nafion-H is an acidic perfluorosulfonic acid resin and PPA is prepared by dissolving P_2O_5 in H_3PO_4 and is a high viscosity liquid. HNO_3 was used as the source of NO_2^+; when Nafion was used, N_2O_4, *n*-butylnitrate, and acetone cyanohydrin nitrate (ACN) were also investigated as sources of NO_2^+. In the presence of sulfuric acid N_2O_4 is an active and selective nitrating agent. Results obtained with other solid (Lewis) acids, e. g. Nafion-H, are, however, moderate. Without an acid catalyst N_2O_4 is a radical oxidation/nitration agent with low selectivity for nitration [12]. The radical mechanism of the nitration is evident from the isomer ratio of

Table 1. Isomer distribution in the-liquid phase nitration of toluene.

Nitrating agent	Solvent	Temp. (°C)	Selectivity (%)	*ortho*/*para*
N_2O_4 [12]	CCl_4	25	5	0.94
N_2O_4/Nafion-H [10]	CCl_4	25	20	1.09
HNO_3 [10]	CCl_4	76	> 95	1.20
HNO_3/Nafion-H [10] azeotrope	Toluene	85	80	1.40
n-butylnitrate/Nafion-H [10]	Toluene	80	> 95	1.06
ACN/Nafion-H [10]	Toluene	110	80	0.94
HNO_3/PPA, 94.7 % (*w*/*w*)H_3PO_4 [11]	Toluene	25	> 95	1.12
HNO_3/PPA, 97.0 % (*w*/*w*)H_3PO_4 [11]	Toluene	25	> 95	1.07

the MNT product: *ortho* 24 %; *meta* 53 %, and *para* 26 %. At high activity the yield of nitroaromatics relative to the amount of nitric acid used is substantially increased by azeotropic removal of water during the reaction.

Use of *n*-butylnitrate and ACN results in enhanced selectivity for the less sterically hindered toluene isomer. The *p*/*o* ratio of the MNT produced increases with increasing P_2O_5 content of the PPA, presumably because of enhanced steric hindrance resulting from the increasing chain length of the polymeric catalyst.

Laszlo and coworkers [13] developed a one-pot nitration method based on the use of 'claycop', cupric nitrate-impregnated acidic montmorillonite clay K-10. Nitration was conducted in the liquid phase under 'Menke' conditions in the presence of acetic anhydride as water-trapping agent; regioselectivity was high for *p*-NT. In a further development, the one-pot polynitration of mainly activated aromatic compounds and in particular toluene was examined using the same catalyst [14]. Interesting features were synthesis at room temperature combined with high 2,4-DNT selectivity (2,4-DNT/2,6-DNT = 9:1). 95 % molar yield of DNT was obtained after 4 h reaction with a huge excess of claycop (480 g mol^{-1} reactant) and addition of fuming nitric acid (18-fold molar excess) in 2:1 CCl_4–acetic anhydride as solvent. In a further communication they reported that the process can be made catalytic by reacting toluene with nitric acid in a mixture of CCl_4, acetic anhydride, and a montmorillonite clay with azeotropic water removal; NT was obtained in 81 % yield with a *o*/*p* product ratio of 0.65 (turnover numbers of > 850). The use of halogenated solvents is, however, a significant concern in large-scale application. Better activity in the nitration of chlorobenzene was claimed by Choudary et al. [15] when an Fe^{3+}-exchanged montmorillonite was used instead of the H-form; this was explained by its greater Lewis acidity.

On the basis of their earlier work with benzoyl nitrate and zeolites [16] Smith et al. [17,18] described a method for the nitration of simple aromatic compounds such as benzene, toluene, and halobenzenes. Using 90 % nitric acid, H-beta zeolite as catalyst, and acetic anhydride as water-trapping agent these aromatics are nitrated in quantitative yield with high *para* selectivity in a solvent-free process by use of a stoichiometric quantity of nitric acid and acetic anhydride at 0–20 °C. The catalyst can be recycled and the only by-product, acetic acid, can be separated by vacuum distillation. By use of different acyl nitrates and HZSM-11, the outer crystal surface of which was deactivated by adsorption of tributylamine, toluene was nitrated with up to 98 % selectivity to *p*-NT [19]. No yields were indicated and the method seems to be of academic interest only.

Kwok and Jayasuriya [20] performed regioselective mono-nitration of toluene with *n*-propyl nitrate in the liquid phase at ambient to reflux temperatures over H-ZSM-5 zeolites with different Si/Al ratios. It was found that high Si/Al ratios enhanced regioselectivity for *p*-NT. The best product distribution was achieved by use of H-ZSM-5 with a Si/Al ratio of 1000. The yield was 54 % with 95 % *p*-NT selectivity. Contrary to literature reports, solvents other than toluene led to sluggish reactions. Enhanced *para* selectivity with a *p*/*o* ratio of up to 4.53 was reported by Zhang et al. [21] for the nitration of chlorobenzene with nitric acid over H-ZSM-5. Conversion was relatively low, however, reaching only 11.9 % at a reaction temperature of 90 °C and a 1:1 reactant ratio (65 % HNO_3).

With a twofold excess of HNO_3 conversion increased to 20 %. Use of > 95 % nitric acid and a 1:1 reactant ratio resulted in an increase in chlorobenzene conversion to 33.4 % at 50 °C, although *para* selectivity dropped substantially ($p/o = 1.91$). No enhanced *para* selectivity was observed for toluene and ethylbenzene with ZSM-5, however, when sulfonated ion-exchange resins were used as catalysts a higher fraction of *para*-substituted products was obtained.

Besides solid acids such as zeolites, clays, or sulfonated resins, supported acids have been proposed as nitration catalysts. Kameo et al. [22] described the use of 2,4-dinitrotoluene sulfonic acid impregnated on various supports for the nitration of toluene with 98 % nitric acid. Again, the objective was to obtain higher *para* selectivity in the conversion of toluene to NT. A catalyst consisting of 33 % (*w*/*w*) 2,4-dinitrotoluene sulfonic acid impregnated on Celite-545 yielded 95 % NT with a *para*-to-*ortho* ratio of 1.61. The catalyst could be reused after regeneration without change in performance; this was demonstrated in six consecutive runs.

Tapia et al. [23] described the use of nitric acid supported on silica gel for the mono-nitration of activated aromatic compounds such as phenols and aryl methyl ethers. Riego et al. [24] used sulfuric acid supported on silica gel for the mononitration of a variety of aromatic compounds. The reaction was performed at ambient temperature with 70 % nitric acid or isopropyl nitrate as reagents and yielded mono-nitrated products within short reaction periods. Toluene was quantitatively converted to NT in 0.1 h, without a solvent, by use of a catalyst containing 10 mmol H^+ g^{-1} as supported 70 % H_2SO_4. A comparative study of the reaction kinetics of the nitration using supported and unsupported liquid acids revealed that the performance of supported sulfuric acid is comparable with that of 90 % sulfuric acid in the classical liquid phase reaction where complete protonation of nitric acid occurs [25].

Kogelbauer et al. [26] studied the nitration of toluene to DNT by use of solid acids in the liquid phase, using 65 % nitric acid, the industrially preferred nitrating agent. Their results obtained by use of silica-supported sulfuric acid demonstrated that a solid acid with a high concentration of acid sites was required and that control of the water level in the reaction mixture was crucial for obtaining reasonable performance. Accordingly, in situ activation of the solid acid significantly improved performance. Although nitration of toluene to DNT was achieved in one step, solvent-free operation was limited because of the large amount of solid acid required. Solvent-free operation for the production of DNT in the liquid phase was, therefore, only feasible in a two-step process. Toluene could act as its own solvent giving quantitative conversion to NT whereas conversion of NT to DNT was limited to about 30 % in one batch.

4.1.6 Vapor-phase Reactions

The advantage of using vapor phase conditions is the continuous thermal removal of water and the simple implementation of a continuous nitration process based on a fixed-bed of the solid acid. Elevated reaction temperatures, however, lead to problems of safety, catalyst stability, and by-product formation, and optimization of the reaction conditions is therefore required. In the nitration of benzene potential fixed-bed processes are about to emerge but for toluene deactivation of catalysts is still the major drawback. Nitration of aromatics with solid acids in the vapor phase was attempted as early as 1936 [27]. More recently, Germain et al. [28] studied nitration over H-beta and silica–alumina with N_2O_4 as nitrating agent. Although H-beta performed well with several aromatic compounds, with toluene complete deactivation was observed within 30 min on-stream at 140 °C accompanied by the formation of numerous by-products. Adding water to the reaction mixture helped to sustain the activity of H-beta; this was explained as a *steam-distillation* effect of strongly adsorbed reaction products such as dinitroarenes [29]. Despite high *para*-nitrofluorobenzene selectivity, it was concluded that shape selectivity did not occur when fluorobenzene was nitrated over a variety of zeolite catalysts.

By use of H-ZSM-5 with a Si-to-Al ratio of 30 and boron ZSM-5, Salakhutdinov et al. [30] conducted the nitration of toluene with N_2O_4. No yields were reported, but boron ZSM-5 increased *p*-NT selectivity from 47 to 67 % at 125 °C. It was concluded that at elevated temperatures ($>$ 125 °C) NB was formed in increasing amounts by dealkylation reactions after *ipso* attack of the aromatic compound by the nitronium ion.

The vapor-phase nitration of benzene with NO_2 was investigated by Suzuki et al. using polyorganosiloxanes bearing sulfonic acid groups and silica-supported benzenesulfonic acid catalysts [31]. Phenylsulfonic polysiloxane was the most active among the polysiloxanes tested, its activity was not related to the concentration of acid sites as determined by a titration method, however. From the partial pressure dependence of the reaction rate it was concluded that the formation of NO^+ as the active species was the rate-limiting step [32].

Bertea et al. [33] studied the vapor phase nitration of benzene over a variety of zeolitic materials with 65 % nitric acid as nitrating agent. Post-synthetic modification of zeolites by high-temperature dealumination in combination with acidic extraction of the non-framework aluminum was reported to give enhanced catalyst performance with respect to activity and stability. This was related to the removal of extra-framework debris blocking the micopores and to the formation of mesopores in the modified zeolites of the mordenite, Y, and ZSM-5 type. Modified clinoptilolite, a naturally occurring zeolite, was of particular interest because of its low cost and showed a constant NB space–time yield of 0.65 h^{-1} in experiments lasting up to 140 h. Another important feature was the complete suppression of the formation of nitrophenolic by-products.

Vassena et al. [34] showed that zeolite H-beta resulted in enhanced *para* selectivity in the vapor phase nitration of toluene at 158 °C with 65 % nitric acid. H-ZSM-5 and Deloxan, a sulfonic acid-bearing polysiloxane, were not selective. Dealumination of H-beta to increase its hydrophobicity was detrimental with regard to activity and *para* selectivity suggesting that catalytic activity was directly related to the acid site concentration. Characterization of the recovered catalyst showed that deactivation was not related to structural damage in the highly acidic reaction medium but rather to pore filling by strongly adsorbed products/by-products.

Kuznetsova et al. [35] studied the vapor phase nitration of benzene with 56 % nitric acid on ZSM-5 at 140–170 °C. Although good yields of NB (ca 90 %) were observed initially at an HNO_3/benzene feed ratio of 3.8, catalysts were rapidly deactivated, presumably because of strongly adsorbed species which decomposed when the catalyst was heated in nitrogen at 220–250 °C. Sato and co-workers [36], studying the vapor-phase nitration of benzene with NO_2 over several mixed metal oxides found that the activity was mainly determined by the acidity of the oxides. To explain the high activity of combinations such as WO_3–MoO_3 additional factors such as BET surface area had to be considered, however. The complete utilization of NO_2 by in situ oxidation of simultaneously produced NO was only feasible when a co-catalyst was used. Although supported sulfuric acid was shown to give good results for the vapor phase nitration of benzene, catalyst activity dropped rapidly after 144 h on-stream [37]. This was related to the slow motion of the catalytically active zone through the catalyst bed, an effect similar to that occurring in the Topsoe fixed-bed alkylation process. Co-feeding a small amount of sulfuric acid (1/2000 of the amount of nitric acid) resulted in highly active (> 95 %) conversion of nitric acid being maintained over a period of 90 days at 140 °C and the exceptionally high overall space velocity of 836 h^{-1} (benzene $SV = 170\ h^{-1}$). It was claimed that the method was applicable for the production of nitrochlorobenzene but was less suitable for the nitration of toluene.

4.1.7 Conclusion

The obvious disadvantages of the commercial manufacturing process currently used has led to a substantial effort to develop viable alternatives, inter alia using solid-acid catalysts, other sources of NO_2^+, organic nitrating agents, other acids replacing sulfuric acid etc. Commercial success of this research effort has yet to be achieved and it seems that, because it is a mature technology, replacement of the existing manufacturing process is an uphill battle. Although an economically competitive aromatic nitration process based on solid acids seems still far away, for benzene at least results from nitration in the vapor phase are very encouraging. For nitration of toluene the situation is less encouraging, particularly if production of DNT is desired. Solid acids with a substantially higher concentration of acid sites are required to compete effectively with liquid sulfuric acid. Azeotropic removal of water in combination with regioselective solid catalysts has a high potential for fine-chemicals production. As a result of fundamental studies of aromatic substitution and exploratory research into the nitration of aromatic compounds, interesting heterogeneous catalytic nitrations are beginning to emerge.

References

[1] Ingold, C. K., 'Structure and Mechanism in Organic Chemistry' 2nd ed., Cornell University Press, Ithaca, New York, 1969.

[2] Olah, G. A., Kuhn, S. J. in 'Friedel–Crafts and Related Reactions', Olah, G. A., ed., Wiley–Interscience, New York, Vol. 2, 1964

[3] Olah, G. A., ACS Symp. Series, Vol. 22, Albright, F., ed., Washington DC, 1976, p. 1

[4] Hoggett, J. G., Moodie, R. B., Penton, J. R., Schofield, K., 'Nitration and Aromatic Reactivity', Cambridge University Press, London, 1971.

[5] Schofield, K., 'Aromatic Nitration', Cambridge University Press, London, 1980.

[6] Olah, G. A., Malhotra, R., Narang, S. C., 'Nitration: Methods and Mechanisms', Feuer, H., ed., VCH Publishers, New York, 1989

[7] Malysheva, L. V., Paukshtis, E. A., Ione, K. G., Catal. Rev. -Sci. Eng., **37**, 179 (1995).

[8] Adkins, R. L., Nitrobenzene and Nitrotoluenes in 'Encyclopedia of Chemical Technology' 4th ed., vol. 17, Wiley–Interscience, New York, 1996, p. 133.

[9] Wright, O. L., Teipel, J., Thoennes, D., J. Org. Chem. **30**, 1301 (1965).

[10] Olah, G. A., Malhotra, R., Narang, S. C., J. Org. Chem., **43**, 4628 (1978).

[11] Moodie, R. B., Schofield, K., Wait, A. R., J. Chem. Soc. Perkin Trans. II, 921 (1984).

[12] Olah, G. A., Overchuck, N. A., Can. J. Chem., **43**, 3279 (1965).

[13] Laszlo P., Acc. Chem. Res. **19**, 121 (1986); Cornelis, A., Delaude, L., Gerstmans, A., and Laszlo, P., Tetrahedron Lett. **29**(44), 5657 (1988); Laszlo P., and Vandormael, J., Chem. Lett. 1843 (1988); Delaude, L., Laszlo, P., and Smith, K., Acc. Chem. Res. **26**, 607 (1993).

[14] Gigante, B., Prazeres, A. O., Marcelo-Curto, M. J., Cornelis, A., and Laszlo, P., J. Org. Chem. **60**, 3445 (1995).

[15] Choudary, B. M., Ravichandra Sarma, M., and Vijaya Kumar, K., J. Mol. Catal. **87**, 33 (1994).

[16] Smith, K., Bull. Soc. Chim. Fr. 272 (1989); Smith, K., Fry, K., Butters, M., and Nay, B., Tetrahedron Lett. **30**, 5333 (1989).

[17] Smith, K., Musson, A., and DeBoos, G. A., Chem. Commun. 469 (1996).

[18] Smith, K., Musson, A., and DeBoos, G. A., J. Org. Chem. **63**, 8448 (1998).

[19] Nagy, S. M., Yarovoy, K. A., Shakirov, M. M., Shubin, V. G., Vostrikova, L. A., and Ione, K. G., J. Mol. Catal. **64**, L31 (1991); Nagy, S. M., Yarovoy, K. A., and Shubin, V. G., and Vostrikova, L. A., J. Phys. Org. Chem. **7**, 385 (1994).

[20] Kwok, T. J., Jayasuriya, K., Damavarapu, R., and Brodman, B. W., J. Org. Chem. **59**, 4939 (1994).

[21] Zhang, P., Guan, J., Li, Y., and Xu, Y., Shenyang Huagong Xueyuan Xuebao **8**(2), 105 (1994).

[22] Kameo, T., Nishimura, S., and Manabe, O., Nippon Kagaku Kaishi **1**, 122 (1978).

[23] Tapia, R., Torres, G., and Valderrama, J. A., Syn. Comm. **16**(6), 681 (1986).

[24] Riego, J. M., Sedin, Z., Zaldivar, J. M., Marziano, N. C., and Tortato, C., Tetrahedron Lett. **37**, 513 (1996).

[25] Marziano, N. C., Tortato, C., Ronchin, L., Martini, F., and Bianchi, C., Catal. Lett. **58**, 81 (1999).

[26] Kogelbauer, A., Vassena, D., Prins, R., and Armor, J. N., Catal. Today **55**, 151 (2000).

[27] Wilhelm, R. H., US Patent 2 109 873 (1938).

[28] Germain, A., Akouz, T., and Figueras, F., J. Catal. **147**, 163 (1994).

[29] Germain, A., Akouz, T., and Figueras, F., Appl. Catal. A: General **136**, 57 (1996).

[30] Salakhutdinov, N. F., Ione, K. G., Kobzar, E. A., and Malysheva, L. V., Zh. Org. Khim. **29**(3), 546 (1993).

[31] Suzuki, S., Tohmori, K., and Ono, Y., Chem. Lett. 747 (1986); Suzuki, E., Tohmori, K., and Ono, Y., Chem. Lett. 2273 (1987); Suzuki, S., Tohmori, K., and Ono, Y., J. Mol. Catal. **43**, 41 (1987).

[32] Ono, Y., Tohmori, K., and Suzuki, E., Proc. 9th Int. Congr. Catal. 4, 1688 (1988).

[33] Bertea, L. E., Kouwenhoven, H. W., and Prins, R., Stud. Surf. Sci. Catal. **78**, 607 (1993); Bertea, L. E., Kouwenhoven, H. W., and Prins, R., Stud. Surf. Sci. Catal. **84**, 1973 (1994); Bertea, L. E., Kouwenhoven, H. W., and Prins, R., Appl. Catal. A: General **129**, 229 (1995).

[34] Vassena, D., Malossa, D., Kogelbauer, A., and Prins, R., Proceedings of the 12th International Zeolite Conference, Vol. II (Treacy, M. M. J., Marcus, B. K., Bisher, M. E., and Higgins, J. B., eds.), Materials Research Society, Warrendale, PA, p. 1471 (1999).

[35] Kusnetzova, T. G., Ione, K. G., and Malysheva, L. V., React. Kinet. Catal. Lett. **63**, 61 (1998).

[36] Sato, H., and Hirose, K., Appl. Catal. A: General **174**, 77 (1998).

[37] Sato, H., Nagai, K., Yoshioka, H., and Nagaoka, Y., Appl. Catal. A: General **180**, 359 (1999).

4.2 Halogenation over Solid Catalysts

P. Ratnasamy, A. P. Singh

4.2.1 Introduction

The use of heterogeneous, solid catalysts in the manufacture of fine chemicals is an area of growing importance. Halogen-containing compounds constitute an important segment of fine and specialty chemicals. Hydrofluorocarbons and hydrochlorofluorocarbons are extensively used in the refrigeration industry. Commodity chemicals such as vinyl chloride monomer (for the manufacture of PVC) and intermediates such as chlorobenzenes and chlorotoluenes are widely used in the chemical industry. Chloro compounds also constitute a significant part of the agrochemicals used as insecticides and herbicides. Bromo compounds, e. g. tetrabromo bis phenol-A, are used as fire-retarding/extinguishing chemicals. Iodine-containing compounds find use in the pharmaceutical industry, especially in thyroid gland therapies. Even though the hydrofluorocarbons (HFCs) are manufactured using solid catalysts, many industrial halogenations of organic compounds are currently performed by use of free halogens either in the absence of catalysts or in the presence of Lewis acid catalysts such as halides of aluminum and iron (aromatic nuclear halogenations). The latter catalysts have shortcomings:

- Strictly anhydrous conditions are required to avoid corrosion problems.
- In the nuclear halogenation of aromatic compounds the operation must be conducted in the absence of light to avoid side-chain halogenation.
- The halides of iron and aluminum, being strong Lewis acids, also catalyze other undesirable side reactions, e. g. alkyl isomerization and transalkylation or displacement of the alkyl group by the halogen. The latter are promoted by increases in temperature, the amount of substitution on the adjacent carbon atom, and the acidity of the catalyst. Another major handicap of Lewis acid catalysts such as $FeCl_3$ or $AlCl_3$ is the difficulty of environmentally acceptable disposal after use in the halogenation reaction.

The use of solid catalysts in halogenation processes will avoid corrosion and disposal problems. Work-up procedures to isolate and recover the desired product will also be easier leading to simpler and cleaner process routes. In addition, the use of zeolites as the solid catalysts in nuclear aromatic halogenations might lead to enhanced yields of the *para* isomer, because of the shape selectivity of the zeolite.

We have already published reviews of the use of solid catalysts [1a], and particularly zeolites [1b], in halogenation reactions covering the literature until the end of 1994 [1]. This review, in addition to covering the period from 1994 to mid-1999, highlights recent advances in this field. After a brief review of the basic principles of halogenation reactions and the properties of commonly used halogenating agents (Section 4.2.2), the available literature on halogenation is summarized in Section 4.2.3. Fluorination, chlorination, bromination and iodination reactions over solid catalysts are then discussed in detail (Sections 4.2.4–4.2.7, respectively.). Both journal/patent literature reports and unpublished results from the authors' laboratory are reviewed.

4.2.2 Halogenation and Halogenating Agents

A comprehensive account of the properties of halogens and their intermediate derivatives is given by Downs and Adams [2] and electrophilic halogenation is reviewed by de la Mare [3]. Halogenation reactions can be, broadly, classified into two categories, halogenation of aliphatic compounds and halogenation of aromatic compounds. Important industrial and fine chemicals such as vinyl chloride monomer, HFCs, HCFCs, CFCs, chloromethanes, chlorosilanes, fluoro- and chloroacetic, and sulfonic acids, etc., fall in the first category whereas chlorotoluenes, chloroxylenes, chlorophenols, chloroanilines, bromo bis-phenols, the chlorine-based pesticides and insecticides, and chloramphenicol, etc., belong to the second. Halogen derivatives of aliphatic compounds can be prepared by a variety of methods: (i) direct halogenation with dihalogen, i. e. substitution reactions (of H or of other halogen atoms) brought about by light, heat or catalysts; a free-radical chain mechanism operates. In both photo- and thermal halogenation no carbon skeleton rearrangement occurs at low temperatures and halogenations beyond the monohalo derivatives can be suppressed by controlling the ratio of the substrate to halogen. The order of ease of substitution is tertiary hydrogen > secondary > primary; (ii) addition of halogen acids to an alkene; (iii) halogen–halogen exchange; this route is especially important in the replacement of chlorine by fluorine in the manufacture of fluorochemicals; and (iv) direct chlorination of alkanes by use of sulfuryl chloride in the presence of light. In the last decade major advances have been made in the manufacture of fluoroaliphatic compounds required by the fine chemicals industry by use of solid catalysts. Since the establishment of a relationship between ozone depletion and chlorofluorocarbons (CFCs) in the early seventies, the industrial production and use of chlorinated aliphatic compounds has been strongly discouraged and in recent years most research effort in the halogenation of aliphatic compounds has been directed toward the discovery and use of solid catalysts for the manufacture of fluoro- and hydrofluorocarbons. This will be discussed in more detail later.

Halogenation of aromatic compounds can lead to: (i) addition compounds, (ii) nuclear substitution products, and (iii) side-chain substitution products. Nuclear substitution occurs in the presence of Lewis acid catalysts such as $AlCl_3$ or $FeCl_3$ by an electrophilic substitution mechanism. These homogeneous catalysts can be replaced by solid-acid catalysts as will be shown later. Side-chain halogenation proceeds by a free-radical mechanism and is, hence, favored by high temperatures and light and the absence of Lewis acid catalysts. Solid catalysts such as silica and Na–Y zeolite also catalyze such halogenations.

A variety of compounds has been used as halogenation agents [3]. Fluorination can be performed with molecular fluorine (F_2), HF, fluoroxy compounds, XeF_2, perchloryl fluoride ($FClO_3$) and metallic fluorides (especially CrF_3 and AlF_3 or their mixtures). Apart from molecular chlorine and HCl, other popular chlorination agents include hypochlorous acids, *t*-butyl hypochlorite, sulfuryl chloride and metallic chlorides such as $InCl_3$ and $SbCl_5$. Similarly, apart from Br_2, brominations can also be performed with hypobromous acid (HOBr), bromine acetate, *t*-butyl hypobromite and *N*-bromosuccinimide. The iodine molecule is the least reactive of all the molecular halogens in effecting addition to or substitution in organic compounds. Apart from I_2, other iodination agents such as iodine chloride (ICl, mainly for aromatic substitutions) and iodine acetate are also commonly used.

4.2.3 Halogenation over Solid Catalysts

The beneficial effects of solid surfaces on the rates of bromination reactions were observed as early as 1923 [4–6]. The polarity of the glass surface was found to enhance the rates of bromination of ethylene. Halogenation reactions over zeolite catalysts have been reviewed [1]. A summary of halogenations over non-zeolite (until mid-1999) and zeolite (1995–mid 1999) catalysts is given in Table 1.

Table 1. Halogenation over solid catalysts.

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
Fluorination					
1	1,1,1 Trifluoro-2-chloroethane (HFCF-133 a)	HFC-134 a	Cr/MgO;Cr/Al_2O_3; Cr/MgF_2; Cr/TiO_2; Cr/ZrO_2	Most active catalyst Cr MgO	7
2	1,1,1-Trifluoro-2-chloroethane (CF_3CH_2Cl)	1,1,1,2-Tetrafluoroethane	CrF_3/MgF_2-AlF_3 CrF_3/MgF_2, CrF_3/ AlF_3	CrF_3/MgF_2 or AlF_3 are more active than CrF_3/MgF_2-AlF_3	8
3	1,1,1-Trifluoro-2-chloroethane (HCFC-133a)	HFC-134a	MgO, Al_2O_3, AlF_3, MgF_2, TiO_2, ZrO_2 or supported chromium oxides	Best activity with CrO_x/MgO	9
4	CFC-113, CFC-113a, CFC-114, CFC-114a, CFC-115/HF and Cl_2	Hexafluoroethane	Cr_2O_3	300–500 °C, vapor phase	10
5	HCFC-133a	HFC-134a	Chromium oxide	Selectivity to HFC-134a is independent of the O/F ratio on the Cr surface	11
6	ClCH:CHCF$_3$ (chloro-trifluoropropene)/HF	1,3,3,3-tetrafluoropropene	Cr_2O_3/carbon	400 °C, Sel = 73.0 %	12
7	$CCl_3CH_2CHCl_2$/HF	1,3,3,3-tetrafluoropropene	Cr_2O_3/carbon	Sel = 28.8 %	13

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
8	2-Chloro-1,1,1,2-tetrafluoroethane	1,1,1,2-tetrafluoro-ethane (CF_3CH_2F)	Metal catalysts/ carbon	100–250 °C	14
9	CH_2Cl_2/HF	CH_2F_2	Supported Cr catalyst	300–450 °C	15
10	CH_2Cl_2/HF	CH_2F_2	AlF_3 on a Cr–Ni	Catalytic gas phase fluorination	16
11	Chlorohydrocarbons/HF	Fluorohydrocarbons	Chromium hydroxide	100–550 °C; conv. = 90 %	17
12	Hydrochlorocarbons/HF	Hydrochlorofluorocarbons	Fluorinated metal oxides	Room temp	18
13	1,1,1-trifluoro-2-chloroethane	1,1,1,2-tetrafluoro-ethane	Transition metals on γ-AlF_3	Vapor phase catalytic fluorination	19
14	SO_3	$S_2O_6F_2$	AgF_2 on copper turnings		20
15	Fluoroalkenes,/F_2	Perfluorinated liquid compounds	Supported NiF_2	Vapor phase, high selectivity	21
16	1,1,1 Trifluoro-2-chloroethane	CF_3CH_2F	Cr_2O_3		22
17	$CF_3CF_2CHCl_2$ by fluorination and reduction of CF_3CF_3CHClF	$CF_3CF_2CH_2F$	halides or oxides of Al,Cr, Mg, Ca, Ba, Sr, Fe, Ni, CO	280 °C, Sel = 73 %	23
18	Chloropentafluoro-ethane/HF	Hexafluoro-ethane	Cr_2O_3,Ni–Cr alloy	Purification of pentafluoro-ethane its major contaminant, Chloropenta-fluoroethane	24
19	Acetylene/HF	Ethylene difluoride (HFC-152a)	Al_2O_3-Bi-Mn	Gas phase	25
20	Hydrocarbon or halogenated hydrocarbon/HF	Fluorinated hydrocarbons	Zn supported on Al, Ni, CO, Mn, Fe or Cu	Vapor phase	26
21	1,1,1-Trichloro-ethane/HF	Fluoro-hydrocarbons	$MeCCl_3$,C_2Cl_4 or $MeCCl_2Me$ supported on SF_4-fluorinated γ-alumina	–	27

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
22	CF_3CH_2Cl/HF	Fluorinated hydrocarbons	Cr_2O_3	350 °C, conv. = 26.9 %	28
23	CF_3CHCl_2, $CClF_2CHClF$, CF_3CHClF, or CHF_2CClF_2	Pentafluoroethane	Cr_2O_3	350 °C, conv. = ~85.9 %	29
24	Tetrahaloethylene/ HF	2,2-Dichloro-1,1,1-trifluoroethane, 2-chloro-1,1,1,2-tetrafluoroethane	Metal fluoride on γ-alumina	250–450 °C, gaseous phase	30
25	Trichloroacetaldehyde /H_2O_2/HF	Trifluoroacetaldehyde (hemiacetal)	Cr catalyst	Gas phase	31
26	1,1,1-Trichloroethane/HF	Chlorofluorohydrocarbons	Fluorinated γ-alumina	Room temp. fluorination	32
27	CCl_3CF_3/HF	$CFCl_2CF_3$	Cr_2O_3-Fe_2O_3	320 °C, conv = 85 %, Sel = 98 %	33
28	Perchloroethylene (C_2Cl_4)/HF	Freon substitutes (R-122, R-123, R-124, R-125)	Cr_2O_3-MgO-Al_2O_3	350 °C, gas phase	34
29	$CF_2ClCHCl_2$ (R-122)/HF	CF_3CHCl_2 (R-123)	Cr_2O_3/γ-Al_2O_3	280 °C, conv = 84.4 %, Sel = 82.6 %	35
30	$MeCF_3/F_2$	C_2F_6,CF_4	Cu-Sn alloy	200 °C, Sel., C_2F_6 = 87.2 %	36
31	$C_2Cl_3F_3/F$	$(ClF_2C)_2$, $ClCF_2CF_3$, C_2F_6	FeF_2/C	553 °C, vapor phase	37
32	CCl_3CHO/HF	CF_3CHO	Cr_2O_3/Al_2O_3	250 °C	38
33	C_2Cl_6/HF	$C_2F_4Cl_2$	Fluorinated N_2O_3 and $CuCl_2$-coated Al_2O_3	400 °C, gas phase	39
Chlorination					
34	1-chloro-1,2,2,2-tetra-fluoroethane (HCFC-124)/ HF and HCl	1,1-dichloro-2,2,2-trifluoro-ethane (HCFC-123)	HF treated $COCl_2$ on Al_2O_3	–	40

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
35	$C_6H_5CH_2Cl/Cl_2$	4-$ClC_6H_4CH_2Cl$	K-L	Conv = 55.7 %, Isomer, 4-/2-ratio = 3.53	41
36	Ethylene/Cl_2	1,2-dichloroethane	$CuCl_2$-Al_2O_3	–	42
37	*o*-Chlorotoluene/Cl_2	*o*-Chlorobenzyl chloride	–	*o*-Chlorophenylacetamide is obtained by cyanation and hydrolysis of product	43
38	Toluene/Cl_2	Benzyl chloride	Composite catalyst	Benzyl chloride produced by catalytic and photochlorination of toluene	44
39	Chlorobenzene, toluene, 1,2-dichlorobenzene, Naphthalene/Cl_2	Mono-chlorinated products	K-L	Mono- and *para*-selective products	45
40	1,2-Dichlorobenzene/Cl_2	1,2,4-Trichlorobenzene	K-L + $ClCH_2COOH$	Nature of active sites and mechanism of the reactions	46
41	4-Chlorotoluene/Cl_2	2,4-Dichlorotoluene	K-L	95 °C, conv. = 57.3 %, isomer ratio 2,4-/3,4- = 3.5	47
42	1,2-Dichlorobenzene/Cl_2	1,2,4-Trichlorobenzene	K-L + $ClCH_2COOH$	Conv. = 90 %, isomer ratio 1,2,4-/1,2,3- = 15.0	48
43	Toluene/Cl_2	Benzyl chloride	Composite catalyst	Yield = 92 %	49
44	4-Chlorotoluene/Cl_2	2,4-Dichlorotoluene	K-L	95 °C, conv = 57.3 % isomer ratio, 2,4-/3,4- = 3.5	50
45	1,2-Dichlorobenzene	1,2,4-Trichlorobenzene	K-L + $ClCH_2COOH$	Conv = 92.1 % Isomer ratio 1,2,4-/1,2,3- = 14.0	51
46	Allylic sulfones/ hexachloroethane or CCl_4	Mono or dichlorinated products	Phase-transfer catalyst	High yields	52
47	CH_3Cl/HCl and air	CH_2Cl_2,$CHCl_3$	Alkali metal or alkaline earth chlorides or rare earth chlorides on γ-alumina	360 °C, conv = 31.9 % Sel. for CH_2Cl_2 = 78.8 %	53

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
48	CH_3Cl/HCl and air	CH_2Cl_2, $CHCl_3$	Cu chlorides on γ-alumina	330 °C, conv = 10.5 % Sel. for CH_2Cl_2 = 81.1 %	54
49	Chlorobenzene/Cl_2	Dichlorobenzene	Silica–alumina, zeolite, bentonite with $FeCl_3$	Sel. to dichlorobenzenes higher over zeolites	55
50	CH_4/Cl_2	CH_3Cl	SO_4^{2-}/ZrO_2, Pt/SO_4^{2-}, ZrO_2, Fe/Mn/SO_4^{2-}/ZrO_2	Continuous flow reactor, atm. pressure, CH_4/Cl = 4; 200 °C, Cl conv.. = 30 %, sel. CH_3Cl = > 90 %	56
51	Trichloroacetic acid	Acid chloride	Silica support	130 °C, 5 h, Yield = 92 %	57
52	[^{14}C]-UL-1,3-Dicyano-benzene/Cl_2	[^{14}C]-UL-2,4,5,6-tetrachloro-1,3-dicyanobenzene (chlorothalonil)	Activated carbon	Tubular reactor, 300 °C, Yield = 90 %	58
53	*m*-Dicyanobenzene/ Cl_2	Tetrachloroisophthalonitrile	Activated carbon-supported catalyst	280–320 °C, gas phase	59
54	Tetrafluoroethylene/HCl	Chlorotrifluoroethylene	Cr_2O_3	150–350 °C, conv = 52 % Sel = 53 %	60
55	Saturated hydrocarbons (CH_4)/HCl	CH_3Cl	Cr(VI)-Cl/SiO_2 and Cr(VI)-Ru(IV)-Cl/SiO_2	120 °C, Yield = 30 %	61
56	Propene/HCl/O_2	1-Chloropropene, 1,2-dichloropropane	MCl/$PdCl_2$/$CuCl_2$/SiO_2	Oxychlorination	62
57	C_6H_6 or C_6H_5Cl/Cl_2	$C_6H_4Cl_2$	γ-Al_2O_3	70 °C, Sel. for *para* = 75.5 %	63
58	Phenol and alkylphenols/Cl_2	*p*- and *o*-chlorophenols, chloroalkylphenols	$CuCl_2/Al_2O_3$	50 °C, *p*-/*o*-chlorophenol = 22	64
59	Ethylene/Cl2/air	Dichloroethane	$CuCl_2$-KCl/γ-Al_2O_3	Gas phase	65
60	CH_4 or chlorinated CH_4/Cl_2	CCl_4	CO/CrO_2	Gas phase	66

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
61	Phthalic anhydride/ Cl_2	Tetrachloro-phthalic anhydride	$COCl_2$, $BaCl_2$/ active carbon	320 °C, Yield = 82.8 mol %	67
62	Propylene/Cl_2	$CH_2{=}CHCH_2Cl$	LiCl/Silica gel, $AlCl_3$-$FeCl_3$/ carborundum	Vapor phase	68
63	C_2H_6/Cl_2	$ClCH_2$-CH_2Cl	$CaCl_2/Al_2O_3$	Vapor phase	69
64	$C_6H_5CH_3/Cl_2$	$C_6H_5CH_2Cl$, C_6Cl_6	Al_2O_3 supported MoO_3, Fe_2O_3, CuO and $CuCl_2$, MoO_3 and $MgCl_2$ on silica gel	260–430 °C	70
65	CH_4/Cl_2	CH_3Cl	Tantalum oxy-fluoride/Al_2O_3	235–300 °C, higher yield for CH_3Cl	71
66	C_6H_6/HCl–O_2	C_6H_5Cl	Cr_2O_3	40 °C, Yield = 35 %	72
67	Cumene/Cl_2	Chloro-cumenes	Chemically modified silica	*para/ortho* ratio higher	73
68	C_6H_6 or $C_6H_5CH_3/Cl_2$	C_6H_5Cl, $C_6H_5Cl_2$, $C_6H_5CH_2Cl$	Activated carbon	25 °C, liquid phase	74
69	Propene/HCl/O_2	CH_2: $CHCH_2Cl$	$SnCl_2$, $PrCl_3$, $MnCl_2$, $CrCl_3/Al_2O_3$	325–525 °C, vapor phase	75
70	C_2H_4/HCl or NH_4Cl/O_2	$ClCH_2CH_2Cl$	$CuCl_2$/TeO and TeO_2	150–230 °C	76
Bromination					
71	Chlorobenzene, toluene, Xylenes (*o*-,*m*-,*p*-)/Br_2 and NBS	Bromochloro-benzene, bromo-toluene, bromoxy-lenes	H-beta, H_2SO_4	nuclear and side-chain products	77
72	1,3,3-Trimethyl-1-phenyl-indan/Br_2	Octabromo-1,3,3-tri-methyl-1-phenylindan	Fe powder	Yield = 97.2 %	78
73	CH_2Cl_2/HBr	Chloro-bromome-thane and dibromo-methane	Al_2O_3	180–250 °C	79
74	CHF_3/Br_2	$CBrF_3$	Quartz rings	600 °C, yield = 72 %	80

Table 1. Continued

No.	Reactant/ Halogenating agent	Product	Catalyst	Remarks	Ref
Iodination					
75	Toluene/ICl	*para*-Iodotoluene	H-beta, H-K-L	90 °C, conv. ICl = 51.5 %, *para*/*ortho* = 2.88	81
76	Naphthalene and aromatic compounds/I_2 and O_2	Iodonaphthalene and iodo-aromatics	K-X	250 °C, conv. naphthalene = 20 %, conv. I_2 = 80–90 %	82

4.2.4 Fluorination using Solid Catalysts

A major impetus to research in this area during the past two decades (especially since the 1987 Montreal Protocol) has been the need to discover catalysts for the synthesis of alternatives to chlorofluorocarbons, specifically hydrofluorocarbons [83], which destroy the protective ozone layer by generating Cl atoms under the influence of UV radiation.

In addition to the destruction of ozone, the CFCs have also been implicated in global warming. Hydrofluorocarbons (HFCs) have all the advantages of the CFCs (inertness, stability and low toxicity) but, unlike the CFCs, do not contain chlorine and, hence, cannot initiate a chlorine atom-catalyzed ozone destruction cycle. 1,1,1,2-Tetrafluoroethane (HFC-134a; CF_3CH_2F) is a typical example of such a HFC alternative to CFCs such as CFC-12 (CF_2Cl_2). HFCs can be synthesized by a variety of methods including addition of HF to olefins, halogen exchange, isomerization, disproportionation, chlorofluorination, and hydrogenolysis. Solid catalysts have been reported for these reactions in both liquid- and vapor-phase processes. For liquid-phase processes, homogeneous catalysts such as SbX_5, BF_3, TaF_5, NbF_5, and $MoCl_5$ had been proposed [85,86]. Vapor-phase processes often use the fluorides or oxyfluorides of chromium or aluminum or their mixture [87]. Compared with liquid phase processes using homogeneous catalysts, vapor-phase fluorinations are less polluting and corrosive. The catalyst is prepared in two separate stages–preparation of the oxide and partial conversion of the oxide into an oxyfluoride phase by use of HF or other fluorinating agents. Oxides of chromium either unsupported or supported on high surface area supports such as Al_2O_3 or MgO are used. In the fluorination of 1,1,1-trifluoro-2-chloroethane (HCFC-133a) to HFC134a over fluorinated chromium catalysts, Cho et al. [88] reported that conversion increases as the crystallinity of the chromia (both unsupported and supported on various solids) decreases. The conversion over supported chromia decreased in the order MgO > Al_2O_3 > AlF_3 > MgF_2 > TiO_2 > ZrO_2. The selectivity to HFC-134a was not highly dependent on the support type, but highest with MgO, Table 2 [88].

Table 2. Conversions of HCFC-133a and selectivities to HFC-134a for chromium oxide on different supports (GHSV = 1800 L kg_{cat}^{-1} h^{-1}).

Catalyst	Surface area after reaction (m^2 g^{-1})	Temperature (°C): 320		350		370	
		Conv. (%)	Select. (%)	Conv. (%)	Select. (%)	Conv. (%)	Select. (%)
CrO_x/MgO	80.0	9.8	98.4	21.4	98.9	25.9	98.8
CrO_x/Al_2O_3	140.0	4.5	98.0	10.5	97.0	17.3	96.2
CrO_x/AlF_3	28.5	2.1	86.8	5.3	93.4	14.2	95.3
CrO_x/MgF_2	60.0	1.1	85.1	4.0	93.0	8.6	97.6
CrO_x/TiO_2	48.3	–	–	–	–	12.0	94.2
CrO_x/ZrO_2	48.0	0.0	0.0	0.0	0.0	0.0	0.0

One of the major drawbacks of the chromium oxide-based catalysts is their rapid deactivation. A probable reason for this is that the fluorination reaction is also accompanied by dehydrofluorination [89]. For example, in the conversion of CF_3CH_2Cl (HCFC133a) into CF_3CH_2F (HFC134-a), a primary product was found [89] to be the olefin $CF_2{=}CHCl$ formed by the dehydrofluorination of CF_3CH_2Cl. The olefin, at the high operating temperatures (above 300 °C) would undergo acid-catalyzed reactions (e. g. oligomerization, polymerization, etc.) on the acid sites of chromia/chromia–alumina leading to the formation of coke which deactivates the catalyst. Co-feeding oxygen or chlorine with the chlorocarbon and HF had been suggested as a means of avoiding such deactivation [90]. As pointed out by Manzer and Rao [83], however, these two co-feeds, while extending catalyst life, can also contribute to chlorination of the molecule. Chromium oxide is a well-known catalyst for the oxidation of HCl to Cl_2 and H_2O. The use of oxygen can oxidize the HCl coproduct to chlorine, again leading to chlorination of the molecule. Perhaps, a less acidic support, e. g. MgO or Al_2O_3, which do not form coke from olefins or readily oxidize HCl to O_2 under these reaction conditions, should be used. Cho et al. [88] have recently found that MgO and Al_2O_3 are among the best supports for chromium oxide for the conversion of HCFC-133a to HFC-134a. Manzer has also claimed that aluminum fluoride or fluorided alumina have longer lives when used as catalysts [91]. There is still significant scope for improvement of the chromia/alumina/chromia–alumina based catalyst for the fluorination of aliphatic hydrocarbons in the vapor phase, especially in reactor throughput and catalyst life.

Because of the corrosive nature of HF, there are few reports of fluorination reactions in the liquid phase using solid catalysts. The use of zeolites in fluorination was reviewed in our earlier publication [1]. An unusual, room-temperature, solid–catalyzed fluorination of CH_3CCl_3 and related species by anhydrous HF has been reported by Thomson et al. [92–94]. He found that fluorination at ambient temperatures is possible in the presence of catalysts derived from fluorinated γ-alumina, chromia, Fe_3O_4, and Co_3O_4 and conditioned before reaction by treatment with 1,1,1-trichloroethane, 1,1-dichloroethane, or a related chlorocarbon. It was postulated that CH_3CCl_3 undergoes initial dehydrochlorination to $CH_2{=}CCl_2$ over the strong Lewis acid sites on the fluorinated oxide surface. The latter is then converted to an oligomeric chlorocarbon species, probably by the acidic sites. The organic layer provides a quasi-liquid medium to trap CH_3CCl_3 and $CH_2{=}CCl_2$, the latter of which reacts further with HF to form CH_3CCl_2F. The long-term behavior (catalyst life and stability) of this system is not known in detail. It would be interesting to investigate this system further because at the low temperatures involved, formation of oligomeric coke precursors might not be favored and, even if they are formed they are likely to remain dissolved in the chlorocarbon liquid phase and, hence, be unlikely to poison the active sites of the solid catalyst.

4.2.5 Chlorination using Solid Catalysts

Chlorination using zeolite catalysts had been reviewed [1]. K-L zeolite was found to be an excellent catalyst for chlorination, with molecular chlorine as the chlorinating agent, of the aromatic nucleus in the liquid phase [1]. Derivatives of benzene and naphthalene containing a variety of alkyl and halo groups were easily chlorinated on the aromatic nucleus [1]. Catalytic chlorination of aliphatic compounds with solid catalysts is carried out in either of two ways–electrophilic chlorination over acidic catalysts [56] or oxychlorination in the presence of dioxygen over copper-based catalysts [42]. Although aliphatic compounds can be easily chlorinated by a radical mechanism (in the presence of light, for example), the reactions are rather non-selective. When alkanes containing different carbon–hydrogen bonds are chlorinated, all possible monochlorinated isomeric products are obtained. Similarly, chlorination of hydrocarbons, such as methane, with a single type of carbon–hydrogen bond leads to a mixture of mono- and polychlorinated products.

Chloromethane is an important industrial chemical. Olah et al. [56] have reported the selective catalytic monochlorination of methane to chloromethane over superacidic sulfated zirconia solid catalysts, for example SO_4^{2-}/ZrO_2, Pt/SO_4^{2-}/ZrO_2, and Fe/Mn/SO_4^{2-}/ZrO_2. The reactions were conducted in a continuous-flow reactor under atmospheric pressure. At 200 °C with 30 % chlorine the selectivity to chloromethane was $> 90\,\%$.The selectivity could be enhanced by adding platinum. The only by-product was CH_2Cl_2. The latter is formed by the subsequent chlorination of chloromethane. No chloroform or carbon tetrachloride was formed. The authors postulated that chlorination occurs by an electrophilic insertion of an electron-deficient, metal coordinated, chlorine molecule into the C–H bond of methane. One drawback of the process was that above 225 °C, part of the metal was removed as the metal chloride [56]. Formation and subsequent loss of volatile metal chlorides is a major pitfall that should be avoided during vapor-phase chlorination over solid catalysts.

The gas-phase oxychlorination of ethylene with HCl to 1,2-dichloroethane (ethylene dichloride or EDC) catalyzed by $CuCl_2$ supported on alumina, followed by the dehydrochlorination of EDC to vinyl chloride monomer (VCM) is a major industrial process for the manufacture of polyvinyl chloride, a commodity polymer.

$$H_2C{=}CH_2 + 2HCL + 0.5O_2 \rightarrow Cl\text{–}CH_2\text{–}CH_2\text{–}Cl + H_2O$$

In a recent study of the $CuCl_2$–Al_2O_3 catalyst system, Finocchio et al. [42] discovered that at 250 °C, whereas the oxychlorination reaction occurs on copper sites, the alumina surface converts the desired product, EDC, to by-products such as vinyl chloride, trichloroethane, and dichloroethylene. The superiority of copper chloride over copper nitrate as the catalyst precursor is probably because metal chlorides are more highly dispersed than metal nitrates on impregnated alumina surfaces and, hence, expose less of the uncovered alumina surface. $CuCl_2$ is also more effective than copper nitrate in poisoning the nucleophilic sites (exposed oxide anions) on alumina.

An extensive literature exists on the characterization and structure–activity correlation of industrial copper–alumina oxychlorination catalysts [95–120]. At least two different major copper species have been identified. At low concentrations of copper (below ca 5 %), a well-dispersed copper species in intimate interaction with the alumina surface is formed. This species has a very low oxychlorination activity. At higher concentrations, a second species, probably formed by the deposition/precipitation of the copper chloro complexes, is observed. The latter gives rise to the active sites during the oxychlorination reaction. On the basis of an FTIR study of the oxychlorination reaction Finocchio et al. [42] postulated the formation of surface copper chloride–ethylene π-complex intermediates (which lead eventually to EDC) and weakly adsorbed HCl during oxychlorination. Formate species associated with copper and probable precursors for formation of the oxides of carbon by combustion were also identified.

More progress has been reported on the halogenation of aromatic compounds over zeolite catalysts. Jang et al. [55] studied the vapor phase catalytic chlorination of chlorobenzene using solid-acid catalysts such as silica–alumina, alumina, zeolites and modified clay (bentonite) impregnated with $FeCl_3$. Dichlorobenzene selectivity was higher over the zeolite catalysts.

The chlorination of benzyl chloride over H-K-L, K-L, K-beta, K-mordenite, K-ZSM-5, K-Y, and K-X, and in the absence of catalyst, at 353 K produces a mixture of 2-chlorobenzyl chloride (2-ClBC), 3-chlorobenzyl chloride (3-ClBC), 4-chlorobenzyl chloride (4-ClBC), and the side-chain chlorinated product a,a-dichlorotoluene (a,a-DCT) [41]. Zeolites H-K-L, K-L, and K-beta produce predominantly nuclear chlorinated products whereas K-ZSM-5, K-mordenite, K-Y, and K-X give mainly the side-chain chlorinated product. The last was also the main product in the absence of the zeolite catalyst. The highest yield of a,a-DCT was observed for the zeolite K-X. The results confirm that zeolite K-L is more active and *para* selective than other zeolites. We mention here that the conventional concept of geometry-related shape-selectivity alone cannot explain the capacity of zeolite K-L to enhance *para* selectivity in the chlorination of benzyl chloride. Zeolites of similar pore diameter but of different structural types behave differently [1,121]. Factors such as size, charge and position of the cations and the electrostatic forces produced by them in the zeolite channels play an additional role. Van Dijk et al. [122] have proposed that selective *para*-substitution in the halogenation of aromatics over zeolite catalysts might also be influenced by the specific orientation of the substrate molecules in the channels of the zeolites. Orientations of the adsorbed molecule wherein steric hindrance at the *ortho* position is enhanced might also lead to higher *para* selectivity.

1,2,4-Trichlorobenzene (1,2,4-TCB) is used as a dye carrier (via 2,4,5-trichloronitrobenzene) in the production of dyes. 1,2,4-TCB and 1,2,3-TCB (1,2,3-trichlorobenzene) were the primary products in the chlorination of 1,2-dichlorobenzene, whereas small amounts of tetra- and pentachlorobenzenes arise from secondary consecutive reactions of trichlorobenzenes [1,123]. Zeolite K-L and K-beta have comparable activity and selectivity. Further, the selectivity for 1,2,4-TCB is strongly enhanced by addition of $ClCH_2COOH$ to K-L (1,2,4-TCB/1,2,3-TCB = 15.0).A similar effect was also reported in the chlorination of biphenyl [124]. Compared with $FeCl_3$ catalyst (1,2,4-TCB/1,2,3-TCB = 2.1), all zeolite catalysts have higher selectivity for 1,2,4-TCB.

The oxychlorination and oxybromination, under near-ambient conditions, of benzene, toluene, phenol, aniline, anisole, and resorcinol, using as catalysts the phthalocyanines of Cu, Fe and Co encapsulated in zeolites X and Y were reported by Raja and Ratnasamy [125]. Both H_2O_2 and O_2 were used as oxidants. HCl and alkali metal chlorides and bromides were used as sources of halogens. Metal phthalocyanines with aromatic rings substituted by Cl or NO_2 groups were more active. There was a dramatic increase in specific activity when the complexes were encapsulated in the zeolites. Oxyhalogenation of both the aromatic nucleus and the alkyl side chain occurred. Oxidation of the aromatic ring (to phenols or cresols, for example) did not occur. Alkyl side-chains, however, were oxidized by the oxidant H_2O_2 or O_2 to alcohols, ketones, and acids. Halogen molecules, formed by oxidative liberation from the corresponding hydrogen or alkali halides by hydrogen peroxide, were presumably, the halogenating agents.

4.2.6 Bromination Using Solid Catalysts

The reactions of bromine and other brominating agents with organic compounds generally resemble those of chlorine, although there are differences because: (i) the larger size of bromine compared with chlorine leads to a greater influence of steric effects on product formation; (ii) bromine has a greater capacity to bear a positive charge; and (iii) the C–Br bond is weaker than the C–Cl bond and molecular bromine is, hence, less reactive than Cl_2. Bromination reactions over zeolite catalysts have been reviewed until the end of 1994 [1]. Bromination over non-zeolite catalysts and the post-1994 literature on bromination over zeolites will be reviewed here.

H-beta is catalytically active in the bromination of chlorobenzene to the 4- and 2-bromo derivatives [77]. The solid catalyst is less active but more selective for the

4-bromo isomer than H_2SO_4. There was no conversion in the absence of the catalyst. The conversion of NBS (*N*-bromosuccinimide), rate of NBS conversion and isomer ratio (4-BCB/2-BCB) over H-beta are 11.2% (*w*/*w*), 0.61 mmol g^{-1} h^{-1} and 7.0, respectively.

The bromination of toluene with NBS over H-ZSM-5, H-mordenite, H-beta, H-Y, conventional catalyst H_2SO_4, and in the absence of any catalyst yields 2-bromotoluene, 4-bromotoluene, and the side-chain product, α-bromotoluene [77]. Zeolite H-beta and H_2SO_4, produce predominantly the bromoaryl products whereas H-ZSM-5, H-mordenite, and H-Y yield mainly the side-chain brominated product in the bromination of toluene. Zeolite H-beta is more *para* selective (*para*/*ortho* = 5.5) than other catalysts. The acidic H–Y resulted in a higher rate of *N*-bromosuccinimide conversion for the side-chain product. H_2SO_4 is found to be more active but less *para* selective than H-beta. The bromination of xylenes (*o*-, *m*-, *p*-) with NBS over H-beta led both to nuclear and side-chain products whereas H_2SO_4 exclusively gave nuclear products. A higher yield of consecutive reaction products is also obtained over H_2SO_4. In the absence of any catalyst, only the side-chain products from the corresponding xylenes are obtained. The bromination of *o*-xylene over zeolite H-beta leads to the formation of 3-bromo-*o*-xylene (3-BOX), 4-bromo-*o*-xylene (4-BOX), and α-bromo-*o*-xylene (alpha BOX). With *m*-xylene the reaction gives 5-bromo-*m*-xylene (5-BMX). Similarly, bromination of *p*-xylene gave mainly a single monobrominated product, 2-bromo-*p*-xylene (2-BPX). Some α-bromo-*p*-xylene is also detected in the bromination of *p*-xylene. The measured product ratios of 4-BOX/3-BOX and 4-BMX/2-BMX are 5.14 and 2.73, respectively.

The selective *para* bromination of phenyl acetate over the sodium forms of zeolites X and Y has recently been reported by Smith et al. [126]. The removal of the HBr formed by the sodium ions prevents the formation of phenol. Bases, acetic anhydride, and some metal acetates also improve the selectivity.

4.2.7 Iodination Using Solid Catalysts

Iodoaromatic compounds are important in metabolism and radiolabeling studies. Thyroid hormones, amphetamines, and corticosteroids have been investigated using radio-iodine derivatives [127]. Although direct chlorination and bromination of aromatic compounds are well known, the direct and selective iodination of aromatic compounds is much more difficult owing to the lower electrophilicity of the iodine molecule. Hence, iodination by molecular iodine in the liquid phase occurs only with phenols and anilines.

ICl is a popular iodinating agent for liquid-phase iodinations. Electrophiles such as I^+ or I_3^+, formed 'in situ' from ICl are the probable iodinating agents The iodination of toluene with ICl over different acidic and basic zeolites is accompanied to some extent by simultaneous chlorination [128–132]. The main products of the reaction are the *para* and *ortho* isomers of iodotoluene and chlorotoluene. The absence of side-chain products (benzyl iodide and benzyl chloride) suggests that halogenation of toluene by ICl occurs by an electrophilic rather than a homolytic process. H-beta and H-K-L zeolites are more *para* selective than other acidic or basic zeolites.

Even though molecular iodine is less reactive than Cl_2 or Br_2, in the presence of oxidizing agents such as dioxygen, HNO_3, H_2O_2, or peracetic acid, iodination of benzene, alkylbenzenes, and even benzene rings with deactivating groups occurs readily. Naphthalene, iodine, and oxygen react in the vapor phase at 225–350 °C over basic faujasite zeolites to produce iodonaphthalenes and water [82]. The product contained 10 % 1-iodonaphthalene, 65 % 2-iodonaphthalene, 19 % 2,6-diiodonaphthalene, 5 % other diiodonaphthalene isomers and 1 % mixed triiodonaphthalene isomers, with 20 % conversion of naphthalene and 80–90 % conversion of iodine. Selectivity for iodination in the 2-position is reduced by substituting sodium for potassium in the zeolite and by altering the Si/Al ratio of the zeolite significantly above or below 1.25. Conventional iodination techniques in the liquid phase using I_2 and nitric acid or other strong oxidants result in preferential iodination in the 1-position. The shape selectivity of the zeolite, probably, causes this effect.

4.2.8 Conclusions

There are significant environmental advantages in the use of solid catalysts, rather than the Lewis acid catalysts (e. g. $AlCl_3$ and $FeCl_3$) currently used, during the manufacture of fine chemicals, especially in *para*-selective nuclear halogenations of aromatic compounds. The use of zeolites in such reactions leads to enhanced yields of the *para* isomer, thereby reducing the formation of by-products and the cost of operation. There is a need for a deeper understanding of the mechanism of halogenation over solid surfaces. There is a major gap in our understanding of aspects of the surface science of the changes undergone by the solid catalyst during the halogenation reaction (either in the vapor or liquid phase). The relatively short cycle lengths of the catalysts used in vapor-phase fluorinations of CFCs, for example, can be enhanced considerably by knowledge of the surface species present on such oxyfluoride catalysts and their interactions with the CFCs and HCFCs. Identification of the nature of the active copper sites in oxychlorination might lead to better processes with greater selectivity for EDC. Similarly, in liquid-phase halogenations, although the superiority of K-L zeolites is well established [1], the structural origins of the phenomenon are not well understood. In view of the increasing general tendency in the chemical industry to replace homogeneous by solid catalysts, activity in this field is expected to grow.

References

[1] (a) P. Ratnasamy, A. P. Singh and S. Sharma in 'Handbook of Heterogeneous Catalysis '(Eds. G. Ertl, H. Knozinger and J. Weitkamp) Wiley–VCH, Germany, 1997, Vol. 5, p. 2848; (b) Ibid., Appl. Catal., A: General 135 (1996) 25.

[2] A. J. Downs and C. J. Adams, in J. C. Bailar Jr., H. C. Emelens, R. S. Nyholm and A. F. Trotman – Dickenson (Editors), Comprehensive Inorganic Chemistry, Pergamon, Vol. 2, 1993, p. 1107.

[3] P. B. D. de la Mare, Electrophilic Halogenation, Cambridge University Press, Cambridge, 1976.
[4] T. D. Stewart and K. R. Edlund, J. Amer. Chem. Soc., 45 (1923) 1014.
[5] R. G. W. Norrish, J. Chem. Soc., 123 (1923) 3006.
[6] G. Williams, J. Chem. Soc., (1932) 1747, 1758.
[7] H. C. Dong, G. K. Young, J. C Moom and S. C. Jong, Appl. Catal, 18 (1998) 251.
[8] L. Hyunjoo, K. H. Sik, K. Honggon, J. W. Sik, S. Inseok, J. Mol. Catal., 136 (1998) 85.
[9] D. H. Cho, Y. G. Kim and J. S. Chung, Catal. Lett., 53 (1998) 199.
[10] B. A. Mahler, PCT Int. Appl. WO 9819981 (1998).
[11] D. H. Cho, Y. G. Kim, M. J. Chung and J. S. Chung, Korean J. Chem. Eng., 14 (1997) 502.
[12] S. Yoshikawa, Y. Tamai and Y. Hibino, Jpn. Kokai Tokkyo Koho JP 10007604 (1998).
[13] S. Yoshikawa, R. Tamai and Y. Hibino, Jpn. Kokai Tokkyo Koho JP 10007605 (1998).
[14] V. N. M. Rao, US Pat. 5602288 (1997).
[15] B. Requieme, E. Lacroix and A. Latz, EP 751107 (1997).
[16] B. Requieme, S. Perdrieux, B. Cheminal, E. Lacroix and A. Lantz, EP 751108 (1997).
[17] K. Tsuji and T. Nakajo, Jpn. Kokai Tokkyo Koho JP 08310980 (1996).
[18] A. Bendada, D. W. Bonniface, F. MeMonagle, R. Marshall, C. Shortman, R. R. Spence, J. Thomson, G. Webb, J. M. Winfield and N. Winterton, Chem. Commun., (1996) 1947.
[19] H. Li Quan, Z. Zhong, Z. Zhao, H. Lu Yang, R. J. Chen, S. K. Chen, H. Fang and H. Li, Appl. Catal. B, 8 (1996) 209.
[20] D. Zhang, C. Wang, F. Mistry, B. Powell and F. Aubke, J. Fluorine Chem., 76 (1996) 83.
[21] V. Yu. Zakharova, A. K. Denisov and M. D. Novikova, Zh. Org. Khim., 30 (1994) 1844.
[22] S. Brunet, B. Requieme, E. Colnay, J. Barrault and M. Blanchard, Appl. Catal., B 5 (1995) 305.
[23] S. Morikawa, K. Oonishi, S. Okamoto and T. Tanuma, Jpn. Kokai Tokkyo Koho JP 06279328 (1994).
[24] E. Lacroix, A. Lantz and B. Cheminal, EP 612709 (1994).
[25] Q. Yu, and X. Huang, Shanghai, 18 (1993) 12.
[26] J. D. Scott and J. M. Watson, PCT Int. Appl. WO 9316798 (1993).
[27] J. Thomson, G. Webb, J. Winfield, D. Bonniface, C. Shortman and N. Wintertan, Appl. Catal. A, general, 97 (1993) 67.
[28] T. Shibanuma, Y. Iwai and S. Koyama, EP 514932 (1992).
[29] V. M. Felix, W. H. Gumprecht and B. A. Mahler, PCT Int. Appl. WO. 9219576 (1992).
[30] D. R. Corbin and V. N. M. Rao, PCT Int. Appl. WO 9216479 (1992).
[31] Y. Tasaka, and T. Nakasora, Jpn Kokai Tokkyo Koho JP 03184933 (1991).
[32] J. Thompson, G. Webb and J. M. Winfield, J. Chem. Soc. Chem. Commun. (1991) 323.
[33] S. Morikawa, S. Samejima, M. Yoshitake and S. Tatematsu, Jpn. Kokai Tokkyo Koho JP 02311429 (1990).
[34] S. Morikawa, S. Samejima, M. Yoshitake and S. Tatematsu, Jpn. Kokai Tokkyo Koho JP 02178237 (1990).
[35] K. Yanagii, S. Yoshikawa and K. Murata, Jpn. Kokai Tokkyo Koho JP 02157235 (1990).
[36] H. Okajima, T. Nakano, F. Ishii and S. Sato, Jpn. Kokai Tokkyo Koho JP 01180838 (1989).
[37] I. Lehms, R. Kaden, D. Mross and D. Hass, Ger. (east) DD 225053 (1985).
[38] B. Cheminal and H. Mathias, Eur: Pat: Appl. EP 145596 (1985).
[39] H. R. Nychka and R. E. Eibek, US Pat. 4088704 (1978).
[40] D. R. Coulson, J. Catal., 142 (1993) 289.
[41] S. M. Kale and A. P. Singh, J. Mol. Catal., 138 (1999) 263.
[42] E. Finocchio, N. Rossi, G. Busca, M. Padovan, G. Leofanti, B. Cremasch, A. Marsella, and D. Carmella, J. Catal., 179 (1998) 606.
[43] T. Xun, L. Xin, Z. Hongsheng and Z. Xiansheng, Xiandai Huagong, 18 (1998) 28.
[44] W. Weihua and Y. Xinshe, Henan Huagong, (2) (1998) 15.
[45] A. P. Singh, Stud. Surf. Sci. Catal., 113 (1998) 419.
[46] S. Sharma, R. C. Deka, A. P. Singh and R. Vetrivel, Stud. Surf. Sci. Catal., 113 (1998) 675.
[47] A. P. Singh, S. Sharma and S. M. Kale, J. Mol. Catal., 127 (1997) 101.
[48] S. Sharma, S. G. Hegde and A. P. Singh, Appl. Catal. 162 (1997) 201.
[49] X. Tang, G. Shi and P. Liu, Xiandai Huagong, 17 (1997) 721.

[50] A.P. Singh, S. Sharma and S.M. Kale, Catal. Lett., 42 (1996) 191.
[51] A.P. Singh, S. Sharma and S.R. Rojatkar, J. Chem. Res (1995) 512.
[52] A. Jonczyk and T. Radwan-Pytlewski, Poly. J. Chem., 69 (1995) 1422.
[53] S. Morikawa, Y. Takagi and N. Yoshida, Jpn. Kokai Tokkyo Koho JP 07206727 (1995).
[54] S. Morikawa, Y. Takagi and N. Yoshida, Jpn. Kokai Tokkyo Koho JP 07206726 (1995).
[55] H.J. Jang, P.H. Choi and S.E. Park, Bull. Korean Chem. Soc., 16 (1995) 507.
[56] P. Batamack, I. Bucsi, A. Molnar and G.A. Olah, Catal. Lett., 25 (1994) 11.
[57] J.P. Senet, EP 545774 (1993).
[58] D. Kantrec, B. Ladesic, Z. Hamersak and V. Sunjik, Appl. Radiat. Isot., 44 (1993) 1133.
[59] D. Lu, Huaxue Fanying Gongcheng Yu Gongyi, (1986) 21.
[60] F. Yamaguchi, T. Otsuka and K. Nakagawa, EP 514920 (1992).
[61] L.K. Volkova, V.N. Tret'Yakov, L.A. Min'ko and E.S. Rudakov, Kinet. Katal., 33 (1992) 321.
[62] Y.M. Bakshi, E.I. Gel'perin, M.P. Dmitrieva and A.I. Gel'bshtein, Kinet. Katal., 32 (1991) 1412.
[63] N. Ito and S. Ishii, Jpn. Kokai Tokkyo Koho JP 01093550 (1989).
[64] M. Kodomari, S. Takahashi, H. Watanabe and S. Yoshitomi, Nippon Kagabu Kaishi, (1987) 1753.
[65] H.D. Eichhorn, C. Jaeckh, W.D. Mross and H. Schuler, Int. Congr. Catal., Proc., 8th, Volume 4, IV 647-IV 656, Verlag Chemie Weinheim, Fed Rep. Ger (1985).
[66] S. Lippert, W. Kochmann, W. Sattelmayer and G. Vogel, Ger (East) DD 229114 (1995).
[67] M. Awashima and O. Kaieda, Jpn. Kokai Tokkyo Koho JP 60161974 (1985).
[68] A.M. Potapov, U.S. Rysaev, S.R. Rafikov and R.B. Valitov, Neftekhimiya (1985)146.
[69] K.M. Hossi and J. Wolstenholme, Eur. Pat. Appl. EP. 113513 (1984).
[70] A.M. Potapov, R.B. Valitov, and A.S. Evolokimova Zh. Prikl. Khim., 57 (1984) 356.
[71] G.A. Olah, PCT Int. Appl. WO 8300859 (1983).
[72] A.D. Ali, F.F. Muganlinskii, V.V. Kas'yanov and E.A. Gazaryan, Azerb. Khim. Zh. (1981) 18.
[73] H. Konishi, K. Yokota, Y. Ichihasli, T. Okano and J. Kiji, Chem. Lett. (1980) 1423.
[74] B.R. Puri, D.D. Singh, N.C. Kaura and S.K. Verma, Ind. J. Chem., 19 (1980) 109.
[75] Anon Res. Discl., 175 (1978) 44.
[76] Anon. Res. Discl. 175 (1978) 31.
[77] A.P. Singh, S.P. Mirajkar and S. Sharma, J. Mol. Catal. 150 (1999) 241.
[78] S. Hussain, US Pat., 5710354 (1998).
[79] V.G. Sharov, B.S. Tanaseichuk, V.N. Shishmin and A.I. Belozerov, USSR DSU 1097590(1984)
[80] H. Bock, J. Mintzer, J. Wittmann and J. Russow, Angew Chem., 92 (1980) 136.
[81] S. Sharma, A.R.A. S Deshmukh and A.P. Singh Catal. Lett., 49 (1996) 257.
[82] G.C. Tustin and M. Rule, J. Catal, 147 (1994) 186.
[83] L.E. Manzer and V.N.M. Rao, Adv. Catal., 39 (1993) 329.
[84] H.-D Quan et al., Appl. Catal., B: Environmental 8 (1996) 209.
[85] A.E. Feiring, J. Fluorine Chem., 14 (1979) 7.
[86] A.E. Feiring, US Pat., 4258225 (1981).
[87] H. Lee, H.S. Kim, H. Kim, W.S. Jeong and I. Seo, J. Mol. Catal., A: Chemical: 136 (1998) 85.
[88] D.H. Cho, Y.G. Kim and J.S. Chung, Catal. Letters, 53 (1998) 199.
[89] S. Brunet et al, J. Catal., 152 (1995) 70.
[90] US Pat., 2030981 (1978).
[91] US Pat., 5051537 (1991).
[92] J. Thomson, G. Webb, J.M. Winfield, D.W. Bonniface, C. Shortman and N. Winterton, Appl. Catal., A:97 (1993) 67.
[93] J. Thomson, J. Chem. Soc., Faraday Trans., 90 (1994) 3585.
[94] A. Bendada, D.W. Bonniface, F. McMonagle, R. Marshall, C. Shortman, R.R. Spence, J. Thomson, G. Webb, J.M. Winfield and N. Winterton, Chem. Commun., (1996) 1947.
[95] A. Arcoya, A. Cortes and X.L. Seone., Can. J. Chem. Eng. 60, (1982), 55

[96] Vetrivel, R., Rao, K. V., Seshan, K., Krishnamurthy, K. R., and Prasada Rao, T. S. R., in "Proc. 9th Int. Congr. Catal., Calgary, Vol. 5 (1988), 1766.
[97] J. Blanco, R. Blanco, A. Cortes, and J. A. Soria, in "Proc. 5th Int. Congr. Catal., Miami Beach, (1973), 905.
[98] J. Blanco, J. Fayos, J. F. Garcia de la Banda, and J. Soria, J. Catal. 31 (1973) 257.
[99] Doston, R. L., J. Catal. 33 (1974) 210.
[100] Yu. M. Bakshi, , M. P. Dmitrieva, , and A. I. Gel'bshtein, Kinet. Katal. 17 (1976) 1023.
[101] J. Valle, A. Vargas, J. M. Ferreira, A. Flores and O. Novaro, Stud. Surf. Sci. Catal. B7 (1981) 1040.
[102] P. Avila, J. Blanco, J, L. Garcia-Fierro, S. Mendioroz, and J. Soria, Stud. Surf. Sci. Catal. B7 (1981) 1031.
[103] R. J. Ott and A. Baiker, Stud. Surf. Sci. Catal. 16 (1982) 685.
[104] G. Zipelli, J. C. Bart, G. Petrini, S. Galvagno, and C. Cimino, Z. Anorg. Allg. Chem. 502 (1983) 199.
[105] A. Baiker, and W. L. Holstein, J. Catal. 84 (1983) 178.
[106] I. G. Solomonik, I. I. Kurlyandskaya, V. I. Yakerson, T. F. Kudryavtseva, G. A. Ashavskaya, M. R. Frid, Yu. A. Treger, and E. V. Sonin, , Izv. Akademii Nauk SSSR Ser. Khim. 11 (1984) 2431.
[107] Yu. M. Bakshi, M. P. Dmitrieva and A. J. Gel'bshtein, Kinet. Katal. 25 (1984) 2785.
[108] P. G. Hall, P. Heaton, and D. R. Rosseinsky, J. Chem. Soc. Faraday Trans. I 80 (1984) 2785.
[109] I. G. Solomonik, I. I. Kurlyandskaya, V. Ya. Danyushevskii, and V. I. Yakerson, Izv. Akad. Nauk. SSSR Ser. Khim. 10 (1984) 2175.
[110] I. G. Solomonik., I. I. Kurlyandskaya, V. Ya Danyushevskii and V. I. Yakerson, Izv. Akad Nauk. SSSr Ser. Khim 10 (1984) 2180.
[111] M. P. Dimitreva, Yu. M. Bahshi and A. I. Gel'bshtein, Kinet. Katal. 26 (1985) 1359.
[112] A. Baiker, D. Monti, and A. Wokaun, Appl. Catal. A: General, 23 (1986) 425.
[113] E. M. Fortini, C. L. Garcia and D. E. Resasco, J. Catal. 99 (1986) 12.
[114] M. Loos, J. Goulon, M. Bertucci and R. J. Bachelard, J. Phys. Coll. C8 Suppl. 47(12), (1986) 285.
[115] I. G. Solomonik, I. I. Kurlyandskaya, G. A. Ashavskaya and V. I. Yakerson, Izv. Akad. Nauk, SSSR Ser. Khim 4 (1986) 766.
[116] I. I. Kurlyandskaya, M. I. Dasheveskii, I. G. Solomonik, T. F. Kudryavtseva and V. I. Yakerswon, Izv. Akad. Nauk. SSSR Ser. Khim 6 (1987) 1220.
[117] P. S. Sai Prasad and P. Kanta Rao, J. Chem. Soc. Chem. Commun., (1987) 951.
[118] P. A. Sermon, K. Rollins, P. N. Reyes, S. A. Lawrence, M. A. Martin Luengo and M. J. Davies, J. Chem. Soc. Faraday Trans. I 83 (1987) 1347.
[119] E. M. Fortini, C. L. Garcia and D. E. Resasco, React. Kinet. Catal. Lett. 36 (1988) 223.
[120] C. L. Garcia and D. E. Resasco., Appl. Catal. 46 (1989) 251.
[121] Th. M. Wortel, D. Oudijn, C. J. Vleugel, D. P. Roelofsen and H. van Bekkum, J. Catal., 60 (1979) 110.
[122] J. Van Dijk, J. J. van Daalen, G. B. Paerels, Recl. Trav. Chim. Pays-Bas, 93 (1974) 72.
[123] A. P. Singh and S. B. Kumar, Appl. Catal. A: General, 126 (1995) 27.
[124] A. Botta, H. J. Buysch and L. Puppe, Angew. Chem. Int. Ed. Engl., 30 (1991) 1689.
[125] R. Raja and P. Ratnasamy, J. Catal., 170 (1997) 244.
[126] K. Smith, P. He, A. Taylor, Green Chem., 1 (1999) 35.
[127] S. Rozen and D. Zamir, J. Org. Chem., 55 (1990) 3552.
[128] H. P. Braendlin and E. T. McBee, in: Friedel–Crafts and Related Reactions, Vol. III, Part 2: Halogenation, ed. G. A. Olah, Wiley Interscience, New York (1964) p. 1531.
[129] L. J. Lambourne and P. W. Robertson, J. Chem. Soc. (1947) 1167.
[130] R. M. Keefer and L. J. Andrews, J. Am. Chem. Soc., 78 (1956) 5623.
[131] L. J. Andrews and R. M. Keefer, J. Am. Chem. Soc., 86 (1964) 4159.
[132] D. E. Turner, R. F. O'Malley, D. J. Sardella, L. S. Barinelli and P. Kaul, J. Org. Chem., 59 (1994) 7335.

4.3 Friedel–Crafts Alkylation

G. R. Meima, G. S. Lee, J. M. Garces

4.3.1 Introduction

Friedel–Crafts reactions are characterized by an extremely broad and difficult to define range of chemistries. One of the best definitions is given by Nobel Prize laureate G. A. Olah in the classical series *Friedel–Crafts Related Reactions* [1] in which he defines these reactions "to be any substitution, isomerization, elimination, cracking, polymerization, or addition reactions taking place under the catalytic effect of Lewis acid type acidic halides (with or without co-catalyst) or proton acids". Initial Friedel–Crafts chemistries were typically related to acidic metal halide catalysts such as $AlCl_3$, BF_3, $FeCl_3$ and $ZnCl_2$. Large-scale industrial applications were developed in the 1930s and 1940s for the manufacture of polyisobutylene, butyl rubber, and ethylbenzene. During World War II butane was isomerized to isobutane using $AlCl_3$, in an intermediate step to produce alkylate for aviation fuel. Since then many other applications have been developed and commercialized. An excellent overview of this field of technology can be found in the *Kirk–Othmer Encyclopedia of Chemical Technology* [2].

Friedel–Crafts reactions are electrophilic in nature and can be divided into two categories–alkylations and acylations. This section will emphasize alkylations; in Section 4.4 attention will be given to acylations.

Today many large volume bulk chemicals are produced using Friedel–Crafts catalysts. Important applications include the production of ethylbenzene and cumene via alkylation of benzene with ethylene and propylene, respectively. Interestingly, $AlCl_3$ is still used as catalyst in some plants although improved technologies have been developed.

The overall reaction scheme for aromatic alkylations using $AlCl_3$ is usually written as follows:

$$C_6H_6 + RX \xrightarrow{AlCl_3} C_6H_6R + HX$$

The primary function of the metal halide is to generate a carbocation. Because this is achieved relatively easily by abstracting a halogen atom from an alkyl halide, alkyl halides are often used or added as co-catalysts during alkylation reactions. A disadvantage of classical Friedel–Crafts chemistry with metal halides is that the catalyst coordinates strongly to basic compounds and eventually becomes exhausted and cannot readily be regenerated. Other drawbacks are intramolecular rearrangements (which reduce selectivity for the desired compound), environmental considerations, and the corrosive nature of the system.

Pure olefins (without co-catalyst) or paraffins (π- or σ-donor agents) can be activated only by strong protic acids or superacids. Although in the classical sense the activation of an olefin by an acid to form a carbenium ion is not a Friedel–

Crafts reaction, in the light of the mechanism described it can be considered a modification thereof.

In non-metal halide chemistry, in particular, enormous progress has been made after the introduction of highly acidic solid acids such as synthetic zeolites. A major breakthrough was the development of the synthetic zeolite ZSM-5 and its application in the Mobil–Badger process for the production of ethylbenzene in 1980 [3]. This event initiated strong research emphasis on the use of acidic zeolite catalysts for the commercial production of petrochemicals. Their advantages over conventional Friedel–Crafts catalysts are clear when taking into account the associated drawbacks mentioned above. Another important feature of zeolites is that the molecular dimensions of the pores enable shape-selective alkylation of aromatics. The formation of bulky molecules, e. g. polyalkylaromatics, does not occur and it is possible to direct polyalkylation to certain (preferred) isomers.

In recent years a tremendous amount of work has been performed in this area and many processes have been commercialized. Tanabe and Hölderich [4] have published an up-to-date overview of many of these processes and so no attempt will be made to give a broad overview of Friedel–Crafts-related chemistries here. Besides the Tanabe and Hölderich paper, reviews on more fundamental aspects are also available [1,2]. An approach we consider more worthwhile is to illustrate the large potential of (modified) zeolite catalysts have in this important field of chemistry through a few illuminating examples. This is a growing field of research with large potential also for the production of fine chemicals.

4.3.2 Dialkylation of Benzene and Polynuclear Aromatics

Valuable products and versatile intermediates are derived from the dialkylates of benzene and polynuclear aromatics. For instance, diethylbenzenes are used for the production of divinylbenzenes that find application in polymer manufacture. *Para* and *meta* isomers of diisopropylbenzene (DIPB) are used for the manufacture of hydroquinone and resorcinol, respectively. Dehydrogenation of DIPB gives rise to diisopropenylbenzenes, which can be polymerized relatively easily [5,6]. Colvin and Muse [7] have given an excellent overview of the possible applications of these molecules. Anionic polymerization with an organometallic initiator leads to a polymer with a pendant isopropenyl group. By grafting onto this group it is possible to prepare novel polymers. Cationic polymerization of diisopropenylbenzenes under the influence of Friedel–Crafts catalysts can give rise to polyindan with a high glass transition temperature. Upon incorporation of the diisopropenyl moiety specialty engineering plastics can be prepared.

Preparation of the starting material DIPB is typically achieved by isopropylation of benzene or cumene by use of conventional Friedel–Crafts catalysts [8] although solid acids [9], resins [10] and, more recently, zeolites [11,12] have also been mentioned as catalysts. Likewise, alkylation of polynuclear aromatics, e. g. biphenyl or naphthalene, gives rise to valuable intermediates. 4,4′-Dialkylbiphenyl can be converted into 4,4′-biphenyldicarboxylic acid, a monomer for a variety of high-performance polymers and liquid crystal applications. Similarly 2,6-dialkylnaphthalene (2,6-DAN) is the raw material for the manufacture of high-quality polyester fibers and plastics. Traditionally, 2,6-DAN is produced by the alkylation of naphthalene over a metal halide Friedel–Crafts catalyst [13].

From the description above it is evident that certain dialkyl isomers are desired and that others can be detrimental to the quality of the product, especially in high-performance polymer applications, and conventional Friedel–Crafts catalysts are not usually totally suitable. This is illustrated in Figure 1, which depicts the possible isomers arising from unrestricted dialkyl substitution of naphthalene. Apart from the low efficiency obtained, the presence of the large number of isomers makes separation by conventional methods virtually impossible.

Selective alkylation is therefore highly desired. Zeolites have proven to have excellent properties in this respect, and shape-selective reactions on these materials are well known [14]. Dow Chemical pioneered the shape-selective alkylation of polynuclear aromatics with olefins such as propylene, using as catalysts modified mordenite zeolites, which were not considered at the time to behave strictly as shape-selective catalysts [15,16]. Mordenite zeolites were not the catalyst of choice for such reactions because the alkylation of aromatics, and in particular of polynuclear aromatics, was recognized already as a first step in the reactions leading to coke formation and catalyst deactivation [17]. How was it possible to convert these unsuitable zeolites into stable and highly shape-selective catalysts for industrial applications? The answer to this question will be used to illustrate the criteria and methods used to develop the so-called 3-DDM catalysts, or 3-dimensional dealuminated mordenites.

Mordenite is known in both natural and synthetic crystalline forms with a guest-free unit cell (uc) composition $Na_8Al_8Si_{40}O_{96}$. This requires eight Al/uc and an Si/

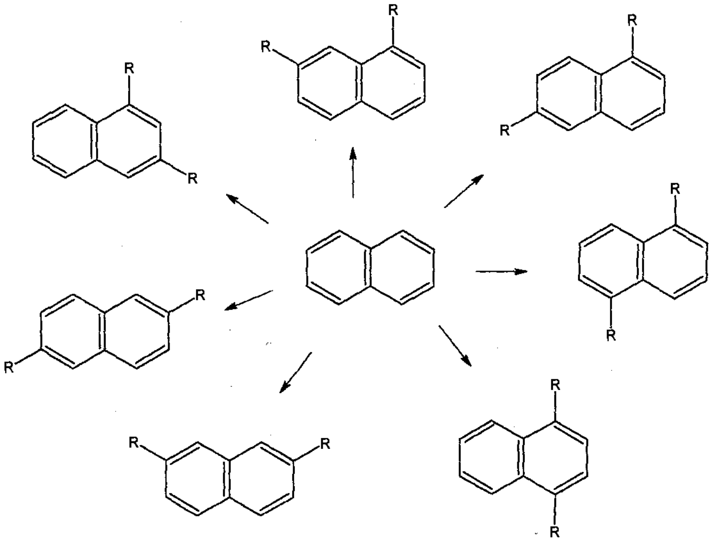


Figure 1. Possible isomers from dialkyl substitution of naphthalene.

Al ratio of 5 {*SAR* = SiO_2/Al_2O_3 = 10 (molar)}. Mordenite is the most siliceous of the natural zeolites and has 12- and 8-ring channels parallel to the *c*-axis connected via staggered eight-ring side pockets. The unit cell has four types of unique tetrahedral (T_i) site, T1, T2, T3, and T4, with relative uc populations of 16, 16, 8, and 8, respectively [18]. The dimensions of the twelve-ring pores are ca 6.7 Å × 7.0 Å and the eight-ring pores are ca 2.9 Å × 5.7 Å [19]. Mordenites can be generally described as having the *Cmcm* symmetry with *Cmmm* contributions resulting from *c*-axis faulting [20]. A practical means of estimating the amount of faulting is by use of the symmetry index (*SI*), defined as the sum of the peak heights of the [111] (13.45, 2θ) and the [241](23.17, 2θ) reflections divided by the peak height of the [350](26.25, 2θ) reflection, all reflections based on Cu Kα X-ray radiation. *SI* values differ for various natural and synthetic mordenites and can change during chemical or physical treatment of mordenite samples.

The dealumination of mordenite by different treatments has been the subject of numerous studies [21–24]. Many of these dealumination studies observed marked differences from sample to sample [25]. Alteration of the lattice symmetry and reduced thermal stability has been observed in acid-dealuminated mordenite heated above 650 K [26]. The variety of changes involved in the dealumination of mordenite, and the problems associated with reproducibility, crystallographic symmetry changes, and the lack of specific knowledge relating to sample source and treatment conditions make interpretation of the literature on this subject a challenge. The introduction of *SI* is an attempt to help clarify differences between data on mordenite and mordenite catalysts.

The procedure for alkylation of polynuclear aromatics with mordenite catalysts developed at Dow Chemical [15,16] requires sodium mordenite with an *SI* from 0.6 to 1.0. The crystalline aggregates of mordenite range in size from 1–20 μm and are formed from crystallites ranging in size from 500–5000 Å. The selected sodium mordenite is treated with inorganic acids to make hydrogen mordenite (HM). HM is calcined at 400–700 °C and further treated with strong acid to produce catalyst precursors. The severity of the thermal and acid treatments, the number and sequence of the treatments, and the type of binder defines the properties of the 3-DDM catalysts.

Dealumination increases the *SAR* of mordenite from values of 10–30, found in natural and synthetic mordenites, to *SAR* from 100–1000, found in highly dealuminated samples. Dealumination also changes *SI* from 0.3–1.0 to 1.5–2.0 or higher. Finally, severe dealumination changes the porosity of mordenites, altering the total pore volume and the pore-size distribution. This combination of changes transforms synthetic mordenites into highly active and selective alkylation catalysts. The 3-DDM catalysts have a new pore structure, such that the eight- and twelve-ring pores in crystalline domains of mordenite are connected by mesopores (ca 50–100 Å). The 3-DDM catalysts were characterized by bifunctional hydroconversion of *n*-decane (BHD) as test reaction. The results indicate an apparent dimensionality change in the channel system from 1-D to higher dimensionality (2-D, 3-D) [27]. Surprisingly, the presence of mesopores modifies the diffusion behavior but has only a small impact on the shape-selective chemistry of the twelve-ring crystalline domains. The meso- and macropores greatly enhance accessibility to the micropore regions resulting in a superior reactant and product mobility and in superior utilization of active sites. An additional benefit of high dealumination is the severe reduction or elimination of active Al sites from the meso- and macropores. This feature constrains the main catalytic reactions to the micropores and helps reduce coke formation and catalyst deactivation. The creation of mesopores within the crystalline domains also reduces the effective length of the twelve-ring pores to 50 to 500-Å segments, which facilitates egress of large product molecules such as 4,4′-diisopropylbiphenyl and reduces pore blockage [15].

The increased activity and stability combined with the shape-selective effect of these tailored mordenites is illustrated beautifully by comparing results for biphenyl alkylation with those obtained using either a more traditional catalyst or nonmodified zeolites. The results are summarized in Table 1 [15]. DHM-2X is a modified mordenite later referred to by Dow as 3-DDM after the more extensive studies described above. The SiO_2/Al_2O_3 molar ratio of this sample was 2600. The Zeolon 100 sample is a standard commercially available mordenite with a SiO_2/Al_2O_3 ratio of 10.

The results clearly demonstrate the improved performance of the tailored mordenite. Typically the selectivity is much lower for other catalysts. The more narrow pores of ZSM-5 limit access of the biphenyl explaining the very low activity of this catalyst. These findings were later confirmed by similar experiments performed by Sugi and Toba [28].

The activity and shape-selectivity of 3-DDM type catalysts can be further directed by careful adjustment of the alkylation conditions. This is illustrated by the results presented in Table 2 [16].

It is apparent that the linear *p,p′*-diisopropylbiphenyl is obtained after short contact times. Longer residence time leads to isomerization to the thermodynamically more stable *p,m* isomer. Another factor of importance in this respect is the presence of external acid sites. Hanaoka et al. [29] recently showed that the low *p,p′*-DIPBP selectivity of H-mordenites with a low SiO_2/Al_2O_3 molar ratio is

Table 1. Alkylation of biphenyl (BP) with propylene at 523 K. Analysis after 20 h in batch experiments using 500 g BP and 10 g catalyst at 8.43 kg cm^{-2} propylene pressure. Stirring rate 2000 rpm (Reprinted with permission from Baltzer Science Publishers).

Catalyst	BP conv. (%)	Sel. (%)[a]	DIPBP yield (%)
H_3PO_4	48	1.9	0.9
Zeolite Y	90	6.7	6.0
Zeolite L	73	3.8	2.8
Offretite	96	14.7	14.2
ZSM-5	5	–	–
Zeolon 100	21	3.8	0.8
DHM-2X (3-DDM)	98	73.5	72

[a] Selectivity to diisopropylbiphenyl isomers (DIPBP).

Table 2. Alkylation of biphenyl (BP) with propylene over a 3-DDM catalyst with an SiO_2/Al_2O_3 molar ratio of 256. Batch experiments were performed using 500 g BP and 10 g catalyst. The stirring rate was as indicated and pressure was maintained at the desired value by use of propylene which was continuously fed on demand.

Time (h)	Temp. (°C)	*P* (psig)	Agitation (rpm)	Conv. (%)	$p,p'/\Sigma di^{a}$ (%)	$(p,p'+p,m')/\Sigma di$ (%)	$\Sigma di/TA^{b}$ (%)	$p,p'/p,m'$	*p,p'* yield (%)	$p,p'+p,m'$ yield (%)
4	250	120	2000	84	86	96	62	8.6	45	50
9	250	120	2000	98	86	96	71	8.6	60	67
20	300	120	2000	89	48	93	47	1.1	20	39
20	250	120	400–500	94	52	95	58	1.2	28	52
20	250	40	2000	90	72	97	52	2.9	34	45
20	120	15	2000	70	15	63	26	0.3	3	11

[a] *di* is the total number of moles of dialkylated isomers.

[b] *TA* represents the total amount (mol) of alkylbiphenyls.

Table 3. Isomerization of *p,p'*-diisopropylbiphenyl over a 3-DDM catalyst with an SiO_2/Al_2O_3 molar ratio of 256 at 270 °C in the presence (120 psig) and absence of propylene. Batch experiments were performed using 500 g *p,p'*-DIPBP and 10 g catalyst.

Time (h)	*p,p'*-DIPBP (% *w/w*)		*p,m'*-DIPBP (% *w/w*)		Others[a] (% *w/w*)		$p,p'/p,m'$	
	p[b]	a[c]	p	a	p	a	p	a
0	98	98	2	2	0	0	49	49
3	88	50	4	25	8	25	22	2
20	85	15	5	45	10	40	17	0.3

[a] Others are mainly monoalkylated products such as 3-IPBP and 4-IPBP.

[b] Propylene present.

[c] Propylene absent.

not because of lack of shape selectivity, but because of non-regioselective isopropylation at the external acid sites. Also, lower propylene partial pressures lead to higher yields of *p,m'*-DIPBP. In another experiment pure *p,p'*-DIPBP was isomerized at 270 °C both in the presence and absence of propylene (120 psig). The results are presented in Table 3. In the presence of propylene the $p,p'/p,m'$ ratio is 17, whereas it is 0.5 in the absence of propylene. This is because of the strong adsorption of propylene by the acid sites, which limits the adsorption and subsequent isomerization of *p,p'*-DIPBP.

Similar shape-selective catalysis has been observed when alkylating benzene over 3-DDM-type catalysts. These results have been presented elsewhere [30]. The combined results clearly indicate that shape selectivity is controlled by the size of the twelve-ring pore of mordenite and the adsorption characteristics of the reactants. The size effect is illustrated in Figure 2 for the *p,p'*- and *p,m'* DIPBP isomers in the alkylation of BP.

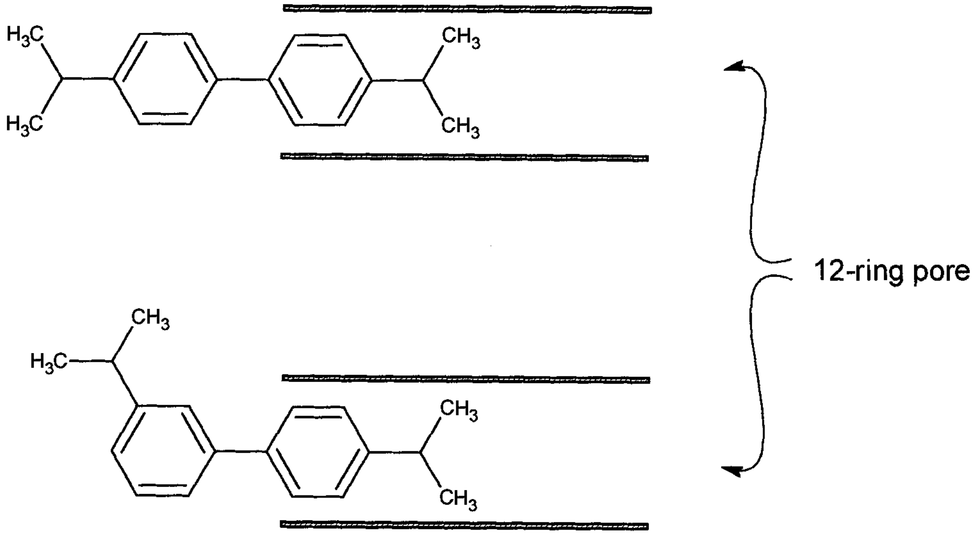


Figure 2. Schematic illustration showing the dimensions of the two DIPBP isomers relative to the twelve-ring pore of mordenite.

The superior activity and stability of these catalysts are caused by the creation of the meso- and macropores during the 3-DDM dealumination process; this greatly enhances access to the twelve-ring pores.

4.3.3 Production of 1,3,5-Trialkylbenzene

A excellent illustration of the practical application of this knowledge in the field of fine chemicals is in the production of 1,3,5-alkylbenzenes. Trialkylbenzenes such as 1,3,5-triisopropylbenzene are useful as high-temperature solvents and as starting materials for the synthesis of agrochemicals. 1,3,5-Triethylbenzene is a useful starting material for the synthesis of K-resins.

Trialkylbenzenes are typically prepared by alkylation of benzene using conventional Friedel–Crafts catalysts or solid acids. A problem with this method is that the desired 1,3,5-trialkylbenzene is obtained in a product mixture with 1,2,4-trialkylbenzene and three dialkylbenzene isomers. Although the dialkylbenzenes can be separated from the trialkylbenzenes relatively easily by distillation, it is much more difficult to separate the two trialkylbenzenes because their boiling points are very close.

A patent awarded to Dow [31] describes an effective process for obtaining pure 1,3,5-trialkylbenzenes. In this process 3-DDM catalysts are used for transalkylating the dialkyl fraction into a monoalkylbenzene in the presence of trialkylbenzenes. The important separation of the pure 1,3,5-trialkylbenzene from the trialkyl

Table 4. Transalkylation of a diisopropylbenzene and tripropylbenzene mix with benzene over a 3-DDM catalyst with a SiO_2/Al_2O_3 molar ratio of 256. Batch experiments were performed using 400 mL benzene, 50 mL diisopropylbenzene (DIPB), 50 mL 1,3,5-triisopropylbenzene (TIPB), and 10 g catalyst. The DIPB contains ca 7.8 % (*w/w*) *meta* isomer, the balance being *para*. Cumene at $t = 0$ is present as an impurity. The 1,3,5-TIPB contains about 2.1 % (*w/w*) of the 1,2,4 isomer. Reactor temp. 250 °C. Concentrations in % (*w/w*).

Compound	Time (h)					
	0	1	2	4	6	20
Benzene	80.5	80.0	79.3	78.6	77.8	76.8
Cumene	0.4	2.1	3.9	6.4	8.3	12.2
m-DIPB	0.8	2.6	3.6	3.6	3.2	0.7
p-DIPB	8.9	5.9	3.9	2.1	1.6	0.3
1,3,5-TIPB	9.3	9.2	9.0	9.2	8.9	9.7
1,2,4-TIPB	0.2	0.2	0.2	0.2	0.2	0.2

mixture is achieved by selective adsorption of the 1,2,4 isomer with a dealuminated Y-zeolite. Subsequently the undesired 1,2,4 isomer is recycled to the 3-DDM catalyst. Importantly, any 1,3,5-trialkylbenzene produced should not be transalkylated further into, e. g., tetraalkylbenzenes or dialkylbenzenes. Again these reactions are prevented by use of 3-DDM catalysts, as is illustrated by the results presented in Table 4.

The concentration of *p*-DIPB decreases as a function of time whereas the concentration of cumene increases; this is indicative of transalkylation. Some isomerization of the *para* isomer into the *meta* also takes place initially. Importantly, no TIPB is transalkylated so it remains available for subsequent separation. Finally, 99 % (*w/w*) pure 1,3,5 isomer can be obtained by passing a TIPB mixture over a dealuminated Y-zeolite with an *SAR* of 630.

4.3.4 Conclusions

The use of traditional Friedel–Crafts catalysts usually leads to complex product mixtures. During alkylation several reactions can take place concurrently, e. g. polymerization, polyalkylation, isomerization, transalkylation, cracking, etc., and complexation of the reactants with the catalyst often occurs. One of the most important drawbacks of these catalysts is probably increasing environmental concern.

As we have shown here, shape-selective solid acids are very capable of replacing traditional Friedel–Crafts catalysts. Besides providing an environmental advantage, the higher selectivity can have economic advantages also. Often separation of the desired product from the product mix is easier, resulting in lower energy costs.

Solid-acid catalysts have now found successful large-scale application in heterogeneous Friedel–Crafts type reactions, especially for the production of bulk chemicals. This field is now rapidly expanding to the area of fine chemicals.

We have shown how zeolites can be tailored to meet increasing demands with respect to both activity and selectivity.

Other Friedel–Crafts catalysts are also being developed; these include clay-supported metal halides [32] and mesoporous silica supported systems [33]. Even enzymes can be used to perform Friedel–Crafts reactions [34].

The use of metal halide catalysts discovered jointly by the French chemist Charles Friedel and the American chemist James Crafts more than one hundred years ago, has evolved into a broad field of chemistry that is still thriving.

Acknowledgments

The mordenite chemistry program at Dow has been a joint effort of many. The authors are much indebted to M. J. M. van der Aalst, M. Olken and others for their contributions.

References

[1] G. A. Olah, ed. in: 'Friedel–Crafts and Related Reactions', Vol. 1–4, Wiley–Interscience, New York, (1963–1965).

[2] G. A. Olah, V. P. Reddy and G. K. S. Prakash in: 'Kirk–Othmer Encyclopedia of Chemical Technology (4th Edition), Wiley–Interscience, New York, Vol. 11, p. 1042–1081.

[3] S. Matar, M. J. Mirbach and H. A. Tayim in: 'Catalysis in Petrochemical Processes', Kluwer Academic Publishers, Dordrecht, (1994), p. 227.

[4] K. Tanabe and W. F. Hölderich, Appl. Catal. A: General, 181 (1999) 399.

[5] P. Lutz, G. Beinert and P. Rempp, Makromol. Chem., 183 (1982) 2787.

[6] A. d'Onofrio, J. Appl. Polym. Sci., 8 (1964) 521.

[7] H. A. Colvin and J. Muse, ChemTech, 16 (1986) 500.

[8] M. Hisaya, EP 0046678 B2 (1990).

[9] G. L. Hervert, US Pat. 3763259 (1973).

[10] G. A. Olah and J. Kaspi, Nouv. J. Chim., 2 (1978) 585.

[11] W. W. Kaeding, EP 0148584 A2 (1985).

[12] P. A. Parikh, N. Subbrahmanyam, Y. S. Bhat and A. B. Halgeri, J. Molec. Catal., 88 (1994) 85.

[13] G. A. Olah and J. A. Olah, J. Am. Chem. Soc., 98 (1976) 1839.

[14] S. M. Csicsery in: 'Zeolite Chemistry and Catalysis', (J. A. Rabo, ed.), ACS Monograph 171, Am. Chem. Soc., (1976), p. 680.

[15] G. S. Lee, J. J. Maj, S. C. Rocke, and J. M. Garces,. Catal. Lett., 2 (1989) 234.

[16] G. S. Lee, J. M. Garces et al., US Pats. 4891448 (1990); 5015797 (1991).

[17] D. E. Walsh and L. D. Rollman, J. Catal., 114 (1988) 136.

[18] W. M. Meier in: 'Natural Zeolites, Occurrence Properties, Uses', (L. B. Sand and F. A. Mumpton, Eds.), Pergamon, Oxford, (1976), p 99.

[19] D. W. Breck in: 'Zeolite Molecular Sieves', Wiley–Interscience, New York, (1974), p. 122–124; p. 162–163.

[20] P. R. Rudolf and J. M. Garces, Zeolites, 14 (1994) 137.

[21] H. G. Karge and J. Weitkamp, Chem.-Ing. Techn., 58 (1986) 946.

[22] I. V. Mishin, H. Bremer and K. P. Wendlandt in: 'Catalysis on Zeolites', (D. Kallo and Ch. M. Minachev, Eds.), Akademiai Kiado, Budapest, (1988) p 231.

[23] I. V. Mishin, T. R. Brueva and G. I. Kapustin in: 'Proc. 12th Int. Zeolite Conf.', (1999), p. 2629.

[24] K.-H. Lee and B.-H. Ha, Microp. Mesop. Mater., 23 (1998) 211.

[25] N. Y. Chen and F. A. Smith, Inorg. Chem., 15 (1976) 295.

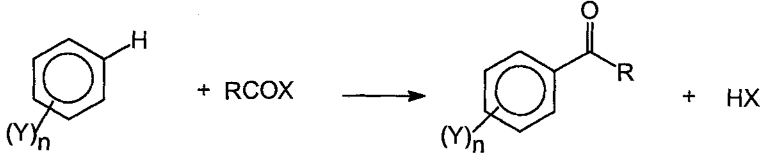
[26] H.K. Beyer, I.M. Belenykaya, I.W. Mishin and G. Borbely, Stud. Surf. Sci. Catal., 18 (1984) 133.
[27] M.M. Olken and J.M. Garces in: 'Proc. 9th Int. Zeolite Conf.', (R. von Ballmoos J.B. Higgins and M.M.J. Treacy, Eds.), Butterworth-Heinemann, (1993), p. 559.
[28] Y. Sugi and M. Toba, Catal. Today, 19 (1994) 187.
[29] T. Hanaoka, K. Nakajima, Y. Sugi, T. Matsuzaki, Y. Kubota, S. Tawada, K. Kunimori and A. Igarashi, Catal. Lett. 50 (1998) 149.
[30] G.R. Meima, M.J.M. van der Aalst, M.S.U. Samson, J.M. Garces and J.G. Lee in: 'Proc. 9th Int. Zeolite Conf.', (R. von Ballmoos J.B. Higgins and M.M.J. Treacy, Eds.), Butterworth–Heinemann, (1993), p. 327.
[31] G.S. Lee, M.M. Olken, J.M. Garces and G.R. Meima, US Pat. 5202516 (1993).
[32] J.H. Clark, A.P. Kybett, D.J. Macquarrie, S.J. Barlow and P. Landon, J. Chem. Soc.; Chem. Commun., (1989) 1353.
[33] J.M. Miller, D. Wails, J.S. Hartman, K. Schebesh and J.L. Belelie, Can. J. Chem., 76 (1998) 382.
[34] J. Rétey, Naturwissenschaften, 83 (1996) 439.

4.4 Friedel–Crafts Acylation

Pascal Métivier

4.4.1 Overview

The Friedel–Crafts reaction (Eq. 1) and the related Fries rearrangement of aromatic compounds are the most important methods in organic chemistry for synthesizing aromatic ketones [1], important intermediates for the production of fine chemicals [2].



(1)

The conventional method for preparation of these aromatic ketones involves reaction of the aromatic hydrocarbon with a carboxylic acid derivative in the presence of a Lewis acid ($AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$, $TiCl_4$) or Brønsted acids (polyphosphoric acid, HF). The major drawback of the Friedel–Crafts reaction is the need to use a stoichiometric quantity of Lewis acid relative to the ketone formed. This stoichiometric quantity is required because the ketone (product of the reaction) forms a stable stoichiometric complex with the Lewis acid. The decomposition of this complex is generally performed with water, leading to total destruction and loss of the Lewis acid.

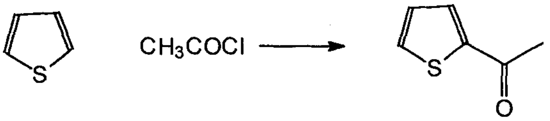
This reaction was discovered at the end of the nineteenth century, and despite intensive studies this drawback has not found a general solution [3]. Studies have been realized to find mild Lewis acids forming less stable complexes with the ketone and still able to catalyze the reaction. Some success has been obtained by use of rare earth triflates [4] or bismuth III salts [5]. These methods, if they prove to be catalytic still require substantial amounts of catalyst (a few percent) and recycling of the catalyst is not simple.

Heterogeneous catalysis seems to be an interesting alternative technique to the homogeneous reaction. The physical and chemical competitive adsorption parameters can in principle be tuned to favor displacement of the product by one of the reagents, reactivity can be promoted by using 'shape' factors to compensate the use of mild acidity of the catalyst. Important work has been performed in the past 10–15 years to find new heterogeneous catalysts for this reaction.

4.4.2 Reactivity

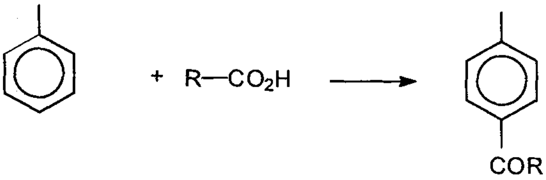
4.4.2.1 Introduction

The use of acidic heterogeneous catalysts for the acylation reaction has rarely been studied until recently. Nevertheless some interesting results were obtained in 1947 [6] for the acylation of the very reactive thiophene with acetyl chloride (Eq. 2) using a montmorillonite clay [7] and in 1982 using a Nafion-H catalyst for the same reaction.



(2)

Pioneering and extensive work in this field was realized in 1985 [8] by use of exchanged Ce^{3+} Y-zeolite as the catalyst for the Friedel–Crafts acylation of toluene (Eq. 3) and xylene with carboxylic acids. Different aspects of this initial work are of interest. Firstly, it shows that the mild acidity of zeolites is sufficient to effect the reaction, and, secondly, it shows that this reaction can be conducted with carboxylic acids and not the corresponding acid chlorides. Only the more lipophilic acids were found reactive whereas no acetylation occurs with acetic acid. The reaction with toluene (Table 1) is extremely *para* selective and more selective than a conventional aluminum chloride homogeneous process. The different reactivities reported in this paper are essentially because of differences between preferential adsorption of the substrates on the catalyst and not their intrinsic activity.



(3)

Table 1. Acylation of toluene with different acids over Ce^{3+}-exchanged Y zeolite (150 °C, 48 h).

Acylating agent	Overall yield (%)	Isomer distribution (%)		
		ortho	*meta*	*para*
Acetic acid	Traces			
Propionic acid	6	3	2	95
Butyric acid	20	3	2	95
Hexanoic acid	30	3	3	94
Octanoic acid	75	3	3	94
Dodecanoic acid	96	3	3	94

Corma's group then published very interesting work on the activity of zeolites in the acylation of anisole with phenyacetyl chloride (Eq. 4) [9]. HY and Hβ Zeolite are active in this reaction, and modification of catalyst parameters has been examined. The amount of zeolite Na^+ exchanged and the silica-to-alumina ratio were examined. It was found that the rate of formation of the reaction product correlates linearly with Na^+ exchange, indicating that all the acid sites are active in the reaction. A material does not, therefore, need to have very strong acid sites to have high activity.

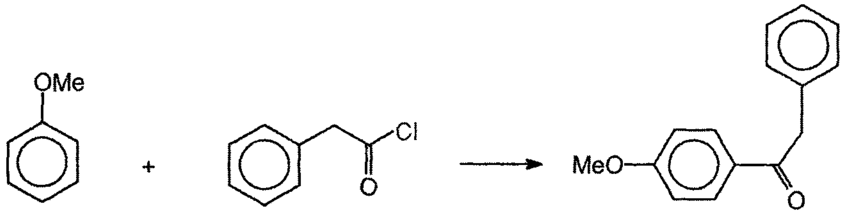

(4)

Table 2. Acetylation of anisole with acetic anhydride and different heterogeneous catalysts (8 h, 90 °C).

Entry	Catalyst	Yield (%)[a]	Selectivity (*para*, %)
1	HZSM5	12	> 98
2	H Mordenite	29	> 98
3	Hβ	70	> 98
4	HY	69	> 98
5	exchanged clay	14	> 98
6	Al clay	16	> 98
7	$H_2PW_6Mo_6O_{40}$	21	> 98

[a] Yield relative to acetic anhydride (initial ratio anisole/anhydride = 5)

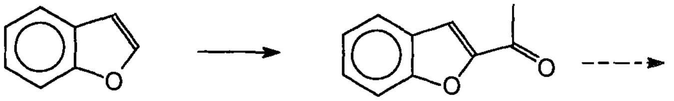
Kouwenhoven's group [10] also worked on acetylation of anisole with various zeolites and found that Hβ has particularly high activity, irrespective of the silica to alumina ratio of the zeolite. Systematic work was then performed in Rhodia [11] to try to rationalize the observed effects. Results obtained using the same reaction conditions changing only the catalyst are depicted in Table 2.

All the catalysts tested were active in this reaction and all had very high *para* selectivity. In conclusion all heterogeneous catalysts can be active toward acylation of anisole with different types of acylation agent, which can be anhydrides, esters, or acids. One important point which is not always discussed in the literature is the ratio of the two reactants, which has a dramatic impact on the adsorption competition of the reactants and on the ability to desorb the formed product.

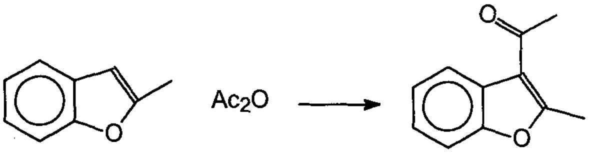
4.4.2.2 Acylation Using Zeolites

The reaction using heterogeneous catalysis which has been studied in greatest depth is the acylation of anisole. Activity, selectivity, deactivation of the catalyst, and recycling have been intensively studied. This activated substrate is an interesting model in this difficult reaction, and because the product is manufactured industrially replacing the conventional $AlCl_3$ method was a challenging target. Many other substrates have been studied, ranging from electron-rich aromatic rings to less reactive compounds such as benzene or toluene. Selective acylation of activated heterocycles has been achieved with benzofurans [12]. Simple benzofuran is extremely reactive and is acetylated at the 2-position (Eq. 5). The product is still reactive and undergoes successive acylation with high conversion. With

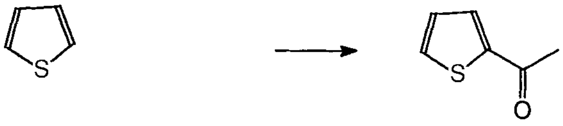
2-methylbenzofuran the reaction is slower and 3-acetyl-2-methylbenzofuran is obtained with high selectivity (Eq. 6).



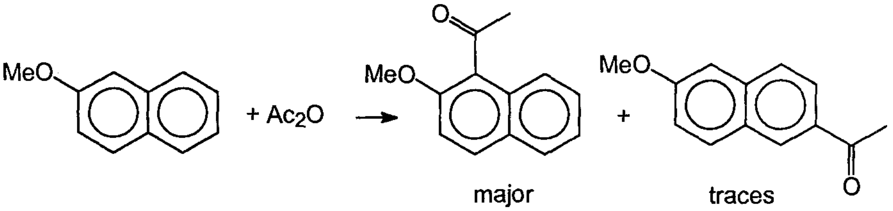
(5)



(6)



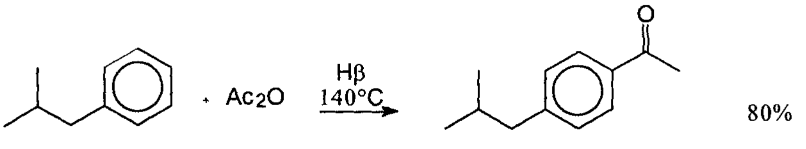
(7)



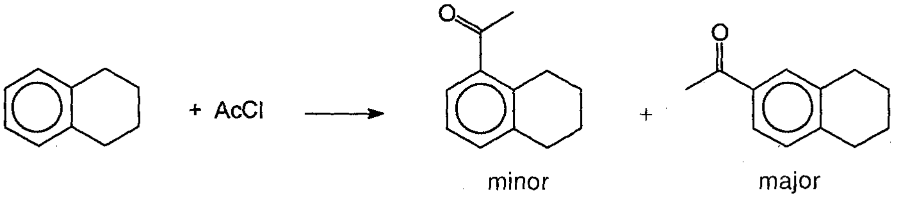
(8)

Acylation of the very reactive thiophene (Eq. 7) with zeolite has been described in the gas phase [13] and more recently in the liquid phase [14,15]. It leads selectively to 2-acetylthiophene. 2-Methoxynaphthalene, which is also very reactive, has been acetylated (Eq. 8) by use of zeolites Y, Hβ, ZSM-12, and MCM-41. The major product is always 1-acetyl-2-methoxynaphthalene [16,17]. For H-MCM-41 the regenerability of the catalyst has been demonstrated [17].

Acylation of isobutylbenzene with acetic anhydride leads with high yield and selectivity to *para*-acetylisobutylbenzene (Eq. 9) which is an intermediate in the synthesis of ibuprofen, an important antiinflammatory drug [18]. With Hβ zeolite at 140 °C after 1 h the yield is 80 % with 96 % *para* selectivity. Acylation of tetralin with acid chlorides and different zeolites has also been studied [19]. For this reaction again acetyl chloride is much less reactive than higher acid chlorides such as butanoyl or octanoyl chloride. The selectivity is in favor of the 2-substituted isomer (85–90 %) and limited quantities of the 1 isomer (10–15 %) are formed (Eq. 10).



(9)



(10)

If the acylation of toluene with acetic acid depicted above [8] failed, use of the more active acyl chlorides instead of acids and La-exchanged Y-zeolite leads to the *para*-acylated product [20].

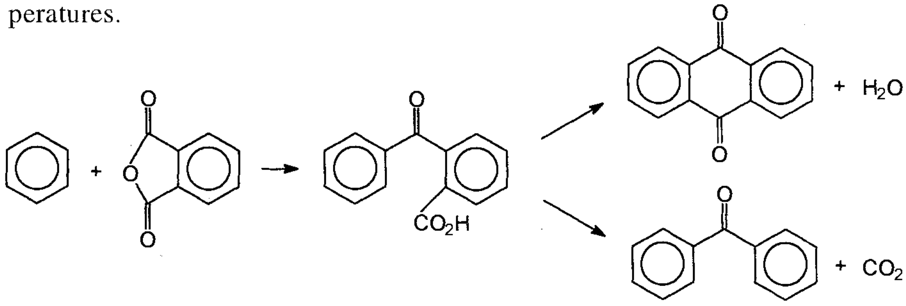
For non-activated aromatic compounds the results obtained from gas-phase reactions by A. P. Singh et al. are of particular interest [21]. H-ZSM5 is very active in the acylation of benzene, toluene, and isopropylbenzene, but fails to give any products with xylene or mesitylene, whereas Hβ proves to be very effective for the acylation of large molecules (Table 3). This greater activity might be explained on the basis of its larger pore openings. At the same time acylation of benzene and toluene was reported using HY, an HZSM5 zeolite, at high temperature in an autoclave [22]. The results are consistent with those obtained in the gas phase. These high-temperature techniques might be the way to progress toward more deactivated aromatic compounds, such as halobenzene or even more deactivated compounds.

In terms of reactivity benzoylation seems to be a much easier reaction. By use of zeolites, benzoylation of toluene [23], xylene [24], and benzene [25] have been described under mild conditions (80–140 °C). It is probable that benzoylation is favored because of the greater affinity of the acylating agent for the heterogeneous catalyst. Interesting results have been found for acylation of benzene with phthalic anhydride to form anthraquinone (Eq. 11) [26]. When the Hβ cata-

Table 3. Acylation of different aromatics in the gas phase using zeolites as catalyst.

Substrate	Catalyst	Acylating agent	Conversion (%)	Product/selectivity
Benzene	HZSM5	CH_3CO_2H	76	Acetophenone 88 %
Toluene	HZSM5	CH_3CO_2H	55.5	*ortho* 41 % *para* 44 %
Isopropylbenzene	HZSM5	CH_3COCl	98.5	*ortho* 52 % *para* 43 %
p-Xylene	Hβ	CH_3COCl	86	79 %
Mesitylene	Hβ	CH_3COCl	97	87 %

lyst is used the selectivity to anthraquinone is favored at rather low temperatures, whereas decarboxylation to form benzophenone (Eq. 12) is favored at higher temperatures.

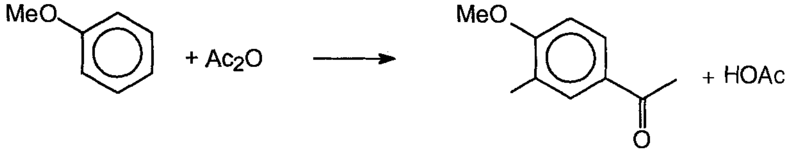


(11)

(12)

4.4.2.3 Acylation Using Other Catalysts

Although zeolites are the catalysts most studied for acylation other acidic materials have also been used and give interesting results. Acylation of anisole (Eq. 13), veratrole, and 2-methoxynaphthalene has been studied using exchanged clays [27]. If the non-exchanged clay is active, clays exchanged with iron, zinc, copper, aluminum, and cobalt have higher activity, as depicted in Table 4 for anisole acylation. Recycling of catalyst has been performed with the iron(III)-exchanged clay and deactivation is low. Leaching of the metal was not investigated and should be carefully studied.



(13)

Table 4. Acylation of anisole using exchanged montmorillonites as catalysts (90 °C, 10 h reaction).

Catalyst	Acylating agent	Yield (%)
Fe^{3+} Montmorillonite	Acetic anhydride	50
Zn^{2+} Montmorillonite	Acetic anhydride	60
Fe^{3+} Montmorillonite	Propionic anhydride	68
Zn^{2+} Montmorillonite	Propionic anhydride	70

In the acylation of 2-methoxynaphthalene, the isomer formed almost exclusively is 1-acetyl-2-methoxynaphthalene and no, or very little, 6-acetyl-2-methoxynaphthalene is formed. The one-step acylation of 2-methoxynaphthalene in the 6 position remains a challenge and is of interest because 6-acetyl-2-methoxynaphthalene is a potential intermediate for the synthesis of naproxen, an important anti-inflammatory drug.

As already mentioned, thiophene has also been acetylated with a variety of heterogeneous catalysts such as montmorillonite clay [28] and Nafion-H [29].

Interesting reactivity has recently been found in the use of Nafion/silica composite material [30]. Nafion resins are active in the acylation of anisole with acetyl chloride, but entrapping highly dispersed nanosized Nafion particles in a silica matrix leads to a much more active catalyst, as indicated in Table 5.

Table 5. Acetylation of anisole with phenylacetyl chloride using Nafion-based materials.

Catalyst	Temperature (K)	Conversion (%)	Selectivity (*para*; %)
Nafion	373	60	97
Nafion/silica composite	373	100	97

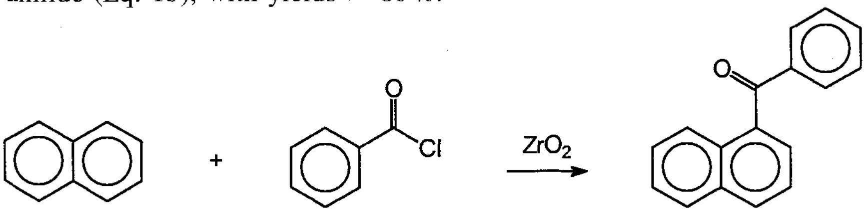
Table 6. Comparison of the activity of different aromatic substrates with Nafion and Nafion/silica composite resins (2 h, 100 °C)

Substrate	Nafion catalyst yield (%)	Nafion/silica composite yield (%)
Toluene	< 1	7
o-Xylene	10	37
m-Xylene	26	58
Anisole	59	97

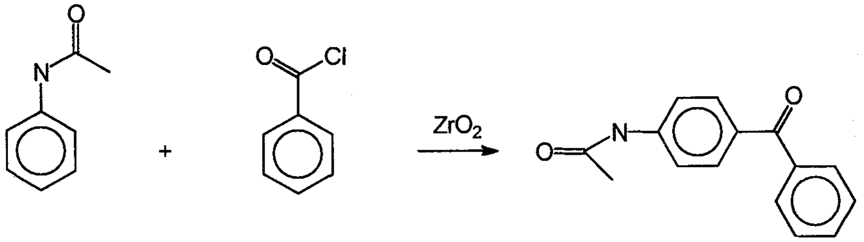
Extension of the scope of the this reaction by use of Nafion/silica composite resin shows that these catalysts can be active in the acylation of xylenes yet have low activity toward toluene (Table 6).

Graphite has also been described as a surprising acylating catalyst whereas carbon black is inactive [31]; again no information was given about the exact composition and metal impurity content, and the results should be considered with caution.

Although most of the literature describes benzoylation with zeolites, most acidic solids are effective in benzoylation with benzoyl chlorides. For example, hydrated zirconia [32] has been used for the benzoylation of naphthalene (Eq. 14) and acetanilide (Eq. 15), with yields > 80%.



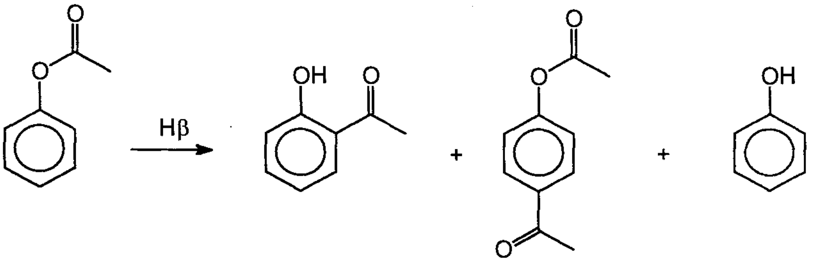
(14)



(15)

4.4.2.4 The Special Case of the Fries Rearrangement

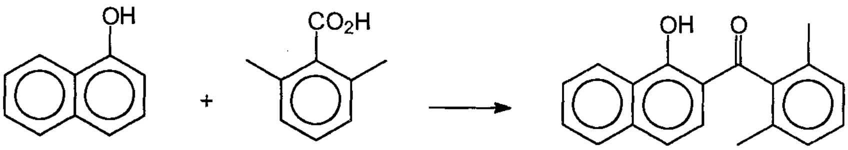
The Fries rearrangement is specific in that published results are not always consistent, and that there is a debate on intra-/intermolecular reactivity. In the Fries rearrangement of phenyl acetate over zeolites (Eq. 16) it was first shown that the reaction is initiated by protonation of the aromatic ester, leading then to the formation of the acylium ion (Scheme 1) [33].



(16)

Scheme 1. Primary (initial) products formed during the Fries rearrangement of phenyl acetate over Hβ catalyst.

Kinetic studies of this rearrangement over Hβ zeolite [34] show that the three primary products are *o*-hydroxyacetophenone, *p*-acetoxyacetophenone, and phenol, suggesting competition between an intramolecular *ortho*-selective rearrangement and an intermolecular *para* acylation of phenyl acetate. Rearrangement of phenyl acetate is much more difficult than rearrangement of phenyl benzoate because of the stability of the acylium ion, which in the case of acetate can be converted to ketene, leading to the formation of side-products and ultimately to tars that will inhibit the catalyst. Benzoylation of different phenols using HZSM5 zeolite is reported to give good yields. For example [35] phenol leads to 3-hydroxybenzophenone with 70 % yield, catechol leads to 3,4-dihydroxybenzophenone with 55 % yield, and 2-naphthol leads to 1-benzoyl-2-naphthol with 82 % yield. In the benzoylation of resorcinol it was shown that most acidic heterogeneous catalysts are active and that 2,4-dihydroxybenzophenone can be formed with good yields [36]. Of particular interest is the use of mesoporous molecular sieves, such as the MCM-41 type. They offer new opportunities for the preparation of bulky products. For example, the acylation of 1-naphthol with 2,6-dimethylbenzoic acid proceeds (Eq. 17) in high yield and selectivity to 1-hydroxy-2-(2,6-dimethylbenzoyl)naphthalene [37].



(17)

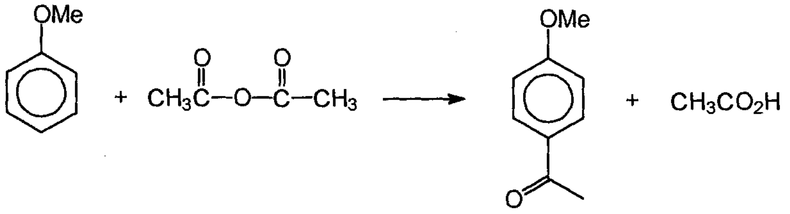
4.4.3 Deactivation

The deactivation of zeolite in the acylation of anisole has recently been studied [38,39]. Both teams agree that the main deactivation is reversible and attributable to non-desorption of the product, acetylanisole, from the catalyst. This problem can be circumvented by modifying the ratio of reagents. Another deactivation which is not reversible is consecutive reaction of the product with the reagents or the product to form a 'heavy' product that remains on the catalyst. Those products will also block the accessibility of the reactants to the micropores of the catalyst. This problem which is second order to the first deactivation causes slow deactivation of the zeolite. The zeolite can be regenerated by calcination with air at high temperature. A third potential deactivation that has been identified is dealumination of the catalyst. It has been shown that when the reaction is performed under harsh conditions (for a long time) acetic acid can extract small quantities of aluminum from the zeolite.

Very few data are available on the deactivation and recycling of catalysts other than zeolites. The main factor is probably the poisoning of the active sites by side-products of the reaction which have a very high affinity toward adsorption on those sites. When using exchanged materials, one should, furthermore, be very careful about possible leaching.

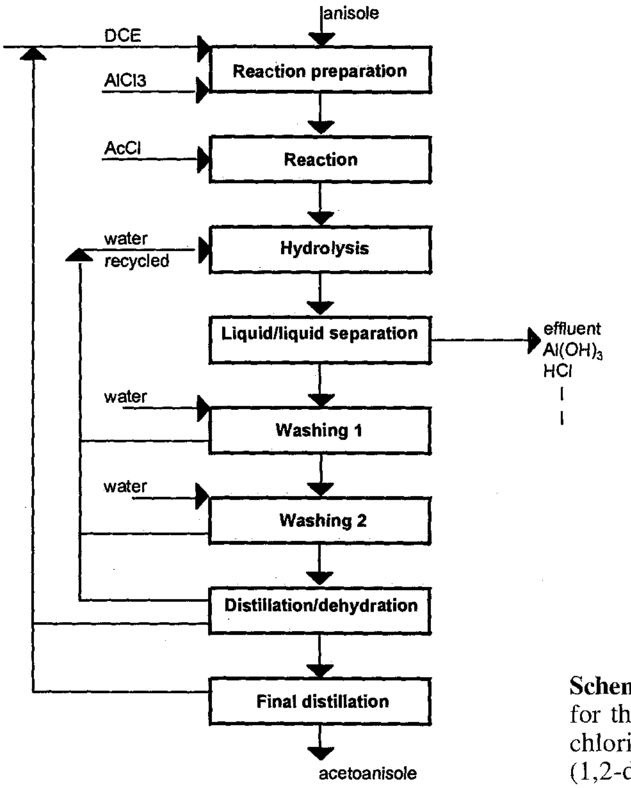
4.4.4 Industrial Processes

The Rhodia company is operating an industrial process for acylation of anisole (Eq. 18) to *para*-acetylanisole using a zeolite [40]. This fixed-bed technology process is a breakthrough in this field. It enables considerable simplification of the process, an increase in *para* selectivity, and thus a reduction of operating cost and dramatic reduction of effluent volume. Comparing of the block diagrams in Schemes 2 and 3 reveals the simplification resulting from the zeolite process.

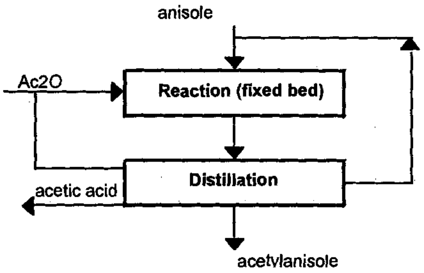


(18)

This process is a good example of how a new procedure can at the same time be cost-efficient and environmentally friendly. The principles of this process have been extended, and Rhodia is also manufacturing acetoveratrole at the same plant by use of a zeolite-based process.



Scheme 2. Simplified flow chart for the conventional aluminum chloride process using DCE (1,2-dichloroethane) as solvent.



Scheme 3. Simplified flow chart for the new zeolite fixed bed process using no solvent

4.4.5 Perspectives and Conclusions

In fifteen years the field of Friedel–Crafts acylation has changed completely. The classical stoichiometric reaction was standard and there was no viable alternative to this reaction. Research performed in recent years has shown that this reaction can often be conducted with heterogeneous catalysts (so far mainly zeolites). These studies have led to the industrialization of at least one process, showing that all the problems of reactivity, catalyst deactivation, and engineering can be solved for such a reaction with zeolites as catalysts. Although one major breakthrough has been achieved, not all difficulties have, of course, been solved. The Friedel–Crafts acylation of deactivated aromatic compounds must still be completely resolved in terms of reactivity and catalyst deactivation. This is a major task for the next ten years. A second point that must be considered is the selectivity of some reactions. For example, the problem of the acylation of 2-naphthol or 2-methoxynaphthalene at position 6 has not yet been solved. Most studies have been performed using a zeolite as the heterogeneous catalyst. Other heterogeneous materials should be able to catalyze this reaction. If the nineties was the pioneering period for this reaction, we have probably now entered the period of expansion of heterogeneous Friedel–Crafts acylation.

References

[1] Olah G. A. in 'Friedel–Crafts and related reactions', Wiley–Interscience, Vol. I–IV, New York (1963–1964); Olah G. A. in 'Friedel–Crafts Chemistry', Wiley–Interscience, New York (1973).
[2] Szmant H. 'Organic Building Blocks of the Chemical Industry', Wiley, New York (1989).
[3] Friedel C. Crafts J. M., Bull. Chem. Soc. Chim. Fr., 27, 482 (1877); Friedel C., Crafts J. M., Bull. Chem. Soc. Chim. Fr., 27, 530 (1877).
[4] Kawada A., Mitamura S., Kobayashi S., J. Chem. Soc., Chem. Commun. 1157 (1993); Hachiya L., Mariwaki M., Kobayashi S., Tetrahedron Lett., 36, 409 (1995).
[5] Desmurs J. R., Labrouillere M., Dubac J., Laporterie A., Gaspard H., Metz F., in 'industrial chemistry library', Vol. 8, Elsevier ,p 15–25, (1996).
[6] Harthough H. D., Kosak A. I., Sardella J. J, J. Am. Chem. Soc., 69, 1014 (1947).
[7] Koniski, H., Suetsugu K., Okano T., Kiji J., Bull. Chem. Soc. Jpn, 55, 957 (1982).
[8] Chiche B., Finiels A., Gauthier C., Geneste P., Graille J., Pioch D., J. Org. Chem., 51, 2128 (1986).
[9] Corma A., Ciment M. J., Garcia H., Primo J., J. Appl. Catal., 49, 109 (1989).
[10] Harvey G., Vogt A., Kouwenhoven H. W., Prins R., in Proc. 9th Int. Zeolite Conf., Vol. II, von Ballmoos R., Higgins J. B., Treacy M. M. J. (eds.), Butterworth, Boston, p. 363 (1992).
[11] Spagnol M., Gilbert L., Alby D. in 'industrial chemistry library', Vol. 8, Elsevier, p 29–38, (1996).
[12] Richard F., Carreyre H., Perot G., J. Catal. 159, 427 (1996); Richard F., Carreyre H., Perot G., J. Mol. Catal. A, 103, 51 (1995).
[13] Lerner H., Hoelderich W., Schwarzmann M., Patent DE 3618964 (1987); Hoelderich W., Hesse M., Naumann F., Angew. Chem., 27, 226 (1988).
[14] Finiels A., Calmettes A., Geneste P., Moreau P., Stud. Surf. Sci. Catal. 78, 595 (1993).
[15] Fripiat J. J, Isaev Y., J. Catal. 182, 257 (1999).
[16] Harvey G., Mäder G., Collect. Czech. Chem. Commun., 57, 862 (1992); Neuber M., Leupold E. I., Patent to Hoechst AG, US 5227529 (1993).
[17] Gunnewegh E. A., Gopie S. S., van Bekkum H., J. Mol. Catal. A: Chemical, 106, 151, (1996).
[18] Vogt A., Pfenninger A., patent to Uetikon AG, EP 0701987 A1 (1996).
[19] Moreau P., Finiels A., Pelorgeas S., Vigneau O., Lasperas M., Catal. Lett., 47, 161 (1997).
[20] Akporiaye D. E., Daastatn K., Solberg J., Stöcker M., Stud. Surf. Sci. Catal., 78, 521 (1993).
[21] Pandey A. K., Singh A. P., Catal. Lett. 44, 129 (1997).
[22] Sreekumar R., Padmakumar R., Synth. Commun. 27, 777 (1997).
[23] Singh, A. P., Bhattacharya D, Sharma S., J. Mol. Catal. A: Chemical 102, 139 (1995).
[24] Fang R., Kouwenhoven H. W., Prins R., in 'zeolites and related microporous materials: state of the art 1994', Elsevier science B. V., Stud. Surf. Sci. Catal., 84, 1441–1448 (1994).

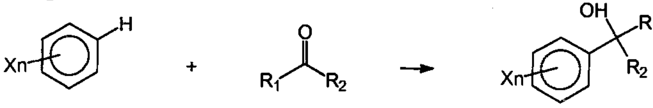
[25] Singh A.P., Bhattacharya D., Catal. Lett., 32, 327 (1995).
[26] Kikhtyanin O.V., Ione K.G., Snytnikova G.P., Malysheva L.V., Toktarev A.V., Paukshtis E.A., Sprichtinger R., Schüth F., Unger K.K., in Zeolites and related microporous materials: State of the art 1994, Weitkamp and all (eds.), Elsevier, Amsterdam, p. 1905 (1994).
[27] Choudary B.M., Sateesh M., Kantam M.L., Prasad K.V.R., Appl. Catal. A, 177, 155 (1998).
[28] Harthough H.D., Kosak A.I., Sardella J. J, J. Am. Chem. Soc., 69, 1014 (1947).
[29] Koniski, H., Suetsugu K., Okano T., Kiji J., Bull. Chem. Soc. Jpn, 55, 957 (1982).
[30] Heidekum A., Harmer M.A., Hoelderich W.F., J. Catal., 188, 230 (1999).
[31] Kodomari M., Suzuki Y., Yoshida K., Chem. Commun., 1567 (1997).
[32] Patil M.L., Jnaneshwara G.K., Sabde D.P., Dongare M.K., Sudalai A., Deshpande V.H., Tetrahedron Lett., 38, 2137, 1997.
[33] Vogt A., Kouwenhoven H.W., Prins R., Appl. Catal. A: General, 123, 37–49 (1995).
[34] Jayat F., Sabatier Picot M.J., Guisnet M., Catal. Lett., 41, 181 (1996).
[35] Paul V., Sudalai A., Daniel T., Srinivasan K.V., Tetrahedron Lett., 35, 2601 (1994).
[36] Hoefnagel A.J., Van Bekkum H., Appl. Catal. A: General, 97, 87 (1993).
[37] Bosàcek E., Gunnewegh A., van Bekkum H., Catal. Lett. 39, 57 (1996).
[38] Rohan D., Canaff C., Fromentin E., Guisnet M., J. Catal. 177, 296 (1998).
[39] Derouane E.G., Dillon C.J., Bethell D., Derouane-Abdamid S.B., J. Catal., 187, 209 (1999).
[40] Spagnol M., Gilbert L., Benazzi E., Marcilly C. Patent to Rhodia WO 96/35655 (1996).

4.5 Hydroxyalkylations

Pascal Métivier

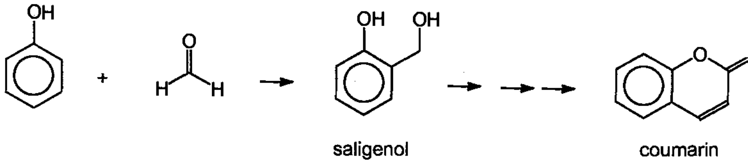
4.5.1 Overview

Hydroxyalkylation reactions are of great interest in fine chemistry, because they enable functionalization of aromatic compounds and access to a wide range of products (Eq. 1).



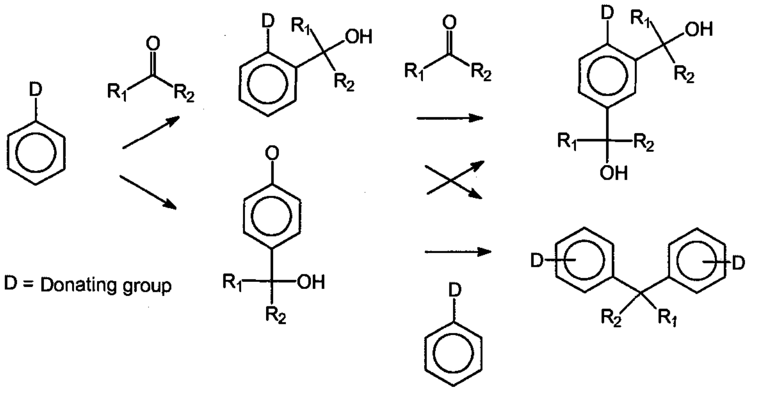
(1)

Saligenol, an intermediate in the synthesis of a variety of products, and a particularly key intermediate in the preparation of coumarin [1], an important perfume base (Eq. 2), is the best example of the industrial synthesis of this type of compound.



(2)

This hydroxyalkylation reaction is difficult to perform in terms of activity and selectivity. Firstly, because the ketone or aldehyde is a mild electrophile the aromatic ring must be activated. Secondly, substitution generally leads to a variety of substituted sites (particularly *ortho*, *para* selectivity for activated aromatic compounds), and last, but not least, consecutive reactions are often observed. These general selectivity and activity problems are depicted in Scheme 1.



Scheme 1. Competing reactions in aromatic hydroxyalkylation.

All these drawbacks probably explain why so few hydroxyalkylations have yet been industrialized, although recent results using heterogeneous catalysis might reverse this tendency in the future. By using specially designed heterogeneous materials, it is possible to favor one reaction over the others.

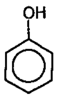
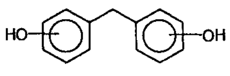
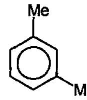
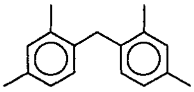
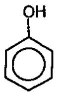
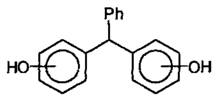
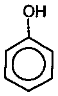
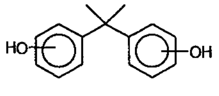
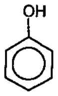
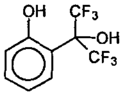
4.5.2 Main Results

In homogeneous media the final product is usually the bis-arylmethane product, which corresponds to the reaction of the formed benzylic alcohol with another molecule of starting aromatic material. Heterogeneous catalysis offers the interesting possibility of avoiding this consecutive reaction. Mild acidity can be used, and tuning of the adsorption affinities of the different moieties in the medium enables preferential adsorption of the starting material over the product, thus limiting consecutive reactions.

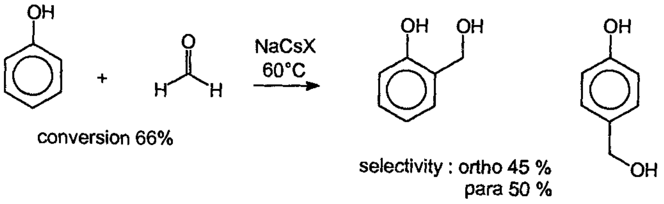
The first work on heterogeneous hydroxyalkylation was conducted by Venuto and Landis [2]. They worked on the hydroxyalkylation of phenol with formaldehyde, benzaldehyde, acetone, and hexafluoroacetone using zeolite HY at 180 °C. Except for hexafluoroacetone (Table 1), the major product was always the bis-arylmethane.

In the eighties Corma and then Van Beckum [3] studied hydroxyalkylation of phenol, toluene, and anisole with formaldehyde [4], acetaldehyde [5], benzaldehyde and acetophenone [6] at high temperature using a variety of acid catalysts. The major product was always the bis-arylmethane adduct. At the end of the eighties Mitsui Toatsu [7] claimed synthesis of *para*-hydroxymethylphenol from phenol and trioxane using and H^+-type Y zeolite at 160 °C for 3 h to give 65 % conversion of trioxane and 88 % *para*-hydroxymethylphenol selectivity. This result is surprising when compared with those of Corma and Van Beckum and should be confirmed. More interesting is the report, by the Asahi Chemical company [8], of the use of a more basic alkali metal-containing zeolite. By use of a CsNaX zeo-

Table 1. Hydroxyalkylations over HY zeolite at 180 °C.

Substrate	Electrophile	Conversion (time)	Main product	Selectivity
	HCHO	80% (1,75 h.)		oo' : 31% op' : 45 % pp' : 24 %
	HCHO	70% (2,0 h.)		> 99 %
	PhCHO	7% (2,5 h)		> 99 %
	CH_3COCH_3	9% (5,7 h)		> 65 %
	CF_3COCF_3	50 % (16,5 h)		> 99 %

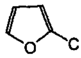
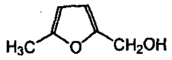
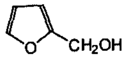
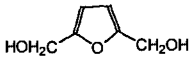
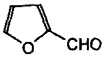
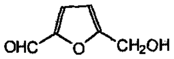
lite at 65 °C in the presence of phenol and paraformaldehyde they obtained a 66 % yield of hydroxybenzylic alcohols with 45 % *para* selectivity and 50 % *ortho* selectivity (Eq. 3).



(3)

The first breakthrough was obtained using furan derivatives and H-Mordenite as the catalyst [9]. The main results obtained are given in Table 2.

Table 2. Hydroxymethylation of furan derivatives using dealuminated H-Mordenite (Si/Al + 100)

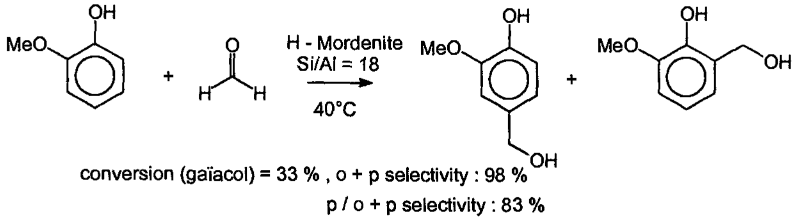
Aromatic	T°C	Product	Conversion	Selectivity
	40		87 %	63 %
	40		80 %	95 %
	90		73 %	30 %

To achieve those results, the conditions required are: excess formaldehyde, a significant proportion of catalyst, and dealumination of the catalyst, mainly to enhance the hydrophobicity of the zeolite [10] (Table 3).

Table 3. Effect of dealumination of H-mordenite on activity and selectivity in the hydroxymethylation of furfuryl alcohol.

Catalyst	Si/Al	Conversion (%)	Selectivity (%)
HMOR	11	4	40
HMOR	49	20	90
HMOR	100	65	85

Reactivity and selectivity observed for furan derivatives have been extended to aromatic phenols. The most interesting results have been obtained for the hydroxymethylation of guaiacol with formaldehyde leading to *para*-hydroxymethylguaiacol, the precursor for vanillin [11]. Use of H-Mordenite type catalyst with an Si to Al ratio of 18, low temperature (40 °C), and well-defined conditions led to very good results–33 % conversion with 98 % alcohol selectivity can be obtained and *para* selectivity of 83 % [12] (Eq. 4).



conversion (gaïacol) = 33 % , o + p selectivity : 98 %
p / o + p selectivity : 83 %

(4)

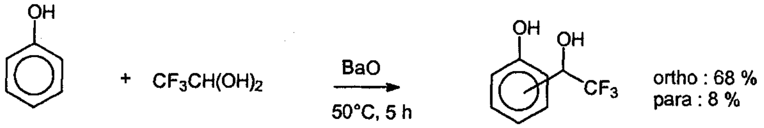
Different studies were then conducted to extend the reaction to more deactivated aromatic compounds, particularly anisole and toluene, as model substrates [13]. With such aromatic compounds hydroxyalkylation always leads to the bisarylmethane type product unless the aldehyde is deactivated. Interesting results have been obtained by use of chloral, fluoral [14], or hexafluoromethylacetone. The reactivity of toluene, anisole, and phenol is compared in Table 4. At 5 % conversion the reaction is very selective with the less active toluene and very 'dirty' with phenol.

Table 4. Hydroxytrichloroethylation of aromatic compounds by use of HY (Si/Al = 5.7) at 50 °C.

Aromatic compound	Toluene (%)	Anisole (%)	Phenol (%)
Selectivity at 5 % conversion	95	47	40
para	100	88	63
Conversion after 4 h	6	41	39

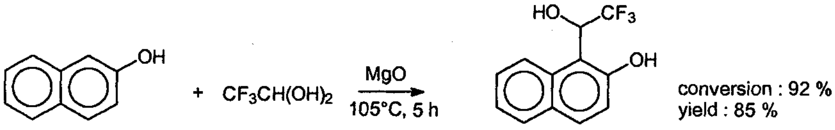
The general explanation of this selectivity is the different stability of the product under acidic conditions. The more donating the aromatic compound the less selective the reaction. Very recently Anthony reported the hydroxyalkylation of benzene with zeolite over ZSM-5 zeolite [15]. Although the results are modest, they indicate that the formation of the bis-arylmethane adduct can be avoided by use of a medium-pore zeolite.

More recently, basic heterogeneous catalysts have been tested for the hydroxyalkylation of phenols [16]. Examples of yields and selectivity obtained with different substrates are shown in Eqs 5 and 6. The reaction in basic medium is much more *ortho*-selective than in acidic medium, and *ortho* selectivity can be enhanced by choice of a suitable catalyst. For example, in the synthesis of 2,2,2 trifluoro-1-



ortho : 68 %
para : 8 %

(5)



conversion : 92 %
yield : 85 %

(6)

(2-hydroxyphenyl)ethanol, La_2O_3 is the most active and selective catalyst and leads to 90 % *ortho*/(*ortho* + *para*) selectivity whereas BaO or $Mg_6Al_2(O_4)_{16}.4H_2O$ leads to 50 % selectivity.

4.5.3 Conclusion and Perspectives

Hydroxyalkylation of aromatic compounds is a reaction that has not yet been studied extensively and many data must still be acquired. Nevertheless, general tendencies can be drawn from existing literature. When acidic conditions are used, consecutive condensation leading to a bis-arylmethane-type product is difficult to avoid. It can be avoided if the ketone or aldehyde is deactivated by use of a zeolite-type material at low temperature (20 to 80 °C) when the reaction is *para* rather than *ortho* selective toward the electron-donating groups of the aromatic compound. Authors have usually reported some deactivation of the catalysts used. Under acidic conditions the challenges to overcome are broadening of the scope of the reaction, enhancing selectivity, and limiting deactivation of the catalyst to an acceptable level. Under basic conditions the reaction has so far been limited to phenolic compounds, but is rather simple to conduct and the selectivity is more oriented toward *ortho* substitution relative to the hydroxy group, although this selectivity can be modified by changing the catalyst.

The scope of this reaction is still limited by important potential side reactions. Heterogeneous catalysis is one technique that could help solve such problems and provide new tools to enable access to this important class of products.

References

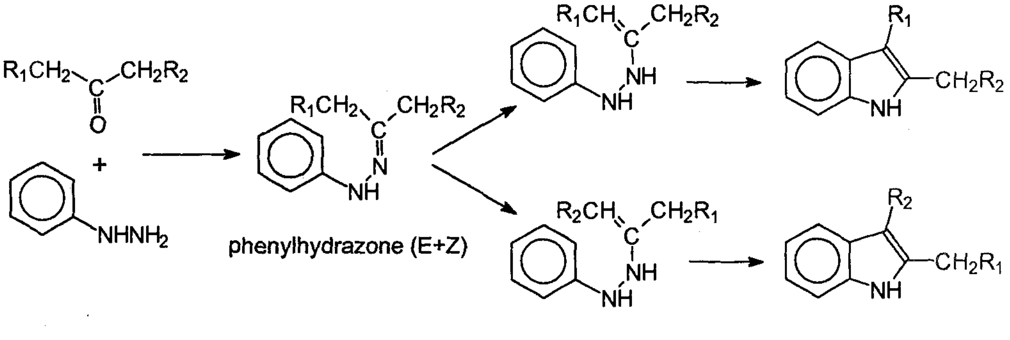
[1] Boisde P.M., Meuly W.C. 'Coumarin' in Encyclopedia of Chemical Technology, Kirk–Othmer, John Wiley and sons, Fourth edition, Vol. 7, p 647–658, 1993.
[2] Venuto P.B., Landis, P.S., J. Catal., 6, 237–244 (1966).
[3] Burgers M.H.W, Van Bekkum H., Stud. Surf. Sci. Catal., 78, 567–574 (1993).
[4] Climent M.J., Corma, A., Garcia H., Primo J., Appl. Catal., 51, 113–125 (1989).
[5] Climent M.J., Corma, A., Garcia H., Primo J., J. Catal., 130, 138–146 (1991).
[6] Climent M.J., Corma, A., Garcia H., Iborra S., Primo J., Appl. Catal., A: Gen., 130, 5–12 (1995).
[7] Kiyora T., Japanese patent JP 63307835 A2, publication 15/12/1988, priority 08/06/1987.
[8] Ishida H., Takamatsu Y., Japanese patent JP 04275246 A2, publication 30/09/1992, priority 01/03/1991.
[9] Lecomte J. These de doctorat, 1996, Université de Montpellier II-ENSCM, France.
[10] Lecomte J. Finiels A., Geneste P., Moreau C., J. Mol. Catal. A: Chem., 140, 147–163 (1999).
[11] Moreau C. Finiels A. Razigade S., Gilbert L., Fajula F., Patent WO 9637452, 1996 to Rhodia.
[12] Moreau C. Finiels A. Razigade S., Gilbert L., Fajula F., Jacquot R., Spagnol M., 'selective hydroxymethylation of guaiacol to vanillic alcohols in the presence of H-Mordenite' in *catalysis of organic reactions*, Marcel Dekker, Inc.: New York, Chapter 5, p. 51–62, 1998.
[13] Barthel N., These de doctorat, Université de Montpellier II-ENSCM, France, 1999.
[14] Jacquot R., Spagnol M., French patent WO 99/64385, priority 11/06/1998, to Rhodia
[15] Wu X., Anthony R.G., J. Catal., 184, 294–297 (1999).
[16] Jacquot R., Spagnol M., French patent WO 99/62853, priority 29/05/1998, to Rhodia.

4.6 The Fischer Indole Synthesis

R. S. Downing, P. J. Kunkeler

4.6.1 Introduction

Indoles are an important class of fine chemicals; derivatives find application as fragrance chemicals. The indole nucleus is present in many biologically active molecules including plant-growth regulators, proteins and pharmaceuticals. The selective synthesis of indole derivatives constitutes an important area of drug research. The well-known Fischer indole synthesis provides a versatile method for synthesizing substituted indoles from the arylhydrazones of aldehydes or ketones [1,2]. In the generally accepted mechanism [3,4] the enehydrazine tautomer of the arylhydrazone undergoes a rapid [3,3]-sigmatropic rearrangement, followed by elimination of ammonia to yield the indole product, as shown in Scheme 1.



Scheme 1. Reaction steps in the Fischer indole synthesis.

Although in favorable circumstances the reaction may be effected thermally, it is usually conducted as an acid-catalyzed reaction. Both Brønsted and Lewis acids are effective. The principal function of the catalyst is to accelerate the formation of the enehydrazine from the arylhydrazone [5,6]. It is not usually necessary to isolate the latter; the reaction can be conducted as a one-pot procedure starting from ketone or aldehyde and arylhydrazine. Catalysts employed include mineral acids (hydrochloric, sulfuric, polyphosphoric), organic acids such as acetic acid, and metal-halide Lewis acids. Among the most generally reported are $ZnCl_2$ and alcoholic hydrogen chloride.

4.6.2 Heterogeneous Catalysis

The homogeneous Brønsted and Lewis acids employed traditionally require neutralization during product work-up and thus generate salt and/or metal-containing wastes, the disposal of which is increasingly subject to environmental restrictions. The heterogeneous catalysis of the Fischer synthesis by solid acids eliminates waste formation and has the advantages of simple separation, recovery, and regeneration of the catalyst. The armory of possible catalysts is large and includes the acidic forms of ion-exchange resins, oxides such as silica, alumina and silica–alumina, and zeolites.

In a series of papers, Suvorov et al. investigated heterogeneous catalysis of the cyclization of isolated aldehyde and ketone phenylhydrazones. γ-Alumina was typically employed as catalyst in the vapor phase reaction at atmospheric pressure and at temperatures around 300 °C. A maximum yield of 60 % was obtained from acetaldehyde phenylhydrazone as a result of thermal decomposition of the hydrazone [7] and the formation of benzene and aniline as by-products [8]. Kinetic studies indicated that the rate-determining step was desorption of product from the surface [9].

Labeling studies were employed to furnish mechanistic insights. By use of ^{15}N-labeled acetaldehyde phenylhydrazone it was established that the nitrogen eliminated as ammonia in the final step was that further from the benzene ring [8]; this is consistent with the elimination mode found for the homogeneous reaction [3]. When the same substrate, labeled with tritium at the methyl group, $PhNHN{:}CHCH_2T$, was cyclized, the tritium was found to be distributed over the 2- and 3-positions and also in the ring; this was attributed to isomerization of the first-formed indole-3-t [10]. A similar distribution of tritium was found when the carbonyl carbon was labeled, $PhNHN{:}CTCH_3$; in this case tautomerization before cyclization was proposed as the mechanism [11].

The effect of substituent groups was also studied. In a series of N-substituted hydrazones, PhNRN:CMeEt, cyclization proceeded with increasing difficulty in the series R = H, Me, Et, Ph; this was ascribed to the effect of increasing steric hindrance [12]. From acetaldehyde phenylhydrazones with methoxy substituents on the aromatic ring, yields were poor, which was attributed to decomposition of the substrate to non-volatile products on the alumina catalyst surface [13]. In contrast, with an acidic ion-exchange resin as catalyst, higher yields were obtained with the 4-methoxy derivative than with the 4-nitro; this was interpreted as the effect of methoxy in facilitating adsorption on the resin [14].

An acidic ion-exchange resin, Amberlite IR-120, was also employed by Yamada et al. to effect the cyclization of the phenylhydrazones of ketones including ethylmethyl ketone, propiophenone, and cyclohexanone in water under reflux [15]. Yields of 60–90 % were obtained but acetone phenylhydrazone proved unreactive under these conditions.

4.6.3 Zeolites as Catalysts

Inspection of Scheme 1 shows that the use of non-symmetrical ketones will result in two isomeric enehydrazine tautomers and hence in two isomeric indoles. When it is desired to obtain a single isomer, either a difficult separation procedure is required or, alternatively, the Fischer synthesis should be conducted with the separated *E* or *Z* arylhydrazone isomer [16]. Selective synthesis of a single isomer would be advantageous and Prochatska et al. recognized that this could, in principle, be achieved by the use of zeolites as catalysts [17]. This is because zeolites, which are microporous, crystalline aluminosilicates with micropores of diameters comparable with molecular dimensions, offer the possibility of *shape selectivity,* which has found wide application in oil refining and bulk chemicals catalysis. With indoles, this could mean the favoring of the less bulky isomeric product by the restrictive environment of the zeolite pore. The compensation by protons of the negative charge introduced by Al^{3+} ions, which replace a proportion of the Si^{4+} ions in the framework, gives rise to catalysts with a wide range of acidity. Thus, in addition to the advantages of easy catalyst recovery and re-use, heterogeneous catalysis of the Fischer synthesis by zeolites might enable the regioselective formation of a single indole isomer. Of the many zeolites known, it is the so-called large-pore zeolite types, such as beta, mordenite and faujasites X and Y, which find the most application in fine-chemical catalysis.

An early, non-shape-selective, application of zeolites in the Fischer indole synthesis was reported by Venuto and Landis [18]. They employed calcium- and rare-earth-exchanged zeolite X as catalysts under continuous-flow conditions at 150 °C. Good yields of indoles were obtained with both acetone and cyclohexanone phenylhydrazones; a 72.5 % yield of indole was obtained from the latter with CaX catalyst.

Prochatska et al. screened (in liquid-phase batch reactions, with cyclohexane under reflux as solvent) fourteen different zeolites with five different unsymmetrical ketones, both in one-pot reactions and with isolated hydrazones as substrates [17]. With large-pore zeolites, yields of 80–90 % were obtained from the phenylhydrazones of 3-hexanone, 3-undecanone, 5-methyl-3-heptanone, and 1-phenyl-2-butanone.

The last substrate seemed to afford the most striking example of shape selectivity. According to Prochazka et al. the use of mordenite as catalyst led to the selective (93 %) formation of the least bulky isomer, 2-benzyl-3-methylindole, from 1-phenyl-2-butanone phenylhydrazine, whereas only 2-ethyl-3-phenylindole was formed when the reaction was performed in acetic acid. In attempts by Rigutto et al. to reproduce these findings, however, mixtures of both isomers were invariably obtained [19] and these workers found that molecular sieves, such as mordenite, with a one-dimensional channel system were ineffective in altering the indole isomer ratio. In their own study of the cyclization of 1-phenyl-2-butanone, Rigutto et al. found that the three-dimensional zeolites H-Na-Y and H-beta significantly altered the isomer ratio, with H-beta resulting in the highest preferential formation (75 %) of 2-benzyl-3-methylindole [19].

Of the various possibilities for realizing preferential formation of a single isomer, *product shape selectivity* is unlikely in this instance, because the indole products do not interconvert, which would rapidly result in plugging of the pores by the bulkier, non-desorbing isomer. This would result in partial catalyst deactivation, residual activity being confined to the unselective external zeolite surface. On the basis of adsorption data for the isomeric indoles from 1-phenyl-2-butanone and phenylhydrazine, Rigutto et al. suggested that *restricted transi-*

tion-state selectivity is the most likely mechanism for determining regioselectivity.

Product isomer distribution in the Fischer synthesis is determined by the complex interaction of several factors, so caution must be exercised in the attribution of changes in product-isomer distribution to specific causes such as shape selectivity. The principal factor determining the distribution of the indole isomers is the structure of the phenylhydrazone, as was shown by Prochazka and Carlson [20]. As summarized by Robinson [2], attempted prediction of the direction of ambiguous indolizations of ketone arylhydrazones must include consideration of the relative steric strain in the two possible enehydrazines involved and the relative steric hindrance in their subsequent reaction, as well as consideration of the stabilization effected by multiple alkyl substitution of the double bonds of the enehydrazine tautomers.

With regard to the effect of variation of the catalyst on isomer distribution, it must be noted that in homogeneous catalysis also substantially different regioselectivity can be engineered by variation of the catalyst. This is especially so with *methyl* ketone phenylhydrazones (R_1 = H in Scheme 1), such as those obtained from 1-phenyl-2-propanone [21] or 3-methyl-2-butanone [22], in which the isomer distribution has been shown to depend on the kind, the concentration, and the excess of Brønsted-acid catalyst used [21,23]. Increasing the concentration and/or excess of acid was shown to enhance the formation of the 2-substituted 3-*H*-indole isomer; this was explained by the investigators in terms of a change in the reaction mechanism, although this does not explain differences between different kinds of acid, such as the remarkably high selectivity towards the 2-substituted 3-*H*-indole isomer obtained with polyphosphoric acid, PPA [2,21].

In attempts to disentangle the different factors contributing to regioselectivity, the systematic studies of Rigutto [19] were extended by Kunkeler et al. [23]. In addition to 1-phenyl-2-butanone these workers also employed 1-phenyl-2-propanone (R_1 = Ph, R_2 = H in Scheme 1) and 3-heptanone (R_1 = Et, R_2 = *n*-Bu in Scheme 1) as substrates, the latter as a non-methyl ketone with no phenyl group, thus obviating the possibility of complications as a result of conjugation in the transition state [2].

Experiments were first conducted with acetic and polyphosphoric acids, and with several concentrations of H_2SO_4. As expected for a methyl ketone, with 1-phenyl-2-propanone phenylhydrazone use of PPA catalyst resulted in a large variation in isomer ratio (see Table 1). With 3-heptanone the variations resulting from use of different acids were much smaller. Of several active zeolite catalysts tested, H-beta was found to be the most selective heterogeneous catalyst for the synthesis of the 'linear' isomer from 3-heptanone and 1-phenyl-2-butanone phenylhydrazones whereas, in contrast, H-Na-Y gave about equal amounts of both isomers.

Appreciable formation of the linear 2-benzyl-3-*H*-indole by the Fischer synthesis with 1-phenyl-2-propanone was only observed with polyphosphoric acid and not at all with zeolite beta, although this product resembles, in bulkiness, 2-benzyl-3-methylindole, the linear indole isomer obtained from 1-phenyl-2-butanone. If the production of the linear isomer depended solely on suppression of the formation of the bulky product, then the trends in the selectivities for 1-phenyl-

Table 1. Ratio of bulky/linear indole isomers in the Fischer indole synthesis[a] [23].

Catalyst	1-Phenyl-2-butanone	1-Phenyl-2-propanone	3-Heptanone
Acetic acid	75/25	100/0	31/69
Polyphosphoric acid	–	59/41–24/76[b]	47/53
H-Na-Y	50/50	100/0	53/47
H-Beta	25/75	100/0	26/74

[a] Experimental conditions: one-pot procedure; ketone and phenylhydrazine react in *p*-xylene under reflux before addition of catalyst; conversion complete after 4 h.

[b] Depending on PPA composition.

2-propanone and 1-phenyl-2-butanone should be comparable, which is not observed. This suggests that selectivity in the 1-phenyl-2-butanone system and 3-heptanone systems is unlikely to be solely the result of intraporous transition-state restriction. An alternative explanation, based on the fact that the intermediate enehydrazine tautomer corresponding to the linear 2-benzyl-3-*H*-indole has an unfavorable terminal double bond, also cannot be valid, because this would be independent of catalyst and should be equally true for both acetic and polyphosphoric acids, which is not as found.

Although adsorption experiments with H-beta gave results in accordance with the preference for the linear product from 3-heptanone phenylhydrazone, with a bulky/linear adsorption ratio of 28/72 being found [23], and similar results were obtained for the indole isomers from 1-phenyl-2-butanone [22], total adsorption was small. Furthermore, when a sample of beta, the external surface of which had been passivated by silylation [24], was employed, no activity was found. This strongly suggests that it is the external surface, rather than the internal pore walls, which is responsible for the activity observed, thus variations in isomer distribution cannot be ascribed to pore-induced shape selectivity. Comparison of the calculated relative stabilities of the isomeric enehydrazines and indoles with the selectivity data of Table 1 indicate that the reactions are kinetically controlled, so that factors such as solvent effects are probably instrumental in establishing the observed product ratios.

On the basis of the examples reviewed above, it can be concluded that heterogeneous catalysis of the Fischer Indole Synthesis provides a practical and environmentally friendly alternative to the acids traditionally employed. Although it has not yet been possible to demonstrate unambiguously the use of a zeolite to effect the shape-selective formation of a single indole isomer, new structural types of zeolite and related materials continue to be synthesized, so that catalysts offering pore access and thus enhanced activity combined with shape selectivity remain a realistic research goal.

References

[1] R. J. Sundberg, 'The chemistry of indoles', Academic Press, New York & London, 1970, Chapter 3.
[2] B. Robinson, 'The Fischer Indole Synthesis', Wiley, New York, 1982.
[3] J. March, 'Advanced Organic Chemistry', 4th ed., Wiley–Interscience, New York, 1992, p. 1141.
[4] A.W. Douglas, J. Am. Chem. Soc. 100 (1978) 6463.
[5] F. P. Robinson, R. K. Brown, Can J. Chem. 42 (1964) 1940.
[6] N. N. Suvorov, N. P. Sorokina, J. N. Sheinker, J. Gen. Chem. USSR, 28 (1958) 1058.
[7] V.Ya. Kanterov, N. E. Starostenko, Yu. G. Oleinikov and N. N. Suvorov, Tr. Mosk. Khim.-Tehnol. Inst. No. 66 (1970) 113; Chem. Abstr. 75 (1971) 75650.
[8] N. N. Suvorov, L. I. Dmitrevskaya, Yu. I. Smushkevich and A. D. Pozdnyakov, J. Gen. Chem. USSR, 42 (1972) 2736.
[9] N. N. Suvorov, A. D. Pozdnyakov, M.Ya. Bykhovskii, V. V. Sadovnikov, J. Org. Chem. USSR, 11 (1975) 2684.
[10] N. N. Suvorov, L. I. Dmitrevskaya, Yu. I. Smushkevich, L.Yu. Petrovskaya, J. Gen. Chem. USSR, 45 (1975) 1565.
[11] N. N. Suvorov, L. I. Dmitrevskaya, Yu. I. Smushkevich, N. M. Przhiyalgovskaya, J. Org. Chem. USSR, 12 (1976) 892.
[12] N. N. Suvorov, V. N. Shkil'kova, N.Ya. Podkhalyuzina, J. Org. Chem. USSR, 17 (1981) 649.
[13] N. N. Suvorov, M.Ya. Bykhovskii, N.Ya. Podkhalyuzina, J. Org. Chem. USSR, 13 (1977) 382.
[14] N. N. Suvorov, V. N. Shkil'kova, N.Ya. Podkhalyuzina, J. Org. Chem. USSR, 19 (1983) 2117.
[15] S. Yamada, I. Chibata and R. Tsurui, Pharma. Bull. (Japan), 1 (1953) 14; Chem. Abstr. (1954) 48:12078.
[16] K. Maruoka, M. Oishi, H. Yamamoto, J. Org. Chem. 58 (1993) 7638.
[17] M. P. Prochazka, L. Eklund, R. Carlson, Acta Chem. Scand. 44 (1990) 610.
[18] P. B. Venuto and P. S. Landis, in: D. D. Eley, H. Pines and P. B. Weisz, Eds., Advances in Catalysis, Academic Press, New York and London, 18 (1968), p. 345.
[19] M. S. Rigutto, H. J. A.de Vries, S. R. Magill, A. J. Hoefnagel and H. van Bekkum, in: M. Guisnet, J. Barbier, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot and C. Montassier, Eds., 'Heterogeneous Catalysis and Fine Chemicals III'; Stud. Surf. Sci. Catal. 78, Elsevier Science, Amsterdam, 1993, p. 66.
[20] M. P. Prochazka and R. Carlson, Acta Chem. Scand. 43 (1989) 651.
[21] N. P. Buu-Hoi, P. Jacquignon and O. Périn, Bull. Soc. Chim. France, 32 (1965) 2849.
[22] H. Illy and L. Funderburk, J. Org. Chem. 33 (1968) 4283.
[23] P. J. Kunkeler, M. S. Rigutto, R. S. Downing, H. J. A. de Vries, H. van Bekkum, in 'Progress in Zeolites and Microporous Materials', Stud. Surf. Sci. Catal. 105, Elsevier Science, Amsterdam, 1997, p. 1269.
[24] P. J. Kunkeler, D. Moeskops and H. van Bekkum, Microporous Mater. 11 (1997) 313.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

5 Solid-acid Catalysis: Rearrangement and Isomerization

5.1 Beckmann Rearrangement

Takashi Tatsumi

5.1.1 Introduction

As an intermediate in the production of Nylon-6, ε-caprolactam is of high industrial importance and commercially produced by a liquid phase Beckmann rearrangement of cyclohexanone oxime in highly concentrated sulfuric acid, oleum. Because of the basicity of ε-caprolactam, it is obtained as a sulfate salt. Ammonia is used to liberate ε-caprolactam, forming ammonium sulfate as a by-product. Cyclohexanone oxime itself is synthesized from cyclohexanone and hydroxylamine sulfate in the presence of ammonia, resulting in the production of ammonium sulfate. As a result, the combined processes furnish 1.6–4.4 tons of ammonium sulfate by-product per ton of ε-caprolactam produced [1]. Although 47th on the list of industrial chemical production, the environmental consequences of this process are significant and have motivated research to find an environmentally acceptable process. Enichem succeeded in converting cyclohexanone to cyclohexanone oxime over a Ti-containing MFI zeolite, TS-1, in the presence of ammonia and hydrogen peroxide (12000 tons year^{-1} demonstration plant), eliminating the formation of ammonium sulfate. In the subsequent Beckmann rearrangement step solid-acid catalysts have been proposed as viable green alternatives to stoichiometric use of oleum.

Although many solid-acid catalysts have been reported for the vapor-phase Beckmann rearrangement [2], their performance has been less than satisfactory from an industrial standpoint and the heterogeneously catalyzed Beckmann rearrangement has not yet been commercialized. In this chapter heterogeneous catalysis of the Beckmann rearrangement, its mechanism, and acid properties and reaction conditions suitable for the reaction will be reviewed.

5.1.2 Catalysts for Beckmann Rearrangements

5.1.2.1 Non-zeolitic Oxide Catalysts

Boria- and Phosphate-based Catalysts

Boria-based catalysts for the Beckmann rearrangement go back to the seventies. Over Al_2O_3-supported B_2O_3 the yield of *N*-methylacetamide from acetone oxime was optimized at ca 20% B_2O_3 [3]. Alumina-supported B_2O_3 prepared by vapor-phase decomposition of $B(OEt)_3$ resulted in greater selectivity for caprolactam from cyclohexanone oxime than did the catalyst prepared by means of H_3BO_3 impregnation [4]. It was suggested that the vapor decomposition technique resulted in more uniform distribution of B_2O_3 on the γ-Al_2O_3 surface than the impregnation method. Silica-supported B_2O_3 catalyst similarly prepared was more efficient than alumina-supported B_2O_3. As shown in Figure 1, the vapor decomposition method had the advantage over the impregnation method [5].

Aluminas modified by the addition of Cl^-, PO_4^{3-}, SO_4^{2-}, Na^+, and B_2O_3 were used for the Beckmann rearrangement of cyclohexanone oxime [6]. Among the aluminas the B_2O_3-modified alumina was the best and that modified with Na^+ the least suitable. B_2O_3 coupled with hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, was more selective than B_2O_3–Al_2O_3 and the enhanced selectivity was ascribed to the basicity of hydroxyapatite [7].

The Beckmann rearrangement of cyclohexanone oxime was tested over phosphates of boron with compositions varying in the range B/P = 0.4–1.6. Catalysts with excess of boron had very high activity whereas catalysts with excess phosphorus had no activity [8]. $AlPO_4$–TiO_2 catalysts were more lactam-selective than $AlPO_4$ catalysts [9].

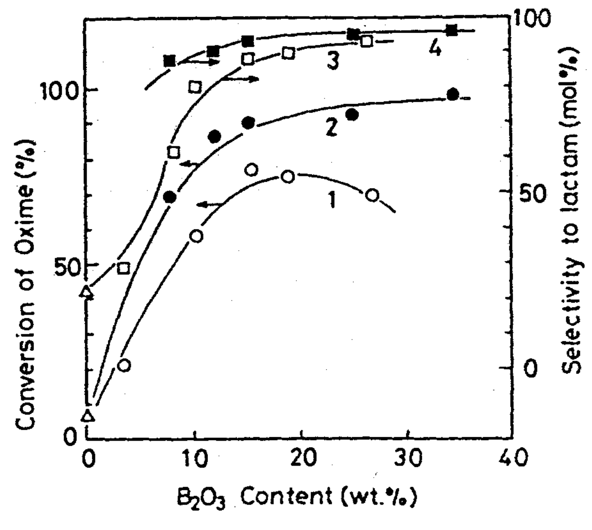


Figure 1. The effect of B_2O_3 content and loading method: (1) oxime conversion by impregnation B_2O_3/SiO_2, (2) oxime conversion by vapor decomposition B_2O_3/SiO_2, (3) lactam selectivity of impregnation B_2O_3/SiO_2, (4) lactam selectivity of vapor decomposition B_2O_3/SiO_2; 523 K [5].

Other Oxide Catalysts

In the early literature it was reported that SiO_2–Al_2O_3 [10,11] and supported tungsten oxide [11] had high activity and selectivity for ε-caprolactam. Tungsten oxide catalysts prepared from the hydrolysis of WCl_6 and supported on silica gel were more caprolactam selective than the catalyst prepared from ammonium tungstate [12]. Silica-supported Ta oxide catalyst prepared by the reaction between Ta alkoxide and surface hydroxy groups of SiO_2 had higher catalytic efficiency than catalysts prepared by impregnation with $TaCl_5$ or hydrated tantalum oxide [13]. Pt/sulfated ZrO_2 is reported in a patent to be active and durable [14].

Mesoporous Molecular Sieves

Use of mesoporous molecular sieves FSM-16 resulted in high conversion of cyclohexanone oxime but the selectivity for ε-caprolactam was low [15]. Dai et al. recently discovered that H-MCM-41 and H-FSM-16 have high activity, selectivity and stability for production of ε-caprolactam when 1-hexanol was co-fed as diluent [16]. Greater selectivity was obtained with the mesoporous catalyst than with amorphous SiO_2–Al_2O_3. Highly siliceous FSM-16 (Si/Al = 640) was inferior to Al-richer FSM-16 (Si/Al = 40) in terms of both selectivity and catalyst life.

5.1.2.2 Zeolite Catalysts

MFI Zeolite

The Beckmann rearrangement of cyclohexanone oxime over ZSM-5 (MFI) was first reported in a patent. High selectivity for ε-caprolactam was not attained [17]. Sato and co-workers found that the catalytic activity and selectivity to ε-caprolactam increased in proportion to the Si/Al ratio of H-ZSM-5 as shown in Figure 2 [18]. Even the extremely highly siliceous ZSM-5 (Si/Al > 27 000) with virtually no acidity resulted in high conversion with 75 % selectivity.

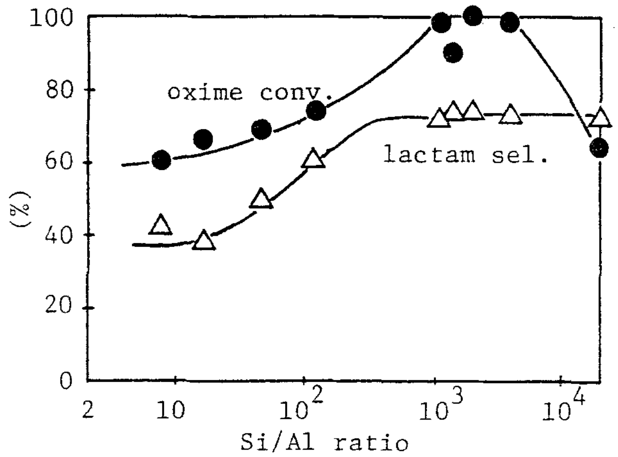


Figure 2. The effect of Si/Al ratio of H-ZSM-5 on the Beckmann rearrangement of cyclohexanone oxime (8 %) in benzene, WHSV = 38.5 h^{-1}, 623 K [18].

A detailed study has been conducted on the effect of synthesis conditions on catalytic properties [19,20]. When sodium silicate and Pr_4NBr were used, a gel was formed before the start of the hydrothermal synthesis and the external surface area of the highly crystalline product was as low as 1–2 $m^2\ g^{-1}$. When $Si(OEt)_4$ (TEOS) and Pr_4NOH were hydrolyzed in ethanol, the hydrothermal synthesis started with a clear solution, giving ZSM-5 materials with extremely low or no acidity, high crystallinity, and large external surface area (30–15 $m^2\ g^{-1}$) because of a small crystal diameter–in the range 0.2–0.3 μm. The total and external surface acidities were small compared with those obtained by use of sodium silicate as the Si source, because of the high purity of TEOS. The catalytic performance of the materials prepared from TEOS was superior to that of the material prepared from sodium silicate and Pr_4NBr. Treatment of highly siliceous ZSM-5 with trimethylchlorosilane improved the lactam selectivity, which increased to 95 % at 100 % conversion [19].

The catalytic performance of metallosilicates with the MFI structure in the Beckmann rearrangement of cyclohexanone oxime was also high. TS-1 was reported to be superior to silicalite-1; both oxime conversion and caprolactam selectivity were increased by increasing the Ti content of the MFI structure [21]. Deactivation was mitigated by incorporation of Ti. An effect similar to that of Ti was also observed for the MEL analog, TS-2 [22]. Takahashi et al. reported that In-MFI was the best catalyst among the metallosilicates (Si/M = 500) containing Al, Ga, In, or Fe [23]. The weakly acidic borosilicate of the MFI type is considered very suitable. Its activity has been studied in detail [24–27] and selectivities up to 95 % were achieved using ethanol as a diluent of the oxime.

Other Small- and Medium-pore Zeolites

Yashima et al. compared the catalytic performance of H-ZSM-5, H-FER, H-MOR, Ca-A, H-B-MFI, and H-SAPO-5 in the Beckmann rearrangement of cyclohexanone oxime [28]. H-B-MFI was calcined at 603 K only and tetra-*n*-propylammonium remained in the pore. The conversions obtained with Ca-A (molecular sieve 5 Å, 8MR) and H-B-MFI were low. As shown in Figure 3, however, the selectivity for ε-caprolactam was higher over Ca-A, H-FER (10 MR) and H-B-MFI and lower over H-SAPO-5 (12-MR), H-ZSM-5, and H-MOR (12-MR), which could accommodate cyclohexanone oxime in their pores. It was concluded that the selective formation of ε-caprolactam proceeded on the active sites on the external surface of zeolite crystallites rather than in the narrow space of the zeolite pore [28]. They even deduced that at higher reaction temperature cyclohexanone oxime would enter the pore, producing undesirable products such as cyclohexanone and 1-cyanopentene, which are smaller than ε-caprolactam, because of the size effect. On the other hand, Curtin and Hodnett reported that caprolactam selectivity was lower over the zeolites with smaller pore diameters [29].

Highly siliceous SAPO-11 (Si/Al > 10000) was a good catalyst in the Beckmann rearrangement compared with H-ZSM-5 and $ALPO_4$-11 on silica, silylated SAPO-11 [30]. UOP constructed a pilot plant using catalysts based on SAPO-11 [31].

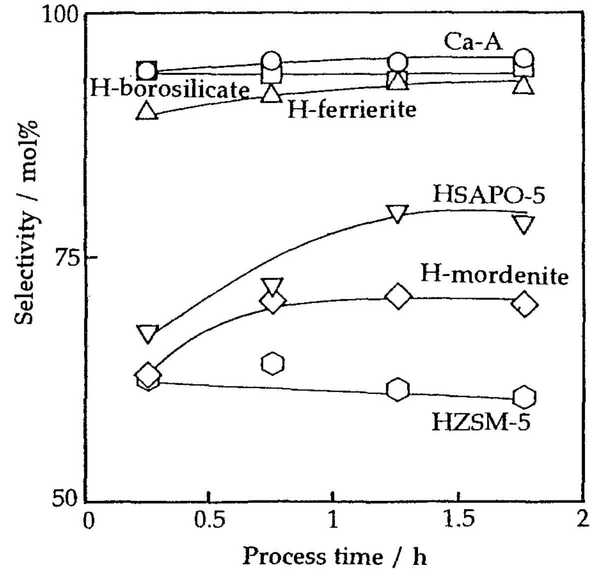


Figure 3. ε-Caprolactam selectivity of different catalysts. W/F = 10.2 g cat h mol^{-1}, 593 K [28].

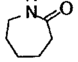
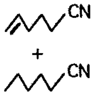
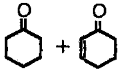
Large-pore Zeolites

The cyclohexanone oxime–caprolactam transformation is also catalyzed by large pore zeolites. H-Y is active in the rearrangement to caprolactam [32]. RE-X (rare-earth exchanged zeolite X), Co-X, Zn-X, and Ni-X also had appreciable catalytic activity whereas Na-X and Cu-X were inactive. H-MOR was inferior to H-Y in respect of both activity and selectivity. The capacity of zeolite Y to cause the Beckmann rearrangement of cyclopentanone oxime decreased in the series H > La > Ca [33]; alkali metal-exchanged zeolites produced only alkenenitriles. On HNa-Y zeolites the rate of caprolactam formation increased with increasing levels of H^+ exchange, at the expense of nitrile formation [34]. Calcination of H-Y at 873 K resulted in the best catalytic performance–high conversion and low activity decay [35], which was ascribed to optimum acid density.

Compared with the MFI zeolites, faujasites (FAU) zeolites such as X and Y had relatively low caprolactam selectivity, which was limited to ca 80 %, although Dai et al. found that use of higher alcohols as diluent greatly improved the catalytic performance of H-Y, depending on the SiO_2/Al_2O_3 ratio, as shown in Table 1 [36]. Thus ultrastable Y with SiO_2/Al_2O_3 ratios of 27 and 62 had excellent activity, selectivity and stability. It should be noted that dehydration of 1-hexanol to hexenes was < 1 % at steady state in the presence of cyclohexanone oxime whereas in its absence extensive dehydration occurred.

It has been shown that BEA zeolites are poor catalysts when benzene was used as diluent [37]. In a similar manner to H–Y, however, BEA zeolites containing Al turned out to be very good catalysts for the Beckmann rearrangement when higher alcohols were used as diluents [38]. Complete conversion and selectivity as high as 96 % were achieved with 1-hexanol and the improving effect increased with in-

Table 1. Product distribution in vapor-phase Beckmann rearrangement reactions[a].

Catalyst[b]	Amount acid (mmol g^{-1})	Diluent	Conv. (%)[c]	Selectivity (%)[c]			Others[d]
							
H-USY(390)	n. d.[e]	Methanol	35.9→12.8	39.5→39.6	29.8→30.4	*19.3→19.1*	*11.4→10.9*
H-USY(97)	0.28	Methanol	75.1→21.4	47.8→63.5	28.5→18.6	16.0→12.6	7.7→5.3
H-USY(62)	0.50	Methanol	97.1→62.5	81.9→86.5	7.7→6.1	5.9→5.0	4.5→2.4
H-USY(27)	0.92	Methanol	98.0→70.1	78.3→85.9	9.1→4.7	6.1→4.5	6.5→4.9
H-USY(6.3)	3.27	Methanol	94.7→78.5	64.5→80.1	3.0→4.4	20.5→8.9	12.0→6.6
H-USY(390)	n. d.[e]	1-Hexanol	45.8→17.6	64.1→80.3	12.3→7.1	10.2→7.6	13.4→5.0
H-USY(97)	0.28	1-Hexanol	89.5→56.5	85.1→87.9	4.3→3.3	3.9→3.8	6.7→5.0
H-USY(62)	0.50	1-Hexanol	100.0→99.9	93.7→94.6	2.1→1.7	2.2→2.7	2.0→1.0
H-USY(27)	0.92	1-Hexanol	99.9→99.9	88.8→93.8	2.6→2.1	1.9→2.8	6.7→1.3
H-USY(6.3)	3.27	1-Hexanol	99.9→99.8	76.6→86.0	3.6→3.1	3.3→6.9	16.5→4.0

[a] Reaction conditions: 623 K, 0.1 MPa, oxime/diluent/N_2 = 1:9:5.9 (molar), W/F = 80 g cat h mol^{-1} oxime.

[b] The number in parentheses presents the SiO_2/Al_2O_3 ratio.

[c] Time on stream = 1 h (left) and 6 h (right).

[d] Mostly dimers; octahydrophenazine and tetrahydrocarbazole.

[e] Not detected.

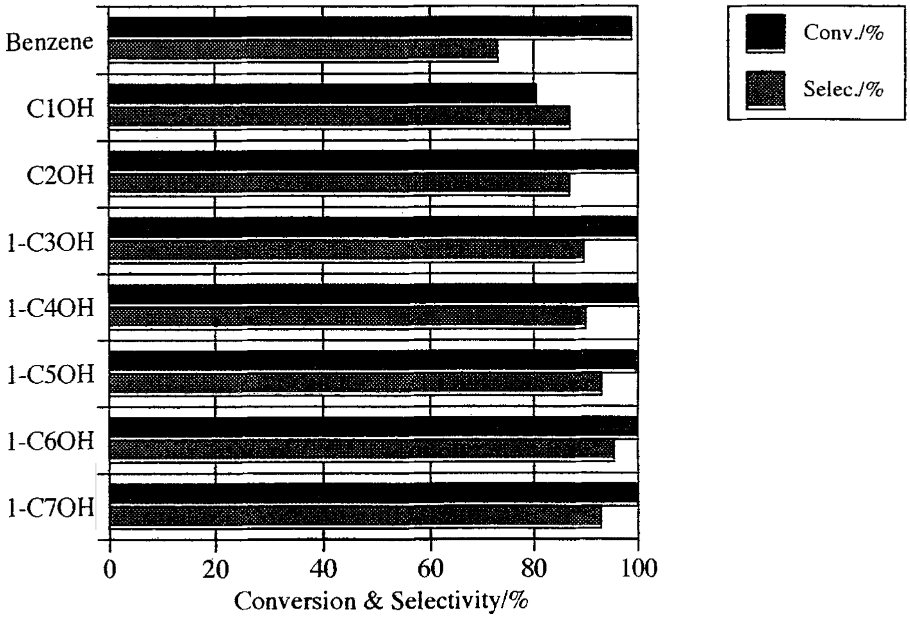


Figure 4. Effect of diluent on cyclohexanone oxime conversion and lactam selectivity over H-BEA. Temp. 623 K, oxime/diluent/N_2 molar ratio 1/9/5.9 and W/F of 80 g cat h moloxime^{-1}, time on stream of 6 h.

creasing alkyl chain length, as shown in Figure 4. The activity was slightly reduced by dealuminating H-beta whereas the selectivity was improved, in contrast with H-ZSM-5, the activity and selectivity of which increased with increasing SiO_2/Al_2O_3 ratio. For beta type borosilicate selectivity was ca 97 % when ethanol was used as diluent; however, the activity loss with time on stream was pronounced [39].

As shown in Figure 5, higher alcohols had a similar effect on other large-pore zeolites such as H-LTL and H-OFF-ERI (OFF-ERI is offretite obtained as mixed crystals with the small pore erionite) [40], whereas the activity of H-LTL slightly decreased with time on stream. H-MTW had poor activity, selectivity, and lifetime, irrespective of diluent. The activity and selectivity of H-MOR were also improved by use of higher alcohols [41], although its activity decreased rapidly with processing time in agreement with the previous findings [29]. The short life of H-LTL, H-MOR, and H-MTW could be because of their monodimensional channel structure.

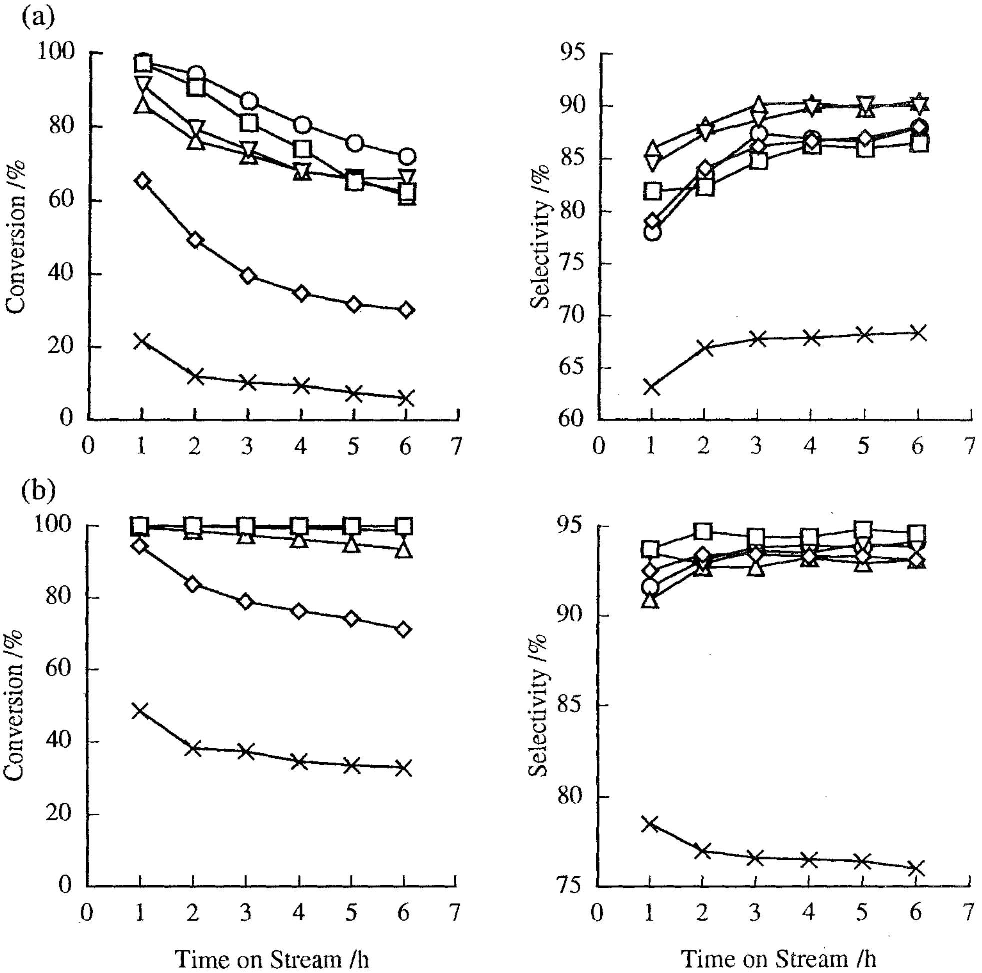


Figure 5. Change in cyclohexanone oxime conversion and lactam selectivity with time on stream in the vapor phase Beckmann rearrangement over 12-MR zeolites. Diluent: (a) methanol, (b) 1-hexanol. (×) H-BEA, (△) H-LTL, (▽) H-OFF-ERI, (□) H-USY ($SiO_2/Al_2O_3 = 62$), (◇) H-MOR, (○) H-MTW; 623 K, oxime/diluent/N_2 molar ratio of 1/9/5.9 and W/F of 80 g cat h^{-1} mol $oxime^{-1}$ [41].

5.1.3 Mechanistic Considerations

5.1.3.1 Reaction Pathway

The reaction pathway for the Beckmann rearrangement is depicted in Figure 6. It is commonly assumed that the Beckmann rearrangement reaction involves initial protonation at the oxygen atom of an oxime (I) giving an oxonium cation (II), followed by a migration of an alkyl group concomitant with liberation of a water molecule affording a nitrilium cation (III). The nitrilium cation (III) is hydrolyzed to form (IV) and, finally, its tautomer (V), an amide. The reaction is highly stereospecific in that the R_1 group *anti* to the hydroxyl group of the oxime always migrates. This stereospecificity is also observed with the heterogeneously catalyzed reaction. In the reaction of acetophenone oxime (R_1 = phenyl, R_2 = methyl) over H–Y at 573 K acetanilide and *N*-methylbenzamide were obtained in a ratio of 19:1 [32]. The small amount of benzamide was considered to arise from isomerization of oxime before rearrangement, rather than from migration of a *syn* methyl group. Aldoximes (R_2 = H) dehydrate to the nitrile under conditions causing ketoximes to rearrange to the corresponding lactams [29].

By use of ab initio calculations energy surfaces of the isolated gas phase systems of the Beckmann rearrangement were mapped out. It was suggested that the formation of the *N*-protonated oxime occurred predominantly, followed by a 1,2-shift leading the easiest way to produce its *O*-protonated isomer (II); the formation of (II) is the rate-determining step for the gas-phase reaction [42].

Cyclohexanone, 2-cyclohexen-1-one, 5-hexenenitrile, and hexanenitrile are commonly observed by-products in the Beckmann rearrangement of cyclohexanone oxime. Aniline and 2-methylpyridine are also occasionally formed. An outline of the reaction scheme is shown in Figure 7. From the selectivity change with time with $AlPO_4$ as catalyst, it was found that ε-caprolactam, cyclohexanone, and 5-hexenenitrile were obtained by parallel reactions [9]. 2-Cyclohexen-1-one, ani-

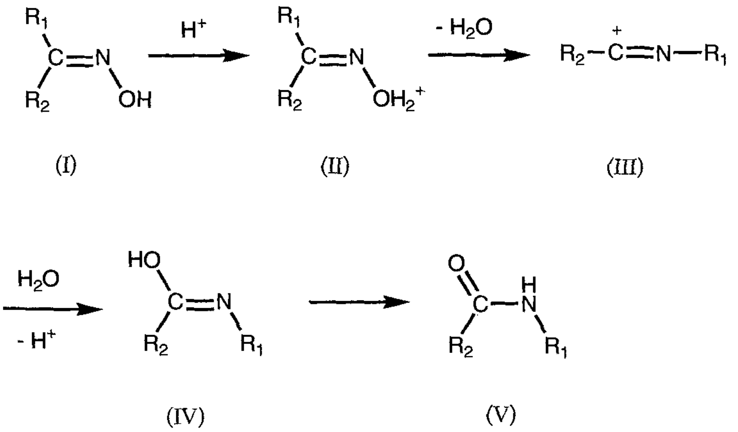


Figure 6. Reaction scheme for conversion of oxime (I) to amide or lactam (V).

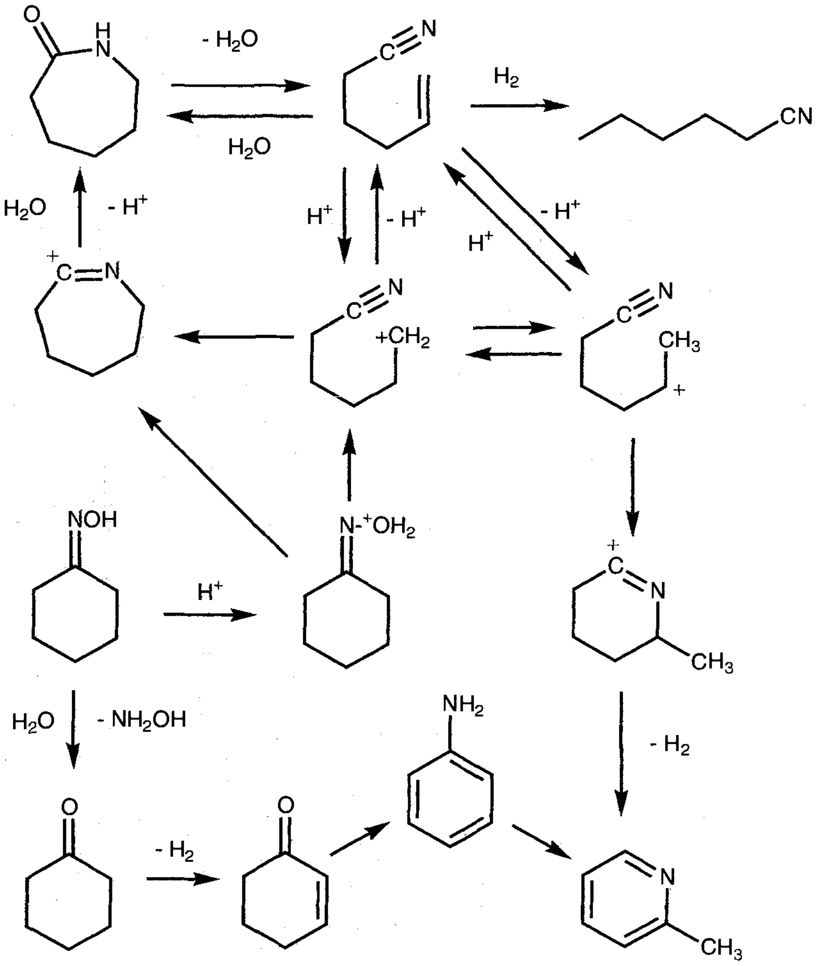


Figure 7. Reaction pathway of cyclohexanone oxime.

line, and 2-methylpyridine were formed as secondary products. Caprolactam was obtained as primary plus secondary reaction product. It was thus proposed that Ritter reaction of the open-chain intermediate contributed to the secondary formation of ε-caprolactam in the vapor phase [9,43] and liquid phase [44]. On dealuminated Y zeolite nitrile formation was enhanced. This was ascribed to the decrease in its transformation to lactam on hydrophobic catalysts, which could not retain water molecules [36,44].

The formation of 2-methylpyridine could be explained by the benzamine rearrangement of aniline or the Ritter reaction of the cyanopentyl carbenium ion. Aucejo et al. observed the disappearance of cyclohexanone and the simultaneous formation of 5-hexenenitrile and explained this by its conversion to 5-hexenenitrile,

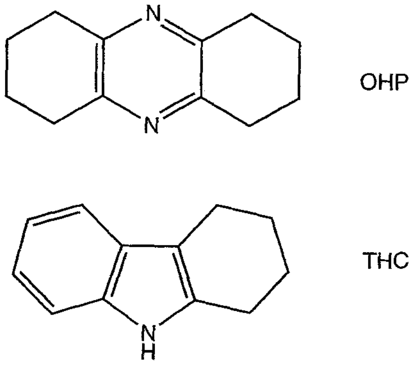


Figure 8. Dimeric products from cyclohexanone oxime.

through pentamethyleneoxaziridine formed by the reaction with NH_2OH [34]. Octahydrophenazine (OHP) and tetrahydrocarbazole (THC) are dimeric products (Figure 8) from cyclohexanone oxime and their formation was appreciable in reactions over the catalyst with high acid density [36].

5.1.3.2 Influence of Acid Type

It is generally accepted that Brønsted acid sites are the catalytic sites for the Beckmann rearrangement [32,34,45]. The reaction apparently involves initial protonation at an oxime, giving an oxonium cation, then migration of an alkyl group. Thus the key role of acid sites is probably to convert the poor leaving OH group of the oxime into a good leaving group by protonation. As described in Section 5.1.3.1, however, the MO calculation suggested that *O*-protonation is preceded by N-protonation.

In contrast, Lewis acids are assumed to be the active sites of boron phosphate catalysts [8]. It has been reported that Brønsted-acid centers which occur in borophosphates containing excess P had no activity in the Beckmann rearrangement whereas Lewis acid centers, which are associated with excess B, had very high activity. It was postulated that the oxime is adsorbed on the trigonal boron (Lewis acid) site to form an intermediate complex and that simultaneous H-bonding of the oxime OH group to the adjacent oxygen connected to tetrahedral boron resulted in migration to give the nitrilium cation intermediate (III). The importance of a Lewis acid site was also proposed for fluorinated Al_2O_3 [46] and Ce-Y [47] catalysts.

5.1.3.3 Influence of Acid Strength

The active site for the Beckmann rearrangement is still the subject of controversy. What is the acid strength suitable for lactam production–strong, weak or intermediate? It has even been suggested that neutral sites are responsible for the rearrangement. For the zeolite catalysts, does the reaction occur inside the pore or on the external surface? If the reaction occurs on the external surface, what is the role of the zeolite structure?

Takamiya et al. reported that B_2O_3-based binary metal oxide catalysts with a large number of acid sites of $-8.2 < H_0 < -3.0$ gave caprolactam preferentially whereas nitrile formation increased over catalysts with acids of $H_0 > -3.0$, which correspond to the acidity inherent to B_2O_3 [3]. Thus it was suggested that stronger acids produce the lactam and weaker acids give rise to the nitrile. Izumi and co-workers, however, reported that the B_2O_3 itself was responsible for the Beckmann rearrangement and that stronger acid sites ($-5.6 < H_0 < -3.0$) formed at lower loadings (< 12 % *w/w*) of B_2O_3 on Al_2O_3 accelerated both the conversion of the lactam to nitrile and the decomposition of the oxime into cyclohexanone [4]. The same authors reached different conclusions for silica-supported B_2O_3 catalyst, for which acid of $H_0 < -5.6$ was responsible for the rearrangement [5]. Curtin et al. found a simple relationship between selectivity for caprolactam over B_2O_3/Al_2O_3 and the surface concentration of intermediate strength acid sites, namely those from which ammonia was desorbed in the temperature range 473–623 K [29].

For the HNa-Y zeolites it was concluded that only Brønsted sites of $H_0 < 1.5$ were active in producing ε-caprolactam [34]. Alkali cations were responsible for the formation of alkene nitriles [33]. For the alkali metal-exchanged Y zeolites the capacity of the cation to promote production of alkene nitrile decreased in the order of decreasing electrostatic field strength, Li > Na > K > Cs. From the presence of alkene nitrile in the total absence of Na^+ it was also suggested that acid centers should also catalyze the ring-opening reaction [34]. For dealuminated Y zeolites selective Beckmann rearrangement was favored by a moderate amount of relatively weak acid sites which showed NH_3 desorption peaks with maxima at ca 436 and 573–603 K [36].

Among the MFI metallosilicates containing Al, Ga, In, and Fe, indosilicate was the best catalyst; this was attributed to its low acid strength [23]. Boria loading on H-ZSM-5 (Si/Al = 50–100) resulted in a decrease in strong acid sites retaining NH_3 at 683 K; this was accompanied by increase in selectivity for the Beckmann rearrangement [48]. The production of polymers over strong acid sites was believed to cause a decrease in the lactam selectivity during the reaction.

Sato et al. found that the yield of caprolactam increased with decreasing Al content of the H-ZSM-5 [20]. In addition, the activity and selectivity were proportional to the external surface areas, as shown in Figure 9 [20]. Thus it was proposed that the active site for the rearrangement is a neutral silanol on the external catalyst surface [20,49]. The proposed neutrality agreed with the negligible influence of the co-fed amines during the reaction [50]. Costa et al. also reported that pyridine and other bases had no poisoning effect on the rearrangement activity of the $AlPO_4/\gamma\text{-}Al_2O_3$ catalyst [51].

The apparent relationship between external surface area and the activity and selectivity of the rearrangement can be interpreted differently. If the reaction occurs in the channels near the pore openings to the external surface, the effectiveness of the catalyst could be increased in line with the external surface area. Another reason for the claim that the Beckmann rearrangement of cyclohexanone oxime occurs on the external surface of the MFI structure is the similar sizes of ε-caprolactam and the pore diameter. It should, however, be noted that the diameter values

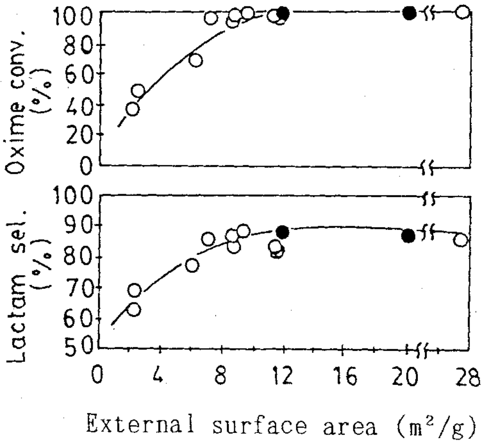


Figure 9. The effect of external surface area of H-ZSM-5 on the Beckmann rearrangement of cyclohexanone oxime. ○ Si/Al = 2000–3000, ● Si/Al = 30 000, 8 % oxime in benzene, WHSV = 38.5 h^{-1}, 623 K [19].

given are based on an oxygen radius of 1.35 Å, which corresponds to ionic oxygen [52] and there seems ample evidence that the framework oxygen is more covalently bound to Si, such that its size is ca 0.85 Å [53]. If this is so the circular pore opening distance might be 1.0 Å larger than the value usually assumed.

Sato et al. also emphasized that the silanol must be located in a crystalline material [20]. Hölderich et al. found that amorphous silica was inactive as a catalyst in the Beckmann rearrangement of cyclohexanone oxime [25], although treatment of inactive silica with HCl led to slightly improved catalytic performance [54]. This was accompanied by an increase in the vicinal H-bonded silanols revealed by IR spectra and thus these vicinal silanols seemed to be more favorable sites for the Beckmann rearrangement than their terminal counterparts. As shown in Figure 10, the IR spectra of the silicalite-1 treated with aqueous NH_4OH or NH_4NO_3 had a peak at 3690 cm^{-1}, assigned to vicinal silanols, and a peak at 3500 cm^{-1}, assigned to silanol nests. The latter were typical of the crystalline structure of the silicalite-1 and their appearance was accompanied by very high caprolactam selectivity; this suggested that these hydroxyl nests are the most favorable active site for the production of caprolactam, even superior to vicinal protons. Their arrangement on the external surface of the silicalite-1 could be most suitable, mainly because of the MFI structure [54].

It is well known that silanol groups are formed upon dealumination of Y zeolites. The excellent catalytic performance of moderately dealuminated ultrastable Y zeolites [36], and of FSM-16 and MCM-41 [16], which contain many hydrogen-bonded silanol groups, for this rearrangement in 1-hexanol diluent is consistent with these findings, although it should also be noted that highly dealuminated Y zeolites gave rise to poor performance, irrespective of diluent–a certain amount of Al favors the rearrangement activity of Y zeolites and mesoporous molecular sieves, in contrast with MFI silicalites.

From the IR spectra of the adsorbed oxime on the highly siliceous ZSM-5, Sato proposed the mechanism via oxime-silyl ether (VI) for the rearrangement at the neutral silanol [1c]. Recently the chemical species formed upon adsorption and

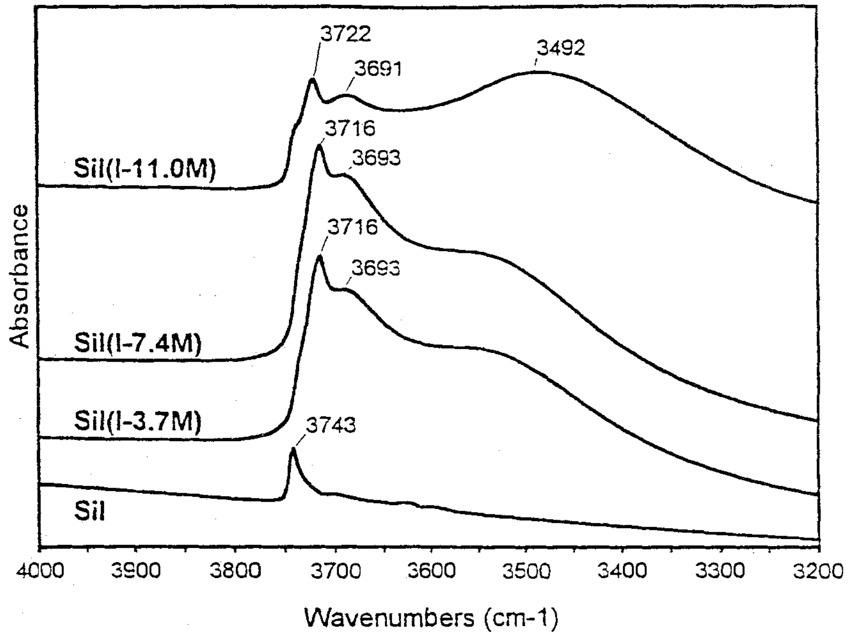
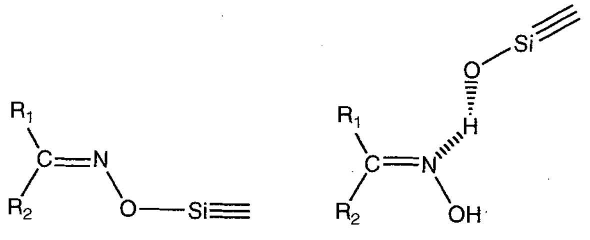


Figure 10. FTIR spectra of Sil (silicalite-1) samples treated with aqueous solutions of NH_3. The number in parentheses indicates the molar concentration of NH_3 solutions [54].

subsequent heat-treatment of 2-butanone [^{15}N]oxime on silicalite-1 were examined by ^{15}N NMR spectroscopy. An H-bonded oxime form (VII) (Figure 11) was detected at 248 K whereas neither (VI) nor amides were detected upon heating [55].

The catalytic performance of highly siliceous ZSM-5 was greatly improved when methanol was co-fed with oxime. Thus it was further claimed that in the presence of methanol the neutral silanol was not the active site for producing ε-caprolactam because they were methylated by methanol [56]. The beneficial effect of trimethylchlorosilane treatment was ascribed to reduction of amorphous silanols and to enhancement of hydrophobicity. The latter could facilitate the smooth desorption of the oxime [19].



(VI)

(VII)

Figure 11. Possible intermediates formed on silicalite surfaces.

5.1.4 Deactivation and Regeneration

5.1.4.1 Deactivation

The decay of catalytic performance in the Beckmann rearrangement with time on stream is a major and common problem associated with all types of catalyst. Two main reasons are suggested for the deterioration in activity–coke formation and irreversible adsorption of basic products.

Coke formation could be a major problem associated with all the acid-catalyzed reactions. Curtin et al. found a direct relationship between amount of coke and loss of catalytic activity [57]. There are different opinions on the mechanism of coke formation. The products can be strongly adsorbed on strong acid sites and lead to polymerization and eventually coke [12]. It has also been proposed that caprolactam polymerization and condensation reactions of by-products, e. g. between cyclohexanone and aniline, involve strongly basic sites [56]. The Schiff base product could condense once again with cyclohexanone via the Mannich reaction, leading eventually to polymer formation. In contrast, Izumi et al. suggested that higher selectivity and less coking can be expected for catalysts containing a basic component because of the desorption thus promoted [7].

The irreversible adsorption of basic products is reported to be common with zeolites. Aucejo et al. reported that the decay of the catalyst was because of the poisoning of the acid sites by basic compounds, rather than deposition of coke [34]. Burguet et al. investigated the catalyst decay accompanying the reaction of cyclohexanone oxime over ultrastable H–Y zeolite [58]. The basic compounds present during the reaction i. e. oxime, ε-caprolactam, methylpyridine, 5-cyanopent-1-ene, hydroxylamine, and aniline were considered to be the catalyst poisons. Hydroxylamine is more basic than the other products and might be more poisonous. Hydroxylamine selectivity decreased with temperature, which could explain qualitatively the apparent decrease in the deactivation constant (k_d) with increasing temperature.

The deactivation of B-MFI catalyst was not attributed to carbon deposition but to pore-blocking caused by an enrichment of nitrogen-containing species inside the pore system [27]. It was assumed that these species were formed by oligomerization or polymerization of alkene nitriles. If this is so the reaction before deactivation occurs mainly inside the pores of the MFI zeolite.

For B_2O_3-based catalysts, in addition to the mechanism already described for the loss of selectivity, evidence has been reported of an additional process whereby the selective sites are converted to amorphous boron species [59] or glassy melt [5].

5.1.4.2 Regeneration

The regeneration procedure is very important in practice. Usually the carbonaceous materials and strongly adsorbed compounds are burned off at elevated temperatures, although this often results in reduced activity and selectivity compared with the starting catalyst. Shimizu et al. treated a spent ZSM-5 catalyst with air in the presence of methanol at 713 K and completely restored catalytic performance [60].

Treating deactivated B_2O_3/Al_2O_3 catalysts in air did not regenerate the catalytic activity [61]. The regeneration temperature must be below 873 K, otherwise supported B_2O_3 is lost by vaporization during regeneration [4]. Crystalline B-MFI was regenerated without such a problem [24].

The possibility of performing the reaction as a continuous reaction–regeneration system has been studied in a fluidized bed reactor on the laboratory scale [24].

5.1.5 Influence of Reaction Conditions

5.1.5.1 Vapor Phase and Liquid Phase

The control of selectivity in the vapor phase Beckmann rearrangement seems to be difficult; this can be ascribed to the drastic experimental conditions required. Liquid-phase reactions over heterogeneous catalysts have been investigated. The Beckmann rearrangement of cyclohexanone oxime in the liquid phase was performed under reflux conditions in a variety of solvents [44]. When chlorobenzene was used solvent conversion and selectivity increased with temperature up to 405 K. From plots of conversion against time it was concluded that catalyst deactivation under liquid-phase conditions is small, in contrast with the rapid deactivation observed when the reaction was conducted in the vapor phase.

A series of BEA zeolites has been applied to the liquid-phase Beckmann rearrangement [62]. As shown in Table 2, activity was observed for BEA catalysts synthesized in OH^- media, with internal silanol groups but no framework Al. The selectivity was, however, dependent on the oxime–for cyclohexanone oxime lactam selectivity was high; for cyclododecanone oxime it was low. Synthesis in F^- media gave samples containing only external silanol groups, which were mainly responsible for the hydrolysis of the oxime to the corresponding ketone. This was explained by assuming that the internal silanol groups were more acidic than the external silanol groups. Brønsted acid sites of the BEA zeolites were very active and selective for formation of the corresponding amides/lactams in the liquid phase. The catalytic performance of H-BEA zeolites for larger oximes was much better than that of H-ZSM-5. These results are inconsistent with the hypothesis of Sato et al. that the external surface of H-ZSM-5 is responsible for the Beckmann rearrangement of cyclohexanone oxime [20,49]; if the reaction occurs on the external surface, there should be no significant difference between the reactivity of cyclohexanone and cyclododecanone oximes. This discrepancy could be ascribed to the difference between the reaction phases.

Table 2. Liquid-phase Beckmann rearrangement.

Catalyst	Synthesis medium	Si/Al	Cyclohexanone oxime (%)		Cyclododecanone oxime (%)	
			Conv.	Sel.[a]	Conv.	Sel.[b]
beta	OH^-	>4000	38	>98	46	39
beta	OH^-	31	68	>98	91	72
beta	F^-	>10000	0.2	80	0	-
beta	F^-	34	54	>98	92	>98
ZSM-5	OH^-	37	67	95	0	-

[a] Selectivity for lactam.

[b] Catalyst 100 mg, oxime 100 mg, chlorobenzene 20 mL, (130 C, 24 h).

Gutierrez et al. compared a variety of catalysts for the solvent-free conversion of oximes at low temperatures (373–433 K) [63]. For acetophenone oxime Al^{3+} montmorillonite resulted in fairly good acetanilide selectivity whereas for cyclohexanone oxime the best results were obtained with Amberlyst-15. The competitive reaction was the hydrolysis of the oxime to carbonyl compounds.

It was very recently reported that cyclododecanone oxime was converted to its corresponding lactam by $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst, the activity of which was much higher than that of either Amberlyst or Nafion–SiO_2. The reaction proceeded at 373 K, indicating it occurred as solid–solid reactions [64].

5.1.5.2 Co-feed Effects

The co-fed gas and solvent have a dramatic effect on the selectivity and service life of the catalysts. With Ni–X, a striking extension of catalyst life was associated with the use of H_2 as carrier gas [32]. The use of H_2 for Pd-containing H–Y improved the Beckmann rearrangement [33]. It was proposed that the prime function of the Pd is to promote formation of Brønsted acid sites.

Sato et al found that over highly siliceous ZSM-5 the selectivity for ε-caprolactam was increased by use of CO_2 as carrier gas [18,20]. Catalytic performance also improved greatly when methanol was co-fed with oxime [56]. Up to a methanol/oxime ratio of unity lactam selectivity increased and then leveled off. Oxime conversion was little changed up to the ratio of unity and decreased beyond this value. It has been claimed [65] that addition of methanol and a small amount of H_2O to cyclohexanone oxime resulted in long catalyst life.

The deactivation rate over In-MFI decreased when a mixture of carbon dioxide and methanol was used as diluent gas [23]. This effect was prominent when the catalysts were modified with noble metals and it was speculated that carbon dioxide or methanol, with the aid of platinum, reduced the carbonaceous deposits.

As described above, favorable effects of higher alcohols were widely observed with large-pore zeolites [40], although the use of 1-hexanol was not so beneficial to 10- or 8-MR zeolites as to 12-MR zeolites [41]. An IR study revealed that the adsorption/interaction of methanol on the H-BEA (Si/Al = 12.8) catalyst was stronger than that of 1-hexanol. The relatively strong Brønsted acid sites, probably responsible for the formation of by-products, might be covered with 1-hexanol preferentially, resulting in increased activity and selectivity for ε-caprolactam formation. Because the adsorption of methanol on H-BEA zeolite was relatively strong, the active sites might be prevented from making contact with the reactant, resulting in low conversion and selectivity to ε-caprolactam. Thus, depending on the Si/Al ratio, the hydrophobicity of the zeolites should be crucial in the choice of diluents.

The solvent effect is not limited to zeolitic catalysts. For WO_3/SiO_2 solvents such as methanol and acetonitrile increased ε-caprolactam selectivity compared with that for benzene [12].

To investigate the active role of the solvent, ab initio calculations were conducted within a supermolecular approach; in the Beckmann rearrangement the solvent molecule interacts with a migrating hydrogen, inducing a significant effect on the barrier height to 1,2-shift as the rate-determining step [42].

5.1.5.3 Temperature Effects

Although the industrial Beckmann rearrangement of cyclohexanone oxime is conducted at 363–393 K in the presence of oleum, heterogeneously catalyzed reactions are usually conducted at much higher temperatures. This could be because of the strong adsorption of the product lactam on the catalyst surface. IR spectra of the zeolite Y surface showed that the rearrangement was substantially complete at 393 K [45]. The strong adsorption of the product lactam would account for the relatively low selectivity observed at temperatures lower than 623 K [9,24]; once formed, the lactam is difficult to desorb and is converted to by-products. Catalyst life also increased with increasing temperature, which was explained by the supposition that coke precursors or deactivating compounds are desorbed more easily at elevated temperatures [24].

On the basis of IR observations of ZSM-5 Sato et al. also concluded that rearrangement was complete at 373 K, irrespective of the Si/Al ratio [49]. There was, however, a large difference between highly siliceous (non-acidic) and acidic samples. The acidity of ZSM-5 (Si/Al = 40) samples prevents the lactam from being desorbed and eventually reduces selectivity, whereas the lactam is readily desorbed from non-acidic ZSM-5.

5.1.6 Concluding Remarks

Strenuous efforts are being made to improve environmental aspects of the heterogeneously catalyzed Beckmann rearrangement. Remaining problems are deactivation after a relatively short time on stream and insufficient lactam selectivity. The solid-acid method must be highly selective to compete with the conventional method because of the extremely high selectivity associated with the latter.

As a novel approach, 'non-catalytic' Beckmann rearrangement was recently reported to occur near the critical temperature (647 K) in subcritical or supercritical water [66].

References

[1] Brownstein A M (1995) Chemtech: 31–32.
[2] For a review see, (a) Hölderich W F and van Bekkum H (1991) Stud Surf Sci Catal 58: 631–726; (b) Hölderich W F (1989) Stud Surf Sci Catal 46: 193–209; (c) Sato H (1997) Catal Rev –Sci Eng. 39: 395–424; (d) Tatsumi T (1997) Curr Opin Solid State Mater Sci 2: 76–83; (e) Tanabe K and Hölderich W F (1999) 181: 399–434.
[3] Takamiya M, Tsunoda H, Suzuki S and Murai S (1978) Nippon Kagaku Kaishi: 799–804.
[4] Sato S, Hasebe S, Sakurai H, Urabe K and Izumi Y (1987) Appl Catal 29: 107–115.
[5] Sato S, Urabe K and Izumi Y (1985) J Catal 102: 99–108.
[6] Curtin T, McMonagle J B, Hodnett B K (1992) Appl Catal 93: 75–89.
[7] Izumi Y, Sato S and Urabe K (1983) Chem Lett: 1649–1652.
[8] Haber J and Szybalska U (1981) Faraday Discuss Chem Soc 72: 263–282.
[9] Bautista F M, Campelo J M, Garcia A, Luna D, Marinas J M and Moreno M S (1993) Stud Surf Sci Catal 78: 615–622.
[10] Murakami Y, Saeki Y and Ito K (1978) Nippon Kagaku Kaishi: 21–26.
[11] Yashima T, Horie S, Saito S, Hara N (1977) Nippon Kagaku Kaishi, 77.
[12] Kob N and Drago R S (1998) Catal Lett 49: 229–234.
[13] Ushikubo T and Wada K (1994) J Catal 148: 138–148.
[14] Mitsubishi Heavy Ind Japanese patent 86-11111.
[15] Nakajima T, Nakajima T and Mishima S (1997) Nippon Kagaku Kaishi: 565–569.
[16] Dai L X, Koyama K and Tatsumi T (1998) Catal Lett 53: 211–214.
[17] Mobil Oil Corp US patent 4359421 (1982).
[18] Sato H, Ishii N, Hirose K and Nakamura (1986) Stud Surf Sci Catal 28: 755–762.
[19] Sato H, Hirose K, Kitamura M and Nakamura Y (1989) Stud Surf Sci Catal 49:1213–1222.
[20] Sato H, Hirose K and Kitamura M (1989) Nippon Kagaku Kaishi: 548–554.
[21] Thangaraj A, Sivasanker S and Ratnasamy P (1992) J Catal 137: 252–256.
[22] Reddy J S, Ravishankar R, Sivasanker S and Ratnasamy P (1993) Catal Lett 17: 139–144.
[23] Takahashi T, Kai T and Nasution M N A (1995) Stud Surf Sci Catal 97: 431–436
[24] Röseler J, Heitmann G and Hölderich W F (1996) Appl Catal A: General 144: 319–333.
[25] Hölderich W F, Röseler J, Heitmann G and Liebens A T (1997) Catal Today 37: 353–366.
[26] Hölderich W F and Heitmann G (1997) Catal Today 38: 223–233.
[27] Albers P, Seibold K, Haas T, Prescher G and Hölderich W F (1998) J Catal 176: 561–568.
[28] Yashima T, Miura K and Komatsu T (1994) Stud Surf Sci Catal 84: 1897–1904.
[29] Curtin T and Hodnett B K (1993) Stud Surf Sci Catal 78: 535–542.
[30] Singh P S, Bandyopaday R, Hegde S G and Rao B S (1996) Appl Catal A 136: 249–263.
[31] Cusumano J A (1992) ChemTech: 482–489.
[32] Landis P and Venuto P B (1966) J Catal 6: 245–252.
[33] Butler J D and Poels T C (1973) J Chem Soc Perkin Trans 2: 1262–1266.
[34] Aucejo A, Bugruet M C, Corma A and Fornes V (1986) Appl Catal 22: 187–200.
[35] Sato S, Takematsu K, Sodesawa T and Nozaki F (1992) Bull Chem Soc Jpn 65: 1486–1490.
[36] Dai L X, Koyama K, Miyamoto M and Tatsumi T (1999) Appl Catal A: General 189: 237–242.
[37] Herrero E R, Anunziata O A, Pierella L B and Orio O A (1994) Lat Am Appl Res 24: 195–202.
[38] Dai L X, Hayasaka R, Iwaki Y, Koyano K A and Tatsumi T (1996) Chem Commun: 1071–1072.
[39] Heitmann G, Dahlhof G and Hölderich W F and (1999) Appl Catal A: General 185: 99–108.
[40] Dai L X, Iwaki Y, Koyama K and Tatsumi T (1997) Appl Surf Sci 121/122: 335–338.
[41] Tatsumi T and L X Dai (1999) Proceedings of the 12th International Zeolite Conference: 1455–1462.
[42] Nguyen M T, Rasport G and Vanquickenborne (1997) J Am Chem Soc 119: 2522–2562.
[43] Costa A, Deya P M, Sinisterra J V and Marinas J M (1980) Can J Chem 58: 1266–1270.

[44] Corma A, Garcia H, Primo J and Sastre E (1991) Zeolites 11: 593–597.
[45] Butler J D and Poels T C (1973) J Chem Soc Perkin Trans 2: 41–47.
[46] Cimino G, Vitarelli P, Alibrandi G, Caristi C and Galvagno S (1982) React Kinet Catal Lett 21: 467–472.
[47] Kowalak S, Laniecki M, Pawlowaka M, Balkus K J and Khanmamedova A (1997) Stud Surf Sci Catal 105B: 1181–1188.
[48] Takahashi T, Ueno K and Kai T (1991) Can J Chem Eng. 69: 1096–1099.
[49] Sato H, Hirose K and Nakamura Y (1993) Chem Lett: 1987–1990.
[50] Sato H and Hirose K (1993) Chem Lett: 1765–1766.
[51] Costa A, Deya P M, Sinisterra J V and Marinas J M (1981) Afinidad 38: 225–227.
[52] Meier W M, Olson D H and Baerlocher Ch (1996) Atlas of Zeolite Structure Types, 4th Ed, Elsevier.
[53] Abrams L and Corbin D R (1995) J Incl Phenom Mol Recog Chem 21: 1–46.
[54] Heitmann G P, Dahlhoff G and Hölderich W F (1999) J Catal 186: 12–19.
[55] Parker W O'N (1999) Magn Reson Chem 37: 433–436.
[56] Curtin T, McMonagle J B, Hodnett B K (1992) Appl Catal 93: 91–101.
[57] Kitamura M and Ichihashi H (1994) Stud Surf Sci Catal 90: 67–70.
[58] Burguet M C, Aucejo A and Corma A (1987) Can J Chem Eng. 65: 944–949.
[59] Curtin T, McMonagle J B, Hodnett B K (1991) Stud Surf Sci Catal 59: 531–538.
[60] Sumitomo Chemical Co, Koei Chemical Co Eur Pat Appl EP 90-302423.
[61] Curtin T, McMonagle J B, Ruwet M and Hodnett B K (1993) J Catal 142: 172–181.
[62] Camblor M A, Corma. A García H, Semmer-Herlédan V and Valencia S (1998) J Catal 177: 267–272.
[63] Gutierrez E, Aznar A J and Ruiz-Hitzky E (1991) Stud Surf Sci Catal 59: 539–547.
[64] Odawara D, Nakato T, Tue, H, Okuhara T (1999) Preprints for the Hokkaido Regional Meeting of the Chemical Society of Japan, B14.
[65] Sumitomo Chemical Co Eur Pat Appl EP 92-310818.
[66] Sato O, Ikushima Y and Yokoyama T (1998) J Org Chem 63: 9100–9102.

5.2 The Benzamine Rearrangement

R. Prins

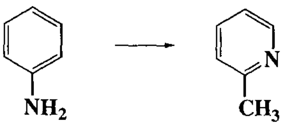
5.2.1 Introduction

Introduction of heteroatoms, e. g. N, S, or O, into hydrocarbon molecules adds substantial value, and new routes for such reactions are of continuous interest to the chemical industry. The two main classes of aromatic N-containing hydrocarbons are the arylamines and the aromatic N-heterocyclic compounds. The arylamines, which are required industrially, are manufactured by nitration of aromatics to nitroaromatics, followed by hydrogenation to arylamines [1,2]. Because of the lower demand for aromatic heterocycles than for arylamines, coal tar is still an important source of pyridine and methylpyridines (picolines). Increasing demand for aromatic heterocyclic compounds has led to processes in which aldehydes and ketones are condensed with NH_3 to furnish pyridine and alkylated pyridines [3,4].

Pyridine derivatives are precursors of many chemical products of medicinal, agricultural, and industrial importance. Pyridine itself is used not only as a solvent, but also as a starting material for pharmaceuticals, herbicides, insecticides, and fungicides. α-Picoline is a precursor for 2-vinylpyridine which is used in the production of an adhesive for textile tire cord. The major use of γ-picoline is in the production of isonicotinic hydrazide, an antituberculosis agent. β-Picoline and 2-methyl-5-ethylpyridine are important intermediates in the production of two members of the vitamin B family, nicotinamide, and nicotinic acid (also known as vitamin B3). All this shows there is a substantial need for the production of picolines. The following text describes a novel route to α-picoline which might in the future lead to new processes.

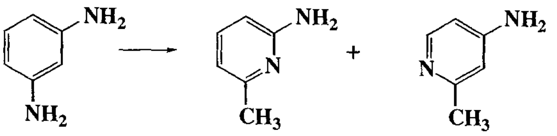
5.2.2 Rearrangement of Aniline and *m*-Phenylenediamine

Two decades ago a process for the conversion of phenol into aniline was patented by Chang and Lang [5]. At 783 K and an NH_3 pressure of ca 1 MPa, reasonable conversion to aniline was obtained over an H-ZSM-5 catalyst in a flow reactor. The two main by-products were diphenylamine, from the reaction of phenol with the aniline product, and 2-methylpyridine. It was suggested that the latter product was the result of a subsequent reaction of aniline. A subsequent patent [6] described the conversion of aniline to 2-methylpyridine under reaction conditions similar to those of the phenol to aniline reaction (Scheme 1). Good selectivity (52 %) was obtained at 783 K, 2.9 MPa NH_3, and an NH_3 to aniline molar ratio of 8, although the conversion was not very high (13 %). By-products were acetonitrile and condensed aromatic heterocyclic compounds such as quinoline and methylindole; the catalyst was rapidly deactivated as a result of coke formation.



Scheme 1. Isomerization of aniline to α-picoline.

A similar isomerization reaction of an arylamine to an aromatic azaheterocycle was described by Le Blanc and Puppe [7]. They succeeded in transforming *m*-phenylenediamine into 2-amino- and 4-amino-6-methylpyridine (Scheme 2) in a flow reactor at somewhat lower temperature (673 K), higher NH_3 pressure (19 MPa) and therefore higher NH_3 to arylamine ratio (60) than in the case of aniline. Conversion (74%) and selectivity (56% 2-amino-6-methylpyridine and 15% 2-amino-4-methylpyridine) were substantially better than for aniline.



Scheme 2. Isomerization of *m*-phenylenediamine to aminomethylpyridines.

The isomerization of an arylamine to an N-containing aromatic heterocyclic compound would, in principle, open a new route from aromatic hydrocarbons, via nitroaromatic compounds and arylamines, to pyridines and quinolines. We were therefore interested to discover the potential of this reaction, and have studied its scope, optimum conditions, and its mechanism [8–11].

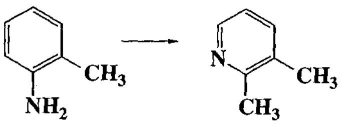
Experiments in autoclaves with *m*-phenylenediamine [9] and microflow reactors with aniline [10] demonstrated that a reasonably high temperature, a high ammonia pressure, and an acid catalyst are required for the benzamine rearrangement. Also non-zeolitic solid acids such as silica–alumina and Lewis acids transformed *m*-phenylenediamine into 2-amino-6-methylpyridine. One-dimensional zeolites (ZSM-12, ZSM-48, ZSM-23, Nu-10, MOR) and three-dimensional zeolites (Y, Beta, ZSM-5) catalyzed the transformation of arylamines to substituted pyridines, but the selectivity of the three-dimensional zeolites was higher. Although ZSM-5 had the narrowest pores of the three-dimensional zeolites studied, it had the highest selectivity. This suggests that the reaction occurs mainly inside the pores and, therefore, that transmethylation and the formation of condensed aromatic compounds are suppressed. Passivation of the external surface area by reaction with triphenylsilyl chloride and subsequent calcination at 773 K indeed reduced the relative amounts of transmethylation and condensed aromatic compounds. The relatively low activity of catalysts other than ZSM-5 is ascribed to blocking of the pores of these catalysts by the condensed aromatic compounds formed in intermolecular side-reactions of the highly unsaturated intermediates.

The acid catalysis, in conjunction with the high NH_3 pressure required, explains why a relatively high reaction temperature is needed. At low temperature all acid sites are occupied by NH_3, and only at elevated temperature will enough NH_3 desorb and acid sites become available for catalysis. Unfortunately, a high temperature also favors acid-catalyzed side reactions such as shifting of methyl groups and transmethylation [12]. These lead to many side-products and to separation problems. Experiments with less acidic catalysts, which adsorb NH_3 less strongly and therefore do not require such high temperatures for NH_3 desorption, indeed gave promising results: The boron, gallium, and iron equivalents of H-ZSM-5 resulted in higher conversions of *m*-phenylenediamine than H-ZSM-5 [13]. In contrast with experiments with H-ZSM-5, with the B-, Ga-, and Fe-MFI catalysts, 4-amino-6-methylpyridine was observed in addition to 2-amino-6-methylpyridine. Experiments with the Fe-MFI catalyst showed that the yield of the 2,4 isomer decreased with increasing temperature, whereas that of the 2,6 isomer increased. This suggests that conditions might be found under which either one isomer or the other can be made with high selectivity.

5.2.3 Rearrangement of Other Benzamines

To discover whether the apparent N-*ortho*–C exchange pattern in the transformation of aromatic amines to substituted pyridines also holds for other aromatic amines, we also studied the reactions of phenylenediamines, toluidines, naphthylamines, and anthracylamines [9]. Batch reactions of *o*-, *m*-, and *p*-toluidine resulted in low conversion, a factor of 2 to 4 higher than for aniline. Much of the conversion was, however, because of isomerization of one toluidine to the other two isomers, and to transmethylation to aniline and xylidines. The yield of substituted pyridines (lutidine and collidine) from *o*- and *p*-toluidine was, therefore, approximately as low as that for the aniline transformation. Conversion of *m*-toluidine to the substituted pyridine was much higher than that of its *ortho* and *para* isomers, however, just as *m*-phenylenediamine results in much higher conversion to aminomethylpyridines than do *o*- and *p*-phenylenediamine.

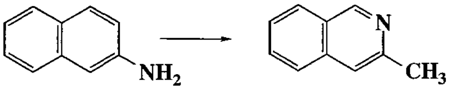
Although the yields of substituted pyridines from the toluidines is low, they suffice to show that in this example also they are formed exclusively by an exchange of the N and *ortho* C atoms. For instance, the only substituted pyridines formed from *m*-toluidine are 2,4- and 2,6-lutidine, plus 2,4,6-collidine as a result of subsequent transmethylation. The main pyridine-type product formed from *o*-toluidine, 2,3-lutidine, is a result of N/*ortho*-C exchange also (Scheme 3). Thus, all three toluidines lead to lutidines and 2,4,6-collidine by the exclusive interchange of the N and *ortho* C atoms in combination with isomerization of the toluidines.



Scheme 3. Isomerization of *o*-toluidine to 2,3-lutidine.

The aza-aromatic products of the reactions of *α*- and *β*-naphthylamine and of *α*- and *β*-aminoanthracene are the result of N/*ortho*–C interchange in combination with equilibration between α- and β-arylamine. Thus 1-methylisoquinoline is the direct product from α-naphthylamine (Scheme 4), and 3-methylisoquinoline is the direct product of β-naphthylamine (Scheme 5). Isomerization of α- to β-naphthylamine explains why 3-methylisoquinoline is a by-product in the reaction of α-naphthylamine. Analogously, 1-methyl-isoquinoline is a by-product in the reaction of β-naphthylamine. It should be noted that almost no 2-methylquinoline was produced. Higher conversions were obtained with the 12-ring zeolite Beta than with the 10-ring zeolite ZSM-5, most probably because of diffusion limitations of the substituted naphthalenes in the 10-ring pores.

Scheme 4. Isomerization of α-naphthylamine to 1-methylisoquinoline.

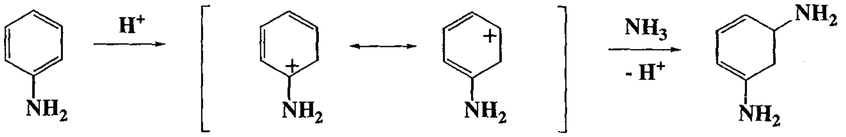


Scheme 5. Isomerization of β-naphthylamine to 3-methylisoquinoline.

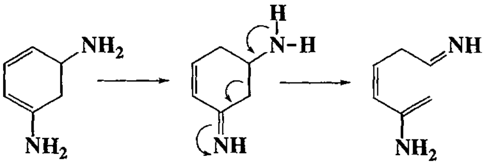
5.2.4 Mechanism of the Rearrangement

The only methyl-aza-aromatic products were those that can be thought of having been formed by interchange of the N atom and a C atom from the *ortho* position of the benzene ring (Schemes 1 and 2). Chang and Perkins proposed that the reaction of aniline to α-picoline occurs via ring enlargement to an aza-7-ring, from which a carbon atom is extruded [5,14]. The seven-ring mechanism cannot, however, explain why the toluidines, *m*-phenylenediamine, the naphthylamines, and anthracylamines react exclusively via exchange of the N atom in the aromatic amine with a ring carbon atom in the *ortho* position [9]. Neither does the seven-ring mechanism explain the need for the high NH_3 pressure. Another mechanism proposed by Chang and Perkins [14] is based on an intramolecular Ritter reaction, the reaction of a carbenium ion with the N atom of a cyano group. The need for a nitrenium ion, and the high strain in the intramolecular Ritter reaction step make this mechanism very unlikely, however, and, again, this mechanism does not explain the need for a high NH_3 pressure, and predicts the wrong products [9].

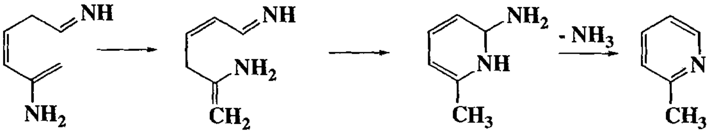
To explain all the results it was necessary to assume that the aromaticity of the arylamine had to be broken by adding an ammonia molecule to the arylamine (Scheme 6). This explains why a high NH_3 pressure is required and why the reaction runs better with naphthylamine than with aniline. Then ring opening occurs through a reverse aldol-type reaction (Scheme 7) and ring closure might occur by addition of the original amino group to an imino group. Finally, the aza-aromatic compound is formed by elimination of NH_3 (Scheme 8).



Scheme 6. Addition of ammonia to aniline.



Scheme 7. Ring opening by reverse aldol reaction.



Scheme 8. Ring closure after rearrangement.

Aniline and ammonia will be present as protonated species at the zeolite surface. If these reactants are adsorbed on separate acidic centers, the reaction cannot occur on zeolites with low Si/Al ratios because the active centers are too far apart. Nevertheless the rearrangement takes place with the same turnover frequency as on zeolites with high Si/Al ratios. It was therefore assumed that the reaction occurs between aniline and ammonia co-adsorbed on a single site [11]. Langmuir–Hinshelwood modeling showed that the maximum yield of picoline in the rearrangement of aniline could be explained with the very reasonable assumptions that aniline is adsorbed more strongly than ammonia and that the adsorption of two or three ammonia molecules by one site is responsible for the rate decrease at high NH_3 pressure.

5.2.5 Outlook

Results obtained so far show that the levels of conversion and selectivity of the rearrangement of aniline to α-picoline and of toluidine to lutidine or collidine are limited; only the rearrangement of *m*-toluidine shows promise for further studies. Results from rearrangements of *m*-phenylenediamine and naphthylamine give hope that further work (with flow instead of batch reactors, and with Fe- and Ga-ZSM-5 catalysts) might lead to efficient syntheses of aminopicolines and methylisoquinolines.

References

[1] H. G. Franck, J. W. Stadelhofer, *Industrial Aromatic Chemistry*, Springer, Berlin, **1988**.

[2] K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, VCH, Weinheim, **1993**.

[3] W. F. Hölderich, in *Proc. 10th Int. Congress on Catal.* (Eds.: L. Guczi, F. Solymosi, P. Tétényi), Akadémiai Kiado, Budapest, **1993**, Part A, p. 127.

[4] S. E. Golunski, D. Jackson, *Appl. Catal.* **1986**, *23*, 1.

[5] Mobil Oil Corp. (C. D. Chang, W. H. Lang), US Pat. 4 380 669 (1980).

[6] Mobil Oil Corp. (C. D. Chang, P. D. Perkins), Eur. Pat. 0 082 613 (1983).

[7] Bayer AG. (H. Le Blanc, L. Puppe), DE 3 332 687A1 (1985).

[8] Th. Stamm, H. W. Kouwenhoven, R. Prins, *Stud. Surf. Sci. Catal.* **1993**, *78*, 543.

[9] Th. Stamm, H. W. Kouwenhoven, D. Seebach, R. Prins, *J. Catal.* **1995**, *155*, 268.

[10] A. Tschumper, R. Prins, *Appl. Catal.* **1998**, *172*, 285.

[11] A. Tschumper, R. Prins, *Appl. Catal.* **1998**, *174*, 129.

[12] J. A. Martens, J. Perez-Pariente, E. Sastre, A. Corma, P. A. Jacobs, *Appl. Catal.* **1988**, *45*, 85.

[13] R. Franck, MSc Thesis, Eidg. Techn. Hochschule Zürich, **1993**.

[14] C. D. Chang, P. D. Perkins, Zeolites **1983**, *3*, 298.

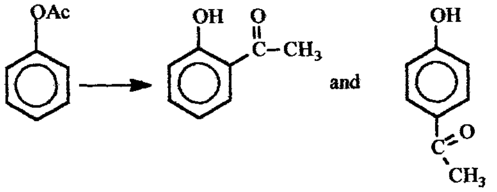
5.3 The Fries Rearrangement

M. Guisnet, G. Perot

The Fries rearrangement is the acid-catalyzed transformation of aryl esters into hydroxyarylketones [1] and often plays an important role in the production of hydroxyarylketones by acylation of phenols with carboxylic acids, anhydrides, or acyl chlorides.

Three different mechanisms have been proposed [1] for the Fries rearrangement with $AlCl_3$: (i) an intramolecular mechanism with a direct acyl shift from the oxygen atom to a carbon atom of the ring; (ii) a monomolecular deacylation–acylation mechanism with an acyl chloride intermediate; and (iii) an intermolecular mechanism (transacylation).

The most simple example of the Fries rearrangement is the transformation of phenylacetate (PA) into hydroxyacetophenones (*o*- and *p*-HAP; Eq. 1).



(1)

The *para* isomer is a key intermediate in the Hoechst Celanese process for the manufacture of paracetamol (*p*-acetaminophenol) [2] ; the *ortho* isomer can be used for the synthesis of salicylic acid. Other hydroxyarylketones of commercial importance also result from the Fries rearrangement, e. g. 2,4-dihydroxybenzophenone, an intermediate in the preparation of UV absorbents [3], and diphenol monomers which can be used for the manufacture of advanced polymers [4], etc.

Traditionally, the Fries rearrangement has been conducted with mineral acids (H_2SO_4, HF) or metal halides as catalysts. $AlCl_3$ was the most extensively used. Because the arylketone forms a stable 1:1 molar adduct with the catalyst, more than stoichiometric amounts of $AlCl_3$ are required. The recovery of the products requires a hydrolysis step with destruction of the catalyst and production of a large amount of inorganic by-products. Substituting these corrosive, polluting, and non-regenerable catalysts by solid acids which do not have these inconveniences is, therefore, an important objective.

Most studies in which acid solids were used concern the synthesis of hydroxyacetophenones either by Fries rearrangement of phenyl acetate [3,5–15] or by acylation of phenol with acetic acid or acetic anhydride [11,16–21]. These reactions were conducted in the gas or liquid phase, zeolites being generally chosen as catalysts (Section 5.3.1). These shape-selective catalysts can also be used [3,4,7,8,22] for the liquid phase synthesis of bulky hydroxyarylketones (Section 5.3.2) even if solid-acid catalysts with larger pores (e. g. MCM-41) are preferred [3,22].

5.3.1 The Fries Rearrangement of Phenyl Acetate, and Related Reactions

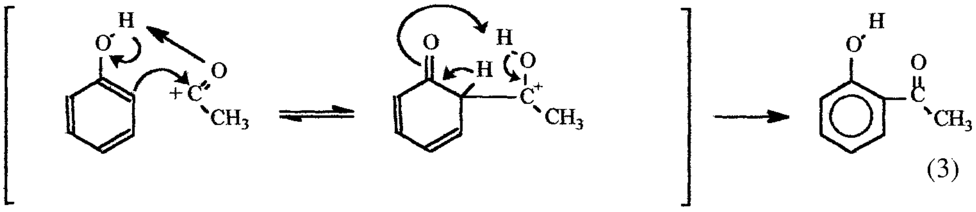
5.3.1.1 Gas-Phase Reactions

The Fries rearrangement of phenyl acetate (PA) over solid-acid catalysts was first studied in a fixed bed reactor at 400 °C by Pouilloux et al. [9,10]. *o*- and *p*-Hydroxyacetophenone (*o*- and *p*-HAP), *p*-acetoxyacetophenone (*p*-AXAP), and phenol (P) were the main reaction products. Fluorinated alumina and H-FAU zeolites afforded approximately the same product distribution, *o*-HAP being highly favored over the *para* isomer. The reaction scheme proposed was that PA dissociates into phenol (P) and ketene and that *o*-HAP results partly from an intramolecular rearrangement of PA and partly from transacylation (Eq. 2) whereas *p*-HAP results from the latter reaction only [10].

(2)

With H-MFI, the *p*-/*o*-HAP ratio was much higher; this is indicative of shape-selectivity effects. With all the catalysts, HAP selectivity was poor, phenol being the main product because of the rapid dissociation of PA [9,10]. Very fast deactivation as a result of coke deposition and zeolite dehydroxylation was also observed. Catalyst stability can, however, be considerably improved by use of equimolar mixtures of PA and water or of phenol and acetic acid (AA) instead of PA [11].

The mechanism of the acylation of phenol with acetic acid over H-MFI (the most stable catalyst) at 280 °C was established from the effect of contact time, hence of conversion, on product distribution [16]. PA and *o*-HAP are the only primary products, O-acylation being much faster than C-acylation. At high conversion the formation of *o*-HAP involves the participation of PA, however, by either an intramolecular or intermolecular process (Eq. 2). Comparison of the transformations of pure PA and of an equimolar mixture of PA and P shows that the latter process is largely predominant. The formation of small amounts of *p*-HAP would result mainly from the hydrolysis of *p*-acetoxyacetophenone (*p*-AXAP) which is selectively formed (no *o*-AXAP is observed) by auto-acylation of PA. The high *ortho*-selectivity of phenol acylation was related to the pronounced stability of the transition state (Eq. 3), whereas the *para*-selectivity of PA autoacylation was attributed to steric hindrance of the approach of the acetyl group in the *ortho* position of PA [16]. Kinetic modeling confirms the reaction scheme and shows that high *o*-HAP selectivity and yield can be obtained by reacting mixtures of AA and P with a high AA/P ratio [18].



(3)

Phenol acylation with acetic anhydride over MFI catalysts is also very *o*-HAP selective, although with this acylating agent *o*-HAP would result from direct C-acylation of phenol rather than secondary transformation of phenyl acetate [21].

5.3.1.2 Liquid-Phase Reactions

A variety of acid solids, particularly zeolites, have been used as catalysts for phenyl acetate (PA) transformation. The reaction is generally performed in a batch reactor. As in the gas phase, *o*- and *p*-hydroxyacetophenones (*o*- and *p*-HAP), *p*-acetoxyacetophenone (*p*-AXAP) and phenol (P) are the main products and deactivation is relatively rapid. Catalyst stability can, however, be significantly improved by continuous extraction of the catalyst with the refluxing reaction mixture [15], by increasing the temperature, and/or by operating with a flow reactor [8]. All this suggests that phenyl acetate transformation is limited by product desorption and thus probably occurs at the outer rim of the crystallites and could even occur mainly on their outer surface when the experiments are conducted in a flow reactor with average pore-size zeolites such as H-MFI [3]. The participation in the reaction of the acid sites of the outer surface could explain why H-BEA zeolites, generally prepared with very small crystallites (hence with a large outer surface), are considered as the best catalysts for PA transformation.

As in the gas phase, *o*-HAP and *p*-HAP result from different reactions [6,8,12,15]–*o*-HAP is a primary product (as are P and *p*-AXAP) whereas *p*-HAP is not formed directly. *o*-HAP could, therefore, result from intramolecular rearrangement of PA whereas the formation of *p*-HAP involves the participation of one primary product in addition to PA. P-AXAP and P result from PA autoacylation, although the production of phenol (P) is greater than is expected from this reaction, indicating either dissociation of PA into P and ketene or its hydrolysis with aqueous impurities or zeolite hydroxyl groups. The secondary formation of *p*-HAP can be explained as acylation of phenol with PA or as dissociation or hydrolysis of *p*-AXAP. To discriminate between these two mechanisms the effect of adding small amounts of P to the PA reactant was determined [12]. *p*-HAP appears as a primary product showing that *p*-HAP probably results from the acylation of P with PA.

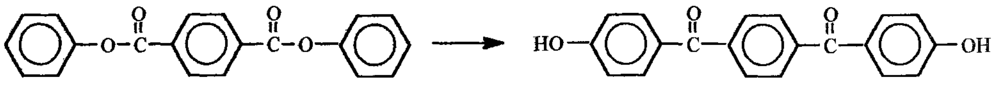
Initial rates of reaction, catalyst stability, and product distribution depend very much on solvent polarity [3,12,13]. Polar solvents such as sulfolane significantly promote the formation of the *para* products (e. g. (*p*-HAP + *p*-AXAP)/*o*-HAP = 7.5 compared with 0.8 with dodecane as the solvent) and also limit the formation of heavy reaction products such as bisphenol A derivatives, and hence catalyst deactivation. These observations can be explained by (i) competition of sulfolane with PA and P for adsorption on the acid sites, and (ii) the solvation of acylium ion intermediates [12,13].

Because the acylation of P by PA over HBEA zeolites in the presence of sulfolane is much faster than the intramolecular rearrangement of PA to *o*-HAP, *p*-HAP can be obtained selectively by transformation of P–PA mixtures: *p*-/*o*-HAP $\simeq$ 10 with an equimolar mixture of P and PA whatever the Si/Al ratio of the zeolite. Maximum in activity was found for Si/Al = 35–40 [13].

5.3.2 Other Fries Reactions

With *p*-tolyl acetate, in which the position in *para* to the acetate group is blocked by the methyl group, no intermolecular reaction is observed and only 2-hydroxy-5-methylacetophenone, resulting from an intramolecular Fries rearrangement, and cresol, resulting from hydrolysis, are formed [8].

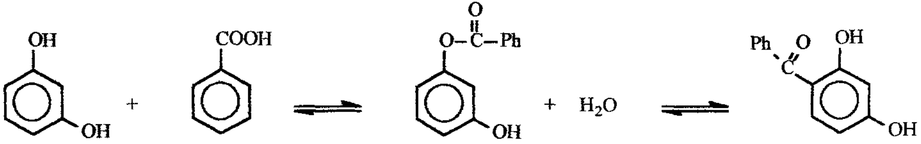
Phenyl benzoate (PB) was chosen as a model for the double Fries rearrangement of diphenyl benzoate into diphenol *para* monomers (Eq. 4) [4] and its transformation over several solid catalysts was investigated [4,8].



(4)

The reaction rate was shown to be related to the accessibility of the acid sites–H-MFI zeolite was practically inactive and Nafion was the most active catalyst. With all the catalysts, not only the desired *p*-hydroxybenzophenone (*p*-HBP) product but also *p*-benzoxybenzophenone (*p*-BXBP) and *o*-hydroxybenzophenone (*o*-HBP) were formed. The *para* products result from benzoylation of phenol (formed by hydrolysis of PB) or of PB and *o*-HBP from the intramolecular rearrangement of PB. The selectivity to *p*-HBP can, therefore, be significantly improved by adding phenol to the reactant mixture [4]. Unfortunately, thermodynamic limitations arising from the low polarity of the medium employed (even with very polar solvents such as sulfolane) seems to preclude the use of a solid acid for the production of diphenol monomers from diphenyl benzoate [4].

The synthesis of 2,4-dihydroxybenzophenone (compound **4**; Eq. 5) was investigated over various solid catalysts by reacting a 1:1 molar mixture of resorcinol with benzoic acid in chlorobenzene as solvent, water resulting from ester formation being removed [3,22].



4

(5)

Sulfonic acid resins, which are the most active catalysts, are less selective for **4** than H-BEA, because the narrow pores of this zeolite limit the formation of bulky secondary products [3,22]. Upon cooling of the reaction mixture **4** crystallizes. This crystallization, and the recycling of the other components of the equilibrium mixture provides an efficient and clean method for the commercial synthesis of 2,4-dihydroxybenzophenone (88 % yield). As for the transformation of the phenol–acetic acid mixture, the esterification is faster than the Fries rearrangement. For this rearrangement an intramolecular α–γ shift seems most likely [22].

The rates and equilibria depend on the substituents of both aromatic rings. Electron-releasing groups on the benzoic acid reactant accelerate the rearrangement whereas electron-attracting substituents on the phenolic reactant deactivate both the esterification and the Fries reactions [3,22]. Acid resins such as Amberlyst 15 and mesoporous aluminosilicates (H-MCM-41) are more active than H-BEA zeolites for the reactions of resorcinol with hindered benzoic acids. Thus, resorcinol and 2,6-dimethylbenzoic acid can be converted over H-MCM-41 to the corresponding benzophenone with a yield higher than 80 %. H-MCM-41 can also convert 1-naphthol and 2,6-dimethylbenzoic acid into the 2-substituted naphthophenone, with excellent yield [3,22].

5.3.3 Conclusion

Fries rearrangements can be catalyzed by a variety of solid acids, particularly zeolitic and mesoporous molecular sieves. The reaction mechanism depends on the hydroxyarylketone produced, *ortho* isomers resulting from an intramolecular rearrangement and *para* isomers from a secondary transacylation process. This explains the large dependence of selectivity on operating conditions and catalyst. Desorption of the hydroxyarylketone from the pores is often important in catalyst activity, selectivity, and stability. The most promising results were obtained by coupling the Fries rearrangement with the synthesis of the ester by O-acylation of the corresponding phenol.

References

[1] A. H. Blatt, *Org. React.* **1942**, *1*, 342.

[2] H. Szmant, Organic Building Blocks of the Chemical Industry, Wiley, New York, **1989**.

[3] H. Van Bekkum, A. J. Hoefnagel, M. A. van Koten, E. A. Gunnewegh, A. H. G. Vogt, H. W. Kouwenhoven in Zeolites and Microporous Crystals, (Eds : T. Hattori, T. Yashima), Elsevier, Amsterdam, **1994**, p.379.

[4] K. R. Lassila and M. E. Ford in Catalysis of Organic Reactions (Ed : W. E. Pascoe), Marcel Dekker, New York, **1992**, p.169.

[5] C. S. Cundy, R. Higgins, S. A. M. Kibby, B. M. Lowe, and R. M. Paton, Tetrahedron Letters, **1989**, 30, 2281.

[6] A. H. G. Vogt and H. W. Kouwenhoven, Collect Czech. Chem. Commun., **1992**, 57,853.

[7] G. Harvey, A. Vogt, H. W. Kouwenhoven and R. Prins, in Proceedings from the Ninth International Zeolite Conference II (Ed : R. von Ballmoos et al.), Butterworth–Heinemann, Boston, **1993**, p.363.

[8] A. Vogt, H. W. Kouwenhoven, R. Prins, Appl. Catal. A : General, **1995**, 123, 37.

[9] Y. Pouilloux, N. S. Gnep, P. Magnoux and G. Perot, J. Mol. Catal., **1987**, 40, 231.

[10] Y. Pouilloux, J. P. Bodibo, I. Neves, M. Gubelmann, G. Perot and M. Guisnet in Heterogeneous Catalysis and Fine Chemicals II, (Eds : M. Guisnet et al.) Elsevier, Amsterdam, **1991**, p.513.

[11] I. Neves, F. R. Ribeiro, J. P. Bodibo, Y. Pouilloux, M. Gubelmann, P. Magnoux, M. Guisnet and G. Perot in Proceedings from the Ninth International Zeolite Conference II (Ed : R. von Ballmoos et al.), Butterworth–Heinemann, Boston, **1993**, p.543.

[12] F. Jayat, M. J. Sabater Picot and M. Guisnet, Catal. Lett., **1986**, 41, 181.

[13] F. Jayat, M. J. Sabater Picot, D. Rohan and M. Guisnet in Heterogeneous Catalysis and Fine Chemicals IV (Eds : H. U. Blaser et al.) Elsevier, Amsterdam, **1997**, p.91.

[14] A. Heidekum, M. A. Harmer and W. F. Hoelderich, J. Catal., **1998**, 176, 260.

[15] U. Freese, F. Heinrich, F. Roessner, Catal. Today, **1999**, 49, 237.

[16] I. Neves, F. Jayat, P. Magnoux, G. Perot, F. R. Ribeiro, M. Gubelmann, M. Guisnet, J. Mol. Catal., **1994**, 93, 169.

[17] I. Neves, F. Jayat, P. Magnoux, G. Perot, F. R. Ribeiro, M. Gubelmann and M. Guisnet, J. Chem. Soc. Chem. Commun, **1994**, 717.

[18] M. Guisnet, D. B. Lukyanov, F. Jayat, P. Magnoux and I. Neves, Ind. Eng. Chem. Res., **1995**, 34, 1924.

[19] I. Neves, F. Jayat, D. B. Lukyanov, P. Magnoux, G. Perot, F. R. Ribeiro, M. Gubelmann and M. Guisnet in Catalysis of Organic Reactions, (Eds : M. G. Scaros and M. L. Prunier), Marcel Dekker, Inc, New York, **1995**, p.515.

[20] F. Jayat, M. Guisnet, M. Goldwasser and G. Giannetto, in Progress in Zeolite and Microporous Materials, (Eds : H. Chon et al.) Elsevier, Amsterdam, **1997**, p.1149.

[21] Y. V. Subba Rao, S. J. Kulkarni, M. Subrahmanyam, A. V. Rama Rao, Appl. Catal. A : General, **1995**, 133, L1.

[22] A. J. Hoefnagel and H. van Bekkum, Appl. Catal. A : General, **1993**, 97, 87.

5.4 Rearrangement of Epoxides

Wolfgang F. Hölderich, Ulf Barsnick

Epoxides are reactive, versatile intermediates in organic chemistry [1,2]. The epoxidation of olefins and subsequent rearrangement in the presence of acidic or basic catalysts is widely used for the preparation of aldehydes, ketones, ethers, or alcohols. The reactions are used for the synthesis of a variety of fine chemicals and are conventionally catalyzed with homogeneous catalysts such as metal halides or mineral acids. Substitution of these homogeneous systems by heterogeneous catalysts is, however, becoming increasingly attractive because they are readily separated from the product and do not usually cause environmental problems.

5.4.1 Catalysts

Catalytic rearrangement of epoxides can be performed over Lewis and Brønsted acidic and basic catalysts. Whereas the ring-opening mechanism in basic media is clearly S_N2, the acid-catalyzed reaction is often termed borderline S_N2 [3] and usually proceeds faster. The pathways to carbonyl compounds are shown in Figure 1.

Acidic activation of the epoxide can be achieved either by Brønsted-acidic catalysis via addition of a proton to the epoxide oxygen or by Lewis-acidic catalysis via coordination of the epoxide oxygen to a multivalent cation. In basic catalysis one of the epoxide carbons is attacked by a nucleophile. Only acid-catalyzed ring-opening leads to an intermediate carbocation (**3**) which can easily result in the mi-

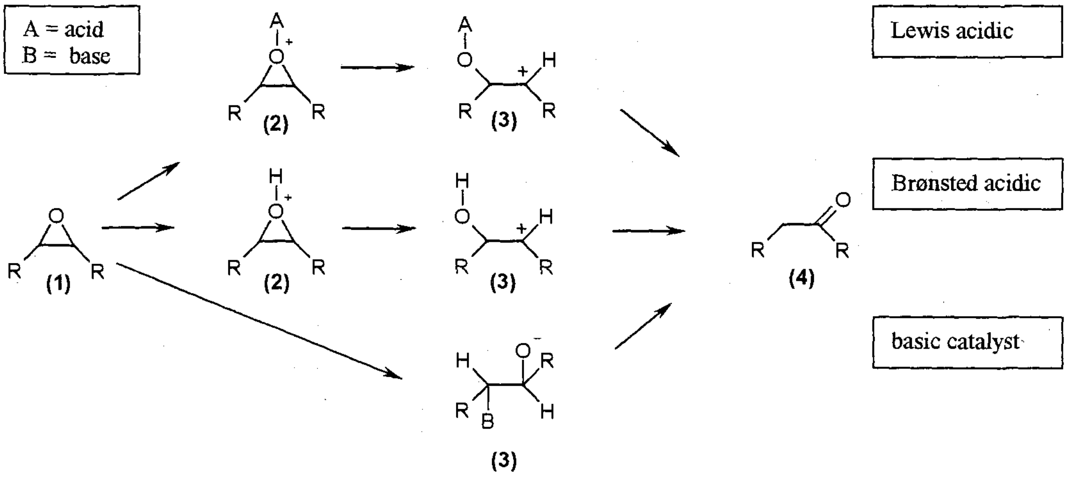


Figure 1. Acid/base catalyzed epoxide rearrangement to carbonyl compounds.

gration of substituents. This might result in unwanted side-products and aldol condensation may occur leading to heavier molecules.

The rearrangement of epoxides to carbonyl compounds or allylic alcohols is catalyzed homogeneously by Lewis (e. g. $ZnCl_2$, $SnCl_2$, $AlCl_3$, $FeCl_3$, and $TiCl_4$) [4] or Brønsted (e. g. H_2SO_4 and HCOOH, HF, HCl, HI, 4-toluenesulfonic acid) [5] acidic catalysts and by strong bases (e. g. lithium diethyl amide, LiBr, LiI, and $LiClO_4$). The application of strong non-nucleophilic bases (e. g. *n*-butyllithium and lithium dialkylamide) as homogeneous catalysts leads to allylic alcohols [6].

Despite the advantages associated with the application of these homogeneous catalysts (e. g. simple reactor construction and good temperature control) their substitution by heterogeneous systems is of great interest. The reason is the several decisive drawbacks of homogeneous catalysis such as the corrosion of reactor vessels, poisoning of bacteria in sludge treatment by, e. g., heavy-metal pollution, and the formation of large amounts of salt during neutralization or, even worse, the ecological damage that results from direct deposition in surface water. In addition, the work-up procedures of homogeneously catalyzed systems are generally difficult and more expensive.

In contrast, heterogeneous catalysts are readily separated from the products; this is essential for fine chemicals such as fragrances, flavors, pharmaceuticals, or their precursors, because they are intended for human consumption and so have to meet the highest standards of quality.

For this reason heterogeneous catalysts such as SiO_2, Al_2O_3, ZnO, and WO_3, supported metals and a variety of precipitated phosphates have been tested for epoxide rearrangement reactions. Use of these conventional catalysts often results in the formation of aldol condensation products and mixtures of ketones and aldehydes as by-products. The heavier molecules formed by aldol condensation are the first step in the formation of coke thus limiting the lifetime of these catalysts.

Consequently, zeolites in their H-form, e. g. [B]-MFI [7–10], and the essentially neutral or weakly Lewis-acidic, titanium containing zeolites [11–13] have many advantages compared with the above mentioned heterogeneous catalysts. The main advantage is their well defined pore system. By carefully choosing the zeolite for a specific reaction, the shape selectivity can suppress the side reactions mentioned above. The greater efficiency also prevents the catalyst from coking thereby increasing its lifetime and resulting in cost savings.

A further advantage of heterogeneous catalysts is, that they can be used in gas-phase reactions so that continuous processes can be created with relatively low technical (equals financial) effort.

Smith [14] has recently reported the successful application of a basic resin-bound catalyst.

5.4.2 Reactor Concepts

When using conventional homogeneous Lewis or Brønsted acidic catalysts only liquid-phase reactions are applicable. With heterogeneous catalysts gas-phase reactions, which are readily performed continuously, can also be realized. The product is readily separated from the catalyst and higher efficiency is usually achieved (space–time yield). The rearrangement of styrene oxides in the gas phase described later in this section [8,15,16] is an example of the improvement of yields by changing the reactor concept from liquid- to gas-phase.

In general, the ease of conducting a reaction continuously in the gas phase must be paid for in terms of increasing costs of energy and plant construction; continuous gas-phase reactions are usually economic only for production of more than several tons per year. For smaller volumes production in multipurpose liquid phase batch reactors is more economical.

5.4.3 Isomerization of Small Aliphatic Epoxides

There is little advantage in the use of acidic zeolites in the rearrangement of simple aliphatic epoxides because of rather low regioselectivity. The intermediate isomerizes, via a hydride shift, to a mixture of aldehydes, ketones, and furans. The rearrangement of small aliphatic epoxides usually yields mixtures of ketones, and aldehydes; aldol condensation and the formation of diols or diethers is also observed. Dehydration might occur, particularly at higher temperatures, leading to dienes which can polymerize. This leads to rapid deactivation of the catalysts as a consequence of coke formation. Shape selectivity can suppress reactions forming bulkier molecules, e. g. furans or aldol condensation products, but does not differentiate between rearrangements to ketones and aldehydes.

In 1968 Venuto and Landis reported on the use of sodium- and rare-earth metal-doped zeolite X in the rearrangement of ethylene oxide and propylene oxide to the corresponding aldehydes [17]. In addition to the desired propanal, acetone was formed with these catalysts because of the hydride shift induced by the intermediate carbocation; consecutive reactions were also observed. Such catalysts also suffer from rapid deactivation.

Better results for the conversion of propylene oxide to propanal can be obtained over basic zeolites such as (Mg, Na)-Y in which 56 % of the Na^+ was substituted by Mg^{2+}. At 300 °C and a WHSV of 2 h^{-1} a conversion of 85 % and selectivities of up to 88 % were obtained. The use of zeolite (Cu, Na)-Y with Na^+ (42 % substituted by Cu^{2+}) results in 98 % conversion and propanal selectivity of 81 % [18].

2-Methyl-2,3-epoxybutene can be converted to methylisopropylketone (51 %), pivalic aldehyde (40 %) and isoprene (7 %) by use of aluminum-containing zeolite MFI (Si/Al =37,6) at 150 °C and a WHSV of ca 2 h^{-1} [8,16]. The pivalic aldehyde is formed via a pinacol-type rearrangement. If the temperature is increased to 300 °C isoprene is the main product [19].

Similarly, butyraldehyde can be prepared from butene-1-oxide with Zn, Cd, and Ag ion-exchanged zeolite A with selectivities between 55 % and 72 % [20].

The bulkier 1,2-epoxyoctane can be rearranged over zeolites HY (Si/Al = 15) and H-OFF (Si/Al 3.6) at 160 °C in an autoclave, with toluene as solvent; this results in 45 % and 46 %, respectively, selectivity to octanal 17 %/25 % to allylic alcohols, and 18 %/14 % to aldolization products, e. g. 2-*n*-hexyldec-2-en-1-al [21]. A kinetic study of this reaction over different acidic heterogeneous catalysts, e. g. phosphoric acid, $ZnCl_2$ immobilized on various supports, sulfated zirconia, zeolites, and dodecatungstenophosphoric acid, was reported by Yadav and Satoskar [22].

5.4.4 Isomerization of Styrene Oxide and Derivatives

The rearrangement of styrene oxides to aldehydes (Figure 2) yields valuable compounds or intermediates for the production of fragrances, pharmaceuticals, and insecticides, fungicides, and herbicides, particularly when halogenated derivatives are needed.

Figure 2. Rearrangement of styrene epoxides (R = alkyl, aryl, haloalkyl, alkoxy, alkylthio).

Different styrene oxides can be rearranged in a fixed-bed reactor under gas-phase conditions. Hölderich et al. [7,8,15,16,23] found that MFI-Type materials are superior to other oxides (e. g. TiO_2, P_2O_5/SiO_2, γ-alumina, B_2O_3/SiO_2, bentonite). A possible reason for the high regioselectivity over the MFI materials might be related to stabilization of the α-carbocation. When conventional oxides are used one of the major side-products is 1,3,5-triphenylbenzene, formed via aldol condensation in the case of γ-alumina (17 % at 300 °C, WHSV = 2.7 h^{-1}, 6 h) [23]. Conventional catalysts are, furthermore, deactivated much more rapidly, because of the formation of the 1,3,5-triphenylbenzene and coke.

This side-reaction can be suppressed by the use of zeolites, such as ZSM-5 (Si/Al = 18.8), which hinder the formation of this aldol condensation and consecutive products because of the steric constraints of the framework. Lower temperatures lead to larger amounts of triphenylbenzene (7.6 % at 200 °C compared with 1.5 % at 300 °C) [23]. This can be explained by a slower desorption of the products at low temperatures.

[B]-MFI zeolite was tested in this reaction because of its mild acidity. In particular, such material doped with cesium yielded 100 % phenylacetaldehyde because of the extremely mild acidity (or possibly even basicity) [8].

The gas-phase reactions of styrene oxide derivatives also gave very good results. 2-Methylstyrene oxide is, however, rearranged to a mixture of 2-phenylpropanal and phenylacetone with selectivity of approx. 20 % aldehyde and 60 % ketone over ZSM-5 (Si/Al = 18.8) and approx. 10 % aldehyde and 80 % ketone for [B]-MFI zeolite. This aldehyde–ketone rearrangement is not observed when pure silica gel is used; this yields 90 % 2-phenylpropanal [8].

Fluoro- and chloro-substituted styrene epoxides can be converted to the corresponding substituted phenylacetaldehydes over ZSM-5 with selectivities of 90 % and higher [23]. These products are not obtainable via the Rosenmund reduction.

Doping of zeolitic materials with elements such as copper leads to bi- or multifunctional catalysts. For example if the epoxide rearrangement of styrene oxides is conducted in the presence of hydrogen and a bifunctional [B]-MFI catalyst with copper as a hydrogenation component, 2-phenylethanol is obtained in a single step. In the gas phase at 250 °C this hydro-isomerization affords high yields ($>$ 85 %). This is an excellent example of multifunctional catalysis in a one-pot reaction for simultaneous rearrangement and hydrogenation. This route might be an environmentally benign alternative to the conventional production of the very important fragrance 2-phenylethanol, which has the odor of roses. Currently this compound is manufactured from ethylene oxide and benzene in the presence of a high excess of $AlCl_3$, with the production of undesired toxic by-products [10]. In addition the work-up procedures are rather complicated.

Liquid-phase rearrangements of styrene oxides and their derivatives over zeolites in their H-form were described by K. Smith et al. [24]. They obtained poor results with protic solvents such as methanol (30 % conversion of styrene oxide). Use of chlorinated aprotic solvents such as dichloromethane led to higher yields of phenylacetaldehyde (74 % over H-ZSM-5 and 78 % over H-β at 20 °C, 8.3 mmol styrene oxide, 0.5 g H-ZSM-5, 10 mL dichloromethane) but results were still inferior to those from the gas-phase reactions described above.

The rearrangement of styrene oxide can also be performed in liquid-phase reactions with the well known catalyst TS-1 [11,25]. The framework-titanium gives the MFI-type zeolite Lewis acidic properties and 100 % conversion and 98 % phenylacetaldehyde selectivity was achieved after 1–2 h at 70 °C in a batch reaction with acetone (100 mL) as solvent, epoxide (50 g), and catalyst (3 g) as feed.

Because TS-1 is also a catalyst for oxidation reactions it can be used for liquid-phase bifunctional catalysis of the oxidation of styrene to styrene oxides with H_2O_2, then in situ rearrangement of the styrene oxides to phenylacetaldehydes [26]. Such reactions are conducted in a batch reactor, containing a solvent, styrene or its derivatives, 36 % *w/w* H_2O_2, and TS-1. H_2O_2 conversions of up to 87 % after 1–2 h and aldehyde selectivities of up to 87 % were obtained with *t*-butanol as the solvent. Acetone could also be used as a solvent but cannot be used with highly concentrated hydrogen peroxide because of the formation of explosive peroxides [26]. Good results were also obtained with 4-methoxystyrene, α-methylstyrene, and 4-methylstyrene as starting materials–conversion was approx. 100 % and selectivities $>$ 90 % [13].

The rearrangement of styrene oxide and derivatives over acidic zeolites has been very successful. The efficient suppression of side-products and the possibility of avoiding salt formation makes the catalytic system based on zeolites such as [B]-MFI environmentally benign and economically superior. Even products that could not be prepared by the conventional Rosenmund reduction are now easily obtained. Although liquid-phase reactions are inferior to the gas phase systems because of their lower selectivities and the systematic advantages of gas-phase systems, bifunctional liquid-phase epoxidation and rearrangement over TS-1 has advantages. Bifunctionality of the catalysts can also be achieved by modification of the zeolitic materials with transition metals such as [Cu,B]-MFI (see above).

5.4.5 Rearrangement of Glycidic Acid Ester

By analogy with the rearrangement of styrene oxide compounds, more complicated substances, e. g. phenylpyruvic acid methyl ester derivatives, can be synthesized from readily available glycidic acid esters, as shown in Figure 3. These esters can be used as intermediates for herbicides (e. g. the triazinones) and for the synthesis of L-amino acids.

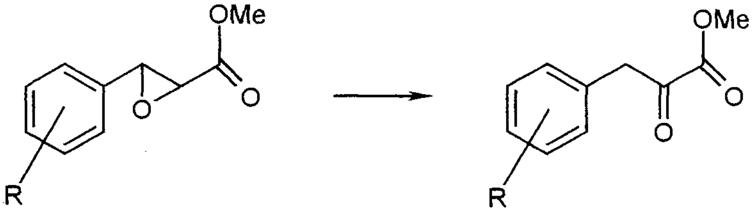


Figure 3. Rearrangement of glycidic acid esters (R = alkyl, alkoxy, halide, hydroxyl).

In gas-phase reactions zeolites are superior to 'non-zeolitic' molecular sieves, metal phosphates, and metal oxides. Over the mildly acidic [B]-MFI (Si/B = 24) the synthesis of phenylpyruvic acid methyl ester yields up to 94 % at 200 °C and WHSV = 3 h^{-1}; 95 % product yield could be achieved with the cesium-doped material (0.6 % *w/w*) [8]. With these concepts α-ketocarboxylic acid esters can be prepared from readily available feedstocks whereas conventional methods require the use of costly and environmentally problematical Grignard reactions.

Increasing the temperature to 350 °C results in decarbonylation of the phenylpyruvic acid methyl ester derivatives and the phenyl acetic ester is formed with a ratio of 65 % α-ketoester to 35 % acetic acid ester. Until now the industrial process for the synthesis of phenylacetic acid ester has started from benzyl chloride, which is converted to benzyl cyanide by KCN, followed by hydrolysis. Every step of this reaction must be performed in a separate reactor and special measures must be taken for handling large amounts of toxic KCN. The new route is certainly an environmentally benign alternative [8,27].

If the phenyl glycidic acid esters contain *t*-butyl- or *i*-propyl groups on the ester residue decarbonylation and elimination of an olefin occurs in the presence of acidic heterogeneous catalysts at temperatures > 200 °C to form phenylacetaldehydes with high selectivity (> 80 % at 100 % conversion) [8].

5.4.6 Isomerization of *α*-Pinene Oxide

α-Pinene oxide (**5**) is a reactive molecule which is readily rearranged by acid catalysis [28–30] affording several different products, e. g. the isomeric aldehyde (**7**), *trans*-carveol (**8**), *trans*-sobrerol (**9**), *p*-cymene (**10**), or *iso*-pinocamphone (**11**) (Figure 4). The most industrially desired compound among these is campholenic aldehyde (**6**), the key molecule in the synthesis of a variety of highly odorous sandalwood-like fragrances [29].

In every acid-catalyzed reaction leading to (**6**) all the molecules shown in Figure 4, and aldol condensation products, can be formed–in total up to 200 compounds can be found. The structural isomers (**6**) and (**7**) are almost always formed in ratios depending on the catalyst used.

Whittaker et al. [31] postulated the reaction mechanism shown in Figure 5 for the formation of these isomers. ^{1}H and ^{13}C NMR experiments and kinetic studies showed that the rate-determining step of the reaction does not involve the opening of the cyclobutane ring.

In the mechanism proposed the first step is the cleavage of the C–C bond in the oxirane ring, followed by hydride shift. The resulting seven-membered heterocyclic ring undergoes C–O cleavage and the resulting carbocation rearranges to (**6**) or (**7**) depending on whether the isopropyl- or methylene bridge is shifted. Because the cyclobutane ring is flexible, unlike the four membered ring in *α*-pinene oxide, the direction of the ring opening reaction is determined by its conformation and the stability of the products. This explains why many homogeneous acidic catalysts do not differentiate between these isomers. An exception is $ZnBr_2$ in benzene which results in selectivities of up to 85 % because of stabilization of the intermediate by forming a complex with zinc [28].

A major drawback of this process is the pollution of water by zinc halides, which cause severe problems in sludge treatment by killing the bacteria. Although $ZnBr_2$ in benzene is well known as an effective homogeneous catalyst with selectivity of ca 85 % for the campholenic aldehyde, many efforts have been made to find a truly heterogeneous system [32].

H. van Bekkum and coworkers found that heteropolyacids, e.g. $H_4SiW_{12}O_{40}$, are very active catalysts for the rearrangement of (**5**). With benzene as solvent conversion of (**5**) was complete after 15 min. Selectivity for (**6**) was, however, low–

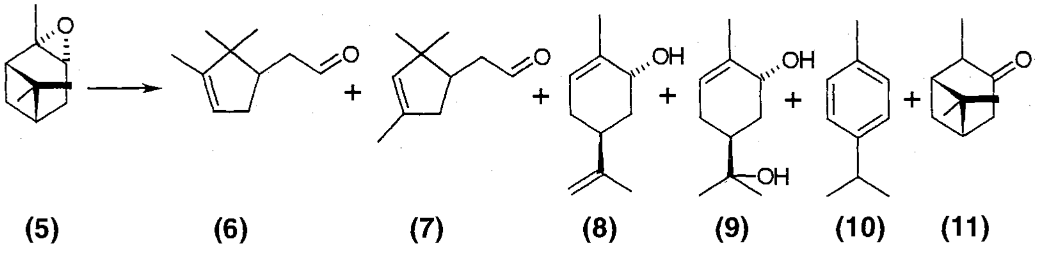


Figure 4. Isomerization products from the acid-catalyzed conversion of α-pinene oxide.

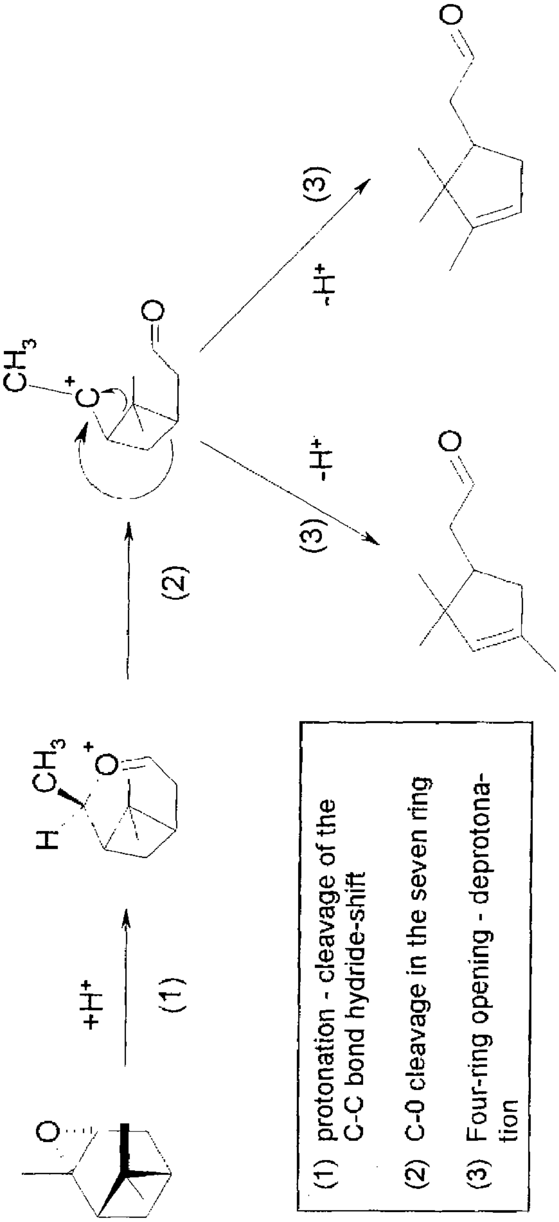


Figure 5. Postulated mechanism for the formation of campholene aldehydes.

Table 1. Influence of acid treatment and Si/Al ratio.

Catalyst	Conversion (%)	Selectivity (%)
H-US-Y (A), Si/Al = 35, Untreated	26	75
H-US-Y (B), Si/Al = 35, Acid-treated	98	76
H-US-Y (C), Si/Al = 20, Acid-treated	95	67

$T = 0$ °C, $t = 24$ h, catalyst load = 7.5 g epoxide (g catalyst)$^{-1}$.

34 % in benzene and 48 % in 1,2-dichloroethane–and (**7**) was not detected. By-products included oligomers and the alcohols (**8**) and (**9**) [28].

With heterogeneous catalysts the selectivity depends on adsorption effects. Hölderich and coworkers found, that some H-US-Y zeolites with many mesopores are suitable catalysts for this reaction [29].

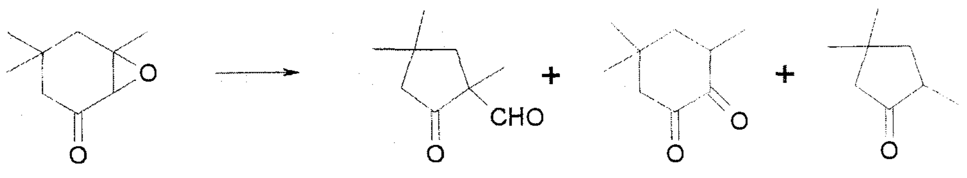
As shown in Table 1, a pretreatment of the mother catalyst (**A**) with dilute acid (0.01 M HCl at 25 °C for 24 h), subsequent washing and calcination at 550 °C gives a better catalyst (**B**), resulting in major enhancement of activity but without any loss in selectivity for the desired reaction to campholenic aldehyde. The performance of these catalysts, especially the high selectivities observed, seem to result from Lewis acid sites [33].

The different performances of catalysts (**A**) and (**B**) was elucidated by characterization of these materials [29]. ^{27}Al and ^{29}Si MAS NMR showed that after treatment with 0.01 M HCl most of the amorphous silica material is removed from the parent catalyst (**A**), leaving extra-framework aluminum species also created by the steaming procedure [29]. This can be readily understood, because the solubility of silica is maximum at pH 2 [34]. It is believed that the silica species blocked most of the catalytically active centers, i. e. the highly dispersed Lewis acidic, extra-framework alumina sites, which seem to be partly bonded to the zeolitic framework of the starting material (**A**). The EFA species are not, therefore, leached out.

After reactivation by calcination in air at 550 °C no loss of activity was observed. By running the isomerization at lower temperatures (down to −30 °C) the selectivity can be improved to 85 % with catalyst (**B**) while maintaining high activity (conversions up to 55 % after 72 h).

It has recently been shown that Lewis acidic zeolites such as Ti-β [12] give excellent results in the rearrangement of (**5**) in both liquid and gas phases [30]. Experiments conducted in the liquid phase with 1,2-dichloroethane as solvent resulted in 81 % selectivity for (**6**) at 29 % conversion after 24 h. Gas-phase tests resulted in further improvements in the catalytic performance of this system. With methylcyclohexane as co-adsorbate 93 % selectivity for (**6**) at an initial conversion of 100 % was achieved at 90 °C. Although the conversion decreases linearly after 6 h on stream, the catalyst can be completely regenerated up to 100 times by an burn-off in air at 480 °C.

Heterogeneous catalysts have been improved by years of research and development and can finally replace conventional homogeneously catalyzed methods using $ZnBr_2$. Heterogeneous catalysis thus contributes to environmental protection.



(12) **(13)** **(14)** **(15)**

Figure 6. Products of the isomerization of isophorone oxide.

5.4.7 Isomerization of Isophorone Oxide

Terpene epoxides are very reactive compounds. Some are prepared conventionally by isomerization using homogeneous catalysts such as $BF_3.Et_2O$ [35,36]. The rearrangement of isophorone oxide (Figure 6) yields the keto aldehyde (**13**), which is an intermediate for fragrance chemicals. If the reaction is performed in the presence of zeolites the keto aldehyde (**13**) and the keto–enol form of the α-diketone (**14**) are the main products [35,36].

Hölderich et al. obtained high yields (up to 81 %) of keto aldehyde (**13**) over H-FER after 6 h in the liquid phase at 110 °C with toluene as solvent [37]. H-US-Y catalysts perform well in the formation of (**13**). The H-US-Y (Si/Al = 48)-HCl catalyst, modified by treatment with dilute HCl (pH 2) according to the method described in the preceding section [35,38] is particularly active, even at high weight hourly space velocities. The performance of this catalytic system is comparable with that of the system described by Sheldon et al. [36]. Reaction in benzene at 80 °C for 2 h over dealuminated H-mordenite gave 100 % conversion and 85 % selectivity for (**13**). The ratio of the two main products (**13**) and (**14**) depends on the type and acidity of the zeolite used. For example, H-BEA with a more acidic outer surface was highly active but the selectivity for (**13**) was lower than for H-FER or H-US-Y catalysts [37].

Hölderich et al. also reported vapor-phase rearrangement of (**12**) [37]. The conversions and selectivities found for different zeolites are shown in Table 2.

Conversions were high for all the zeolites tested except Na-ZSM-5 and silicalite. A shorter contact time seems to have a positive effect on aldehyde formation,

Table 2. Gas-phase isomerization of isophorone oxide.

Catalyst	Conversion (%)	Selectivity (%) (13)	(14)	(15)
H-ZSM-5 (30)	100	72	18	1
H-(B)-ZSM-5 (19)	90	82	10	1
H-US-Y (48)-HCl	100	68	23	3
H-FER (9)	100	66	24	3

TOS = 4 h, $T = 250$ C, toluene/isophorone oxide 2:1 *w/w*; nitrogen flow 8 L h^{-1}, WHSV = 1 h^{-1}, 1 bar pressure, numbers in parentheses are silicon to aluminum or boron ratios.

possibly because of reduced decarbonylation. With H-BEA (Si/Al = 12.5) and a residence time of 1.9 s at 250 °C selectivity for aldehyde (**13**) was 34 %. When residence time was reduced selectivity increased to 49 %. Conversion was complete under both sets of conditions. The highest selectivities for the keto aldehyde (**13**) were obtained with H-[B]-ZSM-5 and H-ZSM-5 (Si/Al = 30) (see Table 2). In conclusion, the heterogeneously catalyzed isomerization of terpene epoxides over zeolites seems slightly better in the vapor phase than in the gas phase.

5.4.8 Rearrangement of Oxaspiro Compounds

Rearrangements of oxaspiro compounds such as 1,5-dioxaspiro-(2,6) octane and 4,4,5,8-tetramethyl-1-oxa-spiro-(2,5) octane are of interest because of the value of the products obtained.

5.4.8.1 Rearrangement of 1,5-Dioxaspiro(2,6)octane

1,5-Dioxaspiro(2,6)octane is readily converted, over a zeolite catalyst, to 4-formyltetrahydropyrane, a valuable intermediate in the production of fragrances, pharmaceuticals, and agrochemicals (Figure 7). This compound is hardly obtainable by other known synthesis routes (Rosenmund reduction). With aluminum- or boron-containing MFI-type zeolites at 300 °C in the gas phase 4-formyltetrahydropyrans are readily produced in high yields (> 97 %) [27,39,40]. This reaction can also be performed successfully in the presence of solvents such as THF, resulting in similar yields under the same conditions [39].

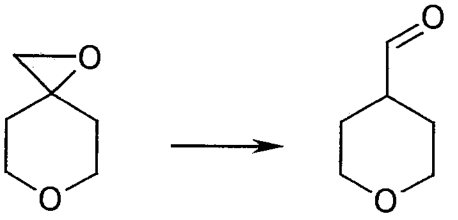
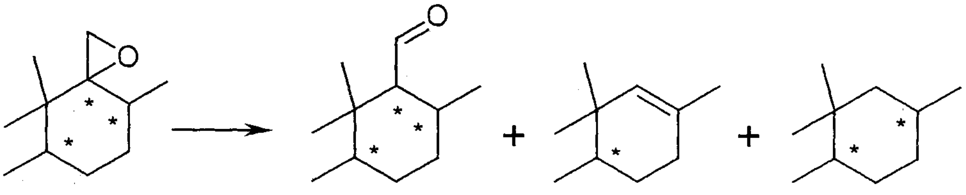


Figure 7. Rearrangement of 1,5-dioxaspiro-(2,6)octane.

5.4.8.2 Rearrangement of 4,4,5,8-Tetramethyl-1-oxaspiro-(2,5)octane

4,4,5,8-Tetramethyl-1-oxaspiro-(2,5)octane is conventionally obtained in a multistep synthesis from readily available (–)-(*S*)-*β*-citronellol or (+)-(*R*)-pulegone (Figure 8) [41]. In the presence of acidic catalysts it rearranges to the industrially-desired 2,2,3,6-tetramethylcyclohexane carbaldehyde (**17**) and many other products.

The aldehyde is a precursor for the synthesis of highly active fragrances such as the saturated alcohol 1-(2,2,3,6-tetramethyl-1-cyclohexyl)-3-hexanol (Figure 9), which has a woody-ambra-like smell [42].



(16) **(17)** **(18)** **(19)**

Figure 8. Main products of the ring opening reaction of 4,4,5,8-tetramethyl-1-oxaspiro(2,5)octane under gas-phase conditions.

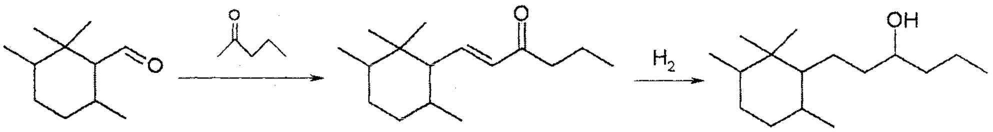


Figure 9. 1-(2,2,3,6-Tetramethyl-1-cyclohexyl)-3-hexanol in two steps from (**2**).

Ring opening of (**16**) can be performed with Lewis acid homogeneous catalysts such as $BF_3.Et_2O$ [8], MgI_2 [41], or $SnCl_4$ [41] with almost quantitative yield at room temperature in toluene as solvent.

The performance of zeolitic catalysts is moderate in liquid-phase slurry reactors, e. g. with H-US-Y (Si/Al = 35) and H-US-Y (Si/Al = 35) modified by HCl treatment (Table 3).

Two main reactions take place, rearrangement of (**16**) to the aldehyde (**17**) then oxidative decarbonylation to the olefin 1,3,3,4-tetramethylcyclohex-1-ene (**18**), presumably as a result of elimination of formaldehyde. Decarbonylation can also occur, leading to 1,1,2,5-tetramethylcyclohexane (**19**). Besides these main products many other side-products can be formed.

The highest selectivities are obtained at low temperatures (ca 0 °C). To obtain high conversion, long residence times are necessary. This means that the space–time yield (STY) in the liquid phase is inferior to that in the gas phase. The catalytic performance of HCl-treated H-US-Y zeolite is better than that of the untreated catalyst, possibly because of the high Lewis acidity and high mesoporosity of this material [29].

Table 3. Liquid-phase reaction for preparation of (**16**) to (**17**).

Catalyst	*T* (C)	*t* (h)	Conv. (**16**) (%)	Sel. (**17**) (%)
H-US-Y (35)	0	24	22.0	59.8
H-US-Y (35) HCl	0	24	79.2	58.6
H-US-Y (35) HCl	Room temp.	24	100	44.0

Catalyst 2.0 g, load 7.5 g, solvent 30 g toluene, $t = 24$ h, 10 mL acid (g catalyst)$^{-1}$.

Examination of gas-phase reactions revealed that the conversion of (**16**) decreases rapidly in the presence of acidic zeolites such as H-B-ZSM-5, H-ZSM-5, and H-US-Y [43]. This behavior is even more apparent over BPO_4 and Nb_2O_5. The best performance was that of the silica catalyst D11-10 (BASF AG), which is mildly acidic–selectivity for **2** was ca 40 % with no decrease in conversion after 8 h on stream, even at 230 °C. The starting material seems to be too bulky to enter the pore system of the medium-sized weakly acid boron–pentasil zeolites [43]. By optimization of reaction temperature and the residence time with respect to the WHSV, and reducing the pressure to 100 mbar the selectivity could be increased to 53 % with complete conversion and no deactivation occurred during 8 h on stream.

The use of mesoporous H-US-Y zeolites as catalysts in this reaction is an environmentally benign alternative to conventional homogeneous catalysts. Because demand for this product is rather low and results from gas-phase reaction are only moderate, the liquid-phase batch reaction is a reasonable choice although it must be performed at 0 °C.

5.4.9 Conclusions

The examples chosen show that heterogeneous catalysis can be tuned to the versatile reactivity of epoxides, affording successful catalysis in the synthesis of the chemical products desired. Because of the manifold methods available for epoxidation, epoxide rearrangement is the most straightforward, and, therefore, cheapest, route to valuable aldehydes and ketones.

Nowadays much production cost results from efforts to reduce or eliminate waste. The rearrangement of styrene oxide to phenylacetaldehyde, for which yields of 100 % have long been achieved as a result of shape selectivity, is a good example of what can be achieved with heterogeneous catalysis. All the examples show how the formation of (heavy metal) salts is prevented, toxic agents are substituted, and energy can be saved by simplifying or avoiding work-up procedures.

Most manufactured zeolites are used as additives in detergents and for petrochemical applications, but there is a marked trend towards the use of zeolite catalysis to obtain high-value-added products. The examples for epoxide rearrangements show the high potential of zeolites in the production of fine chemicals such as insecticides, herbicides, fungicides, fragrances, and starting materials for organic synthesis. It is surprising, therefore, that zeolites are still underutilized tools for the production of intermediates and fine chemicals.

References

[1] J. G. Smith, Synthesis (1984) 629–656.

[2] *Small Ring Heterocycles*; A. Hassner, Ed.; John Wiley Sons New York (1985) Vol. **3**.

[3] J. G. Buchanan and H. Z. Sable *Selective Organic Transformations* John Wiley & Sons New York (1972) Vol. **2**.

[4] G. Kolaczinski, R. Mehren and W. Stein, Fette, Seifen, Anstrichm. **73** (1971) 553–557.

[5] K. Wiechert and P. Mohr, Z. Chem. **7** (1967) 229f.

[6] S. Murata, M. Suzuki and R. Noyori, J. Am. Chem. Soc. **101** (1979) 2738f.

[7] W. F. Hölderich, Pat. US 4990684 (1989) BASF AG (Ludwigshafen, DE).

[8] W. F. Hölderich and N. Goetz, *9th international zeolite conference*, Montreal, (1992), R. v. Ballmoos Ed., Butterworth–Heinemann USA (1993) 309.

[9] *Introduction to Zeolite Science and Practice*; H. v. Bekkum, E. M. Flanigen and J. C. Jansen, Eds.; Elsevier: Amsterdam (1991) Vol. **58**.

[10] W. F. Hölderich and D. Heinz In *Catalysis* Spivey, J. J., Ed. The Royal Society of Chemistry: (1999); Vol. **14**, 149–182.

[11] M. Taramasso, G. Perego and B. Notari, Pat. US 4410501 (1983) Snamprogetti S. P. A. (Milan, IT).

[12] J. C. v. d. Waal, P. Lin, M. S. Rigutto and H. v. Bekkum, *11th International Conf. on Zeolites*, Seoul, South Korea, 1996 Stud. Surf. Sci. Catal. (1997) **105**, 1133.

[13] C. Neri and F. Buonomo, Pat. US 4495371 (1985) ANIC S. p. A. (Palermo, IT).

[14] K. Smith, *Heterogeneous Catalysts and Fine Chemicals*, Lyon, (1999).

[15] H. Smuda, W. F. Hölderich, N. Götz and H.-G. Recker, Pat. US 4929765 (1988) BASF AG (Ludwigshafen, DE).

[16] W. F. Hölderich, N. Götz, L. Hupfer and H. Lermer, Pat. US 4980511 (1987) BASF AG (Ludwigshafen, DE).

[17] P. B. Venuto and P. S. Landis Academic Press: New York (1968); Vol. **18**, 351.

[18] M. K. Faraj, Pat. US 5312995 (1993) Arco Chemical Technology, L. P. (Wilmington, DE).

[19] W. F. Hölderich, W. D. Mross, F. Merger and G. Fouquet, Pat. US 4929765 (1984) BASF AG (Ludwigshafen, DE).

[20] K. Aomura, M. Nitta and S. Matsumoto, Kogakubu Kenkyu Hokoku (Hokaido Daigaku) **67** (1973) 171.

[21] D. Brunel, M. Chamoumi, P. Geneste and P. Moreau, Journal of Molecular Catalysis **79** (1993) 297–304.

[22] G. D. Yadav and D. V. Satoskar, J. Chem. Tech. Biotechnol. **69** (1997) 438–450.

[23] W. F. Hölderich, N. Götz, L. Hupfer, R. Kropp, H. Theobald and B. Wolf, Pat. 0228675 (1990) BASF AG (Ludwigshafen, DE).

[24] K. Smith and M. Al-Shamali, *12th International Conference on Zeolites*, Baltimore Eds. M. M. J. Treacey et al., Material Research Society, Warrendale 1999, **3**, 228.

[25] D. P. Serrano, M. A. Uguina, G. Ovejero, R. V. Grieken and M. Camacho, Microporous Materials **4** (1995) 273–282.

[26] C. Neri and F. Buonomo, Pat. US 4609765 (1986) ANIC S. p. A. (Palermo, IT).

[27] N. Goetz, W. F. Hölderich and L. Hupfer, Pat. US 4968831 (1988) BASF AG (Ludwigshafen, DE).

[28] J. Kaminska, M. A. Schwegler, A. J. Hoefnagel and H. v. Bekkum, Recl. Trav. Chim. Pays-Bas **111** (1992) 432–437.

[29] A. Liebens, C. Mahaim and W. F. Hölderich, *4th Int. Symposium on Heterogeneous Catalysis and Fine Chemicals*, Basel Switzerland, Stud. Surf. Sci. Catal. (1997) **108**, 587.

[30] P. J. Kunkeler, J. C. v. d. Waal, J. Bremmer, B. J. Zuurdeeg, R. S. Downing and H. v. Bekkum, Cat. Let. **53** (1998) 135–138.

[31] G. Carr, G. Dosanjh, A. P. Millar and D. Whittaker, J. Chem. Soc. Perkin Trans. **2** (1994) 1419.

[32] K. Arata and K. Tanabe, Chem. Lett. (1979) 1017.

[33] D. Freude, T. Fröhlich, M. Hunger and G. Scheler, Chem. Phys. Let. **98** (1983) 263.

[34] A. F. Holleman, Textbook in Inorganic Chemistry, de Gruyter: New York, (1985).

[35] A. Liebens, C. Mahaim and W. F. Hölderich, *12th Int. Congr. Catal.*, Baltimore M. M. J. Treacey Ed., Material Research Society, Warrendale 1999, **3**, 1893.

[36] R. A. Sheldon, J. A. Elings, S. K. Lee, H. E. B. Lempers and R. S. Downing, J. Mol. Catal. A **134** (1998) 129–135.

[37] C. Meyer, W. Laufer and W. F. Hölderich, Cat. Let. **53** (1998) 131–134.

[38] W. F. Hölderich, J. Röseler and G. Heitmann, Catal. Today **37** (1997) 353.

[39] W. F. Hölderich In *Acid–Base Catalysis* Kodansha–VCH: Tokyo, (1989) 1–20.

[40] W. Spiegler, W. F. Hölderich, N. Götz, L. Hupfer and J. Wild, Pat. US 4824973 (1986) BASF AG (Ludwigshafen, DE).

[41] C. Chapuis, C. Margot, K. H. Schulte-Elte and H. Pamingle, Pat. EP 374509 (1990).

[42] K. H. Schulte, C. Chapuis, D. Simmons and D. Reichlin, Pat. EP 457022 (1991).

[43] A. Liebens, W. Laufer and W. F. Hölderich, Cat. Let. **60** (1999) 71–75.

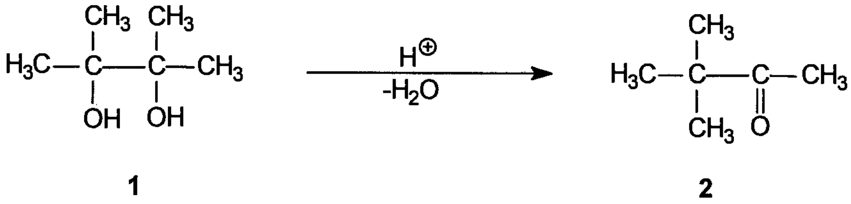
5.5 The Pinacol Rearrangement

Árpád Molnár

5.5.1 Introduction

The pinacol rearrangement is an important and useful transformation in organic synthesis. It enables the preparation of carbonyl compounds from 1,2 (vicinal) diols under mild conditions in good to excellent yields. Although useful, wide-ranging application is limited by the difficulty to obtain diols with complex structures. The practical importance of the reaction and theoretical aspects, including stereochemistry and mechanistic considerations, have been thoroughly treated in numerous reviews [1–9]. Despite its long history recent studies still yield valuable and interesting new information. A particularly burgeoning field is the application of new solid acids.

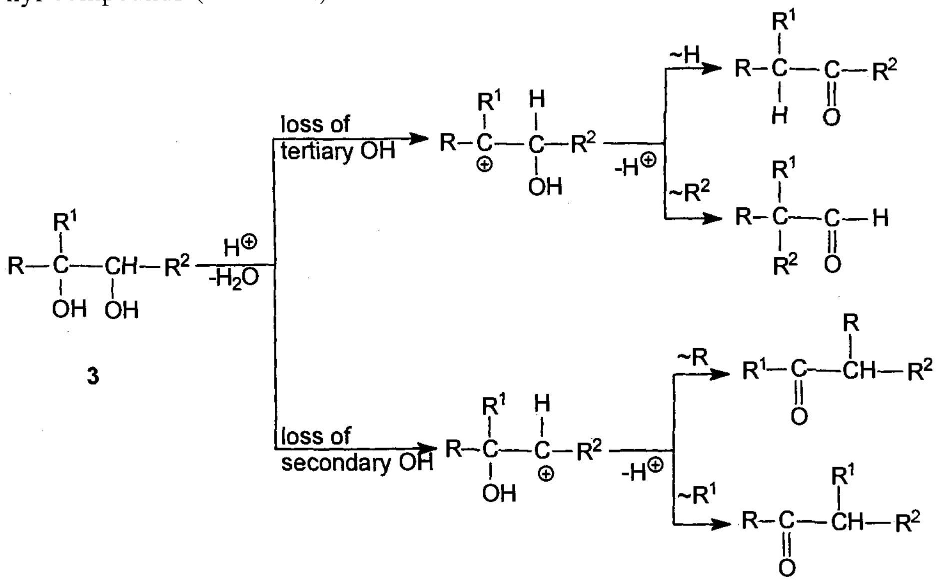
The pinacol rearrangement was first described by Fittig in 1860 [10]–treatment of pinacol (2,3-dimethyl-2,3-butanediol, **1**), a ditertiary 1,2-diol, with sulfuric acid resulted in the formation of pinacolone (3,3-dimethyl-2-butanone, **2**) (Scheme 1). The overall reaction is dehydration with concomitant migration of a methyl substituent.



Scheme 1. The pinacol rearrangement

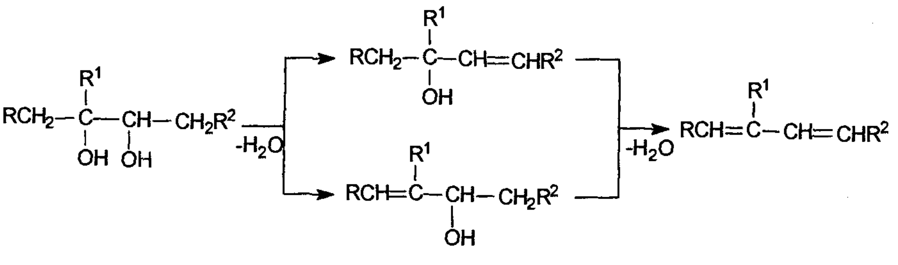
It is now known that the pinacol rearrangement is characteristic of all types of 1,2-diol, and that the process is promoted by most electrophilic catalysts. Most of the available data point to the involvement of a carbocationic intermediate, even when the hydroxyl groups are not tertiary. Evidence for a concerted process, i. e. loss of water with the synchronous migration of the substituent, has also been obtained. Other mechanistic possibilities, e. g. transformation through an epoxide or an enolic intermediate, can either be ruled out or regarded as playing a role in limited cases only [6].

The yield of the product carbonyl compounds can be very high if suitable experimental conditions are applied. The catalyst of choice under homogeneous conditions is sulfuric acid, either dilute or concentrated; this enables the synthesis of pinacolone in almost quantitative yield [11]. Even when selective rearrangement occurs, however, a complex mixture of rearrangement products might be formed, depending on the structure of the starting compound. For example, diol **3** or any compound with four different substituents yields a mixture of four isomeric carbonyl compounds (Scheme 2).



Scheme 2. Mechanism of the pinacol rearrangement.

Side reactions, *β* eliminations yielding unsaturated alcohols and dienes, are often observed (Scheme 3) and can even become the dominant reaction [12]. Appropriate choice of reaction conditions is, therefore, required to achieve the selective formation of rearrangement products.



Scheme 3. Side reactions in the pinacol rearrangement.

It follows from mechanistic considerations that the hydroxyl group removed preferentially determines the general direction of the reaction, because it leads to the more stable intermediate carbocation. The tendency of different substituents to stabilize the developing positive charge might, however, complicate the picture. Another factor affecting the outcome of the process is the mobility of the migrating groups, or the migratory aptitude. The substituent better stabilizing the positive charge at the migration terminus usually has a higher migratory aptitude. The mobility sequence aryl > H > alkyl can be taken as qualitative guidance, because examples of anomalous migratory aptitude are reported. The equilibration of intermediate carbocations, conformational effects, neighboring group participation and the stability of the product carbonyl compounds under the reaction conditions (aldehyde to ketone rearrangement, and interconversion of ketones) also affect the rearrangement. Hence, the control of regioselectivity is often problematic; this limits the synthetic utility of the process.

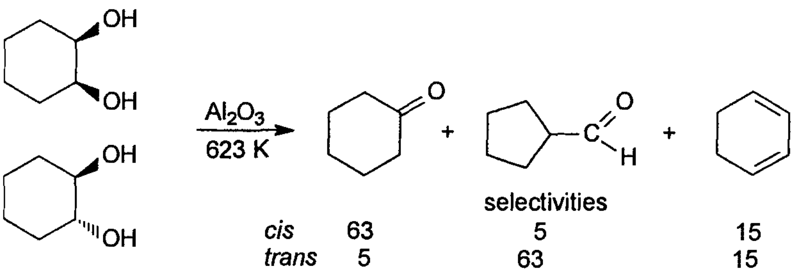
5.5.2 Solid Acids in the Pinacol Rearrangement

Of the solid electrophilic catalysts an acidic clay [13] and alumina were applied in the early history of the pinacol rearrangement. The last two decades, with the development of a variety of new classes of solid acid has, however, brought an upsurge in research activity. Almost all types of solid acid have been tested and found to have high catalytic activity in the transformation of vicinal diols, although selectivity is not always satisfactory.

5.5.2.1 The Use of Alumina

The transformation of ditertiary 1,2-diols was found to be non-selective–a mixture of dienes and ketones is formed and diene selectivity often exceeds that for rearrangement products [14–16]. Increasing surface acidity and increasing temperature have been shown to shift the selectivity toward diene formation [17].

Isomeric 1,2-cyclohexanediols (*cis*- and *trans*-1,2-cyclohexanediol [18–20], *cis*- and *trans*-1-methyl-1,2-cyclohexanediol [21]), in turn, undergo rearrangement with high, usually better than 70 %, selectivity. The *cis* compounds give the corresponding cyclohexanone, whereas ring contraction of the *trans* isomers leads to cyclopentanecarbaldehyde (Scheme 4) [20].



Scheme 4. Pinacol rearrangement of 1,2-cyclohexanediols.

High carbonyl selectivity has also been reported in the transformation of other diols, e. g. disecondary, secondary–tertiary and ditertiary furyl- [22], and ethynyl-substituted [23] compounds, stereoisomeric 2,3-butanediols, and hydrobenzoins [24]. The main product in the dehydration of isomeric 2,3-butanediols is always 2-butanone, formed by hydrogen migration. Interestingly, selectivity in the transformation of *meso*-hydrobenzoin depends on the temperature. Steric interactions in the different conformations leading to the product carbonyl compounds and differences between the migratory aptitude of the substituents (H, Me, and Ph) have been invoked to interpret this observation.

A specific catalyst, an aluminum-containing polymethylsiloxane prepared from aluminum hydroxide and chloromethylsilanes, catalyzes the rearrangement of pinacol in the vapor phase (523 K, pulse technique) [25]. High activity but rapidly decreasing selectivity are characteristic of this catalyst.

5.5.2.2 Application of Molecular Sieves

NaA, NaX, and NaY zeolites, and derivatives prepared by ion exchange (Li, Ca, Co, Sc, La, Zr), were studied first in the transformation of 2-methyl-2,3-butanediol (flow system, 483–583 K) [26]. The small-pore zeolite NaA proved to be completely inactive but the activity of large-pore samples varied, with conversion usually in the range 20–50 %. The best selectivity for 3-methyl-2-butanone (ca 88 %) was achieved over NaCaX. Selectivity, however, was found to decrease with increasing temperature, because of competing β elimination.

High activity and selectivity in the pinacol rearrangement of simple diols were observed in subsequent studies. Y zeolites (HY [27], LaHY [26,28], CaHY [28], NaY, and NaHY [29,30]) had the highest activity, and they were also more selective than X zeolites [29,30]. Though HZSM-5 was less active, its activity remained constant whereas substantial deactivation was observed for Y zeolites [28]. This is explained by the higher resistance of HZSM-5 to coke formation.

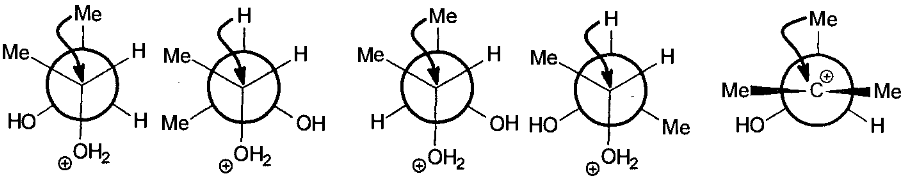
A comparative study of the rearrangement of the stereoisomeric 2,3-butanediols, 2-methyl-2,3-butanediol and pinacol over NaX and NaY zeolites and their hydrogen forms led to some interesting observations in respect of the mechanism of the process [30]. Of the four compounds studied the tendency to form rearrangement products was greatest for racemic 2,3-butanediol (which gave 2-butanone and 2-methylpropanal) (Table 1). The *meso* compound, in contrast, was shown to be less reactive, and the selectivity was much lower. In addition, the ratio of the isomeric carbonyl compounds (2-butanone formed by hydrogen migration compared with 2-methylpropanal formed by methyl migration) was also significantly lower (Table 1). This ratio was even lower for 2-methyl-2,3-butanediol.

These observations for the stereoisomeric 2,3-butanediols can be explained by assuming concerted elimination of water and migration of H or Me. Such an E2-

Table 1. Selectivity in the transformation of racemic and *meso*-2,3-butanediol (flow system, reaction temperature = 523 K) [30].

	Rearrangement/elimination				H migration/Me migration			
	NaX	NaHX	NaY	NaHY	NaX	NaHX	NaY	NaHY
meso-2,3-Butanediol	3.2	3.5	4.1	4.5	13	18	14.6	10.6
Racemic 2,3-butanediol	48.5	18.6	32	48.5	96	46	90	96
2-Methyl-2,3-butanediol	6.1	11.4	15.5	15.2	8.6	6.6	7.5	14.2

type mechanism requires that the molecule adopts a conformation with the leaving group (protonated OH) and the migrating group in the *anti* position. Examination of the four possible conformations reveals significant Me–Me *gauche* interactions in three instances (Scheme 5; **4**–**6**). This accounts for the low reactivity of the *meso* compound and the large amount of elimination occurring via a different transition state. The only conformation without steric crowding (**7**) leads to 2-butanone from the racemic compound with high selectivity and yield (for example, isolated yields of 2-butanone over NaX zeolite from the *meso* and racemic diols are 25 and 71 %, respectively). In contrast, the higher selectivity for aldehyde formation (increased probability of Me migration) from 2-methyl-2,3-butanediol points to the involvement of the carbocationic intermediate, **8**.



4 **5**
meso-2,3-butanediol

6 **7**
racem. 2,3-butanediol

8
2-methyl-2,3-butanediol

Scheme 5. Pinacol rearrangement of 2,3-butanediol stereoisomers

Studies with silicoaluminophosphate molecular sieves showed that SAPO-37 (faujasite geometry) and SAPO-5 (AFI structure) were good catalysts for the transformation of pinacol, with selectivity increasing with reaction time (batch reactor, 423 K) [31]. In contrast, the activity of two other samples (SAPO-11 and SAPO-34) was inferior, possibly because inadequate pore dimensions hindered access of the reacting pinacol to the active sites.

The pinacol rearrangement proceeds over metal-substituted aluminophosphate molecular sieves (APOs) under mild conditions (batch reactor, solvent, g diol/g catalyst = 5, 383 K, 3 h) [32]. Catalytic performance is best for APO-5 (Table 2) and surpasses that that of VPI and APO-11. Of the metals used Fe^{3+}, Ni^{2+}, and Cu^{2+} have the highest activity and selectivity. No direct correlation was found between activity and acidity determined by pyridine TPD. For example,

Table 2. Transformation of pinacol over aluminophosphate molecular sieves (383 K in solvent) [32].

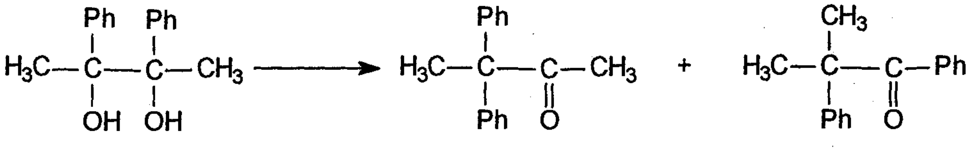
	Rearrangement/elimination		Conversion (%)	
	In toluene	In 2-octanone	In toluene	In 2-octanone
1 % Fe-APO-5	5.9	–	51	–
2 % Fe-APO-5	4.7	16	69	87
4 % Fe-APO-5	4.2	–	60	–
2 % Ni-APO-5	4.8	15	50	83
2 % Cu-APO-5	5.8	9.1	54	85

HY and HZSM-5, with relatively high acid strength, have low activity under these conditions. The activity of all high-silica zeolites (HY, HZSM-5, and Fe-silicalite-1) is, in fact, low; this is attributed to the low adsorption capacity of the hydrophobic surfaces of these samples. The pore diameters of the different catalysts do not affect activity, implying that only the outer surfaces are involved in the transformations. Both activity and selectivity depend on the solvent used. Because solvents of high polarity compete for adsorption sites, toluene and 2-octanone, which are of low polarity, were found to be the best solvents. It has been suggested that high rearrangement selectivity in 2-octanone results from its capacity to remove the product ketone from the surface. The active sites are, thereby, vacated for further rearrangement. The active centers are believed to be metal ions reversibly adsorbing water molecules. Pinacol, displacing water, forms an Fe^{2+}–O bond that stabilizes the carbocation and then back-donates an electron to the C–O bond, regenerating Fe^{3+}. Coordinative and redox capacity of the metal ion center are, therefore, both prerequisites of high catalytic activity.

5.5.2.3 Transformation on Resin Sulfonic Acids

1,2-Diols have been reported to undergo the pinacol rearrangement in the presence of resin sulfonic acids to produce the corresponding carbonyl compounds in 80–90 % yield.

Simple diols have been subjected to the pinacol rearrangement in the presence of Amberlyst 15, a polystyrene sulfonic resin with a high concentration of acidic centers. When excess catalyst is used (g catalyst/g diol = 1.25) pinacol gives 3,3-dimethyl-2-butanone in near quantitative yield (batch reactor, 373 K, 2 h) [33]. Of the two isomeric ketones 3,3-diphenyl-2-butanone (**10**), formed with phenyl migration, is the sole product when 2,3-diphenyl-2,3-butanediol (**9**) is reacted (Scheme 6). This feature is very similar to that observed under homogeneous conditions in the presence of sulfuric acid [2]. An arylsulfonic silica catalyst prepared by grafting and sulfonation proved to be less selective [33].



9 **10** **11**

Scheme 6. Pinacol rearrangement of 2,3-diphenyl-2,3-butanediol.

Nafion-H, a perfluorinated resin sulfonic acid, is also highly selective in the transformation of ditertiary 1,2-diols (benzene solution under reflux, 30 min) [34,35]. A comparative study of simple methyl-substituted diols (flow system or distillation, 448 K) showed that the reactivity of the diols increased with increasing substitution [36]. Under these conditions, however, especially when the distillation (batch) method is used, a secondary transformation occurs–the product carbonyl compounds react with the starting diol to form the corresponding 1,3-dioxolanes. This is the dominant process for 1,2-propanediol (84 % selectivity) but becomes less significant for more substituted compounds. As a result of this tendency, dioxolane formation is not observed for pinacol.

5.5.2.4 The Use of Clay Catalysts

The pinacol rearrangement of simple methyl- and phenyl-substituted diols in the presence of different montmorillonites was examined by Gutierrez and Ruiz-Hitzky [33,37–39]. The transformations were performed in dry media without solvent, with the reacting diols intercalated into the interlamellar space of the montmorillonites. High catalyst/diol ratios (≥ 5) and mild reaction conditions were usually used.

In the transformation of pinacol both activity and selectivity were found to depend on the acidity (expressed as ionic potential, = cation charge/ionic radius) of the metal ions present in M^{n+}-montmorillonites (batch reactor, 373 K, 1 h) [39]. The highest activity was that of Cr^{3+} and Al^{3+} (ionic potentials 4.35 and 6.00, respectively). Selectivity was also shown to increase in the sequence $Na^+ < Ca^{2+} < Cu^{2+} < La^{3+} < Cr^{3+} < Al^{3+}$. Thus, ions with low acidic character (Na^+ and Ca^{2+}) induce increased diene formation (38 % and 19 %, respectively).

M^{n+}-montmorillonites also resulted in the selective formation of 3,3-diphenyl-2-butanone (**10**) from 2,3-diphenyl-2,3-butanediol (Scheme 6), i. e. selective phenyl migration occurred [33,39]. Increasing temperature and increasing acidity, however, brought about a substantial increase in the formation of the isomeric ketone **11**.

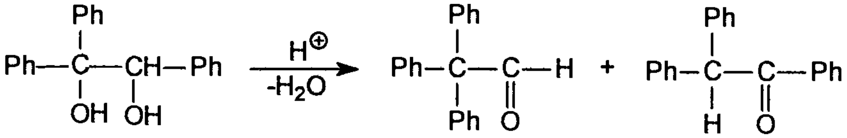
Pillared layered clays (PILC) containing different hydrated cations in the interlayer space are also selective catalysts. Pinacol and 2,3-diphenyl-2,3-butanediol have been studied in the presence of Al-PILC, Zr-PILC, and Cr-PILC [38]. Zr-PILC, with the lowest acidity, gave rise to the largest amount of diene from pinacol (32 % and 22 %, depending on the method of preparation). The rearrangement was selective in the presence of a mixed-metal pillared layered clay (Fe_2Al_{11}-PILC, sealed tube, 398 K, 1 h, catalyst/diol = 5) [40].

Changes in selectivity in the rearrangement of 2,3-diphenyl-2,3-butanediol (Scheme 6; **9**) were similar to those observed with M^{n+}-montmorillonites [38], and selectivity for the isomeric ketone formed by methyl migration (**11**) could also be increased by prolonged reaction (selectivity for **11** as high as 68–70 % could be reached at 433 K after 17 h). This phenomenon was explained by ketone–ketone rearrangement (interconversion of **10** and **11**).

Rapid activation by microwave heating was also studied in the montmorillonite-catalyzed pinacol rearrangement [37,41]. Reactions performed with microwave heating are characterized by very short reaction times–pinacol produced the corresponding ketone selectively in the presence of a variety of M^{n+}-montmorillonites (23–99 % yield in 15 min) [37], whereas diphenylacetaldehyde was formed from hydrobenzoin over K10 and KSF clay via selective phenyl migration (near quantitative yield in 5 min) [41].

5.5.2.5 Miscellaneous Solid Acids

Simple vicinal diols readily undergo the pinacol rearrangement in the presence of heteropoly acids used either neat or in the supported form (batch or flow reactor) [42,43]. Because of their solubility, however, they do not act as true solid acids in these reaction. They can also be employed as solid acids in solid–solid catalytic processes [44,45]. Dodecatungstophosphoric acid ($H_3[PW_{12}O_{40}]$) and its non-stoichiometric acidic cesium salt $Cs_{2.5}H_{0.5}[PW_{12}O_{40}]$ have been used in the pinacol rearrangement of 1,1,2-triphenyl-1,2-ethanediol (**12**). A mixture of reactant and the catalyst was ground for 5 min and kept at room temperature for observation of the selective formation of rearrangement products (Scheme 7). The activity of the salt is good, higher than that observed in the solid–liquid reaction conducted in chloroform as solvent (35 % after 3 h and 63 % after 9 h). Of other solid acids, only Amberlyst 15 and a Nafion-H/SiO_2 nanocomposite had activity (4 % and 12 % conversion, respectively). The key factor in the transformation is to prepare an intimate mixture of the reactant and the catalyst. XRD showed that the diol became nearly amorphous as a result of grinding. The fine particles thus formed could be effectively dispersed on the relatively high surface of the Cs salt. The mesoporous structure of the salt is another important factor in the phenomenon observed.



12

		selectivities		% conversion
$H_3[PW_{12}O_{40}]$	3 h	84	16	21
	9 h	84	16	42
$Cs_{2.5}H_{0.5}[PW_{12}O_{40}]$	3 h	76	24	69
	9 h	76	24	81

Scheme 7. Pinacol rearrangement of 1,1,2-triphenyl-1,2-ethanediol.

The idea of solid-phase acid-catalyzed processes was originally developed by Toda et al. [46,47]. The pinacol rearrangement of aryl-substituted secondary and tertiary diols in the presence of solid *p*-toluenesulfonic acid (333 K) and trichloroacetic acid (293 K) was found to proceed faster and more selectively than in solution (batch reactor) [46].

5.5.3 Conclusions

Solid acids usually have high catalytic activity in the pinacol rearrangement of vicinal diols. Competing β eliminations, however, can affect selectivity. This, and the difficulty of synthesizing starting diols of complex structure, prevent the widespread synthetic application of the pinacol rearrangement. The multiplicity of reaction paths (formation of mixtures of rearrangement products) further limits the use of the process. Despite these complications highly selective formation of carbonyl compounds can be accomplished mainly from symmetrical diols under appropriate reaction conditions.

References

[1] O. Bayer in *Methoden der Organischen Chemie (Houben–Weyl)*, Vol. 7/1, Thieme, Stuttgart, **1954**, pp. 230–236.
[2] C. J. Collins, *Quart. Rev., Chem. Soc.* **1960**, *14*, 377.
[3] C. J. Collins, J. F. Eastham in *The Chemistry of Functional Groups. The Carbonyl Group* (Ed.: S. Patai), Wiley, New York, **1966**, pp. 762–767.
[4] Y. Pocker in *Molecular Rearrangements* (Ed.: P. de Mayo), Wiley, New York, **1963**, pp. 15–25.
[5] D. Dietrich in *Methoden der Organischen Chemie (Houben–Weyl)*, Vol. 7/2a, Thieme, Stuttgart, **1973**. pp. 1016–1034.
[6] M. Bartók, Á. Molnár in *The Chemistry of Functional Groups. Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Sulphur Analogues* (Ed.: S. Patai), Wiley, Chichester, **1980**, pp. 722–728.
[7] B. Rickborn in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Vol. 3 (Ed.: G. Pattenden), Pergamon Press, Oxford, **1991**, pp. 721–732.
[8] Á. Molnár in *The Chemistry of Functional Groups. Supplement E2: The Chemistry of Hydroxyl, Ether and Peroxide Groups* (Ed.: S. Patai), Wiley, Chichester, **1993**, p. 992.
[9] I. Coldham in *Comprehensive Organic Functional Group Transformations* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Vol. 1 (Ed.: S.M. Roberts), Pergamon, **1995**. pp. 384–393.
[10] R. Fittig, *Justus Liebigs Ann. Chem.* **1860**, *114*, 54.
[11] G. A. Hill, E. W. Flosdorf, *Org. Synth., Coll. Vol.* **1932**, *1*, 462.
[12] C. F. H. Allen, A. Bell, *Org. Synth., Coll. Vol.* **1955**, *3*, 312.
[13] R. Lucas, M. F. S. Legagneur, *Compt. rend.* **1928**, *186*, 1848.
[14] W. Reeve, D. M. Reichel, *J. Org. Chem.* **1972**, *37*, 68.
[15] L.Kh. Freidlin, V. Z. Sharf, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1962**, 698.
[16] T. Kuwata, *J. Chem. Soc. Jpn.* **1941**, *62*, 1028, 1035, 1042; *Chem. Abstr.* **1947**, *41*, 3051d.
[17] J. M. Campelo, R. Chakraborty, J. M. Marinas, A. Romero, *Catal. Lett.* **1998**, *54*, 91.
[18] H. Adkins, S. H. Watkins, *J. Am. Chem. Soc.* **1951**, *73*, 2184.
[19] S. Fujita, K. Nomura, *J. Chem. Soc. Jpn.* **1942**, *63*, 510; *Chem. Abstr.* **1947**, *41*, 3063c.
[20] P. Richter, V. Ruzicka, *Chem. Prumysl* **1958**, *8*, 116.
[21] S. Fujita, *J. Chem. Soc. Jpn.* **1951**, *72*, 539; *Chem. Abstr.* **1952**, *46*, 6601c.
[22] G. Dana, J. Wiemann, *Bull. Soc. Chim. Fr.* **1970**, 3994.
[23] J. P. Russell, U. S. Pat. 3,235,602 **1966**; *Chem. Abstr.* **1966**, *64*, 14095c.
[24] S. V. Kannan, C. N. Pillai, *Indian J. Chem.* **1969**, *7*, 1164.
[25] S. Mishima, I. Matsuzaki, T. Nakajima, T. Hiki, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 126.
[26] A. R. Nefedova, Z. V. Gryaznova, G. V. Tsitsishvili, A.Yu. Krupennikova, *Neftekhimia* **1979**, *19*, 113.
[27] W. F. Hölderich, H. van Bekkum in *Introduction to Zeolite Science and Practice* (Eds.: H. van Bekkum, E. M. Flanigen, J. C. Jansen), Elsevier, Amsterdam, **1991**, p. 654.

[28] C. P. Bezouhanova, F. A. Jabur, *J. Mol. Catal.* **1994**, *87*, 39.

[29] Á. Molnár, I. Bucsi, M. Bartók, *Acta Phys. Chem.* **1985**, *31*, 571.

[30] Á. Molnár, I. Bucsi, M. Bartók in *Heterogeneous Catalysis and Fine Chemicals* (Eds.: M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier, G. Pérot), Elsevier, Amsterdam, **1988**, pp. 203–210.

[31] F. A. Jabur, V. J. Penchev, C. P. Bezoukhanova *J. Chem. Soc., Chem. Commun.* **1994**, 1591.

[32] B.-Y. Hsu, S. Cheng, *Microporous Mesoporous Mat.* **1998**, *21*, 505.

[33] E. Gutierrez, A. J. Aznar, E. Ruiz-Hitzky in *Heterogeneous Catalysis and Fine Chemicals*, (Eds.: M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier, G. Pérot), Elsevier, Amsterdam, **1988**, pp. 211–219.

[34] G. A. Olah, P. S. Iyer, G. K. S. Prakash, *Synthesis* **1986**, 513.

[35] G. A. Olah, D. Meidar, *Synthesis* **1978**, 358.

[36] I. Bucsi, Á. Molnár, M. Bartók, G. A. Olah, *Tetrahedron* **1994**, *50*, 8195.

[37] E. Gutierrez, A. Loupy, G. Bram, E. Ruiz-Hitzky, *Tetrahedron Lett.* **1989**, *30*, 945.

[38] E. Gutierrez, E. Ruiz-Hitzky in *Pillared Layered Structures: Current Trends and Applications* (ed.: I. V. Mitchell), Elsevier, London, **1990**, pp. 199–208.

[39] E. Gutierrez, E. Ruiz-Hitzky, *Mol. Cryst. Liq. Cryst.* **1988**, *161*, 453.

[40] I. Pálinkó, Á. Molnár, J. B. Nagy, J.-C. Bertrand, K. Lázár, J. Valyon, I. Kiricsi, *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 1591.

[41] A. Ben Alloum, N. B. Labiad, D. Villemin, *J. Chem. Soc., Chem. Commun.* **1989**, 386.

[42] B. Török, I. Bucsi, T. Beregszászi, I. Kapocsi, Á. Molnár, *J. Mol. Catal. A: Chem.* **1996**, *107*, 305.

[43] B. Török, I. Bucsi, T. Beregszászi, Á. Molnár in *Catalysis of Organic Reactions* (Ed.: R. E. Malz, Jr.), Marcel Dekker, New York, **1996**, p. 393–396.

[44] Y. Toyoshi, T. Nakato, R. Tamura, H. Takahashi, H. Tsue, K. Hirao, T. Okuhara, *Chem. Lett.* **1998**, 135.

[45] Y. Toyoshi, T. Nakato, T. Okuhara, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2817.

[46] F. Toda, T. Shigemasa, *J. Chem. Soc., Perkin Trans. 1* **1989**, 209.

[47] F. Toda, *Synlett* **1993**, 303.

5.6 Terpene Rearrangement/Isomerization

Karl A. D. Swift

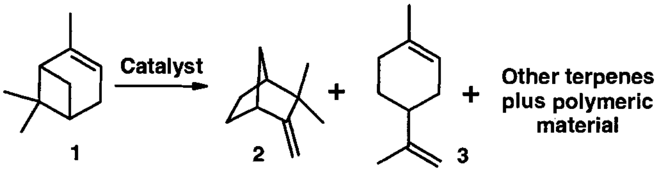
5.6.1 Introduction

The industrial isomerization and rearrangement of terpene molecules is important in the supply of important ingredients and intermediates for the flavor and fragrance industry. Historically, many of these processes have used inorganic or mineral acids and have ultimately generated large volumes of waste. Examples of materials being produced in this way are α-terpineol (via α-terpineol acetate) from the treatment of turpentine oil with acetic acid in the presence of a mineral acid, and campholenic aldehyde which is produced from α-pinene oxide by use of a homogeneous zinc bromide catalyst [1]. It is worth noting that the process used to prepare campholenic aldehyde from α-pinene oxide with a zinc halide catalyst is particularly troublesome because residual zinc salts in the waste water kill bacteria in effluent treatment plants. There is clearly a need for industrial processes which are environmentally more acceptable and the application of heterogeneous solid-acid catalysis to these processes may prove to be a way forward.

5.6.2 Isomerization of pinene (1)

5.6.2.1 Preparation of camphene (2)

By far the greatest amount of work in this area has been centered on the commercially important transformation of α-pinene (**1**) into, primarily, camphene (**2**) and limonene (**3**) (Scheme 1). The first use of a heterogeneous catalyst for the isomerization of α-pinene was reported by Gurvich in 1915 [2] and many forms of solid-acid catalyst have subsequently been studied in relation to this reaction. We shall study just a few of these.



Scheme 1.

Many early literature reports describe the use of clays for this transformation. An interesting example is a 1957 paper by Wystrach et al. [3] who described the isomerization of **1** over 1 % calcined Attapulgus clay to yield **2** and **3** as the major products, and also postulated a mechanism for this transformation [4]. It is also worth noting that they were the first group to realize the importance of the stereochemistry of adsorption in studies relating to isomerization over clays.

Ivanova, Borovskaya, and Rudakov investigated the liquid phase isomerization of β-pinene in the presence of the solid-acid catalysts titanium dioxide, and aluminum silicate [5]. The main products from the reaction were found to be **2** and **3**. They concluded that the isomerization of β-pinene on the two catalytic systems followed zero-order kinetics. They also concluded that the α-pinene formed during the reaction is desorbed from the catalyst surface into the bulk phase where it does not react until the concentration of β-pinene in solution falls to 25–30 %. This means that at this stage of the reaction the camphene and other monocyclic terpenes are being formed directly from β-pinene.

Stanislaus and Yeddanapalli studied the vapor-phase isomerization of **1** over alumina catalysts of different acid strength [6]. They found that the acid strength of the catalyst had a strong influence on the reaction pathway. Over strongly acidic alumina catalysts the selectivity ratio of bicyclic to monocyclic products increased to a maximum, but then decreased rapidly with a prolonged contact time. With the weakly acidic alumina catalysts it was found that once the maximum was reached there was only a small decrease in the selectivity ratio even after prolonged contact times. Conclusions drawn from these results and from the reactions of camphene and tricyclene under the same conditions suggest that the decrease in the selectivity ratio with increasing catalyst acid strength is mainly because of further isomerization of the bi- and tricyclic compounds, which occurs on the strong acid sites only. This work was followed by a Japanese systematic study directed at the discovery of any correlation that might exist between the acidity of the solid acids and their catalytic activity or selectivity [7].

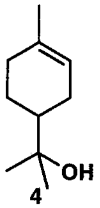
Because acidified titanium oxide is the catalyst usually employed commercially for the transformation of **1** into **2** [8] there has been much investigation of this catalytic system [9]. A 1995 paper by Stefanis et al. [10] reported an investigation of the reaction of **1** in several alumina-pillared clays (PILCs; montmorillonite- and beidellite-based, and their K^+ and Ca^{2+} -exchanged congeners) under Lewis acid conditions (solid is activated by heat to remove all water). The results were compared with those obtained by use of medium-pore zeolites USY, $NH_4{}^+$-ZSM-5, and H-mordenite. Conversion to **2** $> 50\,\%$ was always observed. The aim of the work was to clarify differences between site availability and acidity for the two types of solid.

A recent study [11] into the isomerization of **1** into **2** and **3** using both acid treated polycation-exchanged bentonite clays and their non-polycation-exchanged equivalents found that use of polycation-exchanged clays significantly increased the yield of **2**. For further references related to the use of polycation-exchanged clays the reader is referred to the discussion section in Ref. 11.

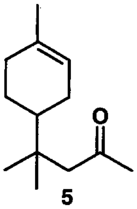
Another recent publication concerning the isomerization of **1** into **2** describes a selective liquid-phase reaction over dealuminated mordenites, Y-zeolites, and a 13 % alumina amorphous aluminosilicate [12]. It found that over microporous zeolite structures the main products were **2** and **3**, but that the wider the pore diameter of the catalyst the greater the amount of unwanted and unidentifiable products obtained. This was worst for the amorphous aluminosilicate, which has a mesoporosity of 90 %. Interesting selectivity was noticed when the dealuminated mordenites were used; the combined yield of **2** + **3** was $> 68\,\%$ and the ratio **2**/(**2** + **3**) was > 0.54.

5.6.2.2 Other Reactions of Pinene

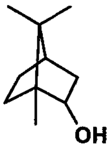
A study of the hydration and isomerization of **1** over zeolite beta in water yielded the expected monocyclic alcohol, α-terpineol (**4**) [13]. This isomerization/hydration in the presence of zeolite beta is a rapid process and yields up to 48 % of **4**.



4



5

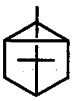


6

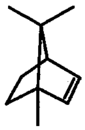
It was found that the rate of the reaction and selectivity towards formation of **4** could both be increased by dealumination of the outer surface of the zeolite with Na_2H_2EDTA. When the solvent was changed to pure acetone a new compound (**5**) was formed. In this study, the coupling of ketones (acetone, butanone, and cyclohexanone) with **1** was found to be catalyzed solely by zeolite beta. The reaction also seems to be exclusive to α-pinene, because no reaction occurred when other terpenes such as **3**, **4**, and borneol (**6**) were used in place of α-pinene. It is also worth noting that borneol (**6**) has also been prepared from **1** by use of a high-silica zeolite [14].

5.6.3 Rearrangement/Isomerization of Other Terpenes

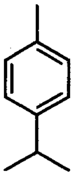
Elangovan and Krishnasamy investigated the isomerization of camphene (**2**) in the vapor phase over different aluminas and zeolites (H-5A, H-ZSM-5, H-Y) and found that the major products were tricyclene (**7**) and bornylene (**8**) [15]. The acidic strength of the catalyst was shown to have a major influence on product distribution–low acid strength yielded only tricyclene (**7**) and bornylene (**8**) whereas high acid strength yielded not only **7** and **8** but also promoted the production of monocyclic compounds such as limonene (**3**), cymene (**9**), and terpinolene (**10**). These are formed from the ring opening of **7** and **8**.



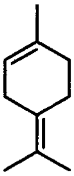
7



8



9

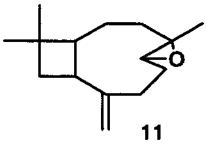


10

5.6.4 Rearrangement of Terpene Epoxides

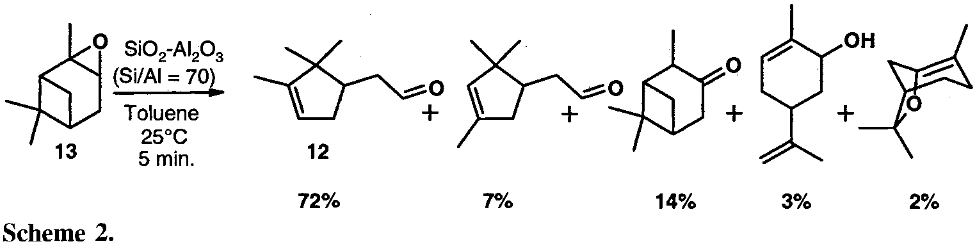
The isomerization of many terpene oxides (see Section 5.4) has been investigated using a wide range of solid acids (and bases). Arata and Tanabe are responsible for much of this work which includes d-limonene oxide [16], 2- and 3-carene oxide [17], and carvomenthene oxide [18].

More recently the isomerization of caryophyllene oxide has been investigated by Arata et al. [19] They reacted caryophyllene oxide (**11**) with a wide variety of solid acids (and some solid bases) and obtained varying ratios of up to five main products. The ratio of products formed was found to depend on the catalyst used. Catalysts such as $FeSO_4$ and $Zr(SO_4)_2$ gave larger quantities of ketone product whereas allylic alcohols were preferentially formed over catalysts such as TiO_2–ZrO_2 and Al_2O_3.



11

The preparation of campholenic aldehyde (**12**) from α-pinene oxide (**13**) is currently a commercial process in which zinc bromide is used as the catalyst. Ravasio et al. [20] have investigated replacing the zinc bromide with a commercial mixed co-gel solid-acid catalyst. They found that by use of SiO_2–Al_2O_3 (1.2 %) or SiO_2–ZrO_2 (4.7 %) they could readily achieve a 72 % yield of **12** under relatively mild conditions (25–60 °C, toluene) although small quantities of several side-products were also still formed (Scheme 2).



Scheme 2.

Another group has also reported a potential zeolite (H-US-Y)-catalyzed production process for preparation of campholenic aldehyde from α-pinene oxide which is described as competitive with the traditional zinc bromide process [21]. Other groups have also looked at this transformation [22].

5.6.5 Conclusion

Heterogeneous solid-acid catalysis has the potential to make a major contribution towards improving the environmental acceptability of terpene rearrangement and isomerization processes. There are potential heterogeneously catalyzed replacement processes for the production of campholenic aldehyde, an important intermediate for many fragrance compounds. With continuing advances in the field of solid-acid catalysis it is likely that other industrially useful heterogeneous catalysts will be discovered.

References

[1] See: Chemistry of Fragrant Substances, Paul J. Teisseire, VCH Publishers, 1994. W. F. Hölderich, D. Heinz, *Catalysis*, 1999, **14**, 148.

[2] L. G. Gurvich, J. Russ. *Phys. Chem. Soc.* 1915, **47**, 827, [C. A. 3005, 1915].

[3] V. P. Wystrach, L. H. Barnum, M. Garber, *J. Am. Chem. Soc.*, 1957, **79**, 5786–5790.

[4] See ref. 2 and also comments in D. V. Banthorpe, D. Whittaker, *Quarterly Reviews*, 1966, 373–387.

[5] L. S. Ivanova, A. G. Borovskaya, G. A. Rudakov, *Zh. Org. Khim.*, 1967, **3**(12), 2114–2118 (English Translation).

[6] A. Stanislaus, L. M. Yeddanapalli, *Can. J. Chem.*, 1972, **50**, 61–74.

[7] R. Ohnishi, K. Tanabe, S. Morikawa, T. Nishizaki, *Bull. Chem. Soc. Jpn.*, 1974, **47**(3), 571–574.

[8] Kirk–Othmer, 1983, *Encyclopedia of Chemical Technology*, 3rd Edition, Volume 22, J. Wiley & Sons, p. 719; A. Severino, J. Vital, L. S. Lobo, 1993, *Heterogeneous Catalysis and Fine Chemicals: III.* Elsevier, Amsterdam, 685–692, M. Guisnet *et al.* (Eds.).

[9] G. A. Rudakov, L. S. Ivanova, T. N. Pisareva, A. G. Borovskaya, *Zh. Org. Khim.*, 1975; **11**(11), 2275–2279, Yu. P. Klyuev, E. S. Nesterova, *Izv. Vyssh. Uchebn. Lesn. Zh.*, 1978, **21**(6), 111–113; A. I. Lamotkin, Yu. P. Klyuev, *Khim. Khim. Tekhnol.* (Minsk), 1982, **17**, 99–102; EP-775682 Hoechst A.-G, 1997.

[10] A. De Stefanis, G. Perez, O. Ursini, A. A. G. Thomlinson, *Applied Catalysis A*, 1995, **132**, 353–365.

[11] C. Breen, R. Watson, *Applied Clay Science*, 1998, **12**, 479–494.

[12] C. López, F. J. Machado, K. Rodríguez, B. Méndez, M. Hasegawa, S. Pekerar, *Applied Catalysis A*, 1998, **173**, 75.

[13] J. C van der Waal, H. van Bekkum, J. M. Vital, *Journal of Molecular Catalysis A*, 1996, **105**, 185–192.

[14] CN85102398, 1986, Guangzhou Institute of Chemistry.

[15] S. P. Elangovan, V. Krishnasamy, *Indian J. Chem.*, 1993, **32A**, 1041–1045.

[16] K. Arata, S. Akutagawa, K. Tanabe, J. Catal., 1976, **41**, 173; K. Arata, H. Takahashi, K. Tanabe, *Rocz. Chem.*, 1976, **50**, 2101; K. Arata, K. Tanabe, *Chem. Lett.*, 1976, 321.

[17] K. Arata, J. O. Bledsoe Jr., K. Tanabe, *Tetrahedron Lett.*, 1976, 3861; K. Arata, J. O. Bledsoe Jr., K. Tanabe, *J. Org. Chem.*, 1978, **43**, 1660.

[18] K. Arata, S. Akutagawa, K. Tanabe, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2289.

[19] K. Arata, K. Hayano, H. Shirahama, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 218–223.

[20] N. Ravasio, M. Finiguerra, M. Gargano, *Chem. Ind. (Dekker)*, 1998, **75**, 513–517.

[21] A. Liebens, C. Mahaim, W. F. Hölderich, *Proceedings of the 4th Int. Symposium on Heterogeneous Catalysis and Fine Chemicals*, Sept. 8–12, Basel, Switzerland, *Stud. Surf. Sci. Catal.*, 1997, **108**, 587.

[22] K. Arata, K. Tanabe, *Chem. Lett.*, 1979, 1017; JP 62.19.549 and JP 62.114.926, 1987 (Toyo Soda Mfg.); W. F. Hölderich, J. Rösler, G. Haitmann, A. T. Liebens, *Catalysis Today*, 1997, **35**, 353.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

6 Solid Acid Catalysis: Miscellaneous

6.1 Metal-Catalyzed Amination of Alcohols

T. Mallat, A. Baiker

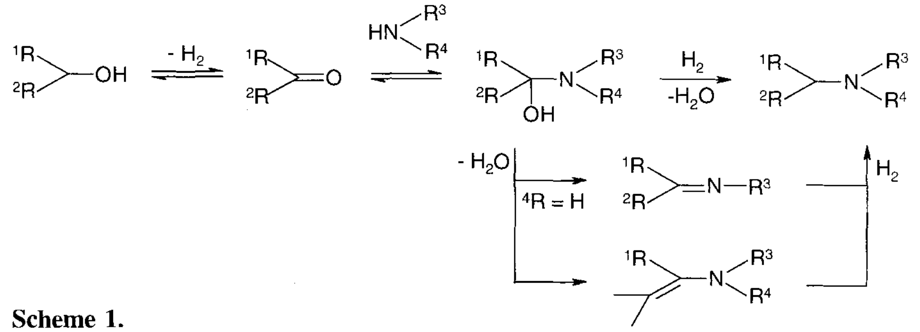
6.1.1 Introduction and Scope

Heterogeneously catalyzed reactions of ammonia or amines with alcohols are industrially important for the production of a variety of amines [1]. Amination catalysts can be divided into two major categories, (supported) metals and solid acids. Metal hydrogenation–dehydrogenation catalysts first transfer the alcohol to the corresponding carbonyl compound which reacts further with ammonia or amine [2–4]. A temperature of at least 150 °C is usually necessary to shift the alcohol–carbonyl compound equilibrium and favor dehydrogenation, which is why amination of alcohols requires considerably higher temperatures than reductive amination of aldehydes and ketones over similar metal catalysts. Because activation of alcohols, and ammonia or amines, by solid acids proceeds at reasonable rates only in the temperature range 250–450 °C, these catalysts, which are robust and highly selective in the synthesis of small chain amines or N-heterocyclic compounds, have limited potential for the transformation of complex, thermally sensitive molecules.

This chapter focuses on the metal-catalyzed amination of alcohols and related compounds such as aminoalcohols, phenols and di- and polyhydroxy compounds. Details of the synthesis of amines with acidic catalysts, including zeolites, mixed oxides and metal phosphates, can be found elsewhere [3,5–7].

6.1.2 Reaction Mechanism

Transformation of an aliphatic alcohol into an amine involves a series of addition and elimination reactions [2–4]. The major steps are shown in Scheme 1, without indicating all the elementary steps and interactions with the metal surface. Initial dehydrogenation of the chemisorbed alcohol to a carbonyl compound is usually the rate-determining step. At high temperature, and especially at low (surface) hydrogen concentration, the final hydrogenation step can be the slowest, leading to the formation of imines, enamines, or even nitriles as dominant products [2,8,9]. This is one reason why hydrogen is added to the reaction mixture when the desired product is the saturated amine, although on a purely stoichiometric basis it would not be necessary.



Scheme 1.

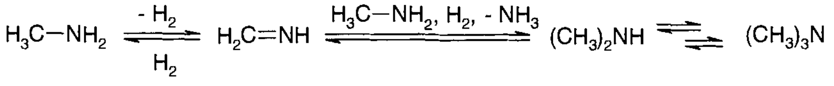
Formation of the tetrahedral intermediate carbinolamine and subsequent elimination of water are amenable to acid–base catalysis and do not require a metal surface. The relative rates of adduct formation and subsequent dehydration to imine or enamine depend on the structure of alcohol and amine, and on the nature and strength of acidic and basic sites on the catalyst surface. It must be stressed that several side-reactions (e. g. dimerization and oligomerization, dehydration) are also acid or base-catalyzed, and good selectivity for the desired product requires proper tuning of the redox and acid–base properties of the catalyst. This is crucial in catalyst development when choosing a suitable support, additive, or modifier. Even traces of impurities remaining on the surface from the catalyst precursor can strongly influence product distribution [10].

When the reactant is ammonia or a primary amine, the product primary or secondary amine, respectively, can further react with alcohol according to Scheme 1, which reduces selectivity. Synthesis of primary amines is especially demanding because the basicity (nucleophilicity) of the product amine is substantially higher than that of ammonia.

6.1.3 Side-reactions, Choice of Catalyst, and Reaction Conditions

All metal hydrogenation catalysts including supported Pt metals, Cu, Co, Ni, Fe, and Cu–Cr_2O_3 are suitable for amination of alcohols [2,11]. There is a wide range of commercially available metal amination catalysts and development of a special multicomponent catalyst might be necessary for demanding reactions only [9]. The choice of a particular catalyst is determined mainly by its selectivity pattern [2]. Pt, Pd, Ru, and Rh are highly active in hydrogenation and dehydrogenation reactions but also catalyze decarbonylation of the intermediate aldehyde, and hydrogenolysis of the C–N bond in amines. Hydrocracking of amines is a favored reaction on Ni and Co also. When these side-reactions are important, Cu-based catalysts might be the appropriate choice.

All metal amination catalysts are active in the disproportionation of amines, which can lead to equilibration of primary, secondary, and tertiary amines. For example, for simple primary amines the initial step is the formation of an aldimine by dehydrogenation (Scheme 2). Subsequent addition of an amine and hydrogenation lead to a mixture of primary, secondary, and tertiary amines. The same active metal sites catalyze alcohol amination and amine disproportionation, which explains why the reactant alcohol inhibits disproportionation and selectivity for the desired amine drops considerably only after consumption of alcohol [2]. It is also evident from Scheme 2 that sufficient hydrogen present on the metal surface can reduce the concentration of imine and thus suppress disproportionation.



$$H_3C{-}NH_2 \xrightleftharpoons[H_2]{-H_2} H_2C{=}NH \xrightleftharpoons{H_3C{-}NH_2,\ H_2,\ -NH_3} (CH_3)_2NH \rightleftharpoons (CH_3)_3N$$

Scheme 2.

A further role of hydrogen in the reaction mixture is to prevent catalyst deactivation by formation of surface nitride, carbide, or unsaturated oligomeric deposit [2]. Aldol condensation of the intermediate aldehyde might be catalyzed by amines or basic sites on the catalyst surface. The unsaturated dimer and oligomers are strongly adsorbed by the metal surface and block the active sites. The usual concentration of hydrogen in the reaction mixture is ca 0.1–2 mol (mol alcohol)$^{-1}$.

The metal catalysts are oxidized during storage in air and have to be reduced (activated) with hydrogen before use. Activation of carbon-supported Pt metals occurs smoothly at ambient temperature but reduction of Cu, Ni, Co, or Fe oxides requires at least 150–200 °C. Major roles of the support (usually Al_2O_3, SiO_2, or carbon) and additives are to stabilize the high surface area of the metal and possibly contribute to acid or base-catalyzed reactions. The amount of catalyst in a batch reactor is usually between 5 and 30 % (*m*/*m*), relative to the alcohol.

The initial alcohol/amine ratio can determine the product distribution. In the synthesis of primary amines a rather high ammonia/alcohol molar ratio (up to 10–25), and usually high pressure, are required to compensate for the low reactivity of ammonia and suppress the formation of secondary amines. Selectivity for primary diamines could be improved in the amination of 1,3-dihydroxy compounds when using supercritical ammonia as solvent and reactant in a continuous fixed-bed reactor [12]. The remarkable changes in selectivity in the near-critical region (100–110 bar) are attributed to the increased concentration of ammonia on the metal surface as a result of elimination of mass-transport limitations in the two-phase system, and to suppression of hydrogenolysis and water elimination reactions which lead to monofunctional by-products. An example is shown in Figure 1.

Both batch reactors (autoclaves) and continuous fixed-bed reactors are suitable for alcohol amination. High pressure in the range 50–150 bar is necessary only for reactions with ammonia. The usual temperature is ca 200 °C, but achieving good selectivity for unsaturated amines, nitriles, or heteroaromatic compounds requires 300–400 °C. Solvents other than ammonia are rarely applied.

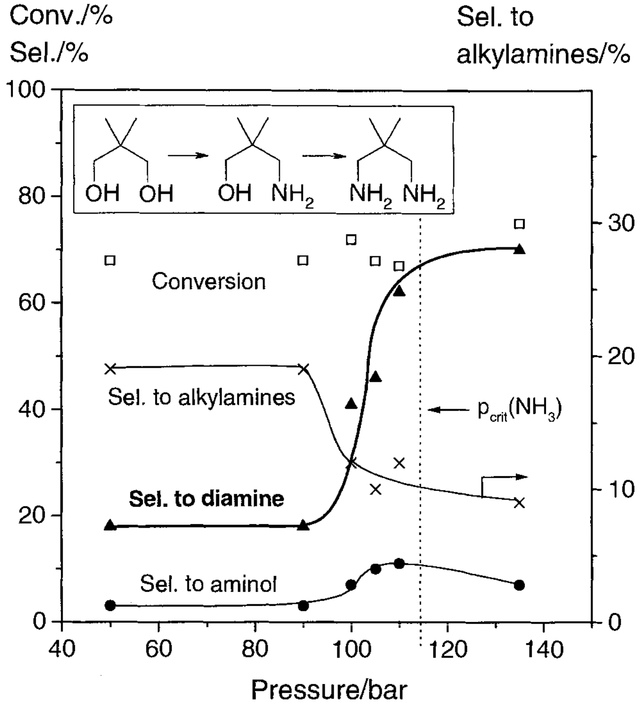
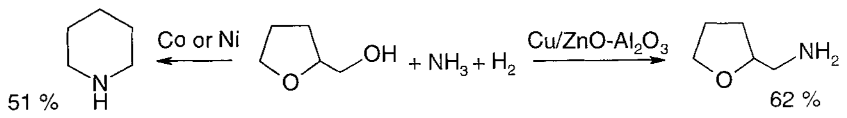


Figure 1. Effect of total pressure on the conversion of 2,2-dimethyl-1,3-propanediol (□), and the selectivity for 2,2-dimethyl-3-amino-1-propanol (●), 2,2-dimethyl-1,3-diaminopropane (▲) and alkylamine by-products (×). The dashed line indicates the supercritical pressure of ammonia [12].

6.1.4 Synthesis of Aliphatic and Aromatic Amines

Numerous examples of the successful use of metal catalysts for the transformation of alcohols to amines can be found elsewhere [1,3,4,11,13–15], although most of the original information is available in the patent literature.

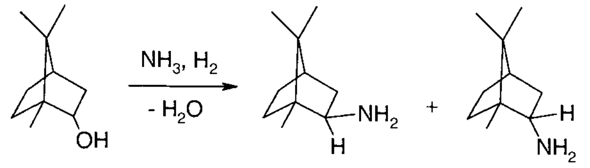
The role of catalyst can be illustrated by the amination of tetrahydrofurfuryl alcohol. Cu/ZnO–Al_2O_3 furnishes mainly the primary amine, whereas piperidine was the major product over Co- and Ni-based catalysts (Scheme 3) [11].



Scheme 3.

Bimetallic Cu/Ni colloids stabilized by Ca and Ba stearates were applied in a simple four-neck round-bottomed flask for the amination of linear and branched oxo-alcohols with dimethylamine [16]. 78–92% yields of tertiary amines were achieved within 3–5 h at 210 °C.

Amination of borneol with ammonia over an Fe-, Cu- and Al_2O_3-containing catalyst afforded bornylamines mainly as *endo* isomers (Scheme 4) [11].



Scheme 4.

Transalkylation of amines with alcohols is usually an undesired side-reaction which reduces amination selectivity. Several metals, e.g. Co, Fe, Ni, or Ru, are good catalysts of interchange between alcohols and amines, including tertiary amines [3]. This reaction can be used for the synthesis of asymmetric tertiary amines. Triethylamine, for example, can be transalkylated with dodecanol over a Ni–Cr alloy catalyst, at 250 °C and 15 bar, to form dodecyldimethylamine in 96 % yield.

Amination of phenols with ammonia is a simple route to aromatic amines. Transformation of 2,6-dimethylphenol in a continuous fixed-bed reactor at 210 °C over Pd/C yielded 90 % 2,6-dimethylaniline after only 6 s contact time [17]. 2,6-Dimethylcyclohexanone and 2,6-dimethylcyclohexylamine were identified as key intermediates; at low contact times the concentration of the latter reached 25 %. Compared with the performance of other metals, Pd-based catalysts have outstanding activity and selectivity in the amination of phenols [4].

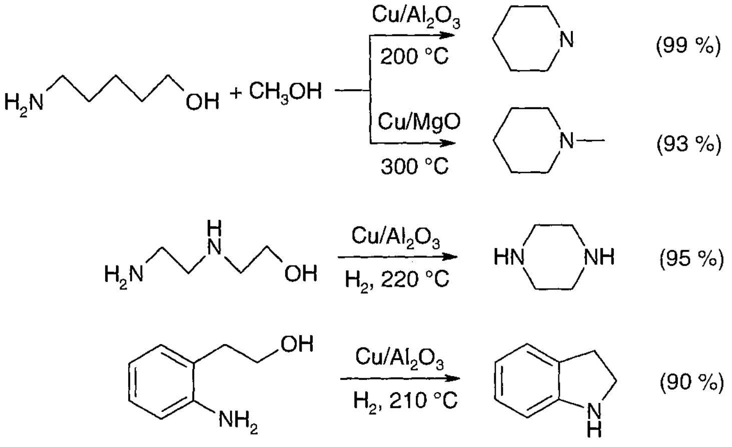
Special multicomponent catalysts were necessary for N-alkylation of sterically hindered anilines with alkoxy alcohols [9]. Doping Cu-chromite with Pd accelerated the hydrogenation of the imine intermediate; this was found to be the rate-limiting step for all the catalysts. Alkali cations (Na^+ and Ba^{2+}) increased the activity whereas acidic centers (e.g. Cr^{6+} and Al^{3+}) favored hydrogenolysis of the ether bond. For N-alkylation with secondary alkoxy alcohols a Pt/SiO_2 catalyst doped with Sn^{2+} and Ca^{2+} ions afforded the best performance. Yields of monoalkylated anilines varied in the range 22–93 % depending on the steric hindrance in the reactants.

When a sufficiently high temperature and a high ammonia/hydrogen ratio are used the selectivity can be shifted from amines to nitriles. For example, reaction of 1-octanol with ammonia over Cu/Al_2O_3 afforded octylamine as the major product below 220 °C, but the yield of octanenitrile was 96–97 % at 260–280 °C [8]. It was proposed that at low temperatures the reaction was kinetically controlled, whereas above 220 °C the thermodynamic equilibrium favored nitrile formation.

When, however, the hydrogen concentration is sufficiently high during amination, the amine or the alcohol reactant can be substituted by the corresponding nitriles, or acids and esters, respectively. The useful intermediate fatty amines were synthesized starting from fatty acids (or esters) and ammonia, and long-chain nitriles instead of amines were used with Cu- and Ni-containing catalysts for the synthesis of N-alkylated amines [15].

6.1.5 Cyclic Amines from Amino Alcohols or Diols

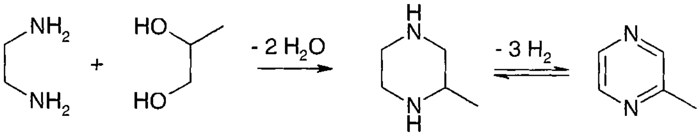
When formation of a five-, six-, or seven-membered ring is possible intramolecular amination is favored on the metal surface. Examples on the cyclization of terminal amino alcohols over supported Cu catalysts are shown in Scheme 5 [18,19]. Cyclization in methanolic solution can afford the N-methylated heterocyclic compound in one step. Reaction conditions, including the temperature, catalyst support, and the presence or absence of hydrogen, had a strong influence on product composition.



Scheme 5.

Similarly, amination of diols with ammonia and hydrogen leads to heterocyclic compounds via the amino alcohol intermediate. A promoted fused Fe catalyst afforded 93 % 2,5-dimethylpyrrolidine from 2,5-hexanediol [11].

A one-step synthesis of the antitubercular drug 2-methylpyrazine has been achieved by cyclization of ethylenediamine with 1,2-propanediol [20]. The role of Pd in the Pd/ZnO–$ZnCr_2O_4$ catalyst is to enhance selectivity by accelerating the final dehydrogenation step (Scheme 6). Aromatization is also favored by the unusually high temperature (350–400 °C). Despite the complexity of the reaction (ca 30 different products are detected) 90 % selectivity at 80 % conversion could be achieved after optimization of the key reaction parameters.



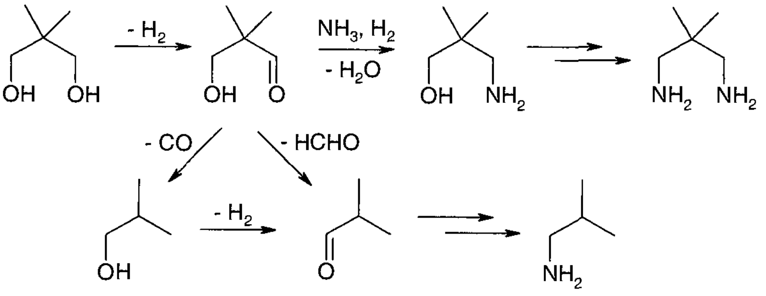
Scheme 6.

6.1.6 Amination of Di- and Polyhydroxy Compounds to Acyclic Amines

Amination of dihydroxy compounds with ammonia to the corresponding primary diamines is considerably more difficult than transformation to cyclic amines. The excellent yields achieved in the synthesis of cyclic amines (see, e. g., Scheme 5) are attributed to the relative stability of the product. In contrast, primary diamines are much more reactive than ammonia and the presence of two functional groups in the reactant, intermediates, and products affords new possibilities for side-reactions.

There are few reports of successful one-step synthesis of primary diamines, and the examples are limited to amines with a special structure. Amination of 1,4-cyclohexanediol in supercritical ammonia (135 bar) over a Co–Fe catalyst afforded 67 % 1,4-diaminocyclohexane [21]. Excess ammonia, as both supercritical solvent and reactant, and short contact time in the continuous fixed-bed reactor favored the desired reactions. In the best example the cumulative selectivity for the diamine and the intermediate amino alcohol was 97 % at 76 % conversion. Recycling of the unreacted diol and amino alcohol can provide an alternative to the current process, the hydrogenation of *para*-phenylenediamine. The high selectivity was because of the rigid structure and the relative positions of OH functionality in the substrate. For comparison, amination of 1,4-butanediol under similar conditions yielded pyrrolidine as the major product; 1,4-diaminobutane was barely detectable. When 1,3-cyclohexanediol was aminated with the same catalyst in the continuous system, the yield of 1,3-diaminocyclohexane dropped below 5 %, mainly because elimination of water led to undesired monofunctional products via *α,β*-unsaturated alcohol, ketone, and/or amine intermediates [22].

The importance of these side-reactions was corroborated by results from the Ni-catalyzed amination of 1,3-propanediols differently substituted at the C2-position [23]. Transformation of 2,2′-dimethyl-1,3-propanediol yielded the corresponding diamine (70 %) and the intermediate amino alcohol (7 %) with 75 % conversion (Figure 2). Temperatures above 210 °C were detrimental to diamine selectivity because of *iso*-butylamine formation by *retro*-aldol or *retro*-formylation reactions (Scheme 7). In the other two substrates, which have an H atom in C2 position, direct elimination of water to form a reactive allylic alcohol (or *α,β*-unsaturated ketone or amine) was the major side-reaction which reduced selectivity.



Scheme 7.

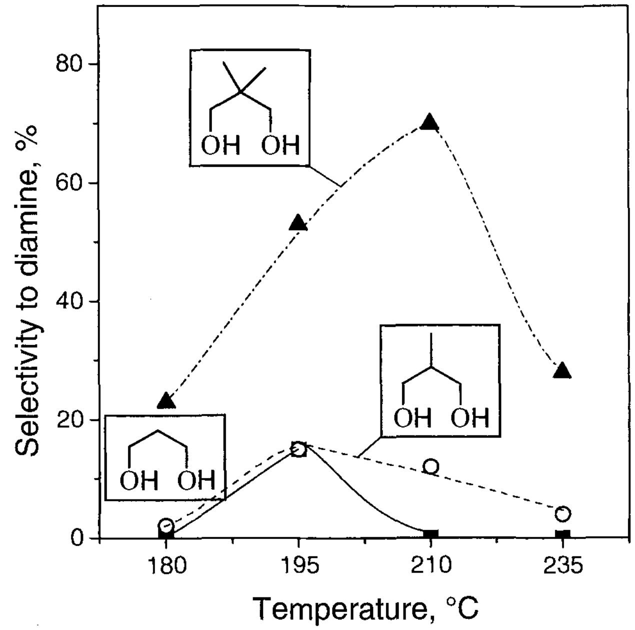
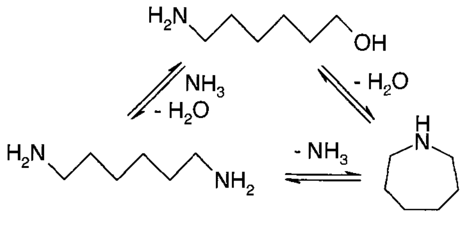


Figure 2. Influence of reactant structure on the amination of different 1,3-propanediols over Ni/SiO_2 at 135 bar [23].

Synthesis of 1,6-diaminohexane from the corresponding diol and ammonia is complicated by cyclization either via the amino alcohol intermediate or by disproportionation of the diamine (Scheme 8) [24]. The best selectivity was achieved with Raney Ni in dioxane – 67 % for the diamine and 33 % for hexamethyleneimine at 58 % conversion. The selectivity for 1,6-diaminohexane could be increased to nearly 100 % by partial recycling of the cyclic imine, i. e. no additional imine was formed in the equilibrium reaction.



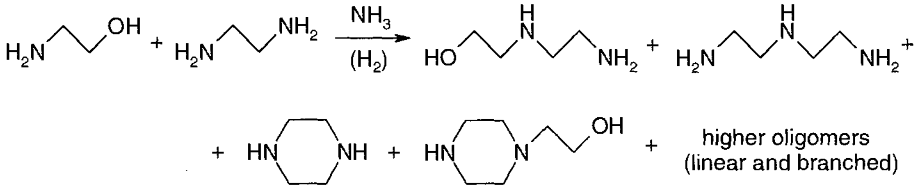
Scheme 8.

Conversion of dihydroxy compounds to diamines requires the repetition of all reaction steps (dehydrogenation, addition, elimination, hydrogenation). Selectivity is much higher when diols are transferred only to amino alcohols or amino alcohols to diamines. This difference is exemplified by the reaction of 1,6-hexanediol with dimethylamine over Cu/Al_2O_3 [25]. Over 90 % selectivity for the intermediate *N,N*-dimethyl-6-amino-1-hexanol was achieved at 180 °C in a continuous fixed-bed reactor. To complete the amination of the second OH group the reactor temperature had to be raised to 230 °C and the highest selectivity for diamine was only 65 %.

Amination of diols with primary and secondary hydroxyl groups showed that the reactivity difference is sufficiently high for selective transformation of the secondary OH group. Under relatively mild conditions reaction with ammonia leads to amino-1-alkanols as the major product. Amination of 1,2-butanediol at 180 °C afforded 93 % selectivity for 2-amino-1-butanol over Co/ThO_2, and Ni/Fe_2O_3 and Ni/La_2O_3 catalysts also afforded selectivity > 90 % [26]. This high selectivity can be explained by the easy formation of the α-hydroxyketone intermediate, compared with the thermodynamically less favored generation of α-hydroxyaldehyde.

Transformation of different polyoxyalkylene diols and triols with ammonia to the corresponding primary amines is of great practical importance. The results have been disclosed almost exclusively in the patent literature; a summary can be found in a previous review [26]. The catalyst of choice is Raney Ni or supported Ni, modified with selectivity and stability promoters such as Fe, Co, Cr, or Mo. The use of a non-porous or mesoporous support is essential to enable access of the bulky reactants to the active sites. Scientific evaluation of these processes is, unfortunately, difficult on the basis of the information available. At best, the conversion is estimated from the amount of water formed and the ratio of primary to secondary amines is determined. On the basis of these data the yields of primary amines are excellent, reaching 85–90 %. It seems that selectivity is barely affected by the conversion, in contrast with general observation in the amination of short-chain alcohols and diols [3,4,14].

Polyalkylene polyamines are typical by-products in the amination of dihydroxy compounds. Some of these oligomers, e. g. diethylenetriamine and triethylenetetramine, are valuable compounds; they are produced industrially from ethanolamine (sometimes directly from ethylene oxide) and ammonia or a mixture of ammonia and ethylenediamine. Over a Ni–Re boride catalyst the selectivity for diethylenetriamine was ca 25 %, almost independent of the conversion [27]. Higher temperatures favored the formation of worthless cyclic products, mainly piperazine and its N-alkylated derivatives (Scheme 9). Recycling the cyclic by-products can minimize their formation and the higher oligomers can be decomposed to useful dimers and trimers [26].



Scheme 9.

Reaction of dihydroxyacetone with ammonia and hydrogen is a good illustration of the different reactivities of hydroxyl and carbonyl groups during amination over metal catalysts. When the reaction is performed at a relatively mild temperature (< 100 °C, 100 bar) in liquid ammonia, Raney Ni affords 2-amino-1,3-propanediol in 99 % yield [28]. Under these conditions activation of hydroxyl groups is negligible. Similarly, the carbonyl group of an aldose or ketose reacts with ammonia and hydrogen to form polyhydroxyamines, e. g. glucamine or isomaltamine from glucose or palatinose, respectively [29]. At ca 50 °C formation of fragmentation products, e. g. ethanolamine and ethylenediamine, is minimal and selectivities up to 90 % have been achieved with Ni catalysts.

References

[1] Heilen, G., Mercker, H. J., Frank, D., Reck, R. A. and Jäckh, R., in: Ullmann's Encyclopedia of Industrial Chemistry, Vol. A2, ed. W. Gerhartz, VCH, Weinheim (1985) p. 1.

[2] Baiker, A. and Kijenski, J., *Catal. Rev. Sci. Eng.* **27,** 653 (1985).

[3] Roundhill, D. M., *Chem. Rev.* **92,** 1 (1992).

[4] Mallat, T. and Baiker, A., in: Handbook of Heterogeneous Catalysis, Vol. 5, eds. G. Ertl, H. Knözinger and J. Weitkamp, Wiley-VCH, Weinheim (1997) p. 2334.

[5] van Bekkum, H. and Kouwenhoven, H. W., *Stud. Surf. Sci. Catal.* **41,** 45 (1988).

[6] Hölderich, W. F., *Stud. Surf. Sci. Catal.* **75,** 127 (1993).

[7] Downing, R. S., Kunkeler, P. J. and van Bekkum, H., *Catal. Today* **37,** 121 (1997).

[8] Card, R. J. and Schmitt, J. L., *J. Org. Chem.* **46,** 754 (1981).

[9] Rusek, M., in: Proceedings 9th International Congress on Catalysis, Vol. 3, eds. M. J. Philips and M. Ternan, Chem. Inst. Canada, Ottawa (1988) p. 1138.

[10] Fischer, A., Maciejewski, M., Bürgi, T., Mallat, T. and Baiker, A., *J. Catal.* **183,** 373 (1999).

[11] Tarasevich, V. A. and Kozlov, N. G., *Russian Chem. Rev.* **68,** 55 (1999).

[12] Fischer, A., Mallat, T. and Baiker, A., *Angew. Chem. Int. Ed.* **38,** 351 (1999).

[13] Herman, R. G., in: Catalytic Conversions of Synthesis Gas and Alcohols to Chemicals, ed. R. G. Herman, Plenum, New York (1984) p. 433.

[14] Baiker, A., in: Catalysis of Organic Reactions, eds. J. R. Kosak and T. A. Johnson, M. Dekker, New York (1994) p. 91.

[15] Barrault, J. and Pouilloux, Y., *Catal. Today* **37,** 137 (1997).

[16] Kimura, H. and Taniguchi, H., *Catal. Lett.* **40,** 123 (1996).

[17] Semikolenov, V. A., Boldyreva, M. E., Shmidt, Y. V. and Stepanov, A. G., *J. Mol. Catal.* **55,** 415 (1989).

[18] Hammerschmidt, W., Baiker, A., Wokaun, A. and Fluhr, W., *Appl. Catal.* **20,** 305 (1986).

[19] Kijenski, J., Niedzielski, P. J. and Baiker, A., *Appl. Catal.* **53,** 107 (1989).

[20] Forni, L. and Nestori, S., *Stud. Surf. Sci. Catal.* **41,** 291 (1988).

[21] Fischer, A., Mallat, T. and Baiker, A., *J. Catal.* **182,** 289 (1999).

[22] Jenzer, G., Mallat, T. and Baiker, A., *Catal. Lett* **61,** 111 (1999).

[23] Fischer, A., Mallat, T. and Baiker, A., *J. Mol. Catal. A*, **149**, 197 (1999).

[24] Horlenko, T. and Tatum, H. W., *US Patent* 3,215,742 (1965).

[25] Vultier, R., Baiker, A. and Wokaun, A., *Appl. Catal.* **30,** 167 (1987).

[26] Fischer, A., Mallat, T. and Baiker, A., *Catal. Today* **37,** 167 (1997).

[27] Burgess, L. M., Gibson, C. A. and Schreck, D. J., *US Patent* 5196588 (1993).

[28] Felder, E., Römer, M., Bardonner, H., Härtner, H. and Fruhstorfer, W., *DE Patent* 3609978 (1987).

[29] Kunz, M., in: Carbohydrates as Organic Raw Materials, ed. F. W. Lichtenthaler, VCH, Weinheim, (1991) p.134.

6.2 Alkylation of Carbohydrates

A. Corma, S. Iborra

6.2.1 Introduction

Alkyl glycosides are compounds formed by the reaction of a sugar with an aliphatic alcohol containing at least four carbon atoms. Because their structure consists of a hydrophilic part (the sugar) and a hydrophobic part (the aliphatic alcohol) they have surfactant properties [1–3]. Any type of sugar can be used as the polar counterpart: glucose, fructose, mannose, xylose, and disaccharides such as lactose, cellobiose, and maltose are interesting candidates. It is possible to expand further the possibilities of these compounds by introducing several units of the same sugar, which is repeated in the hydrophilic part, by performing self-condensation of the sugar. In this reaction the final compound will be an alkyl polyglycoside. Aliphatic alcohols of different chain length can be used for the hydrophobic part, depending on the desired ratio of hydrophilicity to hydrophobicity, the so-called hydrophilic–hydrophobic balance (*HLB*). *HLB* is defined as 20 × the molecular weight of the hydrophilic part/total molecular weight.

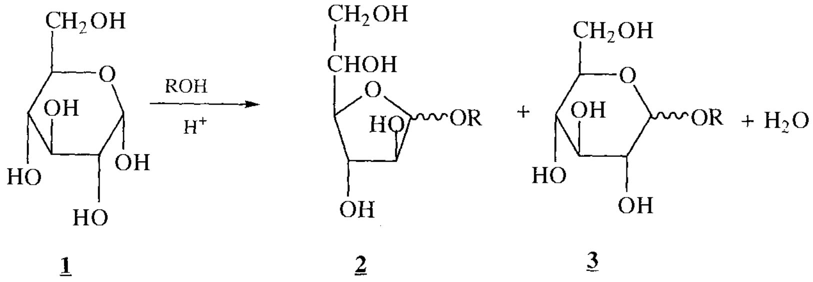
Alkyl glycosides with *HLB* between 13 and 15 are suitable as surfactants; if the value is between 7 and 9 or 1.5 and 3 they are of interest because of their wetting or antifoam properties, respectively. Because alkyl glycosides are obtained from renewable raw materials and are highly biodegradable (their biodegradability is higher than that of alkylbenzene surfactants) they are of commercial and ecological interest.

The first part of this section will present the different possible reactions enabling the formation of alkyl glucosides. This will be followed by discussion of the different types of catalyst used for the synthesis, with special emphasis on solid catalysts.

6.2.2 Synthetic Routes

6.2.2.1 Fischer Synthesis

In 1893 Fischer realized that in the presence of HCl glucose and ethanol react to give ethyl D-glucoside [4], by an acetalization reaction named glucosidation. This reaction produces a mixture of alkyl D-glucofuranosides (**2**) and alkyl D-glucopyranosides (**3**) (α and β isomers) (Scheme 1). It seems that the furanosides are the primary products (or formed with greater initial selectivity) and these then isomerize to give the pyranosides.



Scheme 1.

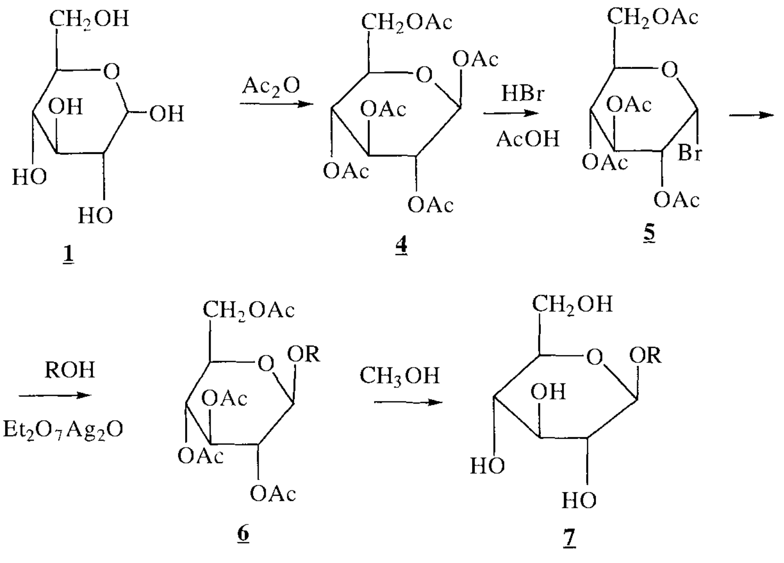
This means that the ratio of furanosides to pyranosides obtained will depend on the conversion–contact time. If reaction of the glucosides is taken to the thermodynamic equilibrium the pyranoside to furanoside ratio is ca 95:5 and the molar ratio of *α/β* is 65:35. The thermodynamic composition of the isomers varies from one monosaccharide to another [5]. A side-reaction is the oligopolymerization of the sugar with formation of alkyl polyglycosides. An average polymerization degree is defined (*APG*) that influences the final hydrophilic–hydrophobic properties [6].

The formation of oligoglucosides seems to be influenced by the low solubility of the sugar in the long-chain fatty alcohol. To solve this problem, the reaction is performed in two steps. In the first step the sugar is reacted with a short-chain alcohol (1-butanol) forming the corresponding butyl glycoside which is subsequently reacted with an alcohol with a longer chain while the shorter-chain alcohol formed is removed from the reaction medium by evaporation. During the transglycosylation, oligomers can still be formed when the ratio of alcohol to butyl glycoside is too low [6,7].

With the objective of reducing the formation of oligoglucosides and also to control the stereoselectivity, Koenigs and Knorr [8] developed another route which involves protection of the hydroxyls in the sugar [9–11].

6.2.2.2 Koenigs–Knorr Route

In this process, the hydroxyl groups of the sugar (**1**) are protected by a peracetylation (product **4**, Scheme 2) then bromination of the anomeric position in an acetic acid solution saturated with HBr at room temperature, giving the *α*-bromide anomer (**5**) in ca 80 % yield. The bromide is reacted with the aliphatic alcohol in a solution of acetic anhydride in the presence of silver salts. Substitution of the bromide group by the alkoxy group takes place with an inversion of configuration yielding a peracetylated alkyl *β*-D-glucopyranoside (**6**). The starting OH groups are then restored by hydrolysis of the esters yielding the alkyl *β*-D-glucopyranoside (**7**).



Scheme 2.

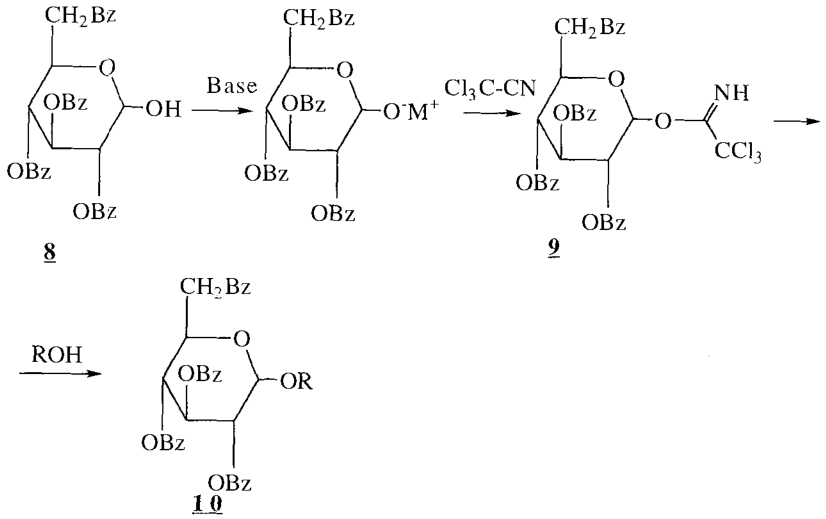
This synthesis is very stereoselective with less than 5 % of the α anomer in the alkyl D-glucoside finally produced. Unfortunately, because of the steps needed and the selectivity in each step the final yield is below 50 %, irrespective of the aliphatic alcohol used [8].

6.2.2.3 Direct Alkylation

Schmidt et al. [12] achieved direct alkylation of the anomeric position of a sugar by performing the reaction in basic media. Then, in the presence of NaH, D-glucose containing OH protecting groups is reacted with an alkylating agent such as the didecyl sulfate $(C_{10}H_{21})_2SO_4$. Owing to its low solubility, glucose is dissolved in *N,N'*-dimethylpropylene urea (DMPU). Yields of decyl D-glucopyranoside close to 60 % are obtained with an α/β ratio of 0.5.

6.2.2.4 Reaction with Trichloroacetamide

This synthetic route entails introduction of a trichloroacetamide group into a protected glucose (**8**) (Scheme 3); which is exchanged by an alkyl chain [13,14].



Bz = benzyl group

Scheme 3.

This procedure enables direction of the reaction toward the formation of either the *α* or *β* anomer. Control is achieved during attachment of the trichloroacetimidate group to the anomeric position of the sugar. If the reaction is performed in the presence of NaH, 96 % of the trichloroacetimidated product (**9**) is obtained with an *α*/*β* ratio of 96:4. In the presence of Na_2CO_3, 80 % of the product is obtained with an *α*/*β* ratio of 25:75. Substitution of the trichloroacetimidate by the alkyl group occurs with inversion of the configuration.

This process, although stereoselective, involves many steps including neutralization, filtration, and separation that strongly reduce its potential commercial interest.

6.2.3 Catalysts for the Synthesis of Alkylglycosides

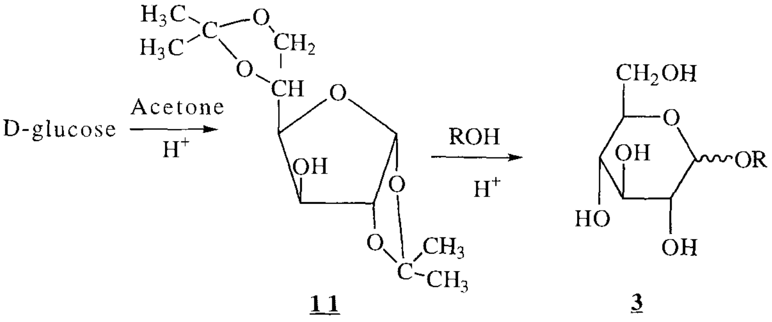
6.2.3.1 Homogeneous Catalysts

The Fischer glycosylation involves the use of acids: mineral acids such as HCl, HF, and H_2SO_4 have been applied successfully [15–23]. *p*-Toluenesulfonic acid can also be used. The use of homogeneous acids results in the need for neutralization and washing steps, and the inconvenience of possible corrosions in the unit [24,25]. Solid acids would be attractive, and an intermediate step has been the use of heteropolyacids as catalysts for the preparing alkyl glycosides [26].

6.2.3.2 Heterogeneous Catalysts

Sulfonic Resins as Solid-acid catalysts

Sulfonic resins have been used for a long time to catalyze the formation of alkyl glycosides [27–30]. In a recent study Van Bekkum et al. [31] used an acid macroporous sulfonic resin (Dowex MSC-1). The D-glucose is treated with acetone (Scheme 4) and the protected glucose (**11**) can then react with an aliphatic alcohol in the presence of the resin to yield the alkyl D-glucosides. The isopropylidene protecting groups increase the solubility of the reactant in the alcohol and consequently reduce secondary oligomerization reactions. Use of 1-butanol as reactant and working at 353 K with a ratio of D-glucose/catalyst of 1.7 and a molar ratio of 1-butanol/D-glucose of 27.5 results in 84 % yield of butyl D-glucopyranosides. The alkylation could also be performed with octanol, decanol, dodecanol, and hexadecanol, but the reaction rate decreases with increasing chain length. The water formed during the reaction hydrolyses the protecting groups forming acetone, which is removed by evaporation. The excess alcohol present enables exchange of the acetal to give the alkyl D-glucoside.



Scheme 4.

When unprotected glucose [32], 1-octanol (1-octanol/D-glucose molar ratio 16 and D-glucose/catalyst weight ratio 2.6), and a sulfonic resin (now Lewatit SPC 108) were reacted at 363 K 98 % glucose conversion was achieved, with 64 % selectivity for octyl D-glucopyranoside. A kinetic study showed that although the two anomers were initially formed at almost identical rates, at high levels of conversion the ratio of α to β was close to the thermodynamic equilibrium ($\alpha/\beta = 2$); small amounts of octyl D-glucofuranosides were also formed. Unfortunately the macroporous acid resins also produce, in the same way as acid catalysts in the homogeneous phase, large amounts of oligoglucosides (ca 30 %).

Anomeric alkylation of D-fructose in 1-octanol has been performed by use of a sulfonic acid resin–Bayer K 2461. Conversion to octyl fructosides was only 14.2 % after 1 h reaction at 548 K [33].

Clays as Catalysts

Laminar clays and, more specifically, montmorillonites have been widely used as solid-acid catalysts for Friedel–Crafts alkylation and acylation reactions [34–36]. Their acidity can be Brønsted acidity generated by isomorphous substitution of Si by Al, or any other trivalent atom, in the tetrahedral sheet, or Lewis acidity originating from trivalent or even divalent cations leached by acid treatment and remaining in the interlayer space as an exchange cation. Coordinated water can, moreover, generate further Brønsted acidity. Montmorillonites have been used as solid catalysts in the glucosidation of butanol or dodecanol by D-glucose [37]. KSF/O was the most active montmorillonite, enabling operation at relatively low alcohol/glucose molar ratios ($\approx$ 10) and with low amounts of catalyst (5 % *w/w* relative to glucose). At 386 K D-glucose is converted in 88 % yield with 89 % selectivity for butyl D-glucosides. The K10 montmorillonite was much less active, affording only 37 % conversion under the same reaction conditions. Remarkably low yields of oligoglucosides were obtained when butanol and glucose were reacted on the montmorillonite catalysts. When the same KSF/O catalyst is used with dodecanol, low yields of dodecyl D-glucosides are obtained (16 %) and larger yields of oligoglucosides (31 %). This is because of the lower solubility of glucose in dodecanol than in butanol and it was thought that selectivity could be improved by use of ultrasounds. Under such conditions, however, only 15 % dodecyl D-glucoside was formed, with 75 % oligoglucosides.

Dodecyl D-fructosides have been prepared by the direct Fischer reaction between D-fructose and dodecanol (alcohol/sugar molar ratio 16) with an acid clay (Tonsil) as catalyst (100 % *w/w* on fructose). The conversion of D-fructose into dodecyl D-fructosides was 45 % after 3.5 h reaction [38].

Supported Enzymes

β-Hydrolase has been tested as a glycosidation catalyst [39,40]. These enzymes hydrolyze the β-glycosidic bonds and the reverse alkylation reaction produces alkyl β-D-glucopyranoside only. The reaction is conducted in a biphasic medium: 90 % alcohol in water. The active form of the enzyme and the D-glucose are in the aqueous phase whereas the aliphatic alcohol is immiscible with H_2O and forms another phase. The glycosylation reaction occurs at the interface or in the aqueous phase if the low miscibility of the alcohol allows this. When the alkyl D-glucoside is formed it migrates to the organic phase, thus shifting the equilibrium. As might be expected, this system works better with short-chain alcohols (1-butanol). When the aliphatic chain becomes longer, the hydrophobicity of the alcohol increases and reaction at the interphase is slower: the concentration of the alcohol in the aqueous phase is too low for any reaction to occur there. As a consequence the reaction rate drops by a factor of four when passing from butanol to octanol and is almost zero for alcohols with more than eight carbon atoms [41]. The use of cosolvents such as *tert*-butanol or acetonitrile did not improve the results [42]: this procedure furnishes the alkyl β-D-glucopyranoside only. The same procedure, but with amylase α-hydrolase as catalyst, gives the α anomer in very low yields [43].

Another route involves the hydrolysis of a mixture of the α and β anomers by one β-hydrolase [44,45]. An interesting procedure is based in the hydrolysis of starch with an amylase α-hydrolase to give maltodextrin which reacts with an α-transglycoside of either *Aspergillus niger* or *Talaromyces duponti* in the presence of an aliphatic alcohol [46].

Irrespective of the enzymatic procedure used, yields are too low ($\leq 60\,\%$). This, and denaturing of the enzymes, limit the practical use of the enzymatic route.

Zeolites as Catalysts

Zeolites are aluminosilicates with a microporous network of channels and cavities. The dimensions of such channels and cavities are in the range 3–14 Å, which enables diffusion of reactants and products to and from catalytically active sites. Acid sites can be introduced by compensating the negative lattice charge with protons. Many zeolite molecular sieves with different pore dimensions, topologies, and acidities have been prepared [47].

Acid zeolites can be used to catalyze the synthesis of alkyl D-glucosides. To design successful catalysts for the above reaction large-pore 12-member ring (MR) zeolites (access 7–7.5 Å) are preferred. It has been reported [48] that glucosidation with 1-butanol and medium pore 10MR zeolites, e. g. ZSM-5 or even the unidirectional 12MR mordenite, mainly occurs on the external surface and consequently conversion is low. Reasonable activity and selectivity for the synthesis of butyl D-glucosides are, on the other hand, obtained with 12 MR tridirectional zeolites such as Beta and Y (Table 1).

During the reaction four butyl glucosides are formed (Scheme 5): the butyl glucofuranosides (α and β) and the butyl glucopyranosides (α and β). Furanosides (**12**) are the kinetic products, the concentration of which passes through a maximum and then decreases with time to give the thermodynamically more stable butyl D-glucopyranosides (**13**) [49] (Figure 1).

Table 1. Initial rates (ro) of disappearance of D-glucose per Brønsted acid site (Ba) and yields of the α,β-butyl furanoside (**12**) and α,β-butyl pyranoside (**13**).

Catalyst	ro/Ba[a] (mol h^{-1} (mmol Py)$^{-1}$) × 10^2	Yield[b] (%) **12**	**13**
MCM-22	2.03	52	14
HY-100	4.49	51	21
H-ZSM-5	2.31	48	9
H-Beta	2.43	33	65
H-Mordenite	0.85	37	14

[a] Brønsted acidity (mmol pyridine (g catalyst)$^{-1}$) of the different zeolites was measured at 623 K and calculated by use of the extinction coefficients given in Ref. 64.

[b] Conditions: 4 h reaction at 383 K, 1-butanol/D-glucose molar ratio 40 and 1.5 % *w/w* catalyst.

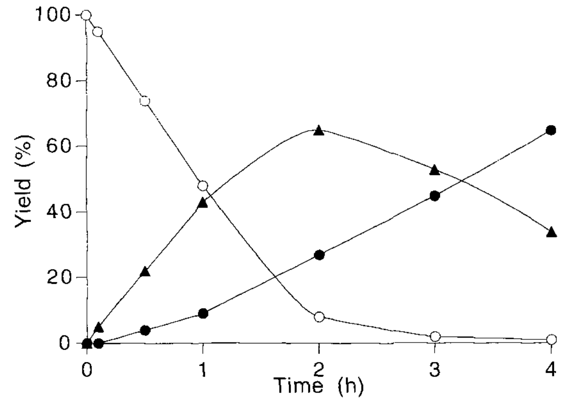


Figure 1. Time conversion plot of D-glucose (**1**, ○) to butyl-D-glucofuranosides (**12**, ▲) and to butyl D-glucopyranosides (**13**, ●) at 383 K in the presence of Beta zeolite.

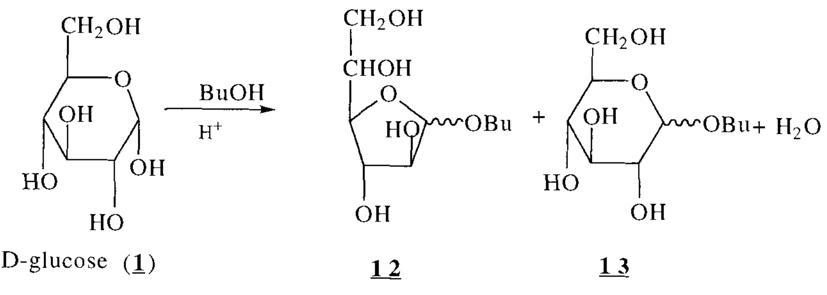
Table 2. Comparison of yield and selectivity for butyl glucoside obtained by use of different 1-butanol/D-glucose (NB/DG) ratios in the presence of H-Beta (Si/Al = 13) and *p*-toluenesulfonic acid (p-TSA) at 393 K.

Catalyst	NB/DG	Catalyst (% *w*/*w*)	Yield (%) **12**	**13**	Other[c]	Selectivity for (**12** + **13**)
H-Beta	10	6	12[a]	77	4	96
H-Beta	5	12	9[a]	78	7	92
p- TSA	5	1	7[b]	74	15	82

[a] Reaction time 2 h.

[b] Reaction time 1 h.

[c] The relative response of oligosaccharides and butyl saccharides to the internal standard was considered to be the same as that to the butyl glucosides.



Scheme 5.

One important fact, inherent in the use of zeolites as acid catalysts for monosaccharide acetalization, is that generation of oligomers is significantly reduced compared with the homogeneous reaction, because the bulkier transition states leading to those products are limited by shape-selective effects (Table 2). As a consequence, the mass balance of the reaction in the presence of acidic zeolites is relatively high ($\approx 90\,\%$) compared with other catalysts such as macroporous ion-exchange resins [32] or *p*-toluenesulfonic acid [48], for which the mass balances are 70 and 80 %, respectively. This behavior has also been observed by other authors in glucosidation with 1-butanol in the presence of HY zeolites [50].

For reactions occurring in the liquid phase on zeolite catalysts and involving reactants and/or products with molecular dimensions close to the pore diameter, the overall reactivity of the catalyst can be strongly controlled by diffusional parameters, and it is clear that if maximum reaction rate is required the influence of diffusion through the micropores must be reduced. For a given zeolite structure this can be achieved by reducing the length of the micropores, i. e. by reducing crystallite size. Study of the influence of the crystal size of a beta zeolite on the acetalization of glucose with 1-butanol has shown that the effectiveness is maximum for samples with a crystallite size $\leq$ 0.35 Å (Table 3) [51]. It has, on the other hand, been found that crystallite size has an important influence on product distribution, such that the ratio of butyl D-furanoside (**12**) to butyl D-pyranoside (**13**) is almost unchanged for samples up to 0.35 μm and then increases when the crystallite size of the sample is increased (Table 3). It thus seems that formation of butyl D-pyranoside is more affected by diffusion than formation of the furanoside. A computer docking study showed that this effect could be a result either of lower diffusivity of the somewhat larger six-membered ring pyranoside compared with the furanoside or, bearing in mind the most probable intermediates in the ring expansion [49–54], geometrical restriction of the isomerization process inside 12-membered ring channels of the beta zeolite. If the furanose–pyranose isomerization were an outer surface reaction the larger outer surface of the small crystals would explain the results.

The influence of the framework Si/Al ratio of Beta zeolites on the glucosidation of 1-butanol has also been studied [51]. The framework Si/Al ratio is a very important property which determines the activity and selectivity of zeolites used as catalysts. The Si/Al ratio not only defines the number of potential protons, and therefore the number and strength of acid sites, but it also determines the hydrophilic–hydrophobic character of the surface, in other words, the adsorption properties of the zeolite. In the formation of alkyl glucosides one must take into account that a highly hydrophilic reactant (the monosaccharide) and a much more hydrophobic reactant (the alcohol) must diffuse through the pores and become adsorbed

Table 3. Influence of zeolite crystal size on the initial reaction rate (ro) and on product distribution from conversion of 60 % D-glucose.

Catalyst	Crystal size (μm)	ro × 10^4 (mol min^{-1} g^{-1})	Yield (%)[a]		
			12	**13**	**12/13**
Beta-1	0.05	4.9	50	10	5
Beta-2	0.35	5.2	48	12	4
Beta-3	0.60	3.7	55	5	11
Beta-4	0.90	1.8	57	3	19

[a] Conditions: 1-butanol/D-glucose molar ratio 40 and 3 % w/w catalyst at 383 K.

Table 4. The influence of the framework Si/Al ratio of the PS and S series of zeolites on the initial rate (ro) and yields in the reaction of D-glucose with 1-butanol.

Catalyst	Si/Al	ro × 10^4 (mol min $^{-1}$ g^{-1})	Yield (%)[a] 12	13
Beta(PS)-1	52	2.14	54	42
Beta(PS)-2	88	3.48	63	35
Beta(PS)-3	118	3.68	55	42
Beta(PS)-4	123	2.43	66	32
Beta(PS)-5	140	2.13	65	25
Beta(PS)-6	200	1.77	54	10
Beta(PS)-7	260	1.68	60	20
Beta(S)-8	12	3.17	48	50
Beta(S)-9	29	7.36	70	30
Beta(S)-10	40	4.16	52	48
Beta(S)-11	52	3.68	65	32
Beta(S)-12	75	3.50	63	30
Beta(S)-13	97	3.17	72	17
Beta(S)-14	184	1.84	65	13

[a] Conditions: 1-butanol/D-glucose molar ratio 40, 3 % *w/w* catalyst, 4 h reaction time at 383 K.

by the zeolite. The different polarities of the reactants make the adsorption properties of the catalyst a property of fundamental importance.

The influence of the hydrophobicity of the catalyst on the alkylation of D-glucose has been studied for two series of Beta zeolites with different hydrophobic character. One series (PS series) contain a large number of external and internal silanol groups, because a large number of crystal defects are generated during the synthesis, dealumination, and calcination processes. The presence of these silanol groups renders the samples hydrophilic and very high zeolite Si/Al ratios are needed in to induce hydrophobicity. The Beta zeolites of the second series (S series) were synthesized in fluorinated media [55] and were prepared free from connectivity defects. Results from glucosidation of 1-butanol using both series are summarized in Table 4. The optimum Si/Al ratio of the Beta zeolite matches two key properties, the number of active sites and the adsorption characteristics. The optimum activity can be reached at lower Si/Al ratios when the catalyst contains few Si–O–Si connectivity defects, and thus high hydrophobicity. In the more hydrophilic zeolites (PS series) D-glucose will be adsorbed preferentially and the reaction will be limited by the diffusion and adsorption of the alcohol; the maximum activity is obtained for much higher framework Si/Al ratio (Si/Al = 118). Deactivation is also strongly influenced by the adsorption properties of the catalyst, the rate being lower the higher the hydrophobicity.

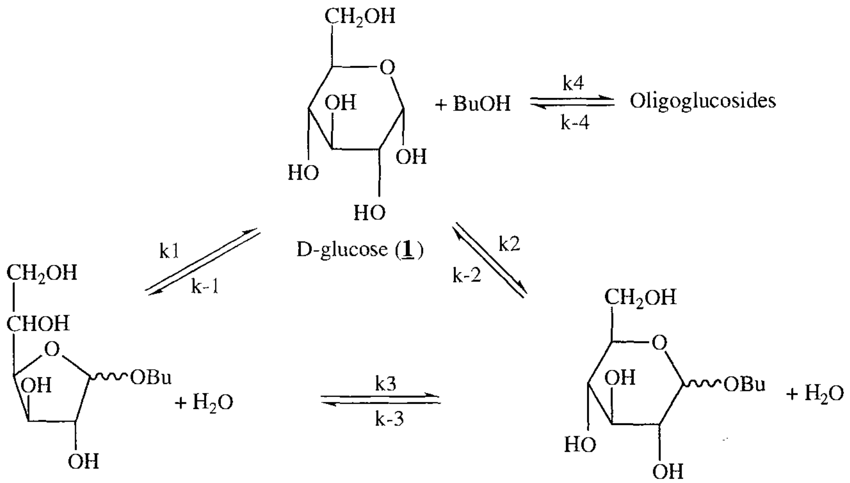
Similar results were obtained by Chapat et al. [56] for the glucosidation of 1-butanol over a series of dealuminated HY zeolites with different framework Si/Al ratios (2.5 to 100) under similar reaction conditions. From Table 5 it can be seen that for dealuminated HY zeolites the activity increases up to an Si/Al ratio of 15, and then decreases significantly.

Table 5. Influence of the Si/Al ratio on the initial rate (ro) of disappearance of D-glucose.

Zeolite (Si/Al ratio)	ro × 10^5 (mol s^{-1})^a	roAnaCin × 10^5 (mol s^{-1})^b
HY(2.5)	0.020	0.020
HY(5.7)	1.080	1.290
HY(15)	1.540	1.780
HY(21)	0.690	0.730
HY(25.5)	0.525	0.560
HY(29)	0.420	0.530
HY(40)	0.270	0.300
HY(100)	0.110	0.130

^{a}Calculation from the slope of the tangent at the origin.
^{b}Calculation by use of kinetic AnaCin modelling software.

The same authors [56] performed a systematic study of the acetalization of glucose with 1-butanol in the presence of HY zeolite and proposed a kinetic scheme for the glycosylation reaction involving both consecutive and competitive steps. Butyl D-glucofuranosides (**12**) and butyl D-glucopyranosides (**13**) are primary products and butyl D-glucofuranosides are then converted quantitatively into their pyranoside form (Scheme 6).



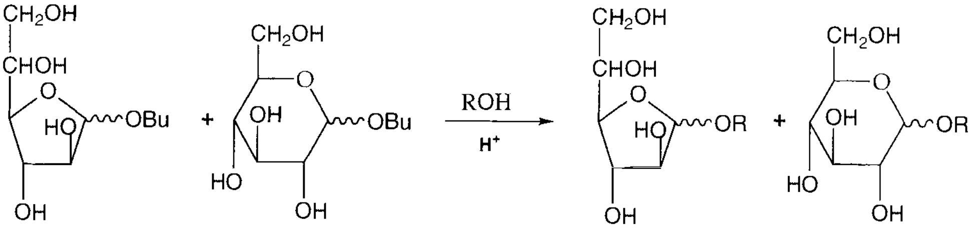
Butyl D-glucofuranosides (12)

Butyl D-glucopyranosides (13)

Scheme 6.

These authors also found that the use of microporous catalysts significantly increases stereoselectivity for butyl β-D-glucopyranosides [50,56]. For instance, the β/α ratio of pyranosides is ca 1.5 for zeolite HY (Si/Al = 15) and ca 0.7 for Beta (Si/Al 12.5), whereas for *p*-toluenesulfonic acid the β/α ratio is intermediate, ca 1. At nearly complete conversion of glucose, however, a thermodynamic ratio β/α of 0.5 is obtained. The kinetic reaction scheme proposed by the authors, involving both consecutive and competitive steps, accounts for the higher *β/α* ratio observed with HY in terms of stereoelectronic effects associated with the shape-selective properties of the catalysts in the transition states.

The preparation of long-chain alkyl glucosides has been achieved by means of a transglucosidation reaction between butyl D-glucosides with different alcohols with Beta zeolite as catalyst [57] (Scheme 7). The transglucosidation of a mixture of butyl D-glucosides **12** and **13** (1:9) with *n*-octanol at 393 K and 400 torr, with an alcohol/butyl D-glucoside molar ratio of **12** gave the octyl glucoside isomers, the *α,β*-octyl D-glucofuranoside (**14a**), and the *α,β*-octyl D-glucopyranoside (**15a**) in yields of 10 and 80 %, respectively. In general, ratios of fatty alcohol to butyl D-glucosides of ≥ 4 were found to give a good initial reaction rate which minimized side-reactions.



12 13 14a,b 15a,b

	R
a	$-(CH_2)_7CH_3$
b	$-(CH_2)_{11}CH_3$

Scheme 7.

Study of the evolution of reactants and products with reaction time showed that octyl D-pyranoside (**15a**) is formed by two different routes: isomerization of octyl D-glucofuranoside (**14a**) to the thermodynamically more stable six-membered ring compound and direct transglucosidation of the butyl pyranoside (**13**). The initial rate of disappearance of the butyl D-glucosides is strongly influenced by feed composition such that starting from a mixture rich in butyl D-furanoside (**12**) (70 %) results in a higher total rate of reaction.

When the reaction was conducted in a single pot, i. e. when, after removal by distillation, of remaining 1-butanol, the 1-octanol was added directly to the reaction mixture without changing the catalyst, it was observed that some deactivation of the catalyst occurred during the glucosidation with 1-butanol, and the initial rate of transglucosidation was 25 % lower (Table 6).

The same study was performed using a much more hydrophobic Beta sample as catalyst, and initial deactivation of the catalyst was again observed. After 4 h reaction, however, the same conversion was achieved with fresh and used catalyst. These results shows that the hydrophobic–hydrophilic properties of the catalysts not only have an impact on catalyst activity but also on catalyst deactivation.

Table 6. Results obtained in the two-step process for production of octyl glucosides without and with addition of fresh catalyst during the transglucosidation step.

Catalyst	Initial rate of disappearance of butyl glucosides (mol h^{-1} g^{-1}) × 10^3	Yield (%)[a] **12**	**13**	**14a**	**15a**
Renovated	5.2	0	19	5	76
Same	4	0	33	7	60

[a]Conditions: initial **13/12** butyl glucoside ratio of 9, in the presence of the H-Beta zeolite at 393 K after 4 h reaction.

The direct reaction of a long-chain alcohol with D-glucose was performed using H-Beta zeolite as catalyst. The main problem is the poor solubility of the monosaccharides in long-chain alcohols, with the corresponding negative effect on the reaction rate and on the quality of the final product. For instance, the solubility of D-glucose in 1-octanol at 363 K is quite low (1.6 g L^{-1}) [32]. It is, nevertheless, possible to overcome this limitation by using excess alcohol and adding incremental amounts of glucose. By operating under these conditions, glucosidation of 1-octanol in the presence of Beta zeolite at 393 K resulted in total conversion of D-glucose with yields of 95 % and 4 % of octyl D-glucopyranoside and octyl D-glucofuranoside, respectively, after 5 h [57]. When the direct glucosidation was performed with 1-dodecanol the yield of dodecyl glucosides (**14b** and **15b**) after 7 h was somewhat lower (80 %), but still significantly higher than those obtained by the transglucosidation process.

Mesoporous Aluminosilicates as Catalysts

MCM-41 is an ordered mesoporous aluminosilicate of the M41-S family which can be synthesized with pore dimensions in the range 20–100 Å and with Si/Al ratios between 10 and infinity [58,59]. It has been established that its acid strength is similar to that of amorphous silica–alumina and its acidity is always much weaker than that of zeolites [60].

MCM-41 materials catalyze the glucosidation of 1-butanol resulting in high conversion to butyl D-glucosides with excellent selectivity [61]. The reactions were conducted in presence of 3 % *w/w* of the catalyst at 393 K. A study of the influence of the Si/Al ratio of the catalyst showed that a higher concentration of acid sites does not guarantee a better catalytic performance. Table 7 shows that the MCM-41 sample with the highest Si/Al ratio and therefore with the lowest content of Brønsted acid sites, gives nevertheless the highest activity which could be correlated with the increased hydrophobicity, in agreement with what is observed when using Beta zeolites [51].

A study of the influence of the pore diameter on activity and selectivity showed that for the same Al content the larger the diameter of the pore the more active is the final catalyst (Table 8). The furanoside to pyranoside ratio (**12/13**) also increases when the pore diameter is reduced; this can be related to the lower diffu-

Table 7. Initial rates for disappearance of D-glucose (ro) and yields of butyl D-glucosides obtained in the glucosidation of 1-butanol in presence of MCM-41 with different Si/Al ratios, at 393 K, after 4 h reaction.

Catalyst (Si/Al)	ro $\times$ 10^4 (mol min^{-1} g^{-1})	Yield (%)		Conversion (%)
		12	**13**	
MCM-41(14)	2.7	55	42	97
MCM-41(26)	3.13	61	33	94
MCM-41(50)	3.68	39	59	98

Table 8. Initial rates (ro) for the disappearance of D-glucose and total conversion in the glucosidation of 1-butanol at 393 K after 4 h in the presence of MCM-41 with Si/Al ratio of 50 and different pore diameters.

Pore diameter (nm)	ro $\times$ 10^4 (mol min^{-1} g^{-1})	Conversion (%)	**12/13**[a]
5.3	3.68	98	2.5
4.5	2.30	94	3.6
2.5	1.38	80	6.0

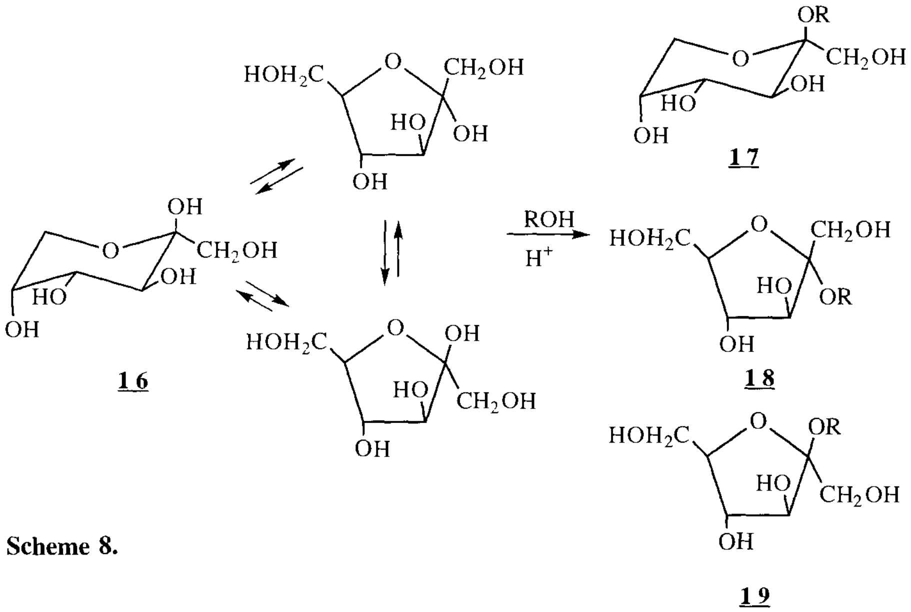
[a] 70 % conversion of glucose.

sivity of the bulkier six-membered ring pyranoside than the five-membered ring furanoside [51].

Finally, the catalyst could be partially regenerated by extraction with methanol then water in a Soxhlet apparatus. That process, however, resulted in loss of crystallinity of the MCM-41. The catalyst could be fully regenerated by calcination in air at 773 K.

De Goede et al. [62] describe a process for the preparation of alkyl glycosides, including di- and oligosaccharides, by reacting an alcohol with a saccharide or a lower alkyl glycoside, with an MCM-41-type material as catalyst. The process is particularly applicable to ketoses, e. g. fructose and sorbose, which are prone to dehydration and other degradation reactions, when treated with conventional strong acid catalysts such as sulfuric and organic sulfonic acids. The glycosylation of 1-butanol with fructose was performed with a 1-butanol/fructose molar ratio of 65, at reflux temperature, in the presence of a MCM-41 (Si/Al = 60) (10 % *w/w* relative to sugar) and after 24 h the yield of butyl fructosides was 100 %. When the glycosylation was performed with 1-octanol and 1-dodecanol at 353 K, the yields of the corresponding alkyl fructosides were 80 and 40 %, respectively.

Depending on the structure of the saccharide, mixtures of alkyl saccharides are formed in which the sugar adopts the furanose or pyranose form. Thus fructose (**16**) yields three main products, the β-D-fructopyranoside (**17**) and the α- and β-D-fructofuranosides (**18**) and (**19**) (Scheme 8).



Scheme 8.

The furanose/pyranose ratio can be modified by varying the Si/Al ratio in the MCM-41 used, (Table 9).

Disaccharides are generally prone to alcoholysis under strong acid catalysis. However the use of MCM-41 as mild acid catalyst enables the selective preparation of alkylated disaccharides in good yield. For instance, butyl leucroside and butyl isomaltuloside were obtained in yields of 92 and 97 % by treating the corresponding sugar with 1-butanol, under reflux, for 24 h and 2 h, respectively, in the presence of an MCM-41 (10 % *w/w* sugar). The transglycosylation of butyl leucroside with 1-octanol at 353 K yields 60 % octyl leucrosides after 24 h.

Silica–alumina cracking catalysts HA-HPV (high alumina–high pore volume) also efficiently catalyze the alkylation of D-fructose with alcohols without perceptible fructose degradation [38,63] (Table 10). With short-chain alcohols up to 1-butanol excellent conversions are obtained. With fatty alcohols, however, the con-

Table 9. Influence of Si/Al ratio of MCM-41 on furanoside/pyranoside ratio in the transglycosidation of butyl fructosides with 1-dodecanol.

H-MCM-41 Si/Al ratio	Yield (%) of alkyl monosaccharide after 4 h	Furanoside/ pyranoside ratio
15	57	n. d.
30	53	2.8
60	57	3.2
118	55	n. d.
100	57	3.9
∞	0	–

Table 10. Effect of the alcohol chain-length on the synthesis of alkyl fructosides.[a]

Alcohol	Time (h)	Yield (**17–19**)
Methanol	24.0[b]	100
Ethanol	4.5[b]	100
1-butanol	1.8[c]	94
n-octanol	4.0	60
n-decanol	5.7	51
n-dodecanol	4.2	43

[a] Reaction conditions: D-fructose (3 g, 16.7 mmol), HA-HPV catalyst (3 g, activated at 703 K for 24 h), alcohol 0.267 mol, 348 K at 15 torr.

[b] Reaction at reflux temperature in 50 mL alcohol. Removal of water by reflux with zeolite KA.

[c] Reaction at 348 K in 50 mL alcohol; reflux at reduced pressure over zeolite KA.

version of D-fructose into alkyl fructosides never exceeds 60 %, as a consequence of deposition of fructose anhydride on the catalyst. This problem was solved by a recirculation procedure entailing transglycosylation of the butyl fructosides with the fatty alcohol. The catalyst containing the deposition product is then isolated by filtration and treated with 1-butanol, resulting in a reaction mixture containing mainly butyl fructosides and nearly clean catalyst. Repeating this procedure results in essentially quantitative conversion of fructose into long-chain alkyl fructosides. Pure alkyl β-D-fructopyranosides can be separated from the reaction mixture by crystallization.

HA-HPV has also been tested as a solid-acid catalyst for Fischer alkylation with common monosaccharides. This proved possible on several occasions (Table 11).

Table 11. HA-HPV-catalyzed reaction of various monosaccharides with 1-dodecanol[a].

Saccharide	Solubility[b] (M)	Initial rate (% **17–19**)[c]	Reaction time[d] (h)	Conversion (% **17–19**)
Ketohexoses				
D-fructose	0.033	43	4.2	43
L-Sorbose	0.017	14	17	23
Aldopentoses				
D-Ribose	0.247	32	27	60
D-Arabinose	0.026	22	29	63
D-Xylose	0.031	17	46	54
Aldohexoses				
D-Mannose	0.020	3	50	14
D-Galactose	0.004	0.8	50	11
D-Glucose	0.012	< 0.1	50	< 1

[a] For conditions see Table 10.

[b] In *n*-dodecanol at 345 K as measured by GC.

[c] Conversion of **17–19** as measured by GC after 4 h.

[d] Reaction time for maximum conversion to **17–19**.

6.2.4 Conclusions

Microporous and mesoporous aluminosilicates are efficient acid catalysts for the alkylation of saccharides. Large-pore 12 MR tridirectional zeolites such as Y and Beta are reasonably active and selective in the synthesis of alkyl glycosides. The use of zeolites as acid catalysts for this reaction reduces the formation of oligomers as a result of shape-selectivity. As a consequence the mass balance of the reaction is relatively high compared with other catalysts, for example macroporous ion-exchange resins and *p*-toluenesulfonic acid.

The framework Si/Al ratio is an important property which controls activity and selectivity when zeolites are used as catalysts. It determines the number and strength of acid sites and the adsorption properties of the zeolite. Because of the different polarities of the reactants (saccharide and alcohol), there is an optimum zeolite Si/Al ratio that matches two key properties, the number of active sites and the adsorption characteristics. Furthermore, the rate of deactivation decreases as hydrophobicity increases.

Mesoporous aluminosilicates are of special interest as catalysts for the alkylation of ketoses, which are prone to degradation when treated with strong acid catalysts. Although disaccharides are generally subject to alcoholysis under strong acid catalysis, the use of MCM-41 as acid catalyst enables the selective preparation of alkylated disaccharides in good yield.

References

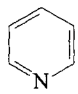
[1] Ruback W and Schmidt in Carbohydrates as Organic Raw Material III, Van Bekkum H, Roper H and Voragen A G J Eds, CRF The Hague, p 231, 1996.
[2] Von Rybinski W and Hill K, Angew Chem Int De 37 (1998) 1328.
[3] Straathof A J J Van Bekkum H and Kieboom A P G, Starch/Stärke 40 (1988) 438.
[4] Fischer E, Ber Dtsch Chem Ges 26 (1893) 2400.
[5] Collins P and Ferier R "Monosaccharides" Wiley, Chichester 1995.
[6] Hill K in "Carbohydrates as Organic Raw materials" II, Descotes G, De VCH, Weinheim p.163, 1993.
[7] Koeltzow D E and Urfer A D, J Am Oil Chem Soc 61 (1984) 1651.
[8] Koenigs W and Knorr E, Ber Dtsch Chem Ges 34 (1901) 956.
[9] Noller C R and Rockwell W C, J Am Chem Soc 60 (1938) 2076.
[10] De Grip W J and Bovee-Geurts P H M, Chem Phys Lip 23 (1979) 321.
[11] Ames G R, Chem Rev 60 (1960) 541.
[12] Schmidt R R, "Modern Methods in Carbohydrate Synthesis–Frontiers in Natural Products Research", p. 20, 1960.
[13] Schmidt R R and Michel J, Tetrahedron Lett 25 (1984) 821.
[14] Schmidt R R, Comprehensive Org Synth 6 (1991) 33.
[15] (a) Karlheinz H, Wenthen and M Koehler H P, US 5480979, 1996. (b) Karlheinz H, Wenthen and M Koehler H P, US 5698684, 1997.
[16] Borsotti M J, Santini C, Nataloni L and Pellizo T, US 5432269, 1995.
[17] Bergeld M J and Seifert J, EP 615974 A1, 1994.
[18] Liiders H, US 4866165, 1989.
[19] Groen J, PTC WO 95/07915, 1995.
[20] McCurry P M and Pickens C E, US 4950743, 1990.
[21] Letton J C, EP 132046 B1, 1988.
[22] Arnandis G, EP 77167 B1, 1985.

[23] Davis J E, EP 132043 B1, 1987.
[24] Wolf G and Wolf H, PTC WO 94/04544, 1994.
[25] Boge K and Tietze L F, Lipid 2 (1998) 36.
[26] Kinomura K, Kitazawa S, Takata Y and Sakakibara T, US 4874852, 1989.
[27] Mowery D F, J Am Chem Soc 77 (1955) 1667.
[28] Boettner F E, US 3219656, 1965.
[29] Yanami T, Murai Y and Oshima R, US 4683297, 1987.
[30] Unilever PLC, EP 378710 A1, 1988 as a data of application.
[31] Straathof A J J, Romein J, Van Rantwijk F, Kieboom A P G and Van Bekkum H, Starch/Stärke 39 (1987) 362.
[32] Straathof A J J, Van Bekkum H and Kieboom A P G, Starch/Stärke 40 (1988) 229.
[33] De Goede A T J W, Van Rantwijk F and Van Bekkum H, Starch/Stärke 47 (1995) 233.
[34] Barlow S J and Bastock T W, Worldwide Solid Acid Process Conference, Houston, TX, Catalyst Consultants Ed, 1993.
[35] Min E, Stud Surf Sci Catal 83 (1994) 443.
[36] Horio M, Suzuki K, Masuda H and Mori T, Appl Catal 72 (1991) 109.
[37] Brochette S, Descotes G, Bouchu A, Queneau Y, Monnier and N, Petrier C, J Mol Catal A 123 (1997) 123.
[38] De Goede A T J W, Van Deurzen M P J, Van Der Leij I G, Van Der Heijden A M, Baas J M A, Van Rantwijk F and Van Bekkum H, J Carbohydr Chem 15 (1996) 331.
[39] Vulfson E V, Patel R Beecher J E , Andrews A T and Law B A, Enz Microb Technol 12 (1990) 950.
[40] Panintrarux C, Adachi S, Araki Y, Kimura Y and Matsuno R, Enz Microb Technol 17 (1995) 32.
[41] Chahid Z, Montet D, Pina M and Graille J, Biotechnol Lett 14 (1992) 281.
[42] Vic G and Thomas D, Tetrahedron Lett 32 (1992) 4567.
[43] Laroute V and Villemot R M, Biotechnol Lett 14 (1992) 169
[44] Wing R E and De Miller J N, Carbohydr Res 10 (1969) 441.
[45] Fabre J, Betbeder D, Paul F, Monsan P and Perie J, Carbohydr Res 234 (1993) 407.
[46] Pelenc V P, Paul F M B and Monsan P F, WO 93/04185, 1993.
[47] Corma A, Chem Rev 95 (1995) 559.
[48] Corma A, Iborra S, Miquel S and Primo J, J Catal 161 (1996) 713.
[49] Capon B, Chem Rev 68 (1969) 407.
[50] Chapat J F and Moreau C, Carbohydr Lett 3 (1998) 25.
[51] Camblor M A, Corma A, Iborra S, Miquel S, Primo J and Valencia S, J Catal 172 (1997) 76.
[52] Bennet A J, Sinnott M L and Sulochana Wijesundera W S, J Chem Soc. Perkin Trans 2 (1985) 1233.
[53] Yamaguchi T and Kojima M, Carbohydr Res 59 (1977) 129.
[54] Post C B and Karplus M, J Am Chem Soc 108 (1986) 1317.
[55] Valencia S, Camblor M A, Corma A, SP 9600625, 1996.
[56] Chapat J F, Finiels A, Joffre J and Moreau C, J Catal 185 (1999) 445.
[57] Corma A, Iborra S, Miquel S and Primo J, J Catal 180 (1998) 218.
[58] Kresge CT, Leonowicz M E, Roth W J, Vartuli J C, and Beck J S , Nature 359 (1992) 710.
[59] Beck J S, Vartuli J C, Roth W J, Leonowicz M E, Kresge C T, Schmitt K D, Chu C T W, Olson DH, Sheppard EW, McCullen S B, Higgins J B and Schlenker J L, J Am Chem Soc 114 (1992) 10834.
[60] Corma A, Fornes V, Navarro M T and Perez-Pariente J, J Catal 153 (1995) 25.
[61] Climent M J, Corma A, Iborra S, Miquel S and Primo J, J Catal. 183 (1999) 76.
[62] De Goede A T J W, Van Der Leij Y G, Van Der Heijden A M, Van Rantwijk F and Van Bekkum H, WO 96/36640, 1996.
[63] Van Bekkum H, Van Deurzen M P J, De Goede A T J W and Van Rantwijk F , WO 94/09019, 1994.
[64] Emeis C A, J Catal 141 (1993) 347.

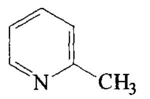
6.3 Heterocyclic Synthesis

Colin H. McAteer, Eric F. V. Scriven

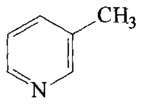
The study of heterocyclic compounds constitutes a major endeavor in the fields of organic chemistry and the life sciences. Although numerous texts on the synthesis, structure, and reactivity of heterocyclic compounds have been written [1,2], the application of solid–acid catalysts to the synthesis of heterocyclic compounds is rarely emphasized in the literature. The authors of this section of the book have chosen not to pursue an exhaustive literature review-type approach to this topic but rather to cover selected areas of this subject from the viewpoint of an industrial chemist. More specifically, an account of the synthesis of pyridines is given which relies heavily on patent literature. Pyridine bases constitute a sizable semi-commodity industry that provides a platform into the pyridine derivatives that are precursors to numerous fine chemicals. In addition, this section includes selected examples of the synthesis of non-pyridine heterocycles which might be of commercial importance.



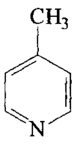
(1)



(2)

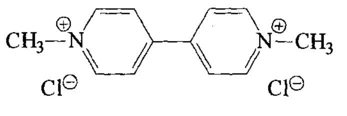


(3)

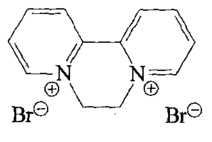


(4)

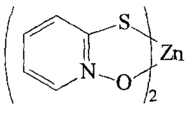
Pyridine bases are by far the largest volume of heteroaromatic compounds to be prepared industrially by use of heterogeneous catalysis [2]. The SRI Chemical Economic Handbook review suggests the global consumption of pyridine (**1**), *α*-picoline (**2**), *β*-picoline (**3**), *γ*-picoline (**4**), lutidines, and collidines was ca 50 000 metric tons in 1995 [3]. Within this group, pyridine and the picolines are dominant, because they are key precursors to a range of agrochemical, pharmaceutical, and consumer products and are used directly in solvent and acid-scavenger applications.



(5)

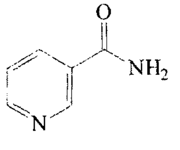


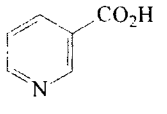
(6)

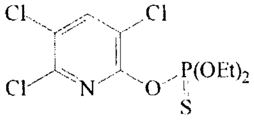


(7)

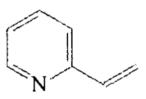
Key products derived from pyridine (**1**) are the non-selective herbicides paraquat (**5**) and diquat (**6**) and the fungicide zinc pyrithione (**7**) used in a well-known *anti*-dandruff shampoo. *β*-Picoline (**3**) is a key precursor to vitamin B3 and both niacinamide (**8**) and niacin (**9**) are produced on the large scale (i.e. several thousand tons per year). The insecticide chloropyrifos (**10**) can be prepared from *β*-picoline.

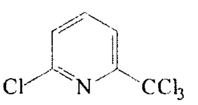

(8)

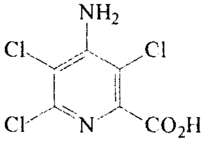

(9)


(10)

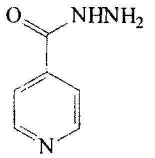
The largest use of α-picoline (**2**) is for production of 2-vinylpyridine (**11**) which, with butadiene and styrene, is converted into a terpolymer latex. This latex provides a coating that stiffens fabrics (e. g. nylon, polyester, rayon) that are incorporated into biased-ply car tires. The 2-vinylpyridine assists in binding the rubber to the fabric carcass. α-Picoline is also used as a precursor to nitrapyrin (**12**), which prevents nitrogen loss from soil, and the herbicide picloram (**13**).

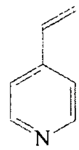

(11)

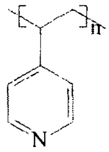

(12)


(13)

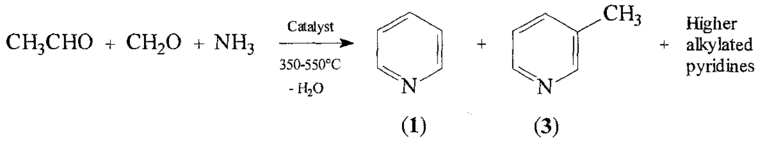
γ-Picoline (**4**) is used to produce isoniazid (**14**), which remains a front-line *anti*-tuberculosis drug despite its being first introduced in the late 1940s. γ-Picoline is also converted into 4-vinylpyridine (**15**) that is used to make Reillex^{TM} resins (**16**); these are used in industry as selective adsorbents and process aids.


(14)


(15)


(16)

Before the 1950s, demand for pyridine bases could be satisfied by coal-tar-derived material. Thereafter growth in the chemical and pharmaceutical industries necessitated the discovery of supplementary supplies of pyridine bases–especially pyridine. Pioneering work by Chichibabin and coworkers in the early 1900s had demonstrated that solid-acid catalysts could be used to make pyridine bases in the vapor phase [4,5]. The industrial-scale production of synthetic pyridine began in 1953 in the United States [6–8]. The early process used fluid-bed technology in combination with a 10 % ZnF_2/Al_2O_3 catalyst (470–480 °C) and formaldehyde–acetylene feed. Later, acetaldehyde became available and was preferred to acetylene for reasons of convenience and safety. Both fluid- and fixed-bed reactor technology are now used by manufacturers of pyridine bases.



Most commercial processes nowadays use CH_2O–CH_3CHO–NH_3 feed combinations to co-produce pyridine and β-picoline [9]. Typically, a C_1/C_2 molar ratio of ca 1.0 is used, but lower ratios can be employed if more pyridine and α-picoline are required [10,11]. If available, acrolein ($CH_2{=}CHCHO$) can be used instead of the C_1–C_2 components and this tends to produce a surplus of β-picoline [3,9]. Addition of propionaldehyde to the C_1–C_2 feed can also be used to increase the amount of β-picoline [12,13]. The yields of **1**, **3**, and 'higher alkylated' pyridine by-products depends on feed composition, reaction conditions, and the choice of catalyst.

Patents and literature reviews reveal that a wide range of catalysts has been investigated for the production of pyridine bases [5,9–11,14–18]. Up to 1980, FCC-based catalysts, often in combination with metal promoters, featured heavily as supports. The list of early solid-acid supports includes Al_2O_3, clays (e. g. montmorillonite), amorphous SiO_2–Al_2O_3, molecular sieves (i. e. LTA), zeolites MOR and FAU (i. e. H^+–Y) [19], and metal phosphates [20].

In 1980, Mobil demonstrated the utility of H^+-MFI for preparing pyridine bases [21]. Compared with amorphous SiO_2–Al_2O_3, zeolite MFI was shown to give ca 10–20 % higher total yields of **1** and **3** and an increased **1/3** ratio in both fluid-bed [22] and fixed-bed reactors [10,11,23]. Shape-selectivity imposed by MFI's medium-size pores reduces the formation of higher alkylpyridines and thus leads to the improved yield. The higher **1/3** ratio afforded by MFI is probably because formation of β-picoline is a higher-order reaction than the formation of pyridine (i. e. a 2:2 CH_3CHO/CH_2O reaction compared with 2:1 CH_3CHO/CH_2O).

In addition to MFI, other zeolites recently investigated for the synthesis of pyridines include MEL [23], TON [24], MCM-22 [25], and BEA [26]. With MCM-22, the combined yield of pyridine and picolines is reported to be higher than with MFI.

The highest pyridine–β-picoline yields with MFI were found with SiO_2/Al_2O_3 ratios in the 150–400 range [10,11,22]. At such low aluminium concentrations it is likely that Brønsted acid sites, rather than Lewis sites, assist in the Aldol condensation, cyclization, and hydrogen transfer (or dehydrogenation) reaction steps. Discussion of the mechanism of formation of pyridine bases in the vapor phase and the nature of the acid site dates back to the time of Chichibabin and remains a topic for debate [5,27].

Before 1980, a range of metals, metal oxides, and metal fluorides was identified as promoting the yield of pyridine bases on amorphous SiO_2–Al_2O_3 supports [9,12,28,29]. A representative list of promoter metals includes Pb, Sn, Cd, Zn, Ni, Co, W, Mo, Cr, and Ag. These metals, which have the potential to cycle between different redox states, might serve to remove dihydrogen from the reaction system in parallel with hydrogen-transfer processes at Brønsted-acid sites. The pa-

Table 1. Comparison of catalyst performance in the synthesis of pyridine bases [18].

Catalyst	Product yields (% carbon basis) Pyridine	Total (pyridine + picolines)	Molar ratio Pyridine/β-picoline
SiO_2–Al_2O_3 (amorphous)	33	52	3.0
H-MOR	17	31	2.1
H-Y	27	54	1.9
H-MFI	42	61	3.8
Tl-MFI	63	81	7.0
Pb-MFI	60	79	7.5
Co-MFI	57	78	8.1

Conditions: fixed-bed reactor, 450 °C, $SV = 1000\ h^{-1}$, $CH_2O/CH_3CHO/NH_3 = 1.0{:}2.0{:}4.0$ (molar).

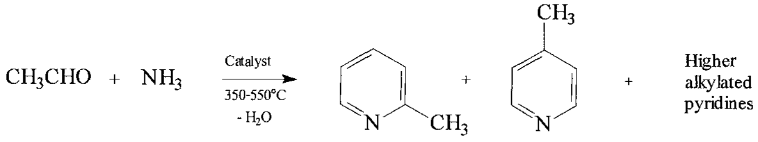
tent literature gives little information about whether the metal loading, method of loading (i.e. impregnation or precipitation), support SiO_2/Al_2O_3 ratio, and pretreatment conditions are important factors affecting performance.

Several patents have recently appeared in which metals have been incorporated into zeolite MFI to promote pyridine–β-picoline yields [21,23,30–32]. Ion-exchange procedures were used to make MO_x/MFI catalysts (M = Tl, Pb, or Co) which, in a fixed-bed reactor, resulted in yields superior to those from the parent MFI and related supports (Table 1) [18,23]. The presence of the same metals also affects product selectivity, as shown by the **1/3** ratios. It is tempting to believe that the proximity of a Brønsted acid site and the redox metal within the MFI channels act in concert to catalyze the sequence of reaction steps. Other MO_x/MFI catalysts (M = Zn, Sn, or W) containing more environmentally benign metals have been investigated for fluid-bed reactor use [30]. Yield promotion has also been observed for related MO_x/BEA catalysts (M = Pb, Cd, Tl, Sn, Ga, or Co) [26].

In commercial pyridine plants, coke deposition will eventually have a detrimental impact on yield. If fluid-bed technology is employed, continuous catalyst removal and regeneration might be possible with a separate regenerator vessel. Average catalyst residence times of minutes to a few hours are routinely employed. With fixed-bed reactors or batch fluid-bed units, intermittent regeneration cycles are necessary. Batch operation is likely to be more demanding on catalysts, because higher coke levels must be tolerated to prolong the pyridine production step. Sustained high coke levels in turn will inevitably affect catalyst longevity.

Extended life has been demonstrated with the doubly promoted M'/MO_x/MFI catalysts (M′ = Pt, Pd, Rh, or Ru; M = Tl, Pb, or Co) in a fixed-bed reactor [31]. The platinum group metal (PGM) presumably prolongs catalyst life by reducing the temperature of coke combustion. The longevity of the same catalyst system has been further extended by dosing the regeneration air with a small amount of methanol [18,32]. This procedure reduces residual coke by a factor of almost ten compared with the standard regeneration procedure. Another approach to extending the pyridine synthesis run-time has been to use M/MFI catalysts (M = Pd, Pt, or Rh) and to co-feed hydrogen with the CH_2O–CH_3CHO–NH_3

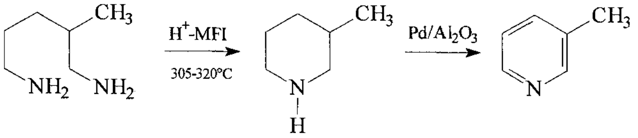
feed [33]. The PGM presumably hydrogenates coke precursors during the reaction cycle and assists coke combustion during the regeneration cycle.



(2) **(4)**

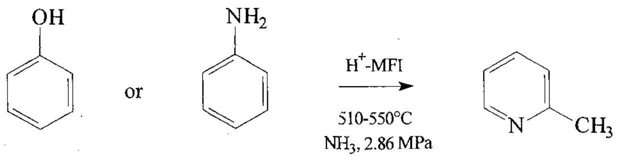
Using an acetaldehyde-only feed, α-picoline (**2**) and γ-picoline (**4**) are co-produced together with higher alkylpyridine by-products. As with the pyridine–β-picoline reaction, similar metal-promoted amorphous SiO_2–Al_2O_3 [28,34–36] and MFI [21,37] catalysts feature in the literature. Phosphate-based catalysts such as $Co_3Al_2(PO_4)_4$, $Co_3Mg_3(PO_4)_4$, and $Pb_3Al_5(PO_4)_7$ are reported to give yields of **2** + **4** of 65–70 % and very high **2/4** ratios of 4.2–5.0 [38]. Substantial loss of yield is observed with these metal phosphates after a few run–regeneration sequences, unless they are impregnated with either H_3PO_4 or $(NH_4)_3PO_4$, which greatly extends catalyst life.

Vapor-phase production of pyridine and picolines from alternative feeds has received much attention. Ethanol has been investigated for production of **1–3**, either as a partial or total substitute for CH_3CHO, over amorphous SiO_2–Al_2O_3 [12] and MO_x/MFI (M = Pb, W) [39] catalysts. It is claimed that the heteropolyacids $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$, when supported on γ-Al_2O_3, convert EtOH to **2–4** with yields of 45–55 % [40]. Feeding air with EtOH, in an attempt to produce CH_3CHO in situ, has also been examined with zeolites TON [24] and MFI [41]. Even with these promising leads, CH_3CHO is preferred to EtOH from a commercial standpoint.



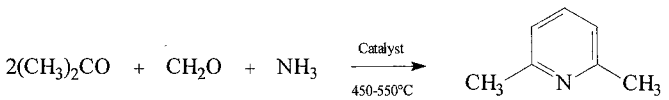
(17) **(18)** **(3)**

An alternative route to β-picoline (**3**) involves a two-step conversion of 2-methyl-1,5-pentanediamine (or Dytek A®; **17**) to 3-methylpiperidine (**18**) over zeolite MFI [42]. This reaction is believed to be in commercial operation in China. α-Picoline (**2**) can be produced by converting either phenol (**19**) [43] or aniline (**20**) [44] over MFI at elevated temperature and pressure. This so-called benzamine rearrangement is discussed in Section 5.2.



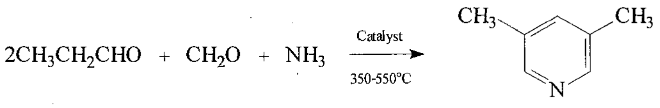
(19) **(20)** **(2)**

Whereas thousands of tons of pyridine and picolines are required for agrochemical, vitamin B3, and consumer product markets, lutidine and collidine derivatives are made on the 10–100 ton scale only, primarily for use as solvents and intermediates in the pharmaceutical industry. Acetone, CH_2O, and ammonia are used commercially to produce 2,6-lutidine (**21**) over metal-promoted catalysts. Zeolites MFI [45] and BEA [26] have featured in the most recent literature.



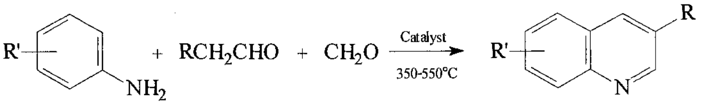
(21)

3,5-Lutidine (**22**) can be used to prepare the *anti*-ulcer drug omeprazole, currently the world's largest selling pharmaceutical. Propionaldehyde, CH_2O, and ammonia can be used to prepare 3,5-lutidine although commercially it is recovered by distillation of the higher alkylpyridines produced in the pyridine reaction. First-intent synthesis of 3,5-lutidine with zeolites MFI [46] and BEA [26] has recently appeared in the literature, together with the use of *n*-propanol–CH_2O as feed [47].



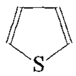
(22)

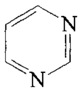
A similar type of carbonyl condensation reaction can be used to produce quinoline derivatives (**24**) in the vapor phase by replacing NH_3 with an arylamine (**23**) [48]. A range of Brønsted acids, including large-pore zeolites and amorphous SiO_2–Al_2O_3, can be used in this reaction.

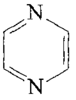


(23) **(24)**

Ring systems with a single heteroatom–e. g. pyridines, quinolines, carbazoles and thiophenes–are usually stable under high-temperature (> 400 °C) syntheses conditions. As an example, thiophene (**25**) and alkylthiophenes are produced from C_4+ oxygenates (alcohols, aldehydes, or α,β-unsaturated aldehydes) and a sulfur source (CS_2 or H_2S) over γ-Al_2O_3-based catalysts above 450 °C [49]. Thiophenes constitute a sizable market of ca 1000 tons per year [50].

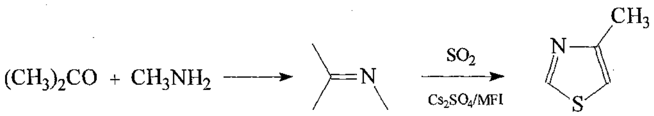

(25)


(26)


(27)

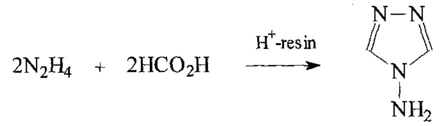
Ring systems containing two heteroatoms tend to feature less in the vapor-phase literature. This is partly because of the greater reactivity (i. e. reduced aromaticity) of these heterocyclic compounds. In addition, there has been less commercial incentive to develop catalyzed processes for these smaller-volume niche products. As an example, both pyrimidine (**26**) [51] and pyrazine (**27**) [52] can be made by catalyzed vapor-phase methods; they can also be recovered from the pyridine-β-picoline reaction. In principle, pyrimidine and pyrazine could then serve as platforms–much like pyridine does–for preparing a wide range of derivatives. The market for these derivatives is, however, best met by traditional convergent syntheses in the liquid phase.

A rare example of a vapor-phase carbonyl condensation reaction leading to a double heteroatom five-membered ring system involves the production of 4-methylthiazole (**28**). This compound is a precursor to thiabendazole, a fungicide used to protect citrus fruit (ca 300 tons is consumed annually). The 4-methylthiazole process is reported to use Cs_2SO_4-doped zeolite MFI [53].



(28)

Solid-acid catalysts can also be used to prepare a three-heteroatom five-membered ring system, but relatively mild reaction conditions are required. A recent example is the liquid-phase formation of 4-aminotriazole (**29**) by reaction of hydrazine and formic acid in the presence of a strong-acid resin [54].



(29)

As well as 3-methylpiperidine (**18**), other ring-saturated five- and six-membered heterocycles can be prepared over zeolites and related solid-acid catalysts [55]. Moderate reaction temperatures (200–300 °C) and elevated pressures can help to minimize acid-catalyzed elimination of the heteroatom from the ring as NH_3, H_2O, or H_2S.

The synthesis of pyridine bases with solid-acid catalysts is of considerable commercial importance. In the future, zeolites and related catalysts can be expected to have an impact on other areas of heterocyclic chemistry, because they bring the combined benefits of high yields and environmentally clean processes. The use of these catalysts to introduce new functions into pre-formed heterocycles or to manipulate their side chains–a topic not addressed here–is an area worthy of more research activity. Hopefully, this brief review provides some insight into heterocyclic chemistry and encourages readers to pursue their own catalysis research in this fascinating and fruitful area.

References

[1] *Comprehensive Heterocyclic Chemistry II–A Review of the Literature 1982–1995* (Eds: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Vols 1–11, Pergamon, **1996**.

[2] E. F. V. Scriven, J. E. Toomey, R. Murugan, Pyridine and Pyridine Derivatives, *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th ed. **1996**, *20*, 641–679.

[3] W. K. Johnson, A. Leder, Y. Ishikawa, Pyridine and Pyridine Bases, *Chemical Economic Handbook Product Review*, SRI International, **1997**, 691.6000 A.

[4] A. E. Chichibabin, *Zh. Russk. Fiz. Khim. O-va.* **1905**, *37*, 1229; *Zh. Russk. Fiz. Khim. O-va.* **1905**, *47*, 703.

[5] R. S. Sagitullin, G. P. Shkil, I. I. Nosonova, A. A. Ferber, *Chemistry of Heterocyclic Compounds*, Plenum, **1996**, *32*, 127–140.

[6] F. E. Cislak, W. R. Wheeler, US Patent 2 744 904, **1956** (Reilly Tar & Chemical).

[7] F. E. Cislak, W. R. Wheeler, US Patent 2 807 618, **1957** (Reilly Tar Chemical).

[8] F. E. Cislak, W. R. Wheeler, US Patent 2 934 537, **1960** (Reilly Tar & Chemical).

[9] F. P. Vatti, P. Pollesel, L. Forni, *La Chimica L'Industria,* **1993**, *75*, 549–557.

[10] H. Sato, S. Shimizu, N. Abe, K. Hirose, *Chem. Lett.* **1994**, 59–62.

[11] H. Sato, S. Shimizu, N. Abe, K. Hirose, *Stud. Surf. Sci. Catal.* **1994**, *84*, 1951–1958.

[12] K. R. Hargrave, Brit. Patent 929 694, **1963** (Distillers Co. Ltd.).

[13] D. Feitler, H. Wetstein, US Patent 5 013 843, **1991** (Nepera, Inc.).

[14] F. Brody, P. R. Ruby, Synthetic and Natural Sources of the Pyridine Ring, *Pyridine and Its Derivatives* (Ed: E. Klingsberg), Interscience, New York, **1960**, 474–496.

[15] N. S. Boodman, J. O. Hawthorne, A. W. Simon, P. X. Masciantonio, Synthetic and Natural Sources of the Pyridine Ring, *Pyridine and Its Derivatives* (Ed: R. A. Abramovitch), Wiley, New York, **1974**, 273–283.

[16] P. B. Venuto, *Microporous Materials*, **1994**, *2*, 297–411.

[17] K. Tanabe, W. F. Hölderich, *Appl. Catal.* **1999**, *181*, 399–434.

[18] S. Shimizu, N. Abe, A. Iguchi, H. Sato, *Catal. Surv. Japan*, Baltzer, **1998**, *2*, 71–76.

[19] A. B. Baylis, US Patent 3 970 655, **1976** (Celanese Corp.).

[20] C. R. Adams, J. Falbe, *Brennstoff Chem.* **1966**, *47*, 184–187.

[21] C. D. Chang, W. H. Lang, US Patent 4 220 783, **1980** (Mobil Oil Corp.).

[22] D. Fietler, W. Schimming, H. Wetstein, US Patent 4 675 410, **1987** (Nepera, Inc.).

[23] S. Shimizu, N. Abe, M. Doba, A. Iguchi, H. Sato, K. Hirose, Y. Umada, US Patent 4 810 794, **1989** (Koei Chemical Co. Ltd.).

[24] R. A. le Febre, A. J. Hoefnagel, H. van Bekkum, *Recl. Trav. Chim. Pays-Bas.* **1996**, *115*, 511–518.

[25] P. J. Angevine, C.T-W. Chu, T. C. Potter, US Patent 5 395 940, **1995** (Mobil Oil Corp.).

[26] C. H. McAteer, D. C. Brown, R. D. Davis, US Patent 5 780 635, **1998** (Reilly Industries).

[27] S. E. Golunski, D. Jackson, *Appl. Catal.* **1986**, *23*, 1–14.

[28] L. E. Cooper, Brit. Patent 900 799, **1962** (Distillers Co. Ltd.).

[29] S. Cane, L.E. Cooper, Brit. Patent 1235390, **1971** (BP Chemicals Ltd.).

[30] G.L. Goe, R.D. Davis, US Patent 5218122, **1993** (Reilly Industries).

[31] S. Shimizu, N. Abe, M. Doba, A. Iguchi, US Patent 5237068, **1993** (Koei Chemical Co. Ltd.).

[32] S. Shimizu, H. Takayasu, N. Osaka, N. Abe, A. Iguchi, H. Ichihashi, M. Kitamura, US Patent 5701802, **1991** (Koei Chemical Co. Ltd.).

[33] W.J Cheng, F.S. Lin, Y.L. Jong, F.J. Huang, US Patent 4866179, **1989** (Dairen Chemical Corp.).

[34] S. Cane, L.E. Cooper, Brit. Patent 1188891, **1970** (BP Chemicals Ltd.).

[35] S.K.R. Roy, N.S. Rawat, P.N. Mukherjee, Catalytic Vapor-Phase Synthesis of Pyridine Bases, *Advances in Catalysis Science and Technology*, The Catalysis Society of India (Ed: T.S.R. Prasada Rao), Wiley, New York **1985**, 121–130.

[36] S.J. Kulkarni, R. Ramachandra Rao, M. Subramanyam, A.V. Rama Rao, *React. Kinet. Catal. Lett.* **1995**, *56*, 291–299.

[37] R. Ramachandra Rao, S.J. Kulkarni, M. Subrahmanyam, A.V. Rama Rao, *React. Kinet. Catal. Lett.* **1995**, *56*, 301–309.

[38] Y. Minato, S. Yasuda, US Patent 3932421, **1976** (Koei Chemical Co. Ltd.).

[39] S.J. Kulkarni, R. Ramachandra Rao, M. Subrahmanyam, A.V. Rama Rao, *Appl. Catal.* **1994**, *113*, 1–7.

[40] R. Potaraju, J.M. Vishnu, Eur. Pat. Application 0209241, **1987** (IEL Ltd.).

[41] F.J. van der Gaag, F. Louter, J.C. Oudejans, H. van Bekkum, *Appl. Catal.* **1986**, *26*, 191–201.

[42] J. Haveling, E. Armbruster, L. Utiger, M. Rohner, H.R. Dettwiler, R.J. Chuck, US Patent 5719045, **1998** (Lonza AG).

[43] C.D. Chang, P.D. Perkins, US Patent 4388461, **1983** (Mobil Oil Corp.).

[44] C.D. Chang, P.D. Perkins, US Patent 4395554, **1983** (Mobil Oil Corp.).

[45] A.V. Rama Rao, S.J. Kulkarni, R. Ramachandra Rao, M. Subrahmanyam, *Appl. Catal.* **1994**, *111*, L101–L108.

[46] S.J. Kulkarni, R. Ramachandra Rao, Y.V. Subba Rao, M. Subrahmanyam, A.V. Rama Rao, *Appl. Catal.* **1996**, *136*, L1–L6.

[47] R. Ramachandra Rao, N. Srinivas, S.J. Kulkarni, M Subrahmanyam, K.V. Raghavan, *Appl. Catal.* **1997**, *161*, L37–L42.

[48] C.H. McAteer, R.D. Davis, J.R. Calvin, US Patent 5700942, **1997** (Reilly Industries).

[49] L.S. Fuller, Thiophene and Thiophene Derivatives, *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th ed. **1996**, *24*, 34–51.

[50] B.W.L. Southward, L.S. Fuller, G.J. Hutchings, R.W. Joyner, R.A. Stewart, *J. Chem. Soc., Chem. Commun.* **1999**, 369–370.

[51] T. Shoji, T. Nakaishi, JP 02011577, **1990** (Koei Chemical Co. Ltd.); *Chem. Abstr.* **1990**, *113*, 40724x.

[52] S. Shimizu, T. Niwa, T. Shoji, JP 63162678, **1988** (Koei Chemical Co. Ltd.); *Chem. Abstr.* **1989**, *110*, 23915f.

[53] B. Beshty, F.P. Gortsema, G.T. Wildman, J.J. Sharkey, US Patent 5231187, **1993** (Merck & Co. Inc.).

[54] G.L. Goe, E.F.V. Scriven, J.G. Keay, L.M. Huckstep, US Patent 5099028, **1992** (Reilly Tar & Chemical).

[55] Y.V. Subba Rao, S.J. Kulkarni, M. Subrahmanyam, A.V. Rama Rao, *J. Org. Chem.* **1994**, *59*, 3998–4000.

6.4 Heterogeneous Catalysis of Diels–Alder Reactions

G. J. Meuzelaar, R. A. Sheldon

6.4.1 Introduction

The Diels–Alder reaction [1] is a versatile tool in synthetic organic chemistry and is widely used in the synthesis of natural products [2]. The reaction can proceed with remarkable regio- and stereoselectivity and up to four stereocenters can be created in one step in the formation of a six-membered ring. Asymmetric Diels–Alder reactions can, moreover, proceed with high enantioselectivity when catalyzed by chiral Lewis acids [3]. Diels–Alder reactions are also ideal in respect of atom utilization [4]. Although many Diels–Alder reactions proceed at room temperature or at slightly elevated temperatures, when less reactive reactants are used, or the reaction involves thermally unstable reactants or products, catalytic methods can be used to enable the reactions to be conducted under mild conditions [5]. Catalysts can also enhance the selectivity of the reaction. Traditional Lewis acids, e. g. $AlCl_3$ and BF_3 etherate, are often used, in stoichiometric amounts, to accelerate Diels–Alder reactions. This makes the work-up procedures laborious and can result in environmentally hazardous waste-streams. The use of solid catalysts, in contrast, facilitates the recovery and recycling of the catalyst.

This contribution provides an overview of known heterogeneous catalysts for Diels–Alder reactions with emphasis on methods which enable efficient synthesis of fine chemicals. It covers the literature up to the end of 1998.

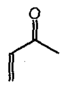
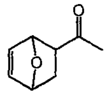
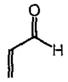
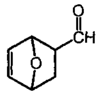
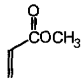
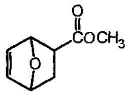
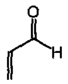
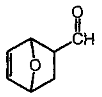
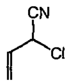
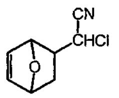
6.4.2 Catalysts

6.4.2.1 Zeolites

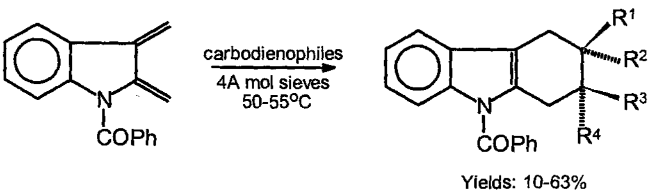
Early reports on zeolite-catalyzed Diels–Alder reactions deal mainly with cyclodimerization reactions of butadiene or 1,3-cyclohexadiene [6] which are of moderate synthetic interest only. For fine chemical synthesis Diels–Alder reactions of substrates with functional groups are of more interest. An early example of a zeolite-catalyzed reaction of this type was patented in 1968 and involves the reaction of butadiene with maleic anhydride in the presence of zeolites X containing an active cation (e. g. rare earth metal ions) and/or H^+ sites [7]. The reaction was performed at 60 °C and gave the adduct in 93 % yield after 3 h. In 1986 Ipaktschi described Diels–Alder reactions catalyzed by Cu^+-exchanged zeolite Y [8]. Among the investigated dienes was furan (see Table 1), many of the Diels–Alder adducts of which are building blocks in the synthesis of biologically active compounds. Furan is acid-sensitive and Diels–Alder reactions with this diene give problems when homogeneously catalyzed by Lewis acids.

Other zeolite-catalyzed Diels–Alder reactions have since been reported; these concentrate mainly on studies of standard model compounds [9]. Pindur and Haber [10] described the reaction of in situ generated *N*-benzoyl-2,3-dihydro-

Table 1. Examples of zeolite-catalyzed Diels–Alder reactions of furan.

Dienophile	Adduct	Catalyst	T(° C)	Yield (%)	*Exo*/*endo*	Ref.
		CuY	0	73	2.5	8
		CuY	0	31	5	8
		CeY	0	40–50	2.3	12
		CeY	0	70	2.2	12
		ZnY	0	55	1.5	12

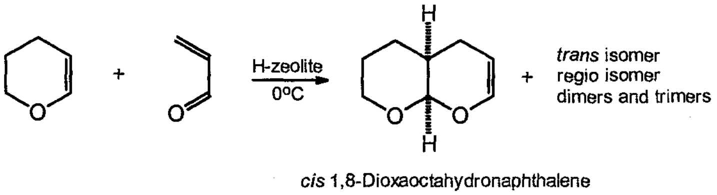
2,3-bis(methylene)indole with several carbodienophiles (Scheme 1) catalyzed by highly activated 4-A molecular sieves. The adducts were difficult to obtain via the thermal reaction.



Scheme 1. Synthesis of 1,2,3,4-tetrahydrocarbazoles by molecular sieve-catalyzed Diels–Alder reactions.

The hetero Diels–Alder reaction of dihydropyran with acrolein (Scheme 2) was performed at 0 °C without solvent in the presence of H-form zeolites [11]. The best catalysts were dealuminated HY (Si/Al = 15; 62 % yield of the desired adduct) and H-beta (Si/Al = 25; 65 % yield). The thermal reaction at 150 °C gave the adduct in 5 % yield only.

A variety of Diels–Alder reactions have been catalyzed by Na-ZSM-5, Na-Y, or Ce-Y [12]. Some results obtained with furan are included in Table 1. Reactions with other dienes were catalyzed more effectively when the zeolites were treated with $ZnBr_2$. Zeolite H-Y modified with anhydrous $ZnCl_2$ has subsequently been used as catalyst in the Diels–Alder reaction of myrcene (7-methyl-3-methylene-1,6-octadiene) and acrolein [13]. Diels–Alder adducts of myrcene are fragrance intermediates.

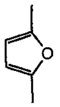
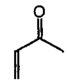
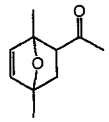
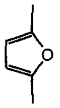
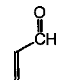
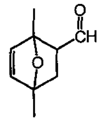
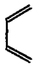
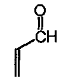
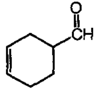
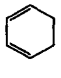
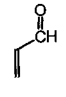
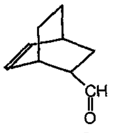
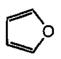
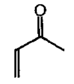
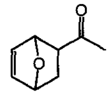
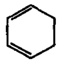
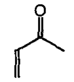
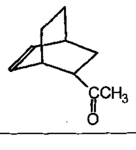


Scheme 2. The Diels–Alder reaction of dihydropyran with acrolein catalyzed by H-form zeolites.

6.4.2.2 Clays

Clay-catalyzed Diels–Alder reactions were thoroughly investigated by Laszlo and co-workers. Of particular interest are reactions with furans [14] or acrolein [15] as substrate catalyzed by iron(III)-exchanged K10 montmorillonite. Some represen-

Table 2. Examples of clay-catalyzed Diels–Alder reactions.

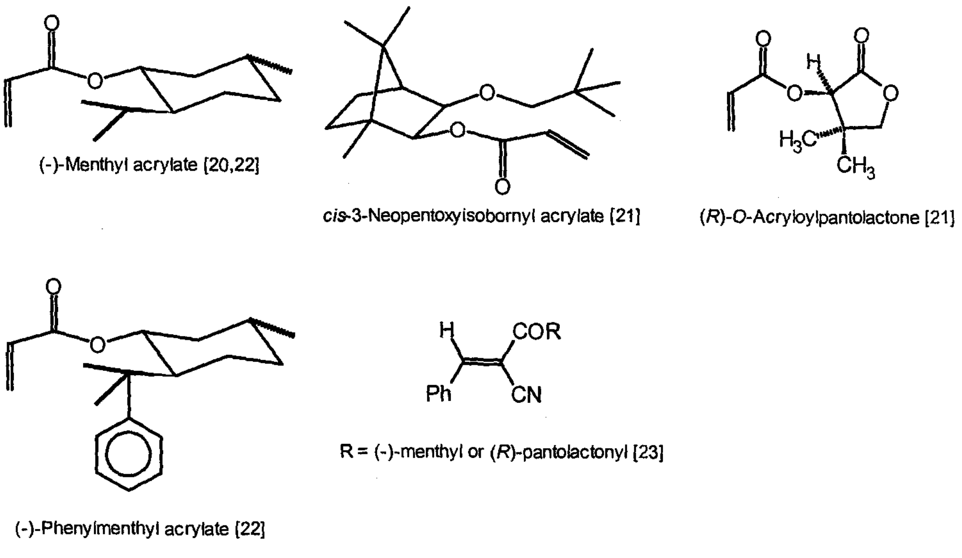
Diene	Dienophile	Adduct	Catalyst	*T* (°)	Yield (%)	*Exo*/*Endo*	Ref.
			Fe(III)-K10	-43	65 (5 h)	0.6	14
			Fe(III)-K10	-43	40 (5 h)	1.0	14
			Fe(III)-K10	20	83 (6 h)	-	15
			Fe(III)-K10	20	55 (24 h)	n.d.[a]	15
			Cr(III)-Tonsil 13	25	14 (20 min)	0.3	18
			Cr(III)-Tonsil 13	25	72 (20 min)	0.12	18

[a] not detected

tative examples are included in Table 2. Laszlo also showed that *N*-benzylidene aniline reacts with vinyl ethers to give tetrahydroisoquinolines in the presence of the same catalyst [16].

Different clay minerals exchanged with different transition metal cations were studied as catalysts in reactions performed at ambient temperatures in several solvents [17,18]. Some results obtained with a chromium(III)-exchanged Tonsil 13 clay are given in Table 2. Surprisingly, clays exchanged with non-transition (e. g. Al^{3+}) or lanthanide (e. g. La^{3+}) cations were ineffective, and a catalytic mechanism which involves constraining of the diene and the dienophile into a suitable configuration by the d-orbitals of the exchanged transition metal was suggested [18].

Diels–Alder reactions of cyclopentadiene with methyl acrylate [19], (–)-menthyl acrylate, or other chiral dienophiles [20–23] catalyzed by cation-exchanged K10 montmorillonites were thoroughly investigated by Mayoral and co-workers. The structures of the chiral dienophiles are depicted in Figure 1. Moderate diastereoselectivities were obtained with (–)-menthyl acrylate (54 %) and (*R*)-*O*-acryloylpantolactone (53 %) in reactions catalyzed by zinc(II)-exchanged K10 montmorillonite at –20 °C.



(-)-Menthyl acrylate [20,22]

cis-3-Neopentoxyisobornyl acrylate [21]

(*R*)-*O*-Acryloylpantolactone [21]

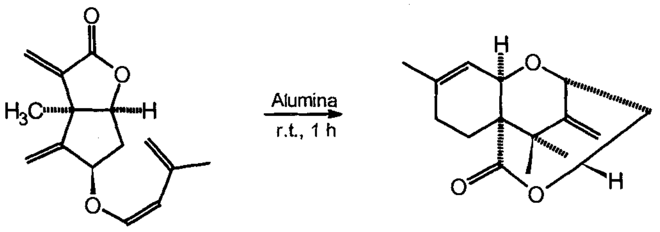
R = (-)-menthyl or (*R*)-pantolactonyl [23]

(-)-Phenylmenthyl acrylate [22]

Figure 1. Structures of chiral dienophiles investigated by Mayoral et al. in Zn(II)–K10-catalyzed Diels–Alder reactions with cyclopentadiene. Reference numbers are given in square parentheses.

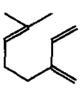
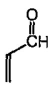
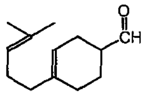
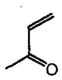
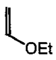
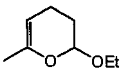
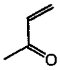
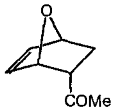
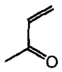
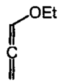
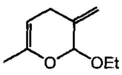
6.4.2.3 Alumina and Silica

The use of alumina and silica to promote Diels–Alder reactions was first reported by Hudlicky [24]. The reactions of 1-acetoxy-1,3-butadiene with tetrafluoro-*p*-benzoquinone or *p*-benzoquinone were considerably accelerated when they occurred inside the pores of the adsorbents. Several other silica- or alumina-catalyzed Diels–Alder reactions, dealing either with investigation of standard model reactions [25] or of reactions of more synthetic utility, were subsequently described. For example, neutral alumina catalyzed the intramolecular reaction of a tetraene to the verrucarol skeleton [26] (Scheme 3). The catalytic action was observed in an attempt to isolate the tetraene by column chromatography. A variety of Diels–Alder reactions were accelerated by silica or the more basic Florisil ($MgO.SiO_2$) in the absence of solvent [27–30]. Table 3 gives some examples of these reactions, which are thought to be catalyzed via multicentered donor–acceptor interactions of the substrates with the active sites of the surface of the adsorbents.



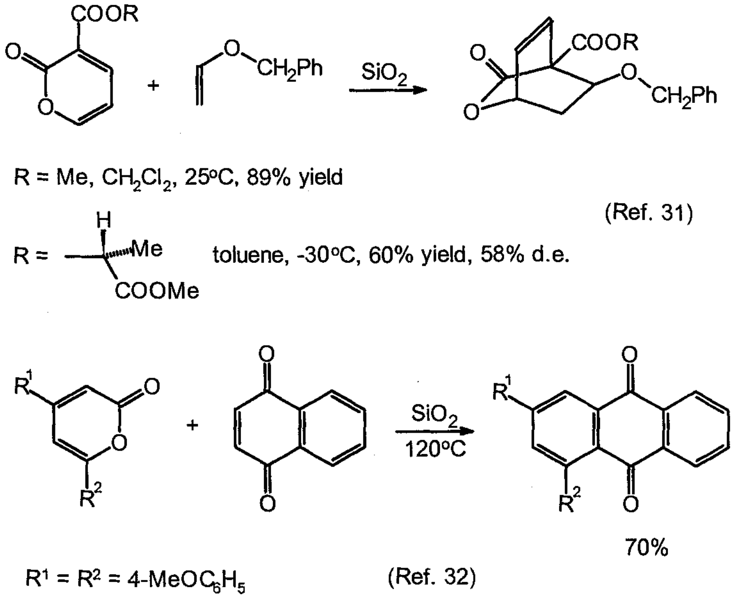
Scheme 3. An alumina-catalyzed intramolecular Diels–Alder reaction to the verrucarol skeleton.

Table 3. Examples of Diels–Alder reactions catalyzed by silica gel or Florisil at 20 °C.

Diene	Dienophile	Adduct	Catalyst	Time (h)	Yield (%)	Ref.
			SiO_2	1	66	27
			MgO-SiO_2	15	50	27
			MgO-SiO_2	70	48	27
			SiO_2	1^{a}	68	28

^{a}Reaction at 50 °C, the non-catalyzed reaction at 50 °C gave the adduct in 62 % yield after 48 h.

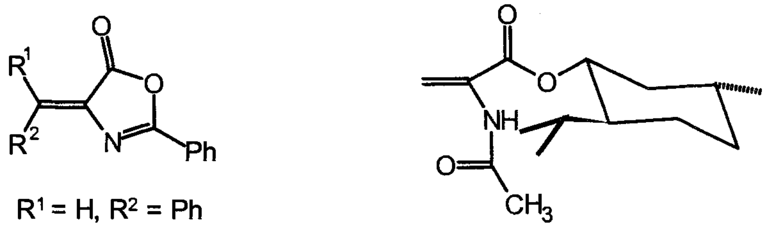
Silica gel has been reported to accelerate Diels–Alder reactions of 3-methoxycarbonyl-2-pyrone and a related chiral dienophile with butyl vinyl ether or benzyl vinyl ether (Scheme 4) [31]. Related dienophiles, 4,6-disubstituted 2-pyrones, were investigated in reactions with naphthoquinone or *N*-phenylmaleimide catalyzed by silica or other heterogeneous catalysts in the absence of solvent [32]. An example is included in Scheme 4.



Scheme 4. Silica gel-catalyzed Diels–Alder reactions of pyrone derivates.

The activity of alumina and silica can be improved by treatment of the support materials with, e. g., $AlEt_2Cl$, $TiCl_4$, $ZnCl_2$, or BBr_3. Reactions of cyclopentadiene were performed with a variety of dienophiles [33–36]. The structures of some of these dienophiles are given in Figure 2. The silica-modified systems were usually found to be the most efficient catalysts; occasionally selectivity was better than that obtained with homogeneous Lewis acid catalysts.

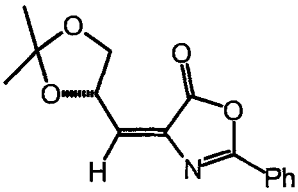
Silica-supported Lewis acids (e. g. $ZnCl_2$, ZnI_2, or $TiCl_4$) were also studied in Diels–Alder reactions of furan [37,38]. Reactions were performed at 25 °C and the best results were obtained in the absence of solvent. The combination of dienophile and supported Lewis acid had a great influence on the outcome of the reactions. Reaction with the chiral dienophile (–)-8-phenylmenthyl acrylate gave the *endo* adduct in 68 % d. e. and the *exo* adduct in 70 % d. e. [37].



R^1 = H, R^2 = Ph
R^1 = Ph, R^2 = H

2-Phenyl-4-benzylidene-5(4*H*)-oxazolones [34]

(-)-Menthyl *N*-acetyl-α,β-dehydro-alaninate [35]



(*E*)-2-Phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolane-4-ylmethylen]-5(4 *H*)-oxazolone [36]

Figure 2. Structures of dienophiles investigated by Mayoral et al. in Diels–Alder reactions with cyclopentadiene catalyzed by Lewis acids supported on alumina or silica. Reference numbers are given in square parentheses.

The performance of alumina-supported BBr_3 as a catalyst in Diels–Alder reactions was studied by Pagni and co-workers [39]. The catalyst gave the adduct of cyclopentadiene and (–)-dimenthyl fumarate in higher diastereoselectivity than alumina itself. When (–)-menthol was added to the BBr_3-treated alumina the diastereomeric excess went up by 50 %; no enantiomeric excess was observed in a reaction of cyclopentadiene with dimethyl fumarate. Mayoral et al. prepared similar catalysts by supporting a (–)-menthol–aluminium Lewis acid on silica gel and alumina via the aluminium atom [40]. A silica-supported catalyst gave the *exo* adduct of cyclopentadiene and methacrolein with 31 % e. e. The authors also studied catalysts prepared by supporting (*S*)-prolinol and (*S*)-tyrosine derivatives on silica or alumina and treatment with BH_3 or $AlEtCl_2$. The e. e. values observed in reactions of cyclopentadiene with methacrolein or bromoacrolein were not higher than 8 %, however.

6.4.2.4 Polymer-supported Lewis Acids

An early example of a Diels–Alder reaction catalyzed by a polymer-supported Lewis acid involves the use of copper-loaded polystyrene-based polymers in the reaction of furan with 2-cyanoacrylonitrile [41]. Nafion-supported scandium [42] and scandium encapsulated in a polystyrene matrix [43] were recently reported as heterogeneous catalysts for Diels–Alder reactions.

Most recent research has been focused on the application of polymers as chiral auxiliaries in enantioselective Lewis-acid-catalyzed reactions. Studies of Itsuno and co-workers [44] culminated in the development of a polymer-supported catalyst containing a chiral oxazaborolidinone with oxyethylene crosslinkages which gave the Diels–Alder adduct of cyclopentadiene and methacrolein in 88 % isolated yield with an *exo/endo* ratio of 96:4 and 95 % e. e. for the *exo* adduct. A variety of polymer-supported chiral Lewis acids was also investigated by Mayoral et al. [45]. Some supported catalysts were more active than their homogeneous analogs, but enantioselectivity was always lower.

6.4.2.5 Miscellaneous Heterogeneous Catalysts

A variety of other heterogeneously catalyzed Diels–Alder reactions has been reported. Nafion-H, a perfluorinated resinsulfonic acid, catalyzed several Diels–Alder reactions and the isolated yield of the adducts was 80–95 % [46]. We have found that a recently described Nafion-silica composite catalyst containing 13 % (*w/w*) Nafion [47] was approximately 30 times more active than the pure resin in the Diels–Alder reaction of 2,3-dimethylbutadiene with 1,4-naphthoquinone [48]. We also showed that another strong heterogeneous Brønsted acid, tungstophosphoric acid supported on silica gel, is a very active catalyst of Diels–Alder reactions of quinones [49] and other enones [50].

An yttrium-based strong Lewis acid, prepared by treatment of aqueous solutions of yttrium nitrate and zirconyl nitrate (molar ratio 16:84) with aqueous ammonia (28 %), was an active catalyst of a wide range of Diels–Alder reactions [51]. Among the reactions investigated was that of acrolein with dihydropyran (Scheme 2). In contrast with reactions with H-form zeolites [11] no regio- and stereoisomers were formed.

Mayoral and co-workers investigated the performance of amorphous $AlPO_4$ in Diels–Alder reactions of cyclopentadiene with various chiral acrylates [52,53]. Amorphous $AlPO_4$ was more efficient than Zn(II)-exchanged K10 montmorillonite and reaction with (–)-8-phenylmenthyl acrylate gave the adduct in relatively high d. e. (74 %). Other heterogeneous catalysts which have been studied in Diels–Alder reactions are a weakly Lewis acidic 1,3-dialkylimidazolium salt [54] and an organic zeolite [55].

6.4.3 Concluding Remarks

A variety of solid Lewis and Brønsted acids has been shown to catalyze Diels–Alder reactions. In several instances the results obtained with heterogeneous catalysts were better than those with homogeneous Lewis acid catalysts. Most of the reported reactions of interest in the synthesis of fine chemicals were catalyzed by (modified) zeolites, clays, alumina, or silica. Catalysts with interesting properties were obtained when support materials such as zeolites, alumina, or silica were treated with Lewis acids. These catalysts were moderately selective in diastereoselective Diels–Alder reactions with chiral dienophiles and induced enantioselectivity (up to 31 % e. e.) in the reaction of cyclopentadiene with methacrolein after treatment with chiral derivatives. Excellent enantioselectivity in this reaction (up to 95 % e. e.) was observed with a polymer-supported chiral oxazaborolidinone. Because of their facile recovery and recycling, we expect that solid-acid catalysts will find increasing use in Diels–Alder reactions in the future.

References

[1] F. Fringuelli, A. Taticchi, "*Dienes in the Diels–Alder reaction*", Wiley, New York, **1990**.

[2] (a) G. Desimoni, G. Tacconi, A. Barco, G. P. Pollini, "*Natural Products Synthesis Through Pericyclic Reactions*", American Chemical Society, Washington, D. C., **1983**. (b) W. Carruthers, "*Cycloaddition Reactions in Organic Synthesis*", Pergamon Press, Oxford, **1990**.

[3] For a recent review, see: K. Ishihara, H. Yamamoto, *Cattech*, **1997**, 51–62.

[4] R. A. Sheldon, "*Catalysis, the Atom Utilization Concept and Waste Minimization*", in: "Industrial Environmental Chemistry", Eds. D. T. Sawyer, A. E. Martell, Plenum Press, New York, **1992**, p. 99–119.

[5] For a review, see: U. Pindur, G. Lutz, C. Otto, *Chem. Rev.* **1993**, *93*, 741–761.

[6] See for example: (a) H. Reimlinger, U. Krüerke, E. de Ruiter, *Chem. Ber.* **1970**, *103*, 2317–2319. (b) I. E. Maxwell, R. S. Downing, S. A. J. van Langen, *J. Catal.* **1980**, *61*, 485–492. (c) R. M. Dessau, *J. Chem. Soc., Chem. Commun.* **1986**, 1167–1168. (d) S. Ghosh, N. L. Bauld, *J. Catal.* **1985**, *95*, 300–304.

[7] P. S. Landis (Mobil Oil Corp.), US. 3359285 (3 Jul **1968**), CA *69*: 10098b.

[8] J. Ipaktschi, *Z. Naturforsch., B*, **1986**, *41B*, 496–498.

[9] See, for example: (a) K. Bornholdt, H. Lechert, *Stud. Surf. Sci. Catal.* **1995**, *94* (Catalysis by Microporous Materials), 619–626. (b) L. Eklund, A-K. Axelsson, Å. Nordahl, R. Carlson, *Acta Chem. Scand.* **1993**, *47*, 581–591. (c) M. Onaka, R. Yamasaki, *Chem. Lett.* **1998**, 259–260.

[10] U. Pindur, M. Haber, *Heterocycles* **1991**, *32*, 1463–1470.

[11] R. Durand, P. Geneste, J. Joffre, C. Moreau, *Stud. Surf. Sci. Catal.* **1993**, *78* (Heterogeneous Catalysis and Fine Chemicals III), 647–652.

[12] Y. V. S. Narayana Murthy, C. N. Pillai, *Synth. Commun.* **1991**, *21*, 783–791.

[13] D. H. Yin, D. L. Yin, Q. H. Li, *Chin. Chem. Lett.* **1996**, *7*, 697–698.

[14] P. Lazlo, J. Lucchetti, *Tetrahedron Lett.* **1984**, *25*, 4387–4388.

[15] P. Laszlo, H. Moison, *Chem. Lett.* **1989**, 1031–1034.

[16] J. Cabral, P. Laszlo, M. T. Montaufier, *Tetrahedron Lett.* **1989**, *29*, 547–550.

[17] J. M. Adams, K. Martin, R. W. McCabe, *J. Inclusion Phenom.* **1987**, *5*, 663–674.

[18] J. M. Adams, S. Dyer, K. Martin, W. A. Matear, R. W. McCabe, *J. Chem. Soc., Perkin Trans. 1* **1994**, 761–765.

[19] C. Cativiela, F. Figueras, J. M. Fraile, J. I. García, M. Gil, J. A. Mayoral, L. C. de Ménorval, E. Pires, *Stud. Surf. Sci. Catal.* **1993**, *78* (Heterogeneous Catalysis and Fine Chemicals III), 495–502, and references cited therein.

[20] C. Cativiela, F. Figueras, J. M. Fraile, J. I. García, J. A. Mayoral, *Tetrahedron: Asymmetry* **1993**, *4*, 223–228.

[21] C. Cativiela, J. M. Fraile, J. I. García, J. A. Mayoral, E. Pires, F. Figueras, *J. Mol. Catal.* **1994**, *89*, 159–164.

[22] J. M. Fraile, J. I. García, J. A. Mayoral, E. Pires, T. Tarnai, F. Figueras, *Appl. Catal. A: General* **1996**, *136*, 113–123.

[23] J. M. Fraile, J. I. García, D. Gracia, J. A. Mayoral, T. Tarnai, F. Figueras, *J Mol. Catal. A: Chemical* **1997**, *121*, 97–102.

[24] M. Hudlicky, *J. Org. Chem.* **1974**, *39*, 3460–3461.

[25] M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jiménez, J. C. Palacios, B. C. Ranu, *Tetrahedron Lett.* **1998**, *39*, 2013–2016, and references cited therein.

[26] M. Koreeda, D. J. Ricca, J. I. Luengo, *J. Org. Chem.* **1988**, *53*, 5586–5588.

[27] V. V. Veselovsky, A. S. Gybin, A. V. Lozanova, A. M. Moiseenkov, W. A. Smit, R. Caple, *Tetrahedron Lett.* **1988**, *29*, 175–178.

[28] M. Conrads, J. Mattay, J. Runsink, *Chem. Ber.* **1989**, *122*, 2207–2208.

[29] M. Prokeöová, E. Solcániová, S. Toma, K. W. Muir, A. A. Torabi, G. R. Knox, *J. Org. Chem.* **1996**, *61*, 3392–3397.

[30] M. Prokeöová , G. Rihs, S. Toma, *Collect. Czech. Chem. Commun.* **1996**, *61*, 364–370.

[31] G. H. Posner, J.-C. Carry, J. K. Lee, D. S. Bull, H. Dai, *Tetrahedron Lett.* **1994**, *35*, 1321–1324.

[32] T. T. Prabhu, S. D. Samant, *Ind. J. Chem.* **1996**, *35B*, 14–18.

[33] C. Cativiela, F. Figueras, J. I. García, J. A. Mayoral, E. Pires, A. J. Royo, *Tetrahedron: Asymmetry* **1993**, *4*, 621–624.

[34] C. Cativiela, J. I. García, J. A. Mayoral, E. Pires, R. Brown, *Tetrahedron* **1995**, *51*, 9217–9222.

[35] (a) C. Cativiela, J. I. García, J. A. Mayoral, E. Pires, A. J. Royo, F. Figueras, *Tetrahedron* **1995**, *51*, 1295–1300. (b) C. Cativiela, J. I. García, J. A. Mayoral, E. Pires, A. J. Royo, F. Figueras, *Appl. Catal. A: General* **1995**, *131*, 159–166.

[36] C. Cativiela, J. M. Fraile, J. I. García, M. Pilar López, J. A. Mayoral, E. Pires, *Tetrahedron: Asymmetry* **1996**, *7*, 2391–2398.

[37] J. M. Fraile, J. I. García, D. Gracia, J. A. Mayoral, E. Pires, *J. Org. Chem.* **1996**, *61*, 9479–9482.

[38] J. M. Fraile, J. I. García, J. Massam, J. A. Mayoral, E. Pires, *J. Mol. Catal A: Chemical* **1997**, *123*, 43–47.

[39] M. B. McGinnis, K. Vagle, J. F. Green, L. C. Tan, R. Palmer, J. Siler, R. M. Pagni, G. W. Kabalka, *J. Org. Chem.* **1996**, *61*, 3496–3500.

[40] J. M. Fraile, J. I. García, J. A. Mayoral, A. J. Royo, *Tetrahedron: Asymmetry* **1996**, *8*, 2263–2276.

[41] F. M. Menger, T. Tsuno, *J. Am. Chem. Soc.* **1989**, *111*, 4903–4907.

[42] S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1996**, *61*, 2256–2257.

[43] S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1998**, *120*, 2985–2986.

[44] K. Kamahori, K. Ito, S. Itsuno, *J. Org. Chem.* **1996**, *61*, 8321–8324, and references cited therein.

[45] B. Altava, M. I. Burguete, B. Escuder, S. V. Luis, R. V. Salvador, J. M. Fraile, J. A. Mayoral, A. J. Royo, *J. Org. Chem.* **1997**, *62*, 3126–3134, and references cited therein.

[46] G. A. Olah, D. Meidar, A. P. Fung, *Synthesis* **1979**, 270–271.

[47] M. A. Harmer, W. E. Farneth, Q. Sun, *J. Am. Chem. Soc.* **1996**, *118*, 7708–7715.

[48] G. J. Meuzelaar, R. A. Sheldon, unpublished results.

[49] G. J. Meuzelaar, L. Maat, R. A. Sheldon, I. V. Kozhevnikov, *Catal. Lett.* **1997**, *45*, 249–251.

[50] G. J. Meuzelaar, L. Maat, R. A. Sheldon, *Catal. Lett.* **1998**, *56*, 49–51.

[51] A. Keshavaraja, V. R. Hegde, B. Pandey, A. V. Ramaswamy, P. Kumar, T. Ravindranathan, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2143–2145.

[52] C. Cativiela, J.M. Fraile, J.I. García, J.A. Mayoral, J.M. Campelo, D. Luna, J.M. Marinas, *Tetrahedron: Asymmetry* **1993**, *4*, 2507–2512.
[53] F.M. Bautista, J.M. Campelo, A. Garcia, D. Luna, J.M. Marinas, J.I. García, J.A. Mayoral, E. Pires, *Catal. Lett.* **1996**, *36*, 215–221.
[54] J. Howarth, K. Hanlon, D. Fayne, P. McCormac, *Tetrahedron Lett.* **1997**, *38*, 3097–3100.
[55] K. Endo, T. Koike, T. Sawaki, O. Hayashida, H. Masuda, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, *119*, 4117–4122.

6.5 Dehydration of Alcohols

Árpád Molnár and Mihály Bartók

6.5.1 Introduction

Dehydration of alcohols over solid catalysts can yield alkenes by intramolecular dehydration, whereas ethers are the product of an intermolecular process. The catalysts used can be acidic or basic solids or bifunctional acid–base materials. Although selective synthesis of any desired product is possible, complications can arise as a result of side-reactions–dehydrogenation and decomposition of the starting alcohol, decomposition and consecutive transformations of intermediates and products (β-cleavage of carbocations, oligomerization of alkenes).

In a similar fashion, diols and polyols can be transformed selectively to important chemicals, e. g. carbonyl compounds, dienes and cyclic ethers. Numerous reviews give adequate treatment of the dehydration both of monohydric alcohols [1–11] and of diols and polyols [12–14].

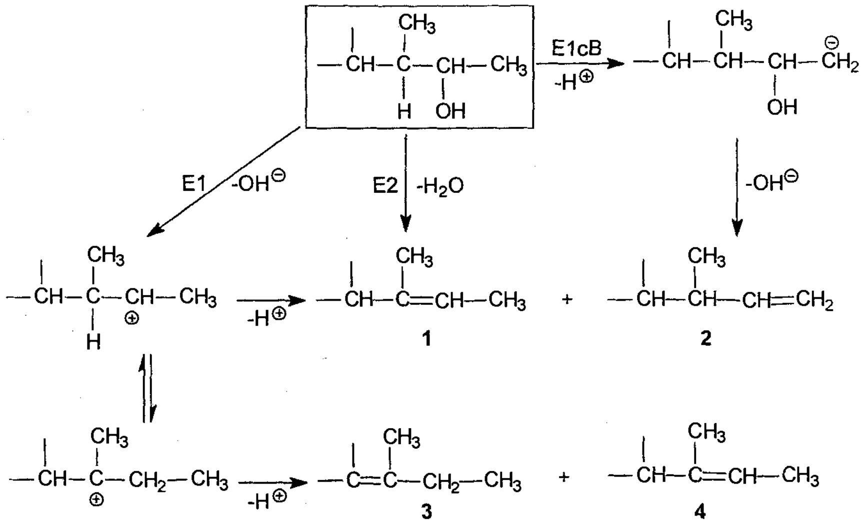
An additional specific dehydration, the transformation of methanol to gasoline-range hydrocarbons (MTG process [15,16]) has been running on a commercial scale for a short time. A partial conversion, the methanol-to-olefin process (MTO process [15,16]), might become more important as selective means of obtaining lower olefins.

6.5.2 Dehydration of Monohydric Alcohols

6.5.2.1 Synthesis of Alkenes

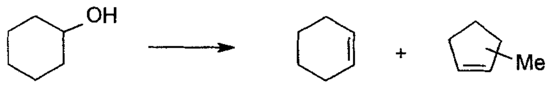
When monohydric alcohols undergo dehydration, isomeric alkenes can be formed by the loss of water by β (or 1,2-) elimination. Selective synthesis of certain alkenes can, however, be accomplished–when primary alcohols are treated with appropriate solid catalysts terminal alkenes are formed. In contrast, either 1- or 2-alkenes can be produced by dehydration of secondary 2-alkanols. The reactivity of alcohols follows the sequence tertiary > secondary > primary.

Thorough mechanistic studies have established that dehydration over acidic oxides follows two major routes. A single-step, concerted E2 mechanism, usually results in alkenes with Saytzeff orientation (more substituted alkene isomers, **1**) (Scheme 1). The E1 mechanism, in turn, is a two-step process which starts with the removal of the OH group. Because carbocationic intermediates are involved they eventually give rise to a mixture of isomeric alkenes (**1**–**4**). A third route of lesser significance (E1cB mechanism), initiated by the removal of a proton from the β carbon, occurs characteristically on basic oxides. In this route the Hofmann orientation (formation of the less substituted alkene, **2**) usually prevails.



Scheme 1.

When used for the dehydration of alcohols most acidic oxides result in the formation of alkenes with Saytzeff orientation, i. e. an E2 mechanism is operative. This means that secondary 2-alkanols are transformed to 2-alkenes. A characteristic catalyst achieving such selectivity is alumina treated with alkali metal cations, ammonia, or organic bases [2]. Such treatment is necessary because pure, strongly acidic alumina induces skeletal rearrangements and double bond migration. The importance of choosing a catalyst with the appropriate characteristics is illustrated in Scheme 2 [17,18].



	conversion (%)	selectivity	
Al_2O_3 (1% K), 683 K	95	100	0
pure Al_2O_3, 623 K	95	89	11
693 K	99	40	60

Scheme 2.

In contrast with alumina, thoria is considered to be a typical ElcB catalyst enabling the synthesis of 1-alkenes from 2-alkanols. Comparative studies including lanthanide and alkaline earth oxides and a variety of labeled alcohols have indicated that selectivity depends on the relative strength and concentration of acidic and basic centers [19–22]. The ElcB mechanism is known to be associated with dehydrogenation [8]. The dehydrating activity of oxides was observed to increase with the covalent character of the metal–oxygen bond, whereas increasing the ionic character was shown to enhance dehydrogenation activity [9]. Thoria with weakly basic sites used at relatively low temperature results in the best 1-alkene selectivity and dehydrogenation is negligible. A specially prepared hydrous zirconium oxide has also been reported to be selective in the formation of 1-alkenes [23]. Oxides with strongly basic sites are, in turn, able to bring about dehydrogenation.

Phosphates are also active dehydration catalysts [6,8,9]. Although a mixed (E1 and E2) mechanism has been reported [24], most of these materials and particularly BPO_4 have typical E1 behavior [25–27]. The involvement of the carbocationic intermediate results in a complex mixture of isomeric alkenes [27,28] and intramolecular and intermolecular dehydration (alkene and ether formation, respectively) are often parallel processes. For example, aluminum phosphates with P/Al < 1 yield a mixture of alkenes and ethers whereas those with P/Al > 1 give alkenes selectively [6,29]. Dehydration activity usually correlated with surface acidity [29–31]. The strongly acidic sites of $AlPO_4$ were found to promote alkene formation [26].

Numerous studies, including mechanistic and kinetic investigations mostly with simple alcohols, have been performed with molecular sieves as dehydration catalysts [8,32–34]. Although highly active these are rarely used for converting alcohols with complicated structures to alkenes. The reason is that these catalysts are not selective–a prevalent E1 mechanism, i. e. the involvement of carbocationic intermediates, and parallel inter- and intramolecular processes result in the formation of isomeric alkenes and ethers. Alcohols with specific structure, however, can be selectively transformed to alkenes. For example, 1-phenyl-1-ethanol is transformed to styrene in 95 % yield over HZSM-5 zeolite at 493 K [34]. Ether formation, however, was shown to be significant when *α*-(*p*-tolyl)ethanol was reacted over zeolite HY [35]. A low concentration of the reactant alcohol inside the zeolite is required to prevent such dimerization-type reaction; a suitable competing solvent should be selected.

Zeolites are also excellent catalysts in the selective dehydration of tertiary alcohols. Shape selectivity, i. e. selective dehydration of 1-butanol to 1-butene over CaA zeolite in the presence of 2-butanol has also been reported [36]. The bulky 2-methylcyclohexanol, in turn, undergoes dehydration over zeolite Y, although resulting in a mixture of alkenes [37].

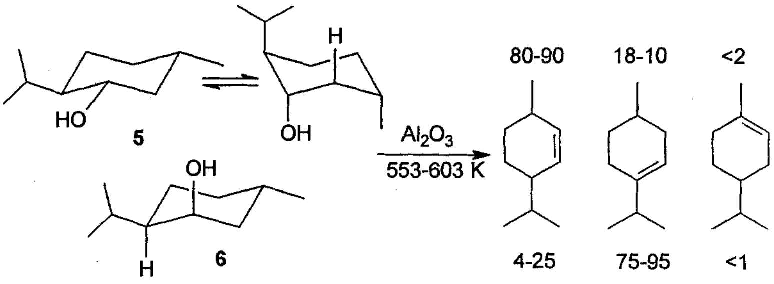
Acidic clays are widely applied in the dehydration of alcohols [38]. Although similar to zeolites in their capacity to induce the formation of both alkenes and ethers, selective alkene synthesis is possible. Various layered materials (clays, ion-exchanged montmorillonite, pillared layered clays) are very active and, in general, selective in transforming primary, secondary, and tertiary aliphatic alcohols to 1-alkenes [39–43]. Al^{3+}-exchanged montmorillonite, however, induces ether formation from primary alcohols and 2-propanol [41]. Substituted 1-phenyl-1-ethanols yield the corresponding styrene derivatives at high temperature (653–673 K) [44].

Ion-exchange resins can also be used for dehydration [8]. The superacidic Nafion-H catalyzes selective alkene formation from 1-propanol, 2-propanol, and *tert*-butyl alcohol at 433 K [45]. Ion-exchange resins have found industrial application in the production of isobutylene from *tert*-butyl alcohol [46].

Specific reagents and methods have recently been reported. *p*-Toluenesulfonic acid adsorbed on silica gel is an excellent catalyst of the dehydration of 3-hydroxy steroids to yield Δ^2-olefins and $\Delta^{3,5}$-dienes [47]. Trisubstituted alkenes are produced in excellent yields when the corresponding benzylic alcohols are treated with trichloroacetic acid in the solid state (room temperature, 5 min) [48].

The stereochemistry of dehydration of alcohols over heterogeneous catalysts differs from that under homogeneous conditions. In the homogeneous phase *cis*-preference (the bulkiest groups in the *cis*-position) usually prevails and *anti* elimination occurs; this involves the thermodynamically more stable antiperiplanar conformation of the leaving groups (H and OH). In contrast, dehydration over solid catalysts is usually characterized by *syn* elimination. In this case the interaction between the OH group and a surface acidic center and, at the same time, between a β hydrogen and a basic center induces the concerted elimination of water. This can occur despite the unfavorable eclipsed conformation required. In this respect the behavior of alumina is anomalous because it favors *anti* elimination. Interpretation of these phenomena is based on results from the transformation of deuterium-labeled stereoisomeric alcohols, careful analysis of product distributions, and consideration of transition states and steric and electronic effects [49–54].

Important information about the stereochemistry of dehydration has been obtained by studying the transformation of cyclic alcohols; many of these reactions have proved suitable for the selective synthesis of alkenes [2]. The dehydration of menthol (**5**) and neomenthol (**6**) illustrates the usefulness of such processes (Scheme 3; axial hydrogens participating in water loss to form the major menthene isomers are shown) [55]. The regioselectivity observed points to an *anti* elimination mechanism. Isomer **6**, with a trans OH/H configuration in the most stable conformation, reacts faster than compound **5**.



Scheme 3.

Recent studies [11,24,56–60] have enabled further understanding of the fine detail of the dehydration process and the nature of the active sites. It is important to emphasize that the preparation and pretreatment of the catalysts, and the reaction conditions used, are of crucial practical importance in achieving selective formation of a given alkene. It has been pointed out that steric effects, the geometry of the catalytic site, and electronic effects may play a role in determining the alkene selectivity [61].

Dehydration to produce alkenes is practiced in industry in the manufacture of ethylene from ethanol over alumina, in the production of isomeric C_4 alkenes from *tert*-butyl alcohol catalyzed by ion exchange resins, and in the transformation of 1-phenyl-1-ethanol to yield styrene in the presence of zirconia (styrene/propylene oxide process) [62].

6.5.2.2 Preparation of α, β-Unsaturated Carbonyl Compounds

α- and β-hydroxy carbonyl compounds both undergo easy dehydration to form α,β-unsaturated carbonyl compounds. Zeolites, and in particular, silica-rich alumino- and borosilicate pentasil zeolites are suitable catalysts for the transformation of α-hydroxy carbonyl compounds [63]. β-Hydroxy carbonyl compounds, produced by aldol condensation, are usually not isolated but transformed in situ. Acidic zeolites (e. g. HZSM-5), again, have recently gained importance in such applications [63].

6.5.2.3 Synthesis of Ethers

Alcohols can undergo dehydration to produce ethers in an intermolecular reaction (Scheme 4) [1,3]. Characteristically only symmetrical ethers can be prepared in this way, usually via a bimolecular reaction (S_N2 mechanism). When a mixture of two alcohols is reacted a mixture of three ethers is produced. Mixed ethers, however may be synthesized by reacting a tertiary alcohol with a primary or secondary alcohol. In this reaction an S_N1 mechanism is operative, with involvement of the tertiary carbocation formed from the tertiary alcohol.

$$2\,\mathrm{R{-}OH} \xrightarrow[\mathrm{-H_2O}]{\text{acidic catalysts}} \mathrm{R{-}O{-}R}$$

Scheme 4.

Intramolecular dehydration (alkene formation) and intermolecular dehydration are competitive processes but selective ether synthesis is possible by applying appropriate catalysts under suitable reaction conditions.

Characteristic examples of the dehydration of primary alcohols are collected in Table 1. Kaolinite containing alumina [67], aluminas, modified aluminas [68,69], silica–aluminas [70] and $AlPO_4$ [26] have also been studied. Ether formation was found to be favored by a high concentration of sites of intermediate or weak acidity.

Nafion-H is a particularly efficient and recyclable catalyst. Surprisingly, even methyl isobutyl ether is formed selectively in the reaction of methanol and 2-methyl-1-propanol over Nafion-H, ruling out the involvement of a carbocationic intermediate [71].

When secondary alcohols are reacted reaction conditions (choice and quantity of catalyst, temperature) are even more important, because of more competitive alkene formation and the unfavorable steric effect. Nafion-H has exceptionally high activity in the formation of ethers from cyclohexanol and *exo*-norborneol (91 % and 99 % yield, respectively) [66]. This is in sharp contrast with Al^{3+}-exchanged bentonite which gave dicyclohexyl ether in mere 15 % yield [72].

The pore structure of the catalyst has been shown to have a large influence in the etherification of 1-phenyl-1-ethanol [73]; the favorable performance of tita-

Table 1. The transformation of primary alcohols to symmetrical ethers.

Alcohol	Catalyst, reaction conditions	Yield (%)
Methanol	Al_2O_3 [1]	100
	Ti^{4+}-layered silicates and TiO_2 (573 K) [64]	41–51
Ethanol	Al_2O_3 (523 K) [1]	81
	Al^{3+}-montmorillonite (433 K) [41]	70
1-Propanol	Al_2O_3 (458 K) [1]	54
	Al^{3+}-montmorillonite (473 K) [41]	67
	ion-exchange resin (438 K) [65]	66
1-Butanol	$AlPO_4$ [6]	54
C_6–C_{10} primary alcohols	ion-exchange resin (408–423 K) [65]	65–80
C_5–C_{10} primary alcohols	Nafion-H (418–423 K or reflux, 7–12 h) [66]	92–98
PhArCHOH	*p*-toluenesulfonic acid (288–323 K) (reaction in the solid state) [48]	74–98

nium-pillared montmorillonite compared with zeolite Y-42 (98.4 % selectivity at 48 % conversion) was attributed to the better accessibility of the acidic sites of the former catalyst.

Methyl *tert*-butyl ether (MTBE) is an important industrial product used as oxygenate additive in reformulated gasoline. Environmental concern makes its future uncertain, however. Although mainly manufactured by reaction of isobutylene with methanol, it is also produced commercially from methanol and *tert*-butyl alcohol, a by-product of propylene oxide manufacture. Numerous observations from the use of heteropoly acids have been reported. These compounds were used either as neat acids [74], or supported on oxides [75], silica or K-10 montmorillonite [76]. They were also used in silica-included form [77] and as acidic cesium salts [74,77]. Other catalysts studied were sulfated ZrO_2 [76], Amberlyst 15 ion-exchange resin [76], HZSM-5 [76], HF-treated montmorillonite, and commercial mineral acid-activated clays [75]. Hydrogen fluoride-treatment of montmorillonite has been shown to furnish particularly active and stable acid sites thereby ensuring high MTBE selectivity (up to 94 % at 413 K) [75].

6.5.2.4 Dehydration of Methanol to Produce Hydrocarbons

Mobil researchers have developed processes to convert methanol to valuable hydrocarbons. The treatment of methanol over HZSM-5 results in the formation of a mixture of gasoline-range hydrocarbons (methanol-to-gasoline or MTG process) [15,16] including many aromatic compounds. The transformation can be modified to produce a large amount ($> 90\%$) of light alkenes by treating methanol with small-pore zeolites (methanol-to-olefin or MTO process) [15,16]. The MTO process ensures future lower olefin monomer supply. The catalyst of choice is SAPO-34 [78]. A detailed discussion of this topic is, however, beyond the scope of this chapter.

6.5.3. Dehydration of Diols

6.5.3.1. Dehydration to Form Carbonyl Compounds

Vicinal diols can be transformed to carbonyl compounds in the presence of electrophilic catalysts. This reaction, called the pinacol rearrangement, is discussed in detail in Section 5.5.

6.5.3.2 Synthesis of Dienes

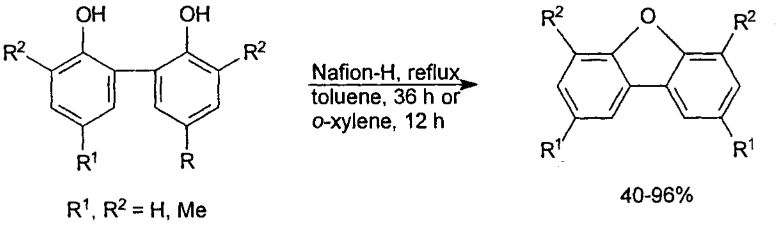
A rather limited possibility is the dehydration of certain 1,2- or 1,3-diols to form conjugated dienes. Pinacol (2,3-dimethyl-2,3-butanediol) can be transformed to 2,3-dimethyl-1,3-butadiene over alumina [79], and the treatment of a variety of 1,3-diols on zeolites also leads to dienes [80,81]. 2,4-Pentadiene is produced in the highest yield (81 %) by reacting 2,4-pentanediol over NaX at 548 K. The synthesis of 1,3-butadiene can be accomplished by the dehydration of 2,3-butanediol or 1,3-butanediol in the presence of a variety of clay catalysts [38].

The behavior of ditertiary diols can be exceptional. Partial dehydration of terpene 1,4- and 1,5-diols over A zeolites gives unsaturated alcohols selectively [82], whereas diene formation can be accomplished by use of Al_2O_3–$AlPO_4$ [83]. As zeolites A give no access to branched or cyclic reactants their activity might arise from the outer surface and/or binder materials.

6.5.3.3 Cyclodehydration

A plethora of reagents including a variety of solid acids is available for transforming higher diol homologs to cyclic ethers [12,13,38]. These include ion-exchange resins, which are used in an industrial process for the production of tetrahydrofuran from 1,4-butanediol [84]. The best yields are achieved in the transformation of 1,4- and 1,5-diols to the corresponding oxolane (tetrahydrofuran) and oxane (tetrahydropyran) derivatives, respectively (Table 2). Larger rings, in general, are formed with lower selectivity.

Nafion-H has especially excellent characteristics [88,89]. It has been shown to ensure high yields under mild conditions even in the cyclodehydration of diphenols (Scheme 5) [92], a reaction which usually requires long reaction times, elevated temperature, and the use of excess acid when performed under homogeneous conditions.

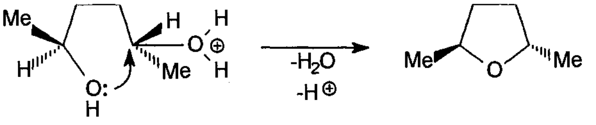


Scheme 5.

Table 2. Cyclodehydration of higher diol homologs to the corresponding cyclic ethers.

Compound	Catalyst, reaction conditions	Yield (%)
1,4-Butanediol	Bentonite (523–573 K) [38]	93–100
	NaHX (493–573 K) [85]	95–98
	Al_2O_3–$AlPO_4$ (distillation) [83]	94
	Al^{3+}-montmorillonite (433–473 K) [86,87]	93–100
	Nafion-H (405 K) [88]	91
	Nafion-H (448 K) [89]	86
	Heteropoly acids on silica (473 K) [90]	99
2,5-Hexanediol (isomeric mixture)	NaHY (573 K) [80]	94
	Al_2O_3–$AlPO_4$ (distillation) [83]	84
	Nafion-H (405 K) [88]	91
	Nafion-H (448 K) [89]	90
meso-2,5-Hexanediol	Dowex 50 (403 K) [91]	100
	$H_3[PW_{12}O_{40}]$ (473 K) [90]	100
1,5-Pentanediol	NaHY (573 K) [80]	95
	Al_2O_3–$AlPO_4$ (distillation) [83]	80
	Al^{3+}-montmorillonite (463–473 K) [86,87]	94–95
	Nafion-H (405 K) [88]	86
	Nafion-H (448 K) [89]	86
2,5-Dimethyl-2,5-hexanediol	Al^{3+}-montmorillonite (433 K) [87]	56
	Nafion-H (405 K) [88]	94
1,6-Hexanediol	Nafion-H (405 K) [88]	72
1,7-Heptanediol	Nafion-H (405 K) [88]	51

Mechanistic studies with stereoisomeric 2,5-hexanediols showed that an intramolecular S_N2 type mechanism is operative; high stereoselectivity with configurational inversion at one stereocenter has been reported [90,91,93]. *meso*-2,5-Hexanediol (**7**), consequently, undergoes dehydration to yield *trans*-2,5-dimethyloxolane (Scheme 6), whereas the racemic compound is converted to *cis*-2,5-dimethyloxolane.

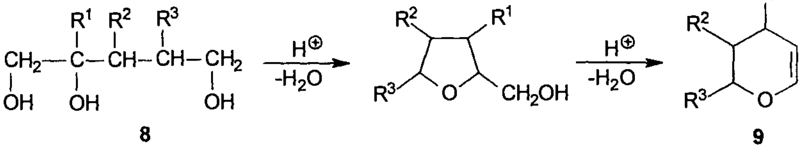


7 *trans*-2,5-dimethyloxolane

Scheme 6.

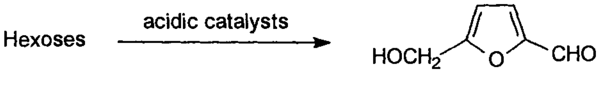
6.5.4 Dehydration of Polyols

One classical polyol dehydration reaction is the transformation of glycerol to acrolein in the presence of fused, powdered $KHSO_4$ [94]. Another important example is the dehydration of substituted 1,2,5-triols (**8**) to dihydropyran derivatives (**9**). The transformation consists of two steps–the conversion of **8** to 2-hydroxymethyltetrahydrofuran which then undergoes a second dehydration step and concomitant ring expansion (the Demyanov rearrangement; Scheme 7). When performed in the presence of zeolites, however, dihydropyrans are formed directly in a single step [63].



Scheme 7.

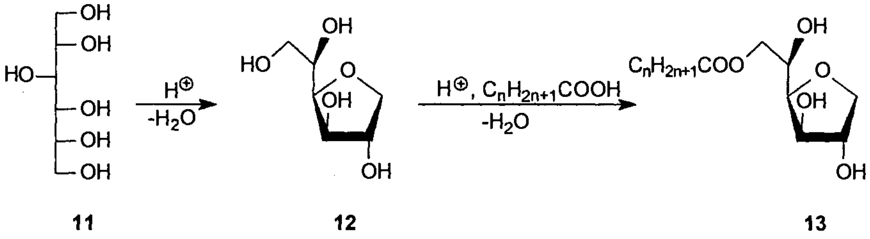
Increasing attention has recently been devoted to the selective dehydration of hexoses, particularly fructose, to 5-hydroxymethylfurfural (**10**, Scheme 8) [14]. This compound, which can thus be derived from renewable biomass and agricultural surpluses, finds application as starting material in the preparation of fine chemicals and polymers.



Scheme 8. **10**

Dehydration is usually performed in aqueous media with continuous extraction. Strongly acidic cation-exchange resins [95–97] and zeolites [98–100] have usually been studied. Zeolites are easy to regenerate and are applicable at higher temperatures. More importantly, they are more selective, because side-reactions including rehydration then C–C bond cleavage and oligomerization are less important. Mordenites have superior characteristics, because of their low mesoporosity and shape selectivity [99,100]. Heterogeneous niobium catalysts (niobic acid, H_3PO_4-treated niobic acid, and niobium phosphate) [101] have recently been found to be highly selective catalysts.

The dehydration of sorbitol (**11**) and the esterification with fatty acids of the resulting anhydrosorbitol or sorbitan (**12**) leads to sorbitan esters (**13**) an early group of fully green surfactants (Scheme 9) [102]. Sold, even in 1938, under the trade name Span$^{(R)R}$, they were patented in 1944 [103]. Dehydration of sorbitol leads, in fact, to isomeric anhydrosorbitols; the main product is 1,4-sorbitan, and 3,6-sorbitan is also formed. Esterification, in turn, is selective, occurring with the participation of the more reactive primary hydroxyl group.



Scheme 9.

Sorbitan esters can be produced by transesterification in the presence of basic catalysts [104]. This process does not, however, give satisfactory results–dehydration of sorbitol is incomplete and, therefore, sorbitol esters can be the major products [105]. Nowadays the acid-catalyzed direct esterification is the major route practiced in industry. Under these conditions both intramolecular dehydration and esterification occur to satisfactory extents [106]. When fatty acids in large excess are reacted for longer times sorbitan triesters are formed; these can be used as water-in-oil emulsifiers.

6.5.5 Conclusions

A wide range of solid catalysts can be used in the dehydration of monohydric and polyhydric alcohols. The materials active in these processes are mostly acidic in nature. Despite competing reactions various valuable products (alkenes, ethers, carbonyl compounds, dienes and cyclic ethers) can be synthesized selectively over carefully selected catalysts under appropriate reaction conditions.

References

[1] H. Meerwein in *Methoden der Organischen Chemie (Houben–Weyl)*, Vol. 6/3, Thieme, Stuttgart, **1965**, pp. 11–19.
[2] H. Pines, J. Manassen, *Adv. Catal.* **1966**, *16*, 49.
[3] H. Feuer, J. Hooz in *The Chemistry of Functional Groups. The Chemistry of the Ether Linkage* (Ed.: S. Patai), Wiley, London, **1967**, pp. 457–460.
[4] H. Knözinger in *The Chemistry of Functional Groups. The Chemistry of the Hydroxyl Group* (Ed.: S. Patai), Wiley, London, **1971**, p. 641.
[5] R. Askani in *Methoden der Organischen Chemie (Houben–Weyl)*, Vol. 5/1b, Thieme, Stuttgart, **1972**, pp. 45–62.
[6] J. B. Moffat, *Catal. Rev.-Sci. Eng.* **1978**, *18*, 199.
[7] S. G. Wilkinson in *Comprehensive Organic Chemistry* (Eds.: D. Barton, W. D. Ollis), Vol. 1, Pergamon Press, Oxford, **1979**, pp. 640–644.
[8] J. M. Winterbottom in *Catalysis, A Specialist Periodical Report*, Vol. 4 (senior reporters.: C. Kemball, D. A. Dowden), The Royal Society of Chemistry, Burlington House, London, **1981**, p. 141.
[9] K. Tanabe, M. Misono, Y. Ono, H. Hattori, *New Solid Acids and Bases*, Kodansha, Tokyo, Elsevier, Amsterdam, **1989**, pp. 260–272.
[10] J. M. Percy in *Comprehensive Organic Functional Group Transformations* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Vol. 1 (Ed.: S. M. Roberts), Pergamon, **1995**, pp. 576–579.
[11] K. I. Zamaraev, J. M. Thomas, *Adv. Catal.* **1996**, *41*, 335.
[12] M. Bartók, Á. Molnár in *The Chemistry of Functional Groups. Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogs* (Ed.: S. Patai), Wiley, Chichester, **1980**, p. 721.
[13] Á. Molnár in *The Chemistry of Functional Groups. Supplement E2: The Chemistry of Hydroxyl, Ether and Peroxide Groups* (Ed.: S. Patai), Wiley, Chichester, **1993**, pp. 992–998.
[14] B. F. M. Kuster, *Starch/Stärke* **1990**, *42*, 314.
[15] C. D. Chang, *Catal. Rev.-Sci. Eng.* **1983**, *25*, 1; **1984**, *26*, 323; *Hydrocarbons from Methanol*, Marcel Dekker, New York, **1983**.
[16] N. Y. Chen, W. E. Garwood, F. G. Dwyer, *Shape Selective Catalysis in Industrial Practice*, Marcel Dekker, New York, **1989**, p. 219.

[17] H. Pines, W. O. Haag, *J. Am. Chem. Soc.* **1961**, *83*, 2847.

[18] C. A. Drake, M. M. Martinovich, S. J. Marwil, *Chem. Eng. Prog.* **1984**, *81*, 52.

[19] P. Canesson, M. Blanchard, *Bull. Soc. Chim. Fr.* **1973**, 2839; *J. Catal.* **1973**, *42*, 205.

[20] K. Thomke, *Z. Phys. Chem.* **1977**, *105*, 75, 87; **1977**, *106*, 225.

[21] R. Schollner, H. Siegel, G. Wendt, *Z. Anorg. Allg. Chem.* **1978**, *432*, 231.

[22] H. Siegel, R. Schollner, D. Dombrowski, G. Wendt, *Z. Anorg. Allg. Chem.* **1978**, *441*, 252.

[23] Chevron Company (W. A. Sweeney), US 5,130,287 (1992); *Chem. Abstr.* **1992**, *117*, 138660f.

[24] R. A. W. Johnstone, J.-Y. Liu, D. Whittaker, *J. Chem. Soc., Perkin Trans. 2* **1998**, 1287.

[25] K. Thomke, *J. Catal.* **1976**, *44*, 339; *Z. Phys. Chem.* **1977**, *106*, 295.

[26] F. M. Bautista, B. Delmon, *Appl. Catal., A.* **1995**, *130*, 47.

[27] M. C. Cruz Costa, L. F. Hodson, R. A. W. Johnstone, J.-Y. Liu, D. Whittaker, *J. Mol. Catal. A: Chem.* **1999**, *142*, 349.

[28] J.-P. Damon, J.-M. Bonnier, B. Delmon, *Bull. Soc. Chim. Fr.* **1975**, 449.

[29] A. Tada, M. Yoshida, M. Hirai, *Nippon Kagaku Kaishi* **1973**, 1379.

[30] J. B. Moffat, A. S. Riggs, *J. Catal.* **1976**, *42*, 388.

[31] S. S. Jewur, J. B. Moffat, *J. Catal.* **1979**, *57*, 167.

[32] M. L. Poutsma in *Zeolite Chemistry and Catalysis*, ACS Monograph 171 (Ed.: J. A. Rabo), American Chemical Society, Washington D. C., **1974**, pp. 535–537.

[33] P. A. Jacobs, *Carboniogenic Activity of Zeolites*, Elsevier, Amsterdam, **1977**, pp. 100–107.

[34] M. Butters in *Solid Supports and Catalysts in Organic Synthesis*, (Ed.: K. Smith), Ellis Horwood–PTR Prentice Hall, New York, **1992**, pp. 133–134.

[35] Th. M. Wortel, W. van den Heuvel, N. A. de Munck, H. van Bekkum, *Acta Phys. Chem.* **1978**, *24*, 341.

[36] P. B. Weisz, *Pure Appl. Chem.* **1980**, *52*, 2091.

[37] J. Ipaktschi, M. Brück, *Chem. Ber.* **1990**, *123*, 1591.

[38] M. Balogh, P. Laszlo, *Organic Chemistry Using Clays*, Springer, Berlin, **1993**, pp. 52–57.

[39] P. Mauret, E. Bordier, *C. R. Acad. Sci., Paris, Series C* **1968**, *266*, 1078.

[40] J. C. Davidtz, *J. Catal.* **1976**, *43*, 260.

[41] J. A. Ballantine, M. Davies, I. Patel, J. H. Purnell, M. Rayanakorn, K. J. Williams, J. M. Thomas, *J. Mol. Catal.* **1984**, *26*, 37.

[42] F. M. Tawfik, D. A. Alsayed, B. M. Hassan, S. A. Wahab, *Trans. Egypt. Soc. Chem. Eng.* **1987**, *13*, 58.

[43] I. D. Johnson, T. A. Werpy, T. J. Pinnavaia, *J. Am. Chem. Soc.* **1988**, *110*, 8545.

[44] A. A. Vansheidt, V. M. Zel'tser, *Zhur. Prikl. Khim.* **1948**, *21*, 512.

[45] G. A. Olah, G. K. S. Prakash, J. Sommer, *Superacids*, Wiley, New York, **1985**, p. 284.

[46] J. N. Armor, *Appl. Catal.* **1991**, *78*, 141.

[47] F. D'Onofrio, A. Scettri, *Synthesis* **1985**, 1159.

[48] F. Toda, H. Takumi, M. Akehi, *J. Chem. Soc., Chem. Commun.* **1990**, 1270.

[49] H. Knözinger, H. Bühl, K. Kochloefl, *J. Catal.* **1972**, *24*, 57.

[50] C. L. Kibby, S. S. Lande, W. K. Hall, *J. Am. Chem. Soc.* **1972**, *94*, 214.

[51] D. Dautzenberg, H. Knözinger, *J. Catal.* **1974**, *33*, 142.

[52] G. Forster, H. Noller, K. Thomke, *J. Catal.* **1976**, *44*, 492.

[53] J. Sedlacek, *Collect. Czech. Chem. Commun.* **1977**, *42*, 2027.

[54] H. Noller, K. Thomke, *J. Mol. Catal.* **1979**, *6*, 375.

[55] H. Pines, C. N. Pillai, *J. Am. Chem. Soc.* **1961**, *83*, 3270.

[56] M. I. Zaki, G. A. M. Hussein, H. A. El-Ammawy, S. A. A. Mansour, J. Polz, H. Knözinger, *J. Mol. Catal.* **1990**, *57*, 367.

[57] B. Shi, B. H. Davis, *J. Catal.* **1995**, *157*, 359.

[58] C. Lahousse, F. Maugé, J. Bachelier, J.-C. Lavalley, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 2907.

[59] A. Auroux, P. Artizzu, I. Ferino, V. Solinas, G. Leofanti, M. Padovan, G. Messina, R. Mansani, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 3263.

[60] A. Auroux, P. Artizzu, I. Ferino, R. Monaci, E. Rombi, V. Solinas, G. Petrini, *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 2619.

[61] B. H. Davis, *J. Org. Chem.* **1982**, *47*, 900.

[62] K. Tanabe, W. F. Hölderich, *Appl. Catal., A.* **1999**, *181*, 399.

[63] W. F. Hölderich in *Heterogeneous Catalysis and Fine Chemicals* (Eds.: M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier, G. Pérot), Elsevier, Amsterdam, **1988**, p. 83–90.

[64] Y. Morikawa, F.-L. Wang, Y. Moro-oka, T. Ikawa, *Chem. Lett.* **1983**, 1849.

[65] N. I. Shuikin, N. A. Pozdnyak, T. P. Dobrynina, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964**, 1705.

[66] G. A. Olah, T. Shamma, G. K. S. Prakash, *Catal. Lett.* **1997**, *46*, 1.

[67] K. Hashimoto, Y. Hanada, Y. Minami, Y. Kera, *Appl. Catal., A.* **1996**, *141*, 57.

[68] E. A. Paukshtis, K. Jirátová, R. I. Soltanov, E. N. Yurchenko, *Collect. Czech. Chem. Commun.* **1985**, *50*, 643.

[69] P. Berteau, S. Ceckiewicz, B. Delmon, *Appl. Catal.* **1987**, *31*, 361.

[70] P. Berteau, B. Delmon, J.-L. Dallons, A. Van Gysel, *Appl. Catal.* **1991**, *70*, 307.

[71] J. G. Nunan, K. Klier, R. G. Herman, *J. Catal.* **1993**, *139*, 406.

[72] D. Chatterjee, H. M. Mody, K. N. Bhatt, *J. Mol. Catal. A: Chem.* **1995**, *104*, L115.

[73] A. Gil, H. L. Del Castillo, J. Masson, J. Court, P. Grange, *J. Mol. Catal. A: Chem.* **1996**, *107*, 185.

[74] M. Matouq, T. Tagawa, S. Goto, *J. Chem. Eng. Jpn.* **1993**, *26*, 254.

[75] J. F. Knifton, J. C. Edwards, *Appl. Catal., A.* **1999**, *183*, 1.

[76] G. D. Yadav, N. Kirthivasan, *J. Chem. Soc., Chem. Commun.* **1995**, 203.

[77] Á. Molnár, Cs. Keresszegi, B. Török, *Appl. Catal., A.* **1999**, *189*, 217.

[78] S. Wilson, P. Barger, *Microporous Mesoporous Mater.* **1999**, *29*, 117.

[79] L. W. Newton, E. R. Coburn, *Org. Synth., Coll. Vol.* **1955**, *3*, 313.

[80] Á. Molnár, I. Bucsi, M. Bartók, *Acta Phys. Chem.* **1985**, *31*, 571.

[81] I. Bucsi, Á. Molnár, M. Bartók in *Heterogeneous Catalysis, Proc. 6th Int. Symposium* (Eds.: D. Sopov, A. Andreev, A. Palazov, L. Petrov), Publishing House of the Bulgarian Academy of Sciences, Sofia, **1987**, p. 158–163.

[82] M. Nomura, F. Yoshihito, *Nippon Nogei Kagaku Kaishi* **1983**, *57*, 139.

[83] A. Costa, J. M. Riego, *Synth. Commun.* **1987**, *17*, 1373.

[84] A. Chauvel, B. Delmon, W. F. Hölderich, *Appl. Catal., A.* **1994**, *115*, 173.

[85] Kh. I. Areshidze, G. O. Chivadze, *Khim. Geterotsikl. Soed.* **1969**, 195.

[86] D. Kotkar, P. K. Ghosh, *J. Chem. Soc., Chem. Commun.* **1986**, 650.

[87] D. Kotkar, S. W. Mahajan, A. K. Mandal, P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1749.

[88] G. A. Olah, A. P. Fung, R. Malhotra, *Synthesis* **1981**, 474.

[89] I. Bucsi, Á. Molnár, M. Bartók, G. A. Olah, *Tetrahedron* **1995**, *51*, 3319.

[90] B. Török, I. Bucsi, T. Beregszászi, I. Kapocsi, Á. Molnár, *J. Mol. Catal. A: Chem.* **1996**, *107*, 305.

[91] Á. Molnár, K. Felföldi, M. Bartók, *Tetrahedron* **1981**, *37*, 2149.

[92] T. Yamato, C. Hideshima, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1991**, *56*, 3192.

[93] M.Lj. Mihailovic, S. Gojkovic, Z. Cekovic, *J. Chem. Soc., Perkin Trans. 1* **1972**, 2460.

[94] H. Adkins, W. H. Hartung, *Org. Synth., Coll. Vol.* **1932**, *1*, 15.

[95] L. Rigal, A. Gaset, J.-P. Gorrichon, *Ind. Eng. Chem., Prod. Res. Dev.* **1981**, *20*, 719.

[96] T. El Hajj, A. Masroua, J.-C. Martin, G. Descotes, *Bull. Soc. Chim. Fr.* **1987**, 855.

[97] L. Rigal, A. Gaset, *Biomass* **1985**, *7*, 267.

[98] P. Rivalier, J. Duhamet, C. Moreau, R. Durand, *Catal. Today* **1995**, *24*, 165.

[99] C. Moreau, R. Durand, S. Razigade, J. Duhamet, P. Faugeras, P. Rivalier, P. Ros, G. Avignon, *Appl. Catal., A.* **1996**, *145*, 211.

[100] C. Moreau, R. Durand, C. Pourcheron, S. Razigade, *Ind. Crops Prod.* **1994**, *3*, 85.

[101] C. Carlini, M. Giuttari, A. M. R. Galletti, G. Sbrana, T. Armaroli, G. Busca, *Appl. Catal., A.* **1999**, *183*, 295.

[102] A. M. van der Heyden, Ph. D. Thesis, Delft University of Technology, 1999.

[103] Atlas Powder Company (K. R. Brown) US 2,322,821 (1943); *Chem. Abstr.* **1944**, *38*, 120.

[104] A. P. G. Kieboom, H. van Bekkum, in *Starch Conversion Technology* (Eds.: G. M. A. van Beynum, J. A. Roels), Marcel Dekker, New York, **1985**, p. 263.

[105] J. A. van Velthuijsen, J. G. Heesen P. K. Kuipers, in *Sucrochemistry*, ACS Symposium Series 41 (Ed.: J. L. Hickson), Am. Chem. Soc., Washington, D. C., **1977**, p. 136.
[106] J. L. Lynn, Jr., B. H. Bory, in *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th ed. (Eds.: J. I. Kroschwitz, M. Howe-Grant), Wiley, New York, **1997**, p. 478.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

7 Solid-base Catalysis

7.1 Zeolites and Related Materials in Knoevenagel Condensations and Michael Additions

A. Corma, S. Iborra

7.1.1 Introduction

7.1.1.1 The Knoevenagel Condensation

The condensation of active methylene compounds of the type Z-CH_2-Z′ or Z-CHR-Z′ with aldehydes or ketones, usually not containing an alpha hydrogen, is as the Knoevenagel reaction [1] (Scheme 1). Ketones are generally less reactive than aldehydes. Imines can also be used instead of aldehydes or ketones, giving the same final product, but eliminating the amine instead of water [2].

R, R′ = H, alkyl
Z, Z′ = CN, COOR, COR, COOH, NO_2, SOR, SO_2R, SO_2OR

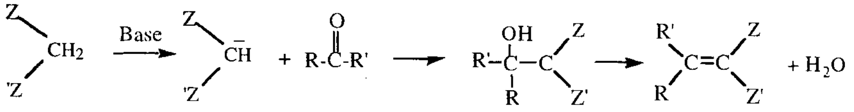
Scheme 1.

The Knoevenagel reaction [3] is one of the most important C–C bond-forming reactions available to synthetic chemists. It is widely used in the synthesis of important intermediates or end-products for perfumes [4], pharmaceuticals [5], e. g. antihypertensive and calcium antagonists [6], and polymers [7]. The reaction is catalyzed by bases, acids, or catalysts containing acid–base sites [8], e. g. bases such as ammonia, primary and secondary amines and their salts [1], and Lewis acids such as $CuCl_2$ [9], $ZnCl_2$ [10], and SmI_3 [11].

In recent years efforts have been focused on the search for new solid catalysts for the Knoevenagel condensation, and numerous types of heterogeneous acidic and basic systems have been reported, including Al_2O_3 [12], silica gel functionalized with amine groups [13], bases derived from organically modified silicas and micelle-templated silicas [14], anionic resins [15], alkaline earth oxides [16], clays [17], calcined hydrotalcites [18], doped xonotlite [19], Mn(II salen) [20], cadmium iodide [21], bismuth(III) chloride [22], AlO_4–Al_2O_3 [23], silicon oxynitride [24], aluminophosphate oxynitride [25], and a series of catalysts based on modified molecular sieves and related materials which will be discussed in this chapter.

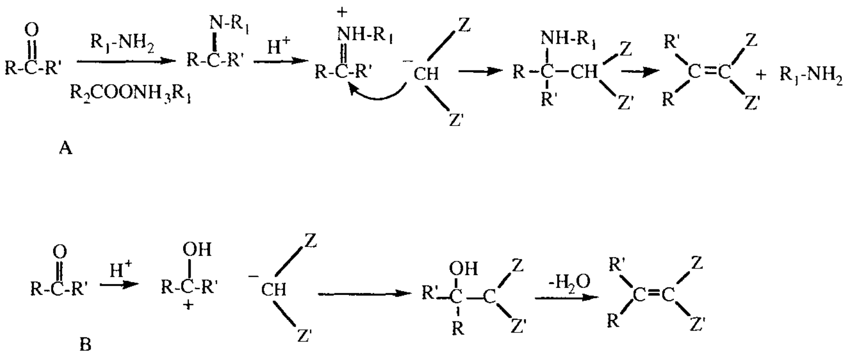
The Mechanism of the Knoevenagel Condensation

The first step in the base-catalyzed condensation is the formation of the carbanion on the methylenic group by abstraction of the proton by the basic catalyst (Scheme 2). This is followed by attack of the carbanion intermediate on the carbonyl group. Finally, elimination of the hydroxyl group takes place to form a C=C bond and water and the basic site is restored.



Scheme 2.

As stated above, Knoevenagel condensations can occur on catalysts combining acidic and basic sites. A well-known system is the combination of an amine and its carboxylic acid salt. Such catalysts seem to activate the carbonyl substrates, usually by imine or enamine formation, and the activated substrate is subsequently activated by protonation. The base assists the deprotonation of a methylene-active compound, forming a carbanion, followed by nucleophilic attack on the protonated imine (Scheme 3A).

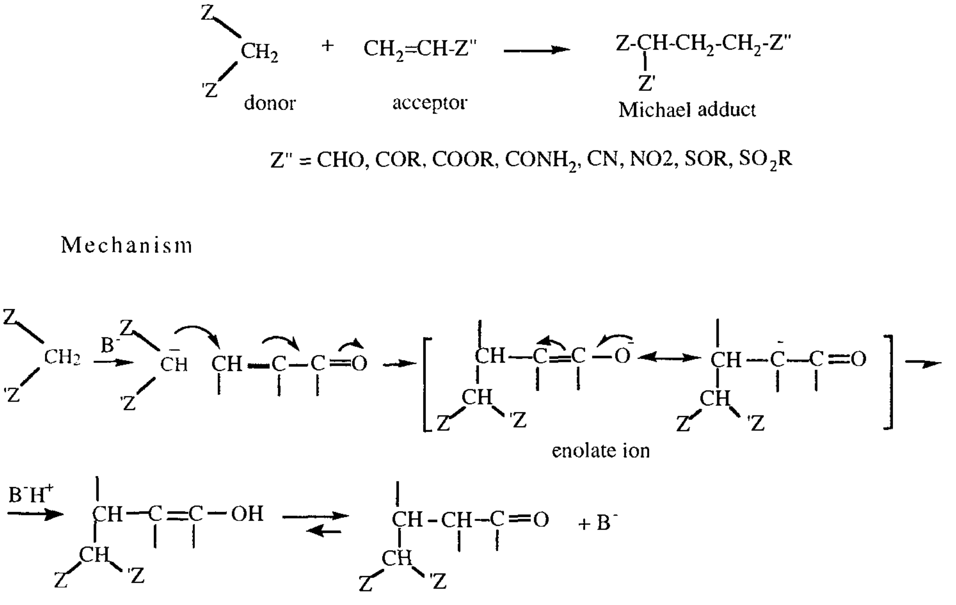


Scheme 3.

When the basic catalyst cannot form imine or enamine intermediates, the Knoevenagel condensation occurs by attack of the carbanion on the carbonyl oxygen, which is activated, by hydrogen bonding or protonation, by the acid component of the catalyst [26] (Scheme 3B). Some examples of the use of heterogeneous catalysts with acid–base sites for the Knoevenagel condensation are reported in the literature. For instance Al_2O_3 [12], clays [17,27], modified Amberlite IRC-50 [28], and even silica gel functionalized with amino groups, for which an acid–base mechanism was proposed [13b], are good examples.

7.1.1.2 The Michael Addition

The Michael addition involves conjugate nucleophilic addition of carbanions to olefins of the type C=C-Z [29]. A base is used to form the carbanion by abstracting a proton from an activated methylene precursor (donor) which attacks the olefin (acceptor) (Scheme 4) forming an enolate ion which is stabilized by delocalization. Protonation of the enolate ion is mainly at the oxygen, which is more negative than the carbon, and this produces the enol, which tautomerizes. The mechanism is 1,4 nucleophilic addition (known as conjugate addition) to the C=C–C=O (or similar) system, although the net result of the reaction is addition to carbon–carbon double bond.



Scheme 4.

The scope of the reaction has been greatly broadened to include the conjugate 1,4-addition of many anions or nucleophiles (e. g. malonates, cyanoacetates, acetoacetates, other β-ketoesters, and compounds of the form Z-CH_3, Z-CH_2R, including carboxylic esters, ketones, aldehydes, nitriles, nitro compounds, sulfones) to many α,β-olefinic or acetylenic ketones, aldehydes, esters, and nitro compounds, etc, in which the anion analogous to enolate ion can be similarly stabilized.

One important characteristic of the Michael addition reaction is that when the donor and acceptor contain suitably different substituents, one or two new chiral centers can be created, producing one or two pairs of enantiomers. When, on the other hand, either or both of the reactants has a chiral substituent, the reaction can be enantioselective. Enantioselective addition has also been achieved by use of chiral catalysts [2]. Indeed, it is interesting to remark that in recent years much attention has been devoted to catalytic asymmetric Michael reactions because of the importance of the products as optically active intermediates for many functional compounds [30]; many types of chiral catalyst have been reported [31].

Together with the Knoevenagel condensation, Michael additions constitute a powerful tool for the synthetic chemist, with numerous applications in many fields such as pharmaceuticals [32], perfumes [33], herbicides [34], polymers [35], dispersant agents [36], and anionic surfactants [37], etc.

Traditionally, the Michael reaction is catalyzed by mild to moderately strong bases such as potassium *t*-butoxide, diisopropylamine [38], and tetramethylguanidine [39] as homogeneous catalysts. The main disadvantages of this type of catalyst are the production of significant amounts of multiple Michael adducts, which are difficult to separate, and problems associated with catalyst recovery. These problems, plus recent interest in environmentally friendly solid catalysts, has led to the development of heterogeneous catalytic systems for this reaction. Examples of heterogeneous catalysts are those based on CsF and KF on alumina [40], or on other solid supports [41], potassium *t*-butoxide on xonotlite [19], Amberlyst A-27 [42], K-10 montmorillonite [43], Li and Cs montmorillonites [44], alkaline earth metal oxides [45], and bases covalently coupled to inorganic supports on aluminosilicates [46,47]; these have been used with varying success.

7.1.2 Zeolites as Catalysts

Zeolites are crystalline aluminosilicates with a regular microporous structure and the general formula $(M^{n+})_{x/n}((Al_2O_3)_x(SiO_2)_y)zH_2O$, where M is a cation which can belong to the groups IA or IIA or can be an organic cation, *n* is the valence of the cation, and *z* denotes the number of water molecules contained in the zeolite voids. In these structures, Al and Si occupy framework positions with tetrahedral coordination. The tetrahedral aluminum has a negative charge which is compensated by the cation M^{n+}. Other microporous structures containing not only Si and Al but also P have been synthesized. Transition metals and other groups elements with valence ranging from I to V, e. g. B, Ge, Fe, Cr, Ti, etc, occupy framework positions; these materials are known as $ALPO_4$-, SAPO-, MeAPO-, and MeAPSO-type molecular sieves [48–53].

The main characteristic of these molecular sieves is their stable crystalline structure enclosing a well-defined system of pores. They are classified according to pore size as ultra-large (those formed with more than a 12 member ring (MR), i.e. the smallest number of O or T atoms which limit the pore structure of their largest channel), large (12MR), medium (10MR), or small (8MR); pore diameters vary between 5 and 20 Å.

The properties of a zeolite depend on its topology, the size and the accessibility of the channels, and the charge and the size of the compensating cation. The presence or lack of an element, and the ratio and environment of the atoms T (Si or Al, for instance) play an important role.

Besides the general advantages associated with heterogeneous catalysts (easy separation, little production of contaminant wastes, inexpensive, possibility of recycling), zeolites can be prepared with different porosity, hydrophobicity, and strength of acidic or basic sites; these characteristics make them very powerful catalysts that can be adapted to particular reactions.

The primary and most important use of zeolites in catalysis is as acid catalysts for petroleum and chemical processes [54,55].

Despite the existence of basic sites in zeolites, the possibility of using zeolites as basic catalysts was forgotten for many years and it was realized only recently that they can also be successful in this field [56,57]. Two approaches have been used to prepare basic zeolites: ion-exchange with alkali metal ions and generation within the pores of small clusters of alkali metals or oxides and alkaline earth oxides. Whereas simple ion-exchange with alkali metal ions produces relatively weakly basic sites, the presence of such clusters results in strongly basic sites.

In the next two sections we will concentrate on the catalytic activity of basic zeolites and mesoporous molecular sieves in the Knoevenagel condensation and Michael addition reactions.

7.1.2.1 Basicity in Alkali Cation-exchanged Zeolites

It is generally accepted that the basic sites on the surface of solid catalysts are of the Lewis type, and can, therefore, be defined as sites able to donate an electron pair to an adsorbed molecule. In zeolites Lewis basicity is associated with the framework oxygens bearing the negative charge of the lattice and consequently the density of negative charge on a given oxygen, i.e. its basicity, will depend both on the chemical composition and on the structure of the zeolite. It can generally be said that the lower the average Sanderson electronegativity of the system the higher the basicity of the zeolite [58–60].

Catalytic Activity: Model Catalytic Reactions

Knoevenagel condensation between benzaldehyde and molecules containing activated methylene groups with different pK_a values has been used as a test reaction to gain insight into the basic properties of solids [60]. In this way it was established that the reaction mechanism is the same in the homogeneously catalyzed reaction in solution as it is when solid catalysts are used; it was found that the rate-controlling step of the condensation reaction on basic zeolites is not proton abstraction, as was first proposed for other basic catalysts [1,2], but attack by the carbanion intermediate on the carbonyl group (Scheme 2).

When, on the other hand, the Knoevenagel condensation is performed between benzaldehyde and a series of methylenic compounds with different pK_a values, e.g. ethyl cyanoacetate (pK_a 9.0), ethyl acetoacetate (pK_a 10.7), and ethyl malo-

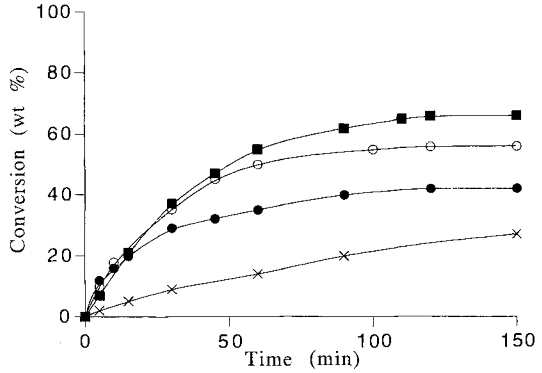


Figure 1. Condensation of benzaldehyde and ethyl cyanoacetate on exchanged X zeolites: LiX (×), NaX (●), KX (○) and CsX (■).

Table 1. Kinetic rate constants (K) for the condensation of benzaldehyde with ethyl cyanoacetate (pK_a 9.0), ethyl acetoacetate (pK_a 10.7), and ethyl malonate (pK_a 13.2) on alkaline-exchanged zeolites, NaGeX, cesium-exchanged sepiolite, and calcined Mg–Al hydrotalcite.

Catalyst	RCH_2COOEt	T (K)	K(mol s^{-1} m^{-2} × 10^{-4})
Hydrotalcite	R = –CN	363	89.7
CsSep			4.6
NaGeX			4.2
CsX			0.24
KX			0.22
LiX			0.037
CsY			0.019
KY			0.017
LiY			0.011
Hydrotalcite	R = –COOEt	443	7.9
CsSep			0.4
NaGeX			0.8
CsX			0.3
Hydrotalcite	R = –$COCH_3$	413	Not reported
CsSep			6.5
NaGeX			5.1
CsX			2.8

nate (pK_a 13.3) not only is it possible to measure the total number of basic sites, but also their strength distribution [57,60]. This study has shown that alkali-exchanged zeolites have a large number of basic sites able to abstract a proton from organic molecules with pK_a in the range $9 < \text{p}K_a < 13.3$ [57].

Figure 1 compares the progress of the Knoevenagel condensation between ethyl cyanoacetate and benzaldehyde on different exchanged X zeolites, and in Table 1 are summarized the rates calculated for the Knoevenagel condensation of different methylenic compounds on basic catalysts.

From these results it is possible to deduce that the activity of the exchanged zeolites increases with decreasing framework Si/Al ratio and increasing counter cation radius. With regard to proton-abstracting capacity, alkali-exchanged zeolites have basic sites with a strength distribution in the range of $9.0 < \mathrm{p}K_a < 10.7$; only a few centers with higher basicities, in the range $10.7 < \mathrm{p}K_a < 13.3$, were detected on the most basic zeolite XCs. Table 1 includes results obtained with a cesium-exchanged sepiolite and a mixed aluminum–magnesium hydrotalcite.

Substitution of Si by Ge in the framework of faujasite substantially increases the catalytic activity in Knoevenagel condensations [61]. Thus, the rates of the reaction between benzaldehyde and ethyl cyanoacetate are one order of magnitude larger over NaGeX than over NaSiX. Significant catalytic activity was, moreover, observed on NaGeX when the methylene-active compound is diethyl malonate ($\mathrm{p}K_a$ 13.3), indicating that incorporation of Ge into the zeolite framework increases the relative proportion of strongly basic sites. The increased activity in this material cannot be related to increased base strength, because of a decrease in the average Sanderson electronegativity (calculated by taking into account only the electronegativity of the compositional elements); it is also related to the T–O–T angle. Consistent with this it has been found that despite its low Al content, Na-exchanged beta zeolite is a more active catalyst of the Knoevenagel condensation than is NaY or NaX. This is related to the relatively small T–O–T angles formed when exchanging the H-beta zeolite by Na^+ [62]. In common with faujasites, Ge-beta, and Ga-beta zeolites in which some Si is replaced by Ge, or Al is substituted by Ga, respectively, are more active than the corresponding Si–Al form [62], indicating that introduction of Ga and Ge increases the basicity.

NaY faujasite has been also exchanged with Ca, La, Ce, and Re, and a systematic and comparative study of their catalytic activity in the Knoevenagel condensation between benzaldehyde and malononitrile has been conducted by Reddy et al. [63]. Two of the catalysts, La (70 %) NaY and Ce (70 %) NaY afforded moderate yields but rare-earth (Re)-exchanged NaY was found to be the optimum zeolite for this condensation in terms of yield, mass balance, and selectivity.

7.1.2.2 Metal Species and Oxide Clusters Encapsulated in Zeolites

Basicity and General Aspects

The basic sites generated in zeolites by alkali cation-exchange can be regarded as weak to medium in strength. Post-synthesis treatment has been used extensively to enhance the basic properties of zeolites while retaining their inherent shape-selectivity. Two different materials have been described: those containing very small oxides particles encapsulated in zeolite cages and those containing metal clusters entrapped within the void spaces of the zeolite.

Alkaline or alkaline earth metal oxides are well known basic catalysts and much of work has been devoted to their characterization and to the study of their catalytic activity [64,65]. Taking into account the strong basic character of these oxides it is possible to enhance the basicity of zeolites by over-exchanging them with alkali [66–69] or alkaline earth metals [70–72] and producing after thermal decomposition the corresponding highly dispersed basic oxides encapsulated in the channels and cavities. Several modes of formation of these clusters have been described, but the most general and applicable to a large number of cations involves the impregnation of the zeolite, within a compatible pH range, with a solution of alkali metal salts or hydroxide. The resulting solid is carefully calcined in the absence of water or CO_2 to form alkaline oxide microcrystals entrapped inside the zeolite cages.

Faujasite zeolites with a three dimensional structure and 12-Å supercavities are the most studied supports. Davis et al. [67,68] prepared catalysts by impregnation of CsNaX and CsNaY with cesium acetate then thermal decomposition. They studied for first time the effect of loading cesium into zeolite on the acid–base properties, by studying the decomposition of propanol. Since then, special emphasis has been devoted to the study of cesium oxide loaded into faujasite zeolites yielding basicities in the range of superbasicity [66–69,73–76].

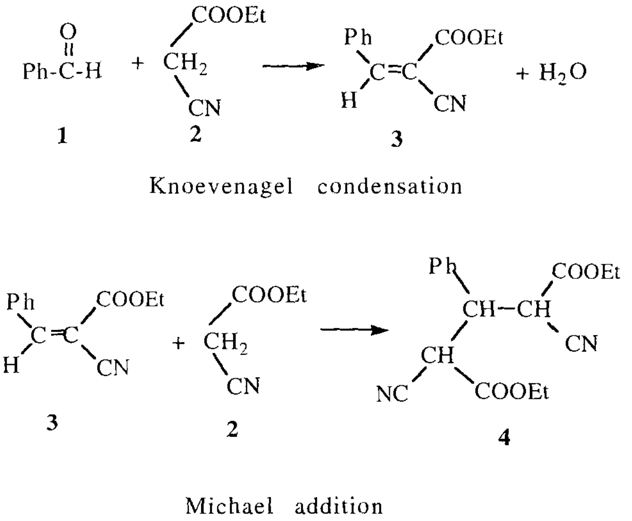
The size of the alkali metal cation has an impact on the basic properties of the final catalysts; this is reflected in the order of basic strength found for several metal oxides encapsulated in X-zeolite: $Na_xO/NaX < K_xO/KX \approx Rb_xO/RbX < Cs_xO/CsX$. This order indicates that stronger basic sites are formed when the radius of the monovalent cation increases; the sites are even stronger than those measured for the corresponding bulk alkaline oxides [67]. A similar order of basicity was observed for a series of alkaline earth oxides occluded inside the cages of faujasite [70].

The chemical composition of the zeolitic host also affects the basic properties. When the basicity of Cs-over-exchanged zeolites X and Y, with Si/Al ratios of 1.2 and 2.5, respectively, were measured by stepwise thermal desorption of CO_2, it was found that different cesium oxide species are present: Cs_2O inside the CsNaX zeolite and $(Cs_2O)_2$ inside the CsNaY zeolite [73,74]. The basicity of the occluded Cs_2O species was, moreover, greater than that of intrazeolitic clusters $(Cs_2O)_2$, as deduced from catalytic activity and TPD results.

Catalytic Activity

The catalytic activity of alkali metal oxide clusters encapsulated in the zeolitic cages of faujasite has been tested in different reactions catalyzed by basic sites, e.g. olefin isomerization [75,77], isopropanol decomposition [67,68], and Knoevenagel condensation [73,74,78].

Lasperas et al. [73,74,78] have studied the Knoevenagel condensation between benzaldehyde (**1**) and ethyl cyanoacetate (**2**) in the presence of over-exchanged CsY zeolites. The reaction was performed under a nitrogen atmosphere in dimethyl sulfoxide (DMSO), the best solvent for eliminating interference from the non-catalyzed reaction. The use of equimolar amounts of each reactant suppressed successive Michael addition between ethyl cyanoacetate and ethyl cyanocinnamate (**3**) to give compound **4** (Scheme 5); this resulted in high selectivity for the Knoevenagel product (**3**) (95 % at 90 % conversion).



Scheme 5.

Kinetic and mechanistic studies in DMSO showed that the reaction is first order in each reactant and that the rate-determining step is the condensation between the adsorbed reactants. Table 2 summarizes the initial rates of reaction as a function of cesium loading in a CsNaX zeolite; the results show that the initial rate increases with increasing cesium loading. The results of activity studies are in good agreement with the TPD results. Cs-over exchanged X zeolites are much more active than Cs over-exchanged Y zeolites, as a result of the different cesium oxide species generated [73,74].

Activity also depends on the crystallinity of the catalyst. When a loss of crystallinity occurs, the entrapped basic species become inaccessible to reactants and catalytic activity decreases [78].

In general two trends are observed in the properties of these materials. Firstly, exchanged zeolites are less basic than those which, in addition, contain clusters of oxides. Secondly, carbonates are formed very easily when the catalyst is exposed to the atmosphere.

Other basic zeolites are those prepared by Baba et al. [79], consisting of low-valent Yb or Eu species introduced into alkali ion-exchanged Y zeolites by impregnation with Yb or Eu metal dissolved in liquid ammonia then heating under vacuum at ca 470 K. These materials catalyze the Michael addition of cyclopent-2-enone and dimethyl malonate at 303 K, without solvent, yielding, after 20 h reaction, 81 % Michael adduct with 100 % selectivity [80,81].

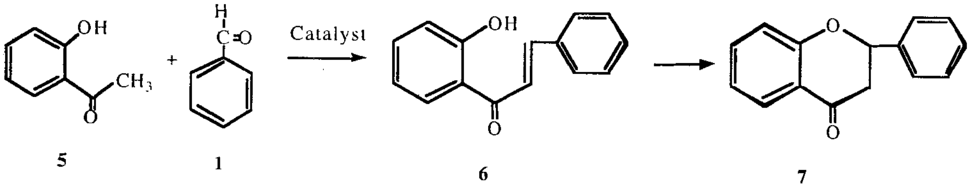
Table 2. Initial rates of condensation (*ro*) of benzaldehyde (0.3 M) with ethyl cyanoacetate (0.3 M) in DMSO solution (55 mL) on over- exchanged zeolites (0.220 g) at 353 K.

CsNaX nCs Zeolite, *n* =	0	4	9	11	16	26
ro (mol L^{-1} (unit cell)$^{-1}$)	15.2	26.2	36.7	43.7	78.5	101.9

7.1.3 Knoevenagel and Michael Reactions on Basic Zeolites and Mesoporous Aluminosilicates for the Production of Fine Chemicals.

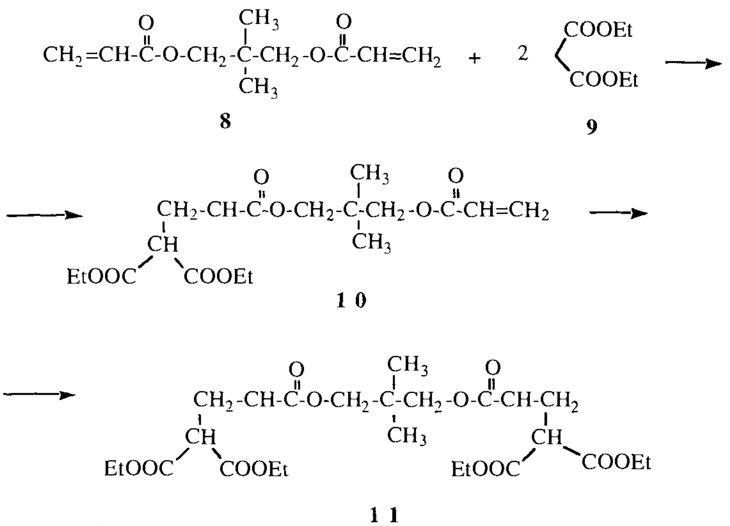
7.1.3.1 Exchanged and Over-exchanged Mesoporous Materials

Pore accessibility is a limitation of zeolitic systems as catalysts in the production of fine chemicals. The mesoporous molecular sieve MCM-41 has proven to be a promising candidate for the conversion of large molecules. Na- and Cs-exchanged MCM-41 are active catalysts in the Knoevenagel condensation [82]. Na-MCM-41 is highly active in the condensation of benzaldehyde with ethyl cyanoacetate whereas with the less acidic diethyl malonate (pK_a 13.3), in a solvent free system at 423 K, conversion was only 6 % after 3 h. Surprisingly, the catalytic behavior of Na-exchanged MCM-41 in Knoevenagel condensations was very similar to that of Cs-MCM-41; it must, therefore, be assumed that both catalysts have basic centers with similar strength distribution (most basic sites of p$K_a \leq 9$ and a few of p$K_a \leq 13.3$). The reason for this unexpected behavior is still not clear, but it seems to be related to the different local order around alkaline cations and/or the different interactions established between the cations and the negatively charged framework oxygens. Na-MCM-41 was also active in the aldol condensation of benzaldehyde with different bulky ketones, including the Claisen–Schmidt condensation of benzaldehyde (**1**) and 2′-hydroxyacetophenone (**5**) to give the chalcone **6**, followed by intramolecular Michael addition to flavanone (**7**) (Scheme 6).



Scheme 6.

The same authors reported [83] that strongly basic sites are created when MCM-41 is impregnated with cesium acetate and then subjected to thermal treatment to produce highly dispersed Cs_2O particles. This material was tested in the Michael addition of neopentyl glycol diacrylate (**8**) with diethyl malonate (**9**). The reactant **8**, with two isolated activated double bonds, can afford a mono adduct (**10**) and/or a bis adduct (**11**) (Scheme 7). Table 3 shows the performance of the catalyst as a function of Cs atom loading and Si/Al ratio.



Scheme 7.

Table 3. Michael addition of diethyl malonate (**9**) to neopentyl glycol diacrylate (**8**) over CsMCM-41.[a]

Catalyst	Cs content (% *w*/*w*)	*T* (K)	*t* (min)	Conversion (% *m*/*m*)	Selectivity **10**:**11**(%)
CsMCM41[b]	23.6	383	15	41	63:37
			60	68	69:31
CsMCM41[c]	19.2	383	60	36	85:15
CsMCM41[c]	27.4	293	30	38	98:0.2
			60	55	58:42
Cs_2O[d]		293	10	100	0:100

[a] Reaction conditions: diethyl malonate (10 mmol), neopentyl glycol diacrylate (5 mmol); toluene as solvent (15 mL); catalyst (6 % *w*/*w* relative to the total amount of reactants).

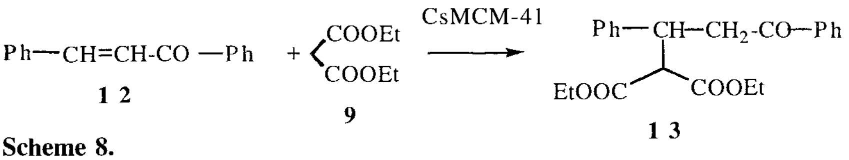
[b] Si/Al = 22.

[c] Si/Al = 13.

[d] 18 % *w*/*w* bulk cesium oxide based on the total amount of substrates.

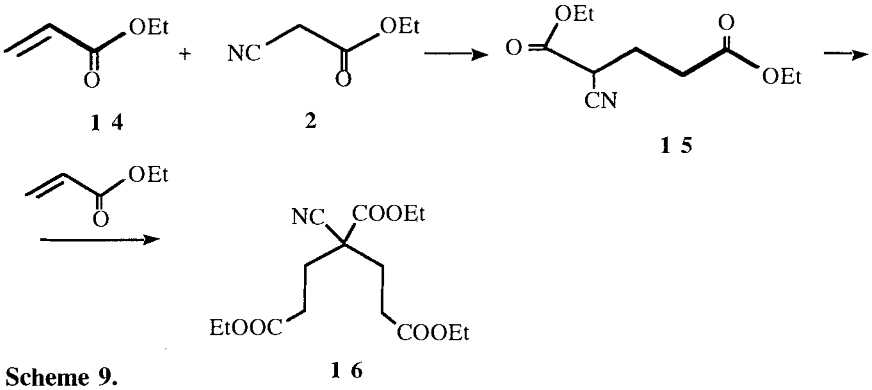
The influence of the mesoporous framework of MCM-41 support is illustrated by the high regioselectivity of the Michael type addition. Selectivity for **10** of up to 98 % is achieved at 293 K. With bulk Cs_2O, in contrast, selectivity is greater for the bis adduct (**11**).

The activity of cesium over-exchanged MCM-41 has also been tested in the base-catalyzed Michael addition of diethyl malonate (**9**) to chalcone (**12**) in a solvent-free system at 423 K [82] (Scheme 8). Conversion of 87 % and selectivity of 91 % to the product **13** were obtained within 30 min. A disadvantage is the poor regenerability of the material, which leads to a drastic decrease in surface area and pore volume.



Scheme 8.

Finally, binary cesium–lanthanum oxides supported on MCM-41 have been tested in the liquid phase as catalysts of the Knoevenagel and Michael reactions [84]. CsLa-MCM-41 catalyzes the Michael addition of ethyl cyanoacetate (**2**) to ethyl acrylate (**14**) (Scheme 9). Besides formation of the mono adduct (**15**), bis adduct **16**, formed by a double Michael addition, is produced consecutively. Although the basicity of CsLa-MCM-41 is quite mild, its performance in this reaction is very good. Table 4 compares the activity and selectivity obtained with different catalysts. Although product selectivity is probably also controlled by the mesoporous MCM-41 support, the basicity of CsLa-MCM-41 is too weak to catalyze the Michael addition of diethyl malonate under the same conditions.



Scheme 9.

Table 4. Michael addition of ethyl acrylate (**14**; 10 mmol) and ethyl cyanoacetate (**2**; 10 mmol) with either MCM-41 or SiO_2-supported cesium oxide, cesium or cesium–lanthanum oxide in ethanol under reflux at 30 % *m/m* ethyl acrylate conversion.

Catalysts[a]	Si/Al	Activity[b] ($mol\,h^{-1}g^{-1}$)	Selectivity **15**:**16** (%)[c]
CsLa/MCM-41[d]	∞	39.3	43:57
Cs-MCM-41[e]	12	948	8:33
Na-MCM-41	12	–	–
CsLa/SiO_2	∞	32	64:36
Cs/SiO_2	∞	289	36:4

[a] 5 % *m/m* catalyst based on total amount of substrates.
[b] Specific activity at 30 % *m/m* ethyl acrylate conversion.
[c] Product selectivity at *t*.
[d] 5 % *m/m* Cs and 5 % *m/m* La on MCM-41.
[e] Cs-exchanged MCM-41.

No reaction between ethyl cyanoacetate and methyl crotonate was observed on CsLa-MCM-41 but with ethyl cinnamate 20 % conversion was achieved after 2 h at high temperature (433 K), giving solely the corresponding mono adduct. In this reaction the effect of pore size on selectivity cannot be excluded.

The Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate was also used to study the performance of LaCs-MCM-41 in aqueous media. The yield was 58 %, with 99 % selectivity for the condensation product.

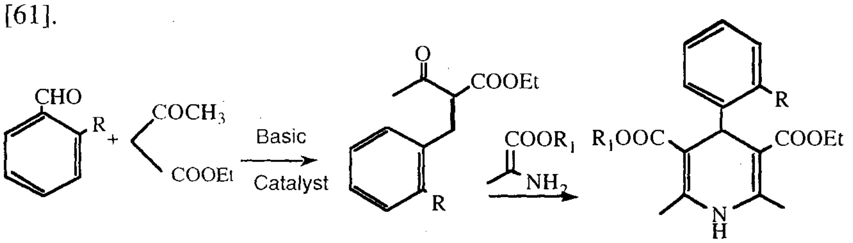
The re-usability of the CsLa-MCM-41 was also studied in Knoevenagel and Michael reactions; the catalysts could be reused after a solvent flush and high temperature cycle without loss of activity.

7.1.3.2 Knoevenagel and Michael Reactions on Cation-exchanged Zeolites

Besides the general advantages associated with zeolites, the use of exchanged zeolites as heterogeneous basic catalysts has the additional advantage that they can be exposed to the atmosphere, because carbon dioxide and water are not absorbed too strongly and can be removed by thermal treatment. They can be used even in systems in which water or CO_2 are involved as reactants or products.

Despite all these advantages, however, exchanged zeolites have rarely been used as basic catalysts in the production of fine chemicals. This is probably because of their weak basic character and because bulky reactants are involved in many chemical processes. Their basicity is, nevertheless, sometimes sufficient to catalyze Knoevenagel condensations and Michael additions.

Preparation of intermediate products for the synthesis of dihydropyridines of the type shown in Scheme 10 (product **20**), which are of interest clinically because of their antihypertensive activity, has been conducted with ion-exchanged zeolites [61].



17a,b **18** **19a,b** **20**

Dihydropyridine derivative

17a, R= NO_2
17b, R= CF_3

Scheme 10.

The synthesis of these compounds involves, as a first step, Knoevenagel condensation between benzaldehyde derivatives (**17**) and ethyl acetoacetate (**18**). The Knoevenagel product (**19**) can be converted in a consecutive step into dihydropyridine derivatives (**20**) by reaction with an aminocrotonic derivative (Scheme 10).

NaX zeolite and NaX zeolite in which the Si had been substituted by Ge during synthesis were used as basic catalysts in a study of the Knoevenagel condensation of 2-nitrobenzaldehyde (**17a**) and 2-trifluoromethyl benzaldehyde (**17b**) with ethyl acetoacetate. NaGeX faujasite was approximately three times as active as NaX zeolite, the selectivity being the same for both. Comparison with pyridine or piperidine as homogeneous basic catalysts (Table 5) showed that the activity of the NaGeX faujasite was higher than that of pyridine and lower than that piperidine; extremely high selectivity for the desired product was obtained by use of the zeolite catalyst.

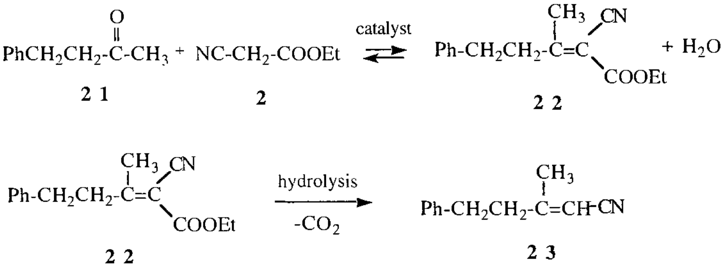
Alkali metal-exchanged zeolites have been used to prepare activated alkenes of interest as prepolymers by Knoevenagel condensation of malononitrile with ketones having different positive charge density on the carbon of the carbonyl group: benzophenone, cyclohexanone, and *p*-aminoacetophenone [85]. The reactivity depends both on ketone structure (the order of reactivity was: benzophenone > cyclohexanone > *p*-aminoacetophenone) and on the catalyst used. For instance, when malononitrile is condensed with cyclohexanone in the presence of a CsY zeolite conversion was very low. CsX zeolite, however, which has a substantial number of basic sites with pK_a in the range $9 < pK_a < 10.7$ and some with $10.7 < pK_a < 13.3$ could be used to perform the reaction, under the same conditions, with high yield (82 %) of activate alkene. When the activity of CsX zeolite in the preparation of prepolymers of malononitrile–ketone was compared with that of stronger basic catalysts, e. g. cesium-exchanged sepiolites and mixed oxides derived from hydrotalcites, the order of activity found was: hydrotalcite > Cs-sepiolite > CsX.

Citronitril (5-phenyl-3-methyl 2-pentenenitrile; **23**) is a fine chemical of interest in the perfume industry. The synthesis of citronitril involves Knoevenagel condensation of benzylacetone (**21**) with ethyl cyanoacetate (**2**). In a second step the Knoevenagel condensation product (**22**) undergoes hydrolysis then decarboxylation (Scheme 11). The Knoevenagel condensation has been performed on Cs-exchanged X zeolite and sepiolite, and on MgO and calcined Al–Mg hydrotalcite [86]. The order of reactivity was hydrotalcite > Cs-sepiolite > CsX, the yield of Knoevenagel product on zeolite and sepiolite being 39 and 49 % respectively. On the oxides the yield was significantly higher (70–75 %), indicating that this reaction requires basic sites stronger than those present in cesium exchange zeolites and sepiolites.

Table 5. Knoevenagel condensation of benzaldehyde derivatives **17a,b** (5 mmol) and ethyl acetoacetate (**18**) (5 mmol) at 473 K with different catalysts.

Catalyst	Yield of **19a** (%)[a]	Yield of **19b** (%)[a]
NaX	16	9
NaGeX	37	32
Pyridine	17	10
Piperidine	82	44

[a] Reaction time 6 h



Scheme 11.

Aromatic aldehydes with a variety of functional groups, e. g. *p*-nitrobenzaldehyde, bromobenzaldehyde, and vanillin react with active methylene compounds, e. g. malononitrile, ethyl cyanoacetate, and 2-cyanoacetamide, in the presence of freshly activated rare-earth-exchanged NaY zeolite and acetonitrile as solvent [63]. The reactions were complete in 8–12 h at 293–333 K and produced the Knoevenagel condensation product in 62–87 % yield. Multicatalytic active sites present inside the supercages are assumed to be involved; the basic site abstracts the proton from the active methylene compound and the Lewis acidic site is responsible for generating the partial positive charge on the carbonyl compound by coordinating with its oxygen, thereby facilitating C–C bond formation.

Na-, La-, and Re-exchanged zeolites have also been used as catalysts of the Michael reaction between silyl enol ethers and α,β-unsaturated carbonyl compounds. This study, performed by Sasidharan et al. [87], focused mainly on the catalytic activity of titanium silicalite molecular sieves (TS-1 and TS-2). They found that TS-1 and TS-2 catalyze 1,4-Michael addition of silyl enol ethers and α,β-unsaturated carbonyl compounds under anhydrous conditions. The zeolites tested as catalysts of this reaction, e. g. ReY, LaY, steamed zeolite Y, and cation-exchanged ZnZSM-5, were less active (or inactive).

Several structurally different diketones (acetylacetone, methyl 2-oxocyclohexane carboxylate) and active methylene compounds (diethyl malonate, ethyl acetoacetate) and thiols (methyl thioglycolate) underwent clean, fast, and efficient Michael addition with methyl vinyl ketone, acrolein, and methyl acrylate over NaY and Na beta zeolites [88] in high yield (70–80 %). The reactions were performed in the absence of solvent, at room temperature, with 1 g catalyst per mmol donor. When HY zeolite was used instead of NaY formation of the desired Michael adduct was low and polymerization of Michael acceptor was the main reaction.

7.1.4 Conclusions

Two approaches have been used to prepare basic zeolites: ion-exchange with alkali metal ions or generation of small clusters of alkali metals or oxides and alkaline earth oxides within the pores of the zeolites. Simple ion-exchange produces relatively weakly basic sites whereas the presence of clusters of alkali metals or oxides and alkaline earth oxides results in strongly basic sites. Special emphasis has been devoted to the study of cesium oxide loaded into faujasite zeolites; basicities in the superbasicity range were obtained.

In both instances the size of the alkali metal cation, the chemical composition, and the structure of the zeolite have an impact on the basic properties of the final catalysts. Hence, zeolites can be prepared with basic sites of different strength, enabling selection of the catalyst most suitable for a particular reaction.

Zeolite catalysts have promise in Knoevenagel and Michael reactions but are not yet widely applied because of the weakly basic character of ion-exchanged zeolites, or the rapid deactivation of over-exchanged zeolites by water and/or CO_2. Another limitation of microporous systems is that bulky reactants are involved in many chemical processes. In this context, we note that the mesoporous molecular sieve MCM-41 is a promising candidate for the conversion of large molecules. Na- and Cs-exchanged MCM-41 have been found to be active catalysts in Knoevenagel and Michael reactions.

References

[1] Jones G., Organic Reactions, Cope A. C. ed., vol. 15, John and Sons: New York 1967, p 204.

[2] March J, Advanced Organic Reactions: Reactions, Mechanisms and Structure 4th Ed. Wiley–Interscience, 1992, 945.

[3] Knoevenagel L, Ber 31 (1898) 258.

[4] (a) Siebenhaar B, WO 9721659, 1997. (b) Hopp R, Thielmann T and Gottsch W, US 5212153, 1992. (c) Lauterbach G Dr , Becker R Dr and Jansen K, EP 0395982, 1990. (d) Siebenhaar B and Casagrande B, EP 0870750, 1998. (e) Manfred K and Slagmulder A, US 4755615, 1988.

[5] (a) Gordeev M F and Patel D V, WO 9633972, 1996. (b) Castelli E, Cascio G and Manghisi E, WO 9807698, 1998. (c) Kesel A J and Oberthür W, WO 9820013, 1998.

[6] (a) Marciniak G, Delgado A, Leedere G, Velly J, Decken N and Schwartz J, J Med 32 (1989) 1402. (b) Enders D, Muller S and Demir A S, Tetrahedron Lett 29 (1988) 643.

[7] (a) Ferraris J P, Lambert T L and Rodriguez S, WO 9305077 ,1993. (b) Schipfer R and Schmolzer G, US 4523007, 1985 and US 4544715, 1985.

[8] Reeves R L, eds. Patai, S. "The Chemistry of Carbonyl compounds", Interscience publishers, New York 1996, p 567.

[9] Attanasi O, Filippone P and Mei A, Synth Commun 13 (1983) 1203.

[10] Shanthan R P and Venkataratnam R V, Tetrahedron Lett 32 (1991) 5821.

[11] Bao W, Zhang Y and Wang J, Synth Commun 26 (1996) 3025.

[12] Texier-Boullet F and Foucaud H , Tetrahedron Lett 23 (1982) 4927.

[13] (a) Angeletti E, Canepa C, Martinetti G and Venturello P, Tetrahedron Lett 29 (1988) 2261. (b) Angeletti E, Canepa C, Martinetti G and Venturello P, J Chem Soc Perkin Trans 1 (1989) 105. (c) Macquarrie D J, Clark J H, Lambert A, Mdoe J E G and Priest A, React Funct Polym 35 (1997) 153.

[14] Brunel D, Microporous and Mesoporous Mat 27 (1999) 329.

[15] Richardhein W and Melvin J, J Org Chem 26 (1961) 4874.

[16] Moison H, Texier-Boullet and Focaud H, Tetrahedron 43 (1987) 537.

[17] Bigi F, Chesini L, Maggi R, Sartori G, J Org Chem 64 (1999) 1033.

[18] (a) Corma A, Fornes V, Martin-Aranda R M and Rey F, J Catal 134 (1992) 58. (b) Kantam L, Choudary B M, Reddy C V, Rao K K and Figueras F, Chem Commun (1998) 1033.

[19] Laszlo P and Pennetreau P, Tetrahedron Lett 26 (1985) 2645.

[20] Kantam M L and Bharathi B, Catalysis Lett 55 (1998) 235.

[21] Prajpati D and Sandhu J S, J Chem Soc Perkin Trans 1 (1993) 739.

[22] Prajpati D and Sandhu J S, Chem Lett (1992) 1945.

[23] (a) Cabello J A, Campelo J M, Garcia A, Luna D and Marinas J M, J Org Chem 49 (1984) 5195. (b) Bautista F M, Campelo J M, Garcia A, Luna D, Marinas J M and Romero A A, Catalysis Lett 19 (1993) 137.

[24] (a) Lednor P W and de Ruiter R, J Chem Soc Chem Commun (1991) 1625. (b) Lednor P W, Catal Today 15 (1992) 243.

[25] (a) Marchand R, Conanec R, Laurent Y, Bastians Ph, Grange P, Gandia L M, Montes M, Fernandes J and Odriozola J A, FR Pat. 9401081, 1994. (b) Climent M J, Corma A, Fornes V, Frau A, Guil-Lopez R, Iborra S and Primo J, J Catal 163 (1996) 392.

[26] Carey F A and Sundberg R, J. Advanced Organic Chemistry, 2nd ed, Plenum: New York, 1984, Chapters 2 and 8.

[27] Delgado F, Tamariz J, Zepeda G, Landa M, Miranda R and Garcia J, Synth Commun 25 (1995) 753.

[28] Saito T, Goto H, Honda K and Fujii T, Tetrahedron Lett 33 (1992) 7535.

[29] Bergmann E D, Ginsburg D and Pappo R, Org. Reactions 10 (1959) 179.

[30] (a) Rossiter B E and Swingle N M, Chem Rev 92 (1992) 771. (b) Perlmutter P, in "Conjugate Addition Reactions in Organic Synthesis", Pergamon Press, Oxford,1992.

[31] Tamai Y, Kamifuku A, Koshiishi E, and. Miyano S, Chem Lett (1995) 957 and references cited therein.

[32] (a) Morishima H, Koike Y, Nakano M, Atsuumi S, Tanaka S and Matsuyama, EP 0309766, 1989. (b) Kleinschroth J, Hartenstein J, Schachtele C and Rudolph C, US 5489608, 1995. (c) Morishima H, Koike Y, Nakano M, Atsuumi S, Tanaka S and Matsuyama K, US 5506356, 1995. (d) Ikeda T, Kawamura M and Ge Y T, EP 0899261, 1999.

[33] Tsuji J, Shiozaki S and Asai H, JP 56022722, 1979.

[34] (a) Hartmann L A and Stephen J F, US 4473696, 1984. (b) Hartmann L A and Stephen J F, US 4584380, 1986. (c) Hartmann L A and Stephen J F, US 4687854, 1987.

[35] (a) Hall Jr H K, Sumitomo H and Okada M, US 4677190, 1987. (b) Famili A, Vratsanos L A and Marten F L, US 5350801, 1994. (c) Famili A, Vratsanos L A and Marten F L, EP 0633271, 1995.

[36] (a) Yada A, Kitada A, Mori Y and Nishiguchi H, JP 08085710, 1994. (b) Yada A, Kawamori Y, Nishiguchi H, Kitada A and Mori Y, JP 08127622, 1995. (c) Nishiguchi H, Watanabe T and Kitada A, JP 10099670, 1996. (d) Yada A, Kawamori Y, Nishiguchi H, Kitada A and Mori Y, EP 0794198, 1997.

[37] Yamamuro A, Takahashi M and Yokota Y, JP 05117216, 1991.

[38] McMurry J E and Melton J, J Org Chem 38 (1973) 436.

[39] (a) Miller D D and Hamada K B , Tetrahedron Lett 24 (1983) 555. (b) Pollini G D, Barco A and De Giuli G, Synthesis (1972) 44.

[40] Clark J H and Cork D G, Chem Lett 26 (1985) 2645.

[41] Campelo J M, Climent M S and Marinas J M, React Kinet Catal Lett 47 (1992) 7.

[42] Ballini R, Marziali P and Mozzicafreddo A, J Org Chem 61 (1996) 3209.

[43] Balogh M, Gonczi C and Hermecz I, Stud Surf Sci Catal 108 (1997) 603.

[44] Martin-Aranda R M, Vicente-Rodriguez M A, Lopez-Pestana J M, Lopez-Peinado A J, Jerez A de D, Lopez-Gonzalez J and Banares-Munoz M A, J Mol Catal. A Chem 124 (1997) 115.

[45] Kabashima H, Tsuji H and Hattori H, Appl Catal A 165 (1997) 319.

[46] Rao Y U S, De Vos E, Jacobs P A, Angew Chem Int Ed Engl 36 (1997) 2661.

[47] (a) Rodriguez I, Iborra S, Rey F, Corma A and Jorda J L, Chem Commun (1999) 593. (b) Rodriguez I, Iborra S, Rey F and Corma A, Appl Catal (in press)

[48] Flanigen E M, Stud Surf Sci Catal 59 (1991) 1.

[49] Wilson S T, Lok B M, Messina C A, Cannan T R and Flanigen E M, J Am Chem Soc. 104 (1982) 1146.

[50] Lok B M, Messina C A, Patton R L, Gajek R T, Cannan T R and Flanigen E M, J Am Chem Soc 106 (1984) 6092.

[51] Davis M E, Montes C, Hathaway P E and Garcés J M, Stud Surf Sci Catal 49 (1989) 199.

[52] Huo Q, Xu R, Li S, Ma Z, Thomas J M, Jones R H and Chippendale A M, J Chem Soc Chem Commun (1992) 875.

[53] Estermann M, McCusker L B, Baerlocher C, Merrouche A and Kessler H, Nature 352 (1991) 320.
[54] Maxwell I E, Cat Tech 1 (1997) 5.
[55] Corma A, Chem Rev 95 (1995) 571.
[56] Barthomeuf D, Catal Rev Sci Eng 38 (1996) 521.
[57] Corma A, Mat Res Soc Symp Proc 233 (1991) 17.
[58] Mortier W J, J Catal 55 (1978) 138.
[59] Barthomeuf D, Stud Surf Sci Catal 65 (1991) 157
[60] Corma A, Fornes V, Martin-Aranda R M, García H and Primo J, Appl Catal 59 (1990) 237.
[61] Corma A, Martin-Aranda R M and Sanchez F, J Catal 126 (1990) 192.
[62] Camblor M A, Corma A, Martin-Aranda R M and Perez-Pariente J, 9th Int Zeolite Conf Eds, Von Ballmoos R et al. (1993) 647.
[63] Reddy T Y and Varma R S, Tetrahedron Lett 38 (1997) 1721.
[64] Hattori H, Chem Rev 95 (1995) 537.
[65] Tanabe K, Misono M, Ono Y and Hattori H, New Solid Acids and Bases, Kodansha, Tokyo – Elsevier, Amsterdam, Oxford, New York, Tokyo, 1989.
[66] Yagi F, Tsuji H and Hattori H, Micropor Mater 9 (1997) 237.
[67] Hathaway P A, and Davis M E, J Catal 116 (1989) 263.
[68] Hathaway P A, and Davis M E, J Catal 116 (1989) 279.
[69] Laspéras M, Cambon H, Brunel D Rodriguez I and Geneste P, Microporous Mater 1 (1995) 343.
[70] Brownscombe T F and Slaugh L H, EU 370553, 1989.
[71] Brownscombe T F, US 5053372, 1991.
[72] Tsuji H, Yagi F, Hattori H and Kita H, Proceed 10th Inter Cong Catal (Budapest) (1993) 1171.
[73] Rodriguez I, Cambon H, Brunel D, Laspéras M and Geneste P, Stud Surf Sci Catal 78 (1993) 623.
[74] Laspéras M, Rodriguez I, Brunel D, Cambon H and Geneste P, Stud Surf Sci Catal 97 (1995) 319.
[75] (a) Kim J C, Li H X, Chen C Y and Davis M E, Microporous Mater 2 (1994) 413. (b)Yagi F, Kanuka N, Tsuji H, Nakata S, Kita H and Hattori H, Microporous Mater 9 (1997) 229.
[76] Yagi F, Kanuka N, Tsuji H, Nakata S, Kita H and Hattori H, Sud Surf Sci Catal 90 (1994) 349.
[77] Tsuji H, Yagi F and Hattori H, Chem Lett, 18 (1991) 81.
[78] Rodriguez I, Cambon H, Brunel D and Lasperas M, J Mol Catal 130 (1998) 95.
[79] Baba T, Kim G J, Ono Y, J Chem Soc, Faraday Trans, 88 (1992) 891.
[80] Baba T, Satoru H, Ryutaro K and Yoshio O, J Chem Soc, Faraday Trans 89 (1993) 3177.
[81] Baba T, Satoru H, Yishio O, Tomoko Y, Tsunehiro T and Satohiro Y, J Mol Catal A 98 (1995) 49.
[82] Kloetstra K R, and Van Bekkum H, J Chem Soc Chem Commun (1995) 1005.
[83] Kloetstra K R, and Van Bekkum H, Stud Surf Sci Catal 105 (1997) 431.
[84] Kloetstra K R, Van Laren M and Van Bekkum H, J Chem Soc, Farad Trans 93 (1997) 1211.
[85] Corma A, Aranda R M, Appl Catal A 105 (1993) 271–279.
[86] Corma A, Iborra S, Primo J and Rey F, Appl Catal 114 (1994) 215.
[87] Sasidharan M and Kumar R, Catalysis Lett 38 (1996) 251.
[88] Sreekumar R, Rugmini P and Padmakumar R, Tetrahedron Lett 38 (1997) 6557.

7.2 Aldol Condensations Catalyzed by Hydrotalcites

François Figueras, Joseph Lopez

7.2.1 Introduction

Aldolization is widely used in organic chemistry, because it enables the creation of C–C bonds. It is commonly used to manufacture solvents (diacetone alcohol, isophorone), intermediates for the manufacture of perfumes and pharmaceuticals (chalcones and more generally α,β unsaturated ketones), and plasticizers. This reversible reaction can be catalyzed by acids or bases [1], but basic catalysis is usually preferred. The substitution of the homogeneous bases by solids in the process is environmentally highly desirable.

7.2.1.1 Thermodynamics of Aldolization

One of the difficulties in performing aldolization is the reversibility of the reaction, which limits the equilibrium conversion. The thermodynamic equilibrium has been investigated by Craven [2] for the industrially important aldolization of acetone to diacetone alcohol (DA). Because the reaction is exothermic, the yield of aldol obtained from pure acetone decreases with temperature: 23.1 % at 273 K, 16.9 % at 283 K, 12.1 % at 293 K and 9.1 % at 303 K. The same conclusions can be drawn from the work of Guthrie [3–6] who reported equilibrium constants in the aqueous phase, in relation to the pK_a of the substrates, for a series of aldol condensations at room temperature. For the aldolization of acetaldehyde at 298 K the values relative to the reaction are $\Delta G° = -2.4$ kcal mol^{-1}, $\Delta H° = -9.84$ kcal mol^{-1}, and equilibrium constant $K = 57$ M^{-1}. The results for a few specific reactions performed in the aqueous phase are reported in Table 1 where K_1 and K_2 represent the equilibrium constants for the formation of the aldol and for its dehydration, respectively.

According to these thermodynamic data, significant conversion can be obtained for the condensation of acetone with formaldehyde. Diacetone alcohol can be formed in low yield only and has a lower tendency to dehydrate than the aldols formed from benzaldehyde. The energy balance of the process is so displaced by the formation of water that the unsaturated ketone is usually obtained. The

Table 1. Free enthalpies of formation of aldols and equilibrium constants K_1 (M^{-1}) for aldolization and K_2 (M) for dehydration at 298 K, for some characteristic reactions.

Reaction	ΔG_f aldol (kcal mol^{-1})	K_1 aldolization (M^{-1})	K_2 dehydration (M)
Acetone–formaldehyde	–4.58	–	0.043
Acetone–acetone	+1.92	0.039	0.063
Benzaldehyde–acetone	–1.27	8.5	31
Acetophenone–benzaldehyde	+0.16	0.76	87

ease of dehydration on one side and the decrease of the equilibrium constant with temperature accounts for the difficulty in preparing aldols. Another factor of importance related to the solid is possible catalysis or inhibition of some of the steps.

7.2.1.2 Structure and Surface Properties of Hydrotalcites and Calcined Hydrotalcites

Hydrotalcite (HDT) is a natural mineral of ideal formula $Mg_6Al_2(OH)_{16}$ $(CO_3{}^{2-}).4H_2O$. Solids with the same structure, denoted by extension hydrotalcites (HDT), have been synthesized with Al/(Mg + Al) ratio between 0.2 and 0.33 [7,8]. Outside this range the material is a mixture of HDT and gibbsite or hydromagnesite. Hydrotalcite corresponds to a solution of Al atoms in the lattice of brucite (Figure 1) and the solid solutions thus obtained have lattice parameters which follow Vegard's law [7–9]. Isostructural solids can also be obtained by dissolving Fe^{3+} and Cr^{3+} in $Mg(OH)_2$ or the same trivalent cations in the lattice of the divalent hydroxides of Ni, Cu, Zn, Co, and Mn [8–10]. The structure then consists of a positively charged layer, compensated by anions which retain some mobility and can be exchanged. The OH form of MgAl HDT is also a natural mineral called meixnerite.

Because of their basicity, hydrotalcites stored in air become carbonated, then neutral. They can be decarbonated by treatment above 673 K, and a mixed oxide of MgO structure is then obtained which has basic properties. The basic strength can be estimated from the temperature of decarbonation, and it is then observed that this temperature is affected by the presence of chlorine on the surface, even in trace amounts [11]. This temperature is shifted by ca 30 K towards high temperatures when Cl^- has been fully exchanged by carbonate. Because chlorine is normally present at trace levels only, these anions must have a long-range influence and reduce the basicity of the stronger basic sites.

The original structure can be restored by rehydration. This phenomenon is called the memory effect of hydrotalcite, and suggests that dehydration induces a small displacement of the cations only and not complete rearrangement of structure. Dehydration is accompanied by a spectacular increase of surface area, as illustrated in Table 2, and gas phase rehydration with water-saturated nitrogen by a decrease to very low values of surface area and porosity [12].

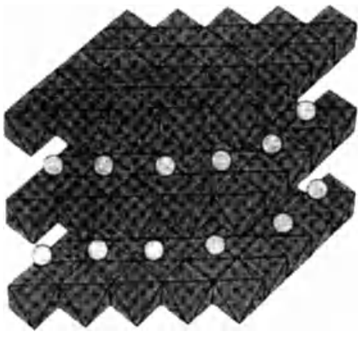


Figure 1. Structure of hydrotalcite: Al or Mg occupies the centers of the octahedra, and anions (circles) the interlayer space.

Table 2. Surface area and porosity of a synthetic hydrotalcite after calcination at 723 K and further rehydration at room temperature for different periods.

	HT1A	Treated at 723 K	Rehydration 5 h	15 h	48 h
S_{BET} ($m^2\ g^{-1}$)	95.3	265.2	50.2	19.1	11.7
V_{PC} ($mL\ g^{-1}$)	0.415	0.857	0.261	0.0991	0.0636

The acid–base properties of the material depend on the treatment: HDT which has first been converted to the carbonate form, then calcined at about 723 K adsorbs CO_2 and thus shows basicity. Basicity has been estimated by calorimetric measurement of adsorption of CO_2. The enthalpy of adsorption is related to the basic strength and the amount adsorbed to the number of sites. An example of a thermogram is shown in Figure 2. CO_2 uptake after rehydration, depends on the temperature of evacuation. Figure 2 reports the results obtained after evacuation at 353 K up to 0.01 Pa [11].

After evacuation at 373 K the thermogram of the rehydrated samples is similar to that of the calcined sample. Thermogravimetric analysis, however, shows that the surface is still highly hydroxylated, which leads to the conclusion that hydroxyl groups and oxygen have basicities of the same order of magnitude, at least relative to CO_2.

HDT can be regenerated without loss of properties [13]. Regeneration is much easier for the fully carbonated samples, because after calcination at 723 K significant amounts of Al can be extracted, by basic treatment, from solids containing Cl. Fortunately the most basic samples are those which can be reactivated.

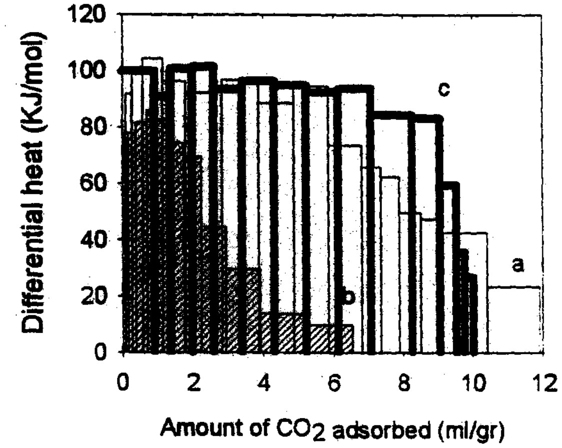


Figure 2. Differential heats of adsorption of carbon dioxide over HDT(2.7) (a) calcined at 773 K, or (b) calcined, rehydrated at room temperature, then evacuated at 353 K (gray bars), and (c) rehydrated and evacuated at 373 K.

7.2.1.3 Aldolizations on Calcined Hydrotalcites

Most results relate to this catalyst, after the pioneering work of Reichle [14–17] on the use of calcined hydrotalcites in the conversion of acetone to isophorone above 523 K. Indeed in a 1-inch pilot-plant reactor operated at 573 K conversion reached 23 %. Because mesityl oxide can be converted to isophorone the efficiency, as the sum of both, was 77 mol%. A further refinement of catalyst preparation [18] increased the conversion to 31 % with the same efficiency, or the efficiency to 85 % with a lower conversion of 20 %. Similar results have also been described by Ishino et al. [19], who also reported 5.2 % conversion of cyclohexanone into (mainly) 2-cyclohexylidenecyclohexanone at 573 K.

The aldol condensation of formaldehyde and acetone to methylvinylketone has been investigated by Suzuki and Ono [20] on a series of solids; MgAl hydrotalcite was found to be the best catalyst, leading to 21 % conversion of acetone at 673 K, with 96 % selectivity for acetone and 64 % for formaldehyde. The carbonate form was the most suitable. Exchange by sulfates or chromates resulted in poor activity.

The aldolization of acetaldehyde on calcined hydrotalcites of different composition has been studied by Kagunya and Jones [21] in a flow reactor at 10 bar and LHSV = 4 at temperatures between 363 and 403 K. MgAl carbonate was the best catalyst; conversion reached ca 40 % at 110 °C with a broad range of products with a larger selectivity to C_6 isomers.

The condensation of formaldehyde and acetaldehyde has been studied by Dimitriu et al. [22] in the vapor phase at 453–598 K using a pulse type microreactor. The main product was acrolein, obtained with a selectivity of ca 82 % with conversion of 45 % acetaldehyde at 573 K. With such reactors it is difficult to make a good material balance because the products retained by the solid are not detected. Because of this the technique probably gives too optimistic a view of the catalytic results (selectivity and stability to coke deactivation).

The direct conversion of butyraldehyde to 2-ethylhexanal-1 has also been reported to proceed on calcined HDT of low Mg/Al ratios in the range 373–473 K, in a flow reactor. [23,24]. At 373 K both conversion and selectivity increased with reaction temperature. At 463 K conversion reached 71 % and selectivity 81 %. At constant temperature the conversion decreased slowly with time on stream. Addition of palladium to HDT, and operation in hydrogen enabled the performing of a bifunctional process in which butyraldehyde was converted to 2-ethylhexanol-1 with 90 % conversion and 75 % selectivity.

An exhaustive kinetic investigation of the aldol condensation of benzaldehyde and acetone on calcined MgAl HDT has been performed in the liquid phase with a batch reactor at 383 K [25]. The aldol, benzalacetone, and dibenzalacetone in small amounts were observed as products. Benzalacetone resulted from dehydration of the aldol, and dibenzalacetone from the addition of a second mole of acetone to benzalacetone.

A kinetic study of the reaction was performed by measuring the initial rates as a function of concentration for three samples, all decarbonated at 723 K–an HDT non-exchanged by carbonates and containing trace amounts of chlorine (HT(2.5)NE), a sample obtained from HT(2.5)NE by exchanging Cl^- by carbonates (HT(2.5) E), and MgO. The results reported on Figure 3 show that the initial rate of reaction goes through a maximum as a function of the concentration of benzaldehyde or acetone, characteristic of a Langmuir–Hinshelwood mechanism with competitive adsorption of the reactants. The maximum is observed at a benzaldehyde concentration of 0.25 mol L^{-1} for the two hydrotalcite samples and near 0.38 mol L^{-1} for MgO. It is well known that the ratio of the concentrations C_B/C_A at the maximum of the curves is equal to the ratio, λ_A/λ_B, of the adsorption coefficients, the maximum rate being related to the rate constant, k, of the reaction.

The shift of the maximum from 0.25 to 0.38 mol L^{-1} when going from hydrotalcite to MgO corresponds to a change in the adsorption coefficient for benzaldehyde. This shift suggests that MgO would be of lower basic strength than HDT, but calorimetry shows the initial enthalpy of adsorption of CO_2 to be 100 kJ mol^{-1} for both, with more sites on HDT. The apparent discrepancies between these results probably originate from the relatively high acidity of CO_2 compared with that of the reactants–CO_2 is too acidic for detection of the small differences of basicity to which the reactants are sensitive. The kinetic results also suggest that exchange of Cl^- by $CO_3{}^{2-}$ increases the number of sites and shifts their strength slightly.

The kinetics can be analyzed quantitatively by assuming competitive adsorption of the two reagents–the set of values $k = 153$, $\lambda_A = 1.3$, and $\lambda_B = 53$ obtained by variation of the concentration of benzaldehyde was consistent with the set obtained by variation of the concentration of acetone ($k = 124$, $\lambda_A = 1.2$, and $\lambda_B = 41$). Benzaldehyde is, therefore, adsorbed much more than acetone under these conditions. This model suggests that the rate-determining step is the condensation of benzaldehyde and acetone, both adsorbed on the same active sites of the hydrotalcite, to form a C–C bond. Whereas acetone would give a carbanion, benzaldehyde should be adsorbed by hydrogen bonding. This mechanism was previously proposed for the same reaction on barium hydroxide [26].

In the presence of a large excess of acetone the kinetics reduced to a pseudo-first order in benzaldehyde. According to the classical mechanism in solution,

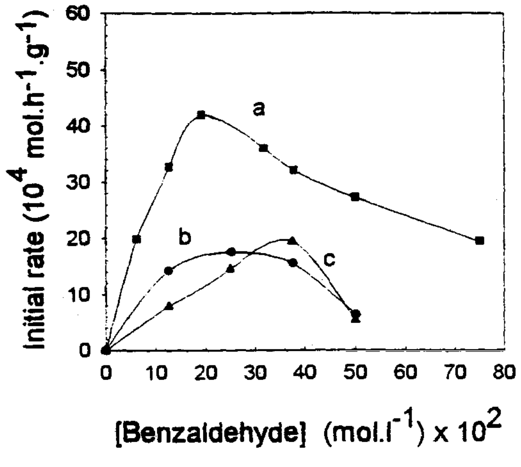


Figure 3. Variation of the initial rate of reaction with the concentration of benzaldehyde, at constant concentration of acetone (7.5 mol L^{-1}) at 383 K for samples calcined at 723 K: (a) hydrotalcite (Mg/Al = 2.5) exchanged by carbonates, (b) the same non-exchanged and containing traces of chlorine, and (c) magnesia.

the first step of the condensation reaction between benzaldehyde and acetone on hydrotalcite as a catalyst would be proton abstraction from acetone by the basic sites of the solid. When the reaction was performed with substituted benzaldehydes, the experimental rate constant increased as a function of the nucleophilic strength of the substituents (p-NO_2 > m-Cl > p-Cl > Me > p-OMe). A linear relationship was, indeed, obtained when the logarithm of the experimental pseudo first-order rate constants was plotted against the corresponding Hammett substituent coefficients. Better correlation was obtained by use of σ^+ values with a reaction constant, ρ, of 0.7.

The positive value of the reaction constant, ρ, is indicative of a reaction facilitated by a low electron density at the reaction center. The sign and the value of ρ are of the same magnitude as those found for homogeneous catalysis with NaOH [27] or for heterogeneous catalysis with Al_2O_3 [28]. The homogeneous acid-catalyzed aldolization and aldol dehydration are, moreover, characterized by a negative value of the ρ constant. These results (pseudo-first order in benzaldehyde with a positive value of the Hammett reaction constant) support the assumption that the rate-determining step is indeed nucleophilic addition of the carbanion to the CO of benzaldehyde to yield the corresponding aldol (4-hydroxy-4-phenylbutane-2-one).

These results, which are highly analogous with those from the homogeneous base-catalyzed condensation reaction, imply that the condensation of benzaldehyde and acetone is base-catalyzed on hydrotalcites.

Comparison of the performance of HDT (HT(2.5)E-1 or 2 denotes HDT with an Mg/Al ratio of 2.5, exchanged once or twice by carbonate) with that of NaY at similar reactant concentrations shows that NaY zeolite is much less active. The specific activities follow the pattern:

$$\text{HT(2.5)E-2} > \text{HT(2.5)E-1} > \text{MgO} > \text{NaY}$$

suggesting again that HDT is more basic than MgO and NaY.

The condensation of substituted benzaldehydes with 2-hydroxyacetophenones to give α,β unsaturated ketones (hydroxychalcones) of industrial interest has been reported by Climent et al. [29] to reach a yield of 85 % at a temperature of 443 K on hydrotalcite. The rate went through a maximum for a Al/(Mg + Al) ratio close to 0.3. The presence of electron-acceptor groups in the aromatic ring of benzaldehyde increased the reaction rate in proportion to the value of the Hammett constant, although bulky substituents such as NO_2, Cl, or OCH_3 resulted in geometrical effects as a result of diffusional problems or steric restrictions.

7.2.1.4 Aldolizations on Hydrotalcites First Calcined then Rehydrated

As discussed above rehydration enables the restoration of the hydroxyls and it can be assumed that the compensating anions are OH^-, as in meixnerite. This solid has been described only recently [30] and few of its potential applications have been studied.

This solid is the first heterogeneous catalyst yet reported for the aldolization of acetone to diacetone alcohol at 273 K. The products of the batch reaction are diacetone alcohol (selectivity > 96 %) and triacetone dialcohol (4 %) with traces of mesityl oxide (MO). The productivity was 3.7 kg DAA kg^{-1} solid h^{-1} and the catalyst could be recycled seven times without any loss of activity. Hydrated HDT reached thermodynamic equilibrium in < 1 h and was more active than MgO, calcined HDT, or even solutions of NaOH (Figure 4). The selectivity is also much better because mesityl oxide was not formed on the rehydrated sample.

The non-formation of MO is indeed very beneficial, because the reaction is dramatically inhibited by this product (Figure 5); thus a non-selective catalyst also has low activity because of self inhibition by the products [11].

Chlorine, has a deleterious effect on strong basicity, and might even promote acidity. Even in trace amounts it inhibits the reaction of acetone, as evidenced by Figure 6. Fortunately Cl^- can be readily exchanged by carbonates which decompose during thermal treatment.

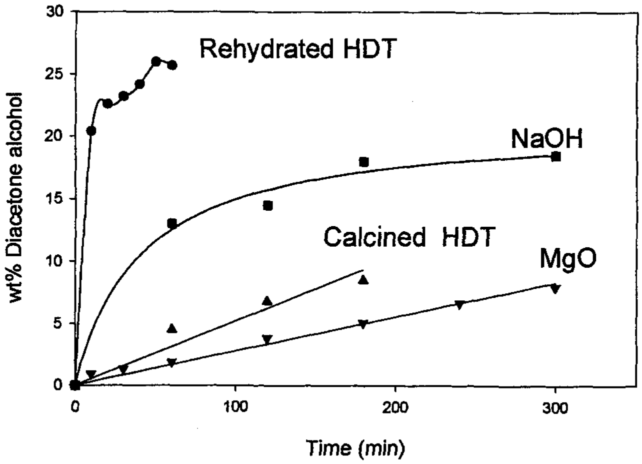


Figure 4. Formation of diacetone alcohol from acetone at 273 K, using NaOH and different solid bases.

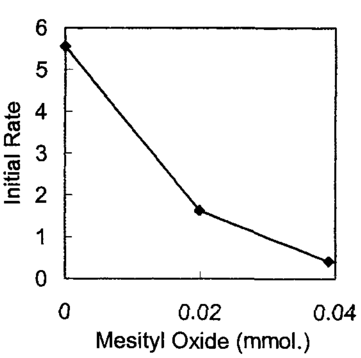


Figure 5. Influence of the addition of mesityl oxide to the reaction mixture on the initial rate of reaction of aldol formation, using HDT (Mg/Al = 2.89) exchanged twice by carbonates.

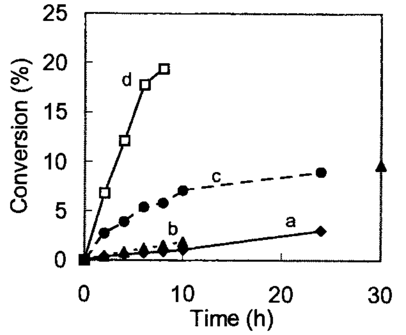


Figure 6. Conversion of acetone on non-exchanged samples–curves a (HDT (2.85) and b (HDT (4.68)–and on the solids obtained from these by anion exchange–c (exchanged HDT(2.85) and d (exchanged HDT (4.68).

The specific properties of hydrated hydrotalcites appear not only in the aldolization of acetone, but in many other aldolization reactions. For example, in the aldol condensation of benzaldehyde with acetone the hydrated form catalyzes the reaction at 273 K, yielding aldol as the main product instead of benzalacetone, obtained on the calcined sample. Competitive adsorption kinetics are still observed, with a much greater adsorption coefficient for benzaldehyde. As suggested earlier from Hammett relationships, this reaction can be generalized with success to many substituted benzaldehydes [32], although the reaction could be performed selectively at 273 K with benzaldehyde only, and substituted benzaldehydes required a reaction temperature of 333 K. Because of this 'high' temperature the reaction usually gives *a,β* unsaturated ketones; isolated yields are > 95 %.

Because the mechanism of this reaction is supposed to be ionic, it should be affected by the nature of the solvents. This is indeed so for the condensation of benzaldehyde and acetone [33]–rate changes by a factor of 50 are observed when heptane or toluene are substituted by DMF (Table 3). The initial rate, unaffected by possible inhibition by the products, is higher in polar solvents. Acetone also is highly polar and thus a good solvent for these reactions.

Good catalytic properties have also been reported by Teissier and Kervenal [34] for the synthesis of isophorone on an hydrotalcite first calcined then rehydrated. The superiority of the rehydrated solid in the experiment is apparent from the observation that the reaction performed in a batch reactor at 473 K reaches about

Table 3. Effect of the solvent on the initial rate of the aldol condensation of benzaldehyde with acetone in the liquid phase at 273 K.

Solvent	Polarity (*D*)	Rate × 10^6 (mol g^{-1} s^{-1})
Heptane	0	0.31
Toluene	0.3	0.34
Anisole	1.3	1.3
THF	1.7	5.2
DMF	3.2	16.4
Water	1.8	0

40% conversion with the same overall efficiency of ca 80% to isophorone + mesityl oxide and a higher selectivity to isophorone. Indeed, despite partial dehydration at this temperature, at 473 K this rehydrated solid has more activity than the calcined solid at 573 K, which clearly shows that the presence of hydroxyl groups is beneficial to this reaction also.

7.2.1.5 Aldolizations on Other Solid Catalysts

MgAl hydrotalcite impregnated with potassium *t*-butylate has recently been used for aldolization reactions [35]. The results are summarized in Table 4 for the condensation of acetone on benzaldehydes of general formula R_2CHO.

This modified catalyst is more active than decarbonated and rehydrated HDT because it catalyzes the reaction very quickly at 273 K whereas HDT required a slightly higher temperature and a longer time. As a result of operation at 273 K the aldol can be formed selectively.

Table 4. Aldol condensation of acetone with substituted benzaldehydes at 273 K on HDT modified with tBuOK. Reaction conditions: 2 mmol aldehyde in 10 mL acetone with 0.05 g catalyst.

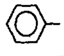
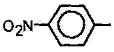
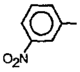
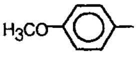
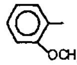
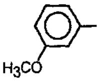
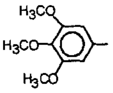
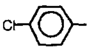
R_2	Time (min)	Conversion (%)	Isolated yields (%)
	15	100	95
	30	100	91
	10	100	97
	30	90	88
	15	100	93
	10	100	97
	10	100	92
	20	100	93

Table 5. Aldol condensation catalyzed by a modified MCM-41 catalyst.

Nucleophile	Electrophile	Time (h)	Conv. (%)	Selectivity (%) Aldol adduct	Dehydrated product
Me_2CO	PhCHO	3	79	52	48
Me_2CO	$2\text{-}MeOC_6H_4CHO$	9	81	47	53
Me_2CO	$3,4,5(MeO)_3C_6H_2CHO$	9	86	34	66

Aldolization with MCM 41, a mesoporous material modified by anchoring of 3-trimethoxysilylpropylethylenediamine, has also been reported [36]. This solid is expected to have the medium basicity of a diamine. Results for some aldolization reactions are reported in Table 5. The temperature was 323 K and relatively long times are required to reach high conversions, so these solids seem to be weaker bases than activated hydrotalcites. The high selectivity for dehydrated products is, moreover, evidence of the residual acidity of the solid.

The aldol condensation of benzaldehyde with acetophenone has been used to compare hydrated hydrotalcites with many solids claimed to be strong solid bases–KF and KNO_3 supported on alumina, X zeolites containing excess Cs or Mg, and lanthanum oxide. Only hydrated HDT and KF/Al_2O_3 could be used to perform this reaction at 273 K–HDT with 100 % selectivity for chalcone and KF with lower selectivity, because of secondary Michael addition of the chalcone to acetophenone. The other solids were inactive, but could induce comparable conversions at 423 K.

After activation at their optimum temperature (723 K for HDT, 923 K for La_2O_3, 823 K for Mg and Cs zeolites), the pattern of activity observed at 423 K, expressed on a weight basis, was:

$$\text{HT calcined} < \text{MgNa X} < La_2O_3 < \text{HT rehydrated} < \text{CsNaX} \\ < KNO_3/Al_2O_3 < KF/Al_2O_3$$

although when activity was expressed per unit surface area La_2O_3 was the most active.

The selectivity for the unsaturated ketone changes differently:

$$\text{HT (sel 100\%)} > La_2O_3\ (96) > \text{KF}\ (94) > KNO_3/Al_2O_3(92) \\ > \text{MgX}\ (89) > \text{CsNaX}\ (82).$$

The low activity of HDT at 423 K is because of its dehydration; conversion at 298 K after 3 h decreases from 70 % for the hydrated form to 4.6 % after dehydration at 423 K, with the same selectivity [33].

In conclusion, for thermodynamic and kinetic reasons aldolizations are difficult to perform with good yields. In several examples a spectacular increase in catalytic activity upon rehydration shows that this reaction is very specific for OH^- or F^- groups. The effect of substituents and the rate law both suggest that the mechanism can be described in terms of conventional organic chemistry.

References

[1] Carey F A and Sundberg R J (1990). *"Advanced Organic Chemistry"* Part B, 3rd edition, Plenum Press New York.
[2] Craven E C (1963) *J. Appl. Chem 13*; 71–77.
[3] Guthrie J P (1973) *J. Am Chem. Soc 113*; 7249–7255.
[4] Guthrie J P (1973) *Can. J. Chem 52*; 2037–2040.
[5] Guthrie J P (1978) *Can. J. Chem 56*; 962–973.
[6] Guthrie J P (1981) *Can. J. Chem 59*; 45–49.
[7] Miyata S (1975), *Clays Clay Miner 23*; 369–375 and (1980) *28*; 50–56.
[8] Cavani F, Trifiro F, and Vaccari A (1991) *Catal. Today 11;* 173–303.
[9] Rey F, Fornes V and Rojo J M (1992) *J. Chem. Soc. Faraday Trans. 88;* 2233–2238.
[10] De Roy A, Forano C, El Malki, K and Besse J-P (1992) in: M L Occelli and H Robson (Editors), *Synthesis of Microporous Materials* Van Nostrand-Reinhold, New York, 2, p 108–169.
[11] Tichit D, Lhouty M H, Guida A, Chiche B, Figueras F, Auroux A, Bartalini D, Garrone E (1995) *J. Catal. 151*; 50–59.
[12] Figueras F, Tichit D, Bennani Naciri M, Ruiz R (1998) in *"Catalysis of Organic Reactions"* (F E Herkes ed) Marcel Dekker Inc, New York, p. 37–49.
[13] Tichit D, Naciri Bennani M,. Figueras F, and Ruiz J R (1998) *Langmuir 14*, 2086.
[14] Reichle W T (1985) *J. Catal. 94*; 547–557.
[15] Reichle W T (1986) *ChemTech 16*; 58–63.
[16] Reichle W T and Millington N J (1978) *US* 4086188, pp. 9.
[17] Reichle W T and Warren N J (1984). *US* 4458026, pp. 14.
[18] Braithwaite J and Colakyan M (1995) *US* 5627303, pp. 7.
[19] Ishino M, Fukao M, Sasaki K, Suzukamo G and Sasaki M (1992) *US* 5237107, pp. 4.
[20] Suzuki E, Okamoto M and Ono Y (1990) *J Mol Catal 61;* 283–294.
[21] Kagunya W and Jones, W. (1995) *Applied Clay Science* 1095.
[22] Dumitriu E, Hulea V, Chelaru C, Catrinescu C, Tichit D, and Durand R (1999) *Applied Catal. A 178*; 145–147.
[23] Arena B J and Holmgren J S (1992) *US* 5144089, pp. 6 and *US* 5258558, pp. 6.
[24] Holmgren J S and Arena B J (1992) *US* 5254743, pp. 9.
[25] Guida A, Lhouty M H, Tichit D, Figueras F, Geneste P (1997) *Appl. Catal. 164;* 251–264.
[26] Aguilera A, Alcantara A R, Marinas J M and Sinisterra J V (1987) *Can. J. Chem.* 65; 1165.
[27] Coombs E and Evans D P. (1940) *J. Chem. Soc*; 1295–1300.
[28] Nondek L and Malek J (1980) *Collect Czech Chem Commun 45*; 1812.
[29] Climent M J, Corma A, Iborra S and Primo J (1995) *J. Catal. 151*; 60–66.
[30] Tessier R, Tichit D, Figueras F, and Kervenal J (1995) *French Patent* 95 00094 to Atochem.
[31] Koteswara Rao K, Gravelle M, Sanchez Valente J, Figueras F (1998) *J. Catal. 173*; 115–121.
[32] Choudary B M, Kantam M L, Kavita B, Venkat Reddy Ch , Koteswara Rao K and Figueras F (1998) *J. Chem Soc. Chemical Commun. 39*; 1033–1034.
[33] Lopez J, PhD thesis (1999) University Claude Bernard Lyon.
[34] Teissier R and Kervenal J (1997) *French Pat* 2745566 A1, pp. 5.
[35] Kantam M L, Choudary B M, Venkat Reddy Ch., Koteswara Rao K and Figueras F (1998) *Tetrahedron Lett. 39*; 3555–3558.
[36] Choudary B M, Kantam M L, Sreekanth P, Bandopadhyay T, Figueras F and Tuel, A (1999) *J. Mol. Catal. A: Chemical 142*; 361–365.

7.3 Organic Bases Attached to Mesoporous Silicas as Solid Catalysts

Duncan J. Macquarrie, Daniel Brunel

7.3.1 Introduction

The nineties saw enormous advances in the synthesis of inorganic oxides with high structural control. After original work performed at Mobil on M-41S materials, and subsequently by many others, the potential of these new solids for catalysis is steadily being realized. The initial breakthrough came in 1992 from the Mobil Corporation [1], who discovered that polymerizing silica and alumina precursors around cylindrical micelles of quaternary ammonium surfactants according to a cooperative assembly [2,3] led to a composite material consisting of an aluminosilicate framework with hexagonally tessellated cylindrical pores filled with the surfactant micelle. Calcination of this material led to removal of the surfactant, and to highly ordered silica, both in terms of uniform pore size and, in good samples, long-range order (Figure 1).

Surface areas are very high, typically ca 1000 m^2 g^{-1}, and the pore size is monodisperse and varies predictably with surfactant chain length. In this way alumino-

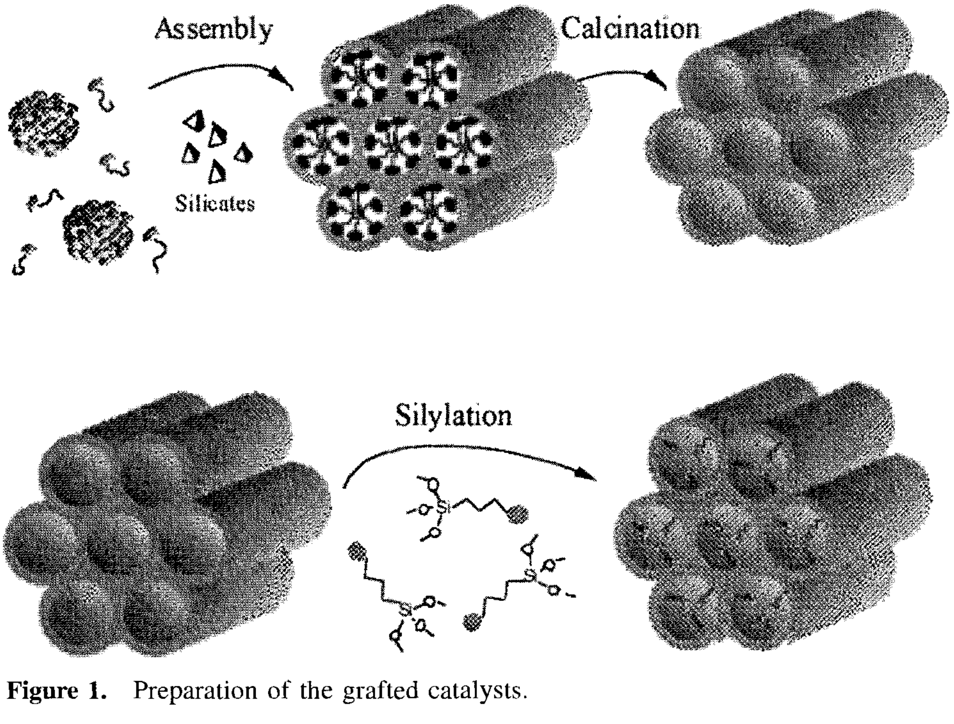


Figure 1. Preparation of the grafted catalysts.

silicates with pore sizes ranging from 2 to 5 nm can be prepared. Larger pore sizes are also accessible by modification of the original procedure, whereby a hydrocarbon (i. e. mesitylene) is added to the synthesis solution. This partitions itself inside the micelles, expanding them and leading to a larger-diameter pore. Increasing the amount of mesitylene leads to increased expansion of the micelle, and to larger pores.

These materials, which were initially designed as large-pore zeolites, are not strongly acid but are, rather, quite effective as mild acid catalysts [4], catalyzing reactions such as the oligomerization of propene [5,6] and butene [7], the alkylation of aromatic hydrocarbons [8–10], the acylation of activated aromatics [11,12], and the tetrahydropyranylation of alcohols [13].

Much effort has thus been expended in two other directions. Many mesoporous silicates have been prepared containing silicon and a second element, e. g. titanium, vanadium, zirconium, and a range of other first row transition metals, and their uses in catalysis have been examined [14–16]. The scope of this section is, however, to cover organic modification of the silica framework, both by post-synthesis grafting and in-situ functionalization, and to discuss applications of the products as basic catalysts.

7.3.2 Preparation of Materials

The surface of the materials obtained after calcination of the micelle-templated silicates (MTS) has been functionalized by covalent linkage of organic moieties; this has been achieved by silylation of the surface with organotrialkoxysilane (Figure 1) [17].

It is noteworthy that anchorage of alkylsiloxy chains takes place mainly on the hydrophobic part of the surface comprising the siloxane and isolated silanol groups. Hence the grafted chains are surrounded by a hydrophilic environment consisting of adjacent silanol groups of the uncovered surface [18–20]. This can be made more hydrophobic by end-capping. By this method of silylation, organic bases such as amine or diamine functions have been directly anchored to the MTS surface by use of the corresponding functionalized propyltrialkoxysilane as silylating agent (Figure 2) [17].

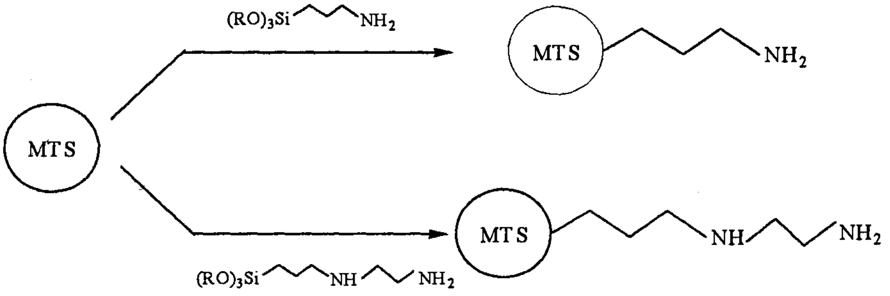


Figure 2. Direct anchoring of amines.

More recently, quaternary organic tetraalkylammonium hydroxides have been grafted on to an MTS surface by reaction with 3-trimethoxysilyl(trimethyl)ammonium chloride then treatment of the resulting solid with a methanolic solution of tetramethylammonium hydroxide [21].

Another method of functionalization effects multistep anchoring by coupling organic bases to previously grafted moieties containing an appropriate function. Hence, piperidine [17,22] and guanidine [23] have been anchored by substitution of halogen on the grafted chains and guanidine has been also linked by epoxide ring opening of previously anchored glycidyl functions (Figure 3) [24].

Although the grafting route can utilize calcined MCMs, direct incorporation of organic functionality requires a different strategy. The approach adopted exploits the tendency of organically functionalized silica precursors–e. g. $RSi(OR')_3$–to copolymerize with silica precursors–e. g. $(RO)_4Si$ (Figure 4).

This approach precludes the calcination of the initially formed silica–surfactant composite because of the similar (in)stability of the organic groups R, which contain the active center. Removal of quaternary templates by solvent-extraction procedures is known to be difficult, and this limits the utility of the original MCM route. Nonetheless, this route has been used for successful preparation of some organically modified materials [25,26]. Two other routes have been developed for the preparation of mesoporous silicas, namely the S^0I^0 and the N^0I^0 routes developed by Pinnavaia [27], involving the use of long-chain amines and non-ionic surfactants (end-capped polyethers) as structure determinants. In both routes the template can be easily removed by extraction with solvents, and this enables the preparation of organically modified materials under conditions in which the organic group remains intact during removal of the template [28,29]. It has, furthermore, been shown that the extractive S^0I^0 route enables essentially quantitative recovery of the template where R is aminopropyl [30].

This method of preparation involves the co-condensation of two silanes via a series of hydrolyses and condensations. It might be expected that the nature of

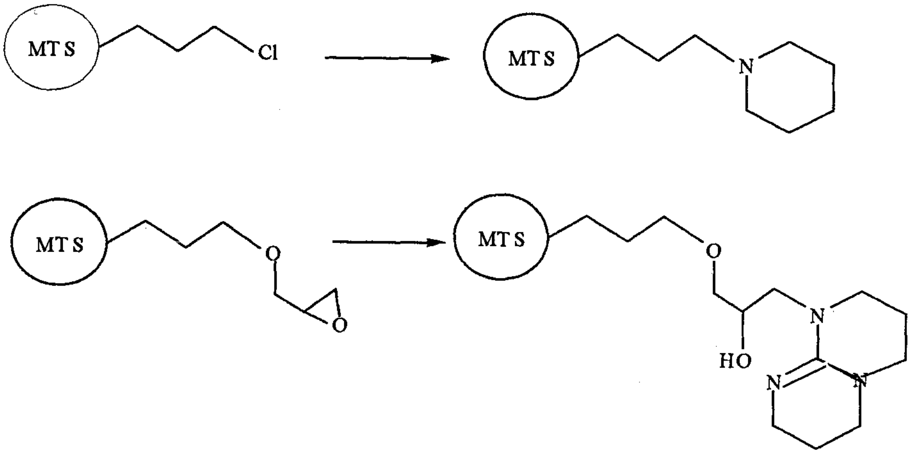


Figure 3. Anchoring of basic sites by two-step procedures.

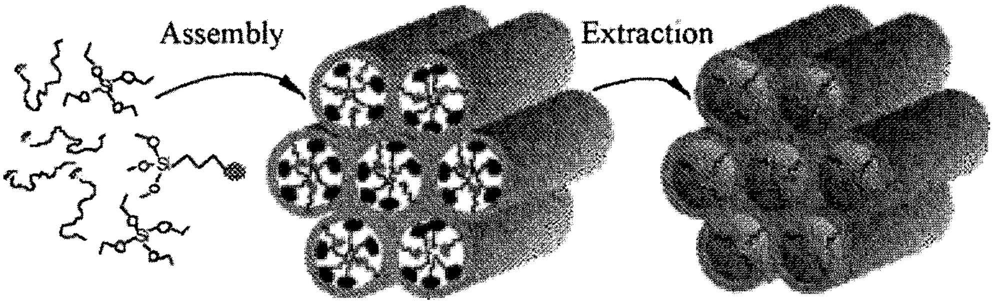


Figure 4. Preparation of the in-situ hybrid catalysts.

the material will differ significantly from the corresponding material prepared from the pre-formed support by reaction of the surface groups with silylating agent. Whereas elemental analysis (for aminopropyl) indicates that the C:N ratio is 5–6 (i.e. almost double the theoretical value of 3 for full hydrolysis–the figure found for the grafted materials) ^{29}Si MAS NMR indicates that the organosilane is attached predominantly by either 2 or 3 bonds to the structure, as compared to 1 or 2 for the grafted material [31]. The remaining alkyl groups seem to be mostly EtO groups distributed throughout the structure. One further difference which is expected from the preparation arises because the sol–gel preparation does not involve a calcination step. The evolution of surface species such as, e.g., siloxane bridges and hydrophobic (and hydrophilic) islands is thus not expected to occur to the same extent. Because attachment of silane during grafting is considered to occur on some of these areas only, the distribution of basic sites on the surface might well be quite different in the two materials–the in-situ sol–gel materials might thus be expected to have a more random structure, whereas the grafted materials could have concentrated islands of basicity. The detailed steps of the in-situ sol–gel method have not yet been elucidated, and thus no definitive conclusions can be drawn about this aspect of surface chemistry.

Another facet of the different nature of the two materials can be obtained from potentiometric titration of aqueous suspensions of the two materials [31]. The titration curve of the grafted material is similar to that shown in the reference for the corresponding amorphous silica material, suggesting that the grafting process produces similar materials both from amorphous silica and from preformed MTS. This differs significantly from the curve of the in-situ material, which has a definite inflection (at ca the pK_a of SiOH groups in silica) [32]. This might indicate that the surface of the material could be described more accurately as SiO^- H_3N^+–R. Such a (reversible) process has been postulated as occurring on aminopropyl groups grafted on to silica under water-rich conditions, and a similar solution-phase process in the water-rich sol–gel environment might be expected to lead to such a surface site [33]. Such a description of the basic center fits well with the lack of nucleophilicity of the nitrogen atom [34]. Aminopropyl groups grafted on to amorphous silica are poisoned by nucleophilic attack on the ester groups of one of the reaction partners in the Knoevenagel condensation [35].

The poisoning mechanism of the in-situ sol–gel materials does not involve nucleophilic attack, rather, it might be a result of selective adsorption of one of the reaction components at the active site.

7.3.3 Reactions Catalyzed by Organic Bases Attached to Mesoporous Silicas

7.3.3.1 Knoevenagel Reaction

The Knoevenagel reaction is one of the oldest C–C bond forming reactions (see also Section 7.1) [36]. It involves the condensation of a carbonyl component (typically benzaldehyde) with a C-acid (typically ethyl cyanoacetate)–Figure 5. This classical reaction is usually catalyzed by organic bases (primary, secondary, and tertiary amines), ammonia, and ammonium salts [37].

Under homogeneous conditions, the reaction proceeds by addition of a carbanionic species to the carbonyl group, then dehydration.

In some special cases, the carbonyl function could be previously activated during the process [38]. The rate-controlling step could be either the ionization of the methylene-activated reactant or the addition of the so-formed carbanion to the carbonyl group; the dehydration step is nearly always assumed not to be rate-determining [39].

Under heterogeneous conditions, the Knoevenagel reaction has been used as a well-adopted test reaction to check the activity of the basic sites of different solids, mainly basic zeolites such as alkali-exchanged zeolites [40] or zeolites containing occluded metal oxides [41]. The basic activity of alkali-containing MCM-41 [42] or binary cesium–lanthanum oxide supported on MCM-41 [43] has, moreover, also been evaluated in the Knoevenagel condensation.

Kinetic investigations have shown that during heterogeneous catalysis performed with metal oxides the associated acid site (metal cation) can also activate the carbonyl group, leading to cooperative acid–base catalysis. With organic bases attached to a mineral support such an effect would not be so pronounced.

In this respect, Brunel and co-workers compared grafted AMP-MTS [44] silica-grafted aminopropyl materials (AMPS) [45]. They found that AMP-MTS efficiently catalyzed the reaction of ethyl cyanoacetate and benzaldehyde, that the catalysts could be easily recovered and reused after a simple regeneration step, and that the activity was a simple linear function of catalyst loading within the limits 0.8–1.9 mmol g^{-1}–the highest loading achievable with these materials. Tertiary amines attached via displacement of a halogen substituent with piperidine were

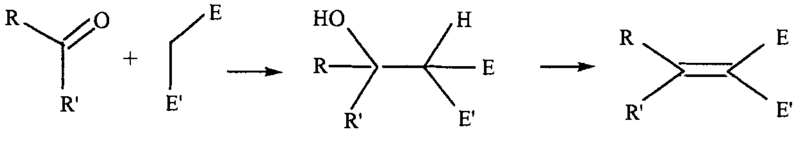


Figure 5. The Knoevenagel Reaction.

also active catalysts. The catalytic activity was lower for the tertiary amine, and it was postulated that the mechanism of catalysis involved the classical deprotonation mechanism then attack of the conjugate base of the C-acid on the carbonyl component. Catalysis by the grafted primary amine functions is thought to proceed via the imine [44]. This assumption was supported by the greater activity observed in this example, which is consistent with that observed in homogeneous conditions and similarly explained. On the other hand the TOF of these catalytic sites does not depend on the site or on their local environment density. Hence, a concerted mechanism is consistent with the involvement of a single amine site during each catalytic site.

The Knoevenagel reaction is, moreover, sensitive to both electronic and steric effects, making aryl carbonyls less reactive than alkyl-substituted analogs, and ketones much less active than aldehydes. Macquarrie et al. studied the condensation of a range of carbonyl components with ethyl cyanoacetate, using AMPS, and found that the order of activity of the carbonyl component was as expected [35]. Solvent effects were pronounced, and there was a distinct trend towards higher activity in low polarity solvents, indicating that partitioning of substrate on to the catalyst surface was important. With this grafted catalyst, no imine intermediate was seen and, although the imine could be prepared easily, it was unreactive under the conditions of the reaction. Although this is in contradiction to the results for the grafted MTS, it is known that even relatively small changes in the reaction medium can cause the Knoevenagel reaction to switch mechanism [37]. Interestingly, the same set of reactions using sol–gel-prepared aminopropyl–HMS (AMP–HMS) was characterized by one remarkable difference from the grafted materials [46]. The reaction of benzaldehyde, one of the easiest substrates, was one of the slowest studied, benzaldehyde being considerably less active than even acetophenone, which is ordinarily a very challenging substrate. This unusual change in activity has not yet been explained, but might be a result of selective adsorption phenomena. It does, however, highlight the dangers inherent in using one example of a reaction to evaluate a catalyst. A second significant difference is that turnover numbers (defined as moles of product per mole of active site) are 4–5 times higher for the AMP–HMS catalysts than for AMPS, and the mechanism of poisoning is different. AMPS is poisoned by acylation of the amine group by the cyanoacetate ester, but this does not happen with the sol–gel materials. Higher loaded materials result in higher enhanced reaction rates, when the same amounts are used (the rate per active site increases and then decreases from 1.1 mmol g^{-1} up to the highest studied, 4.9 mmol g^{-1}). Loadings above 2.5 mmol g^{-1} are no longer structured, but have high surface areas and broad pore-size distribution. [30].

A further modification to these catalysts involves the incorporation of a third, polarity-modifying silane (e. g. $PhSi(OMe)_3$) alongside the aminopropyl silane. The effect of this is quite pronounced, and increases both rate of reaction and the turnover number [30].

Choudary et al. have investigated the Knoevenagel reaction by use of diamine-functionalized MCM-41 [47]. This grafted material was effective in the condensation of several aldehydes with both ethyl cyanoacetate and with malononitrile. Interestingly, only malononitrile condensed efficiently with a ketone when this catalyst was used; ethyl cyanoacetate was obtained in low yields only.

Jacobs group has described the use of a supported guanidine catalyst in the Knoevenagel reaction [24]. This material is derived from a much stronger base than the simple amines, but there seems to be no real advantage in its use for the Knoevenagel condensation of the aldehydes quoted. Indeed yields are modest, although selectivities are claimed to be excellent. The real benefit of this material seems to be its performance in more demanding types of reaction.

A. Corma et al. have also recently used the Knoevenagel condensation as a test reaction for their MTS-quaternary tetramethylammonium hydroxide [21]. The turnover number of NMe_4OH sites remains constant even though the loadings were different, indicating total accessibility of reactants to the active sites. Moreover, the higher the polarity of the solvent, the higher is the reaction rate. That indicates that charged species are involved in the transition state. On the other hand, the catalyst kept the same activity upon recycling and reuse.

7.3.3.2 Michael Additions

Macquarrie et al. have demonstrated that in-situ copolymerized dimethylamino-substituted HMS materials are active in the Michael addition of nitroalkanes and enones [48]. Yields and selectivities are high, and the activity of the catalysts is much higher than that of the corresponding silica-grafted materials. (Figure 6)

Jacobs et al. [24] have shown that their supported guanidine catalyst is effective in a range of Michael additions involving both ethyl cyanoacetate and diethyl malonate as C-acid. Selectivity was variable and depended on the nature of the acceptor, with the very active acceptors, such as acrolein and ethyl acrylate, giving substantial quantities of the double-addition products.

The Michael reaction was also investigated by Corma's group, who used a variety of donor and acceptor substrates [21]. High selectivity to the 1,4 adduct was always obtained, showing the well-defined strong basicities of the hydroxide sites [21b]

A further application of this catalyst is the related base-catalyzed epoxidation of electron-deficient alkenes. The supported guanidine is capable of significant conversion of enones such as cyclopentenone, with hydrogen peroxide as oxidant (Figure 7).

Brunel et al. have investigated transesterification reactions catalyzed by grafted guanidine [23]. Although the turnover frequency of the anchored guanidine is of the same order of magnitude as that of the homogeneous material during the first run, the stability of this solid-base catalyst warrants further investigation.

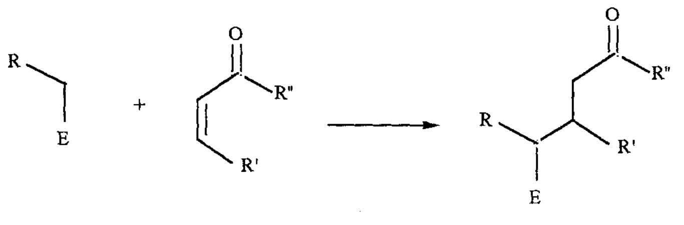


Figure 6.
The Michael addition.

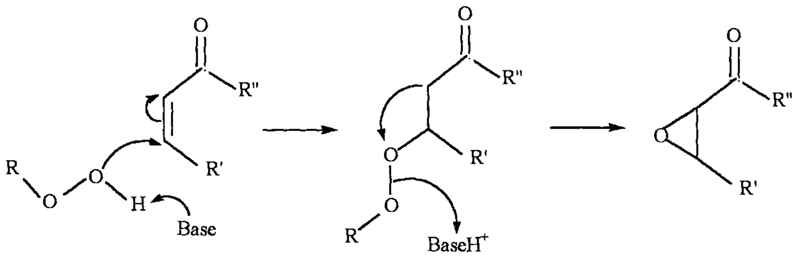


Figure 7. Base-catalyzed epoxidation of electron-deficient alkenes.

7.3.3.3 The Aldol Reaction

Choudary et al. have used diamine-functionalized MCM-41 for the aldol reaction of a variety of aliphatic aldehydes with acetone. [47]. Conversions were good, although the ratio of aldol product to dehydrated product was quite variable, depending on the nature of the aldehyde. There does not seem to be any definite pattern in the selectivity achieved as a function of substitution of the aldehyde (Figure 8).

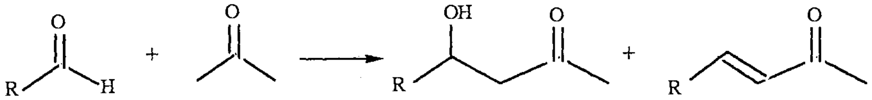


Figure 8. The aldol reaction.

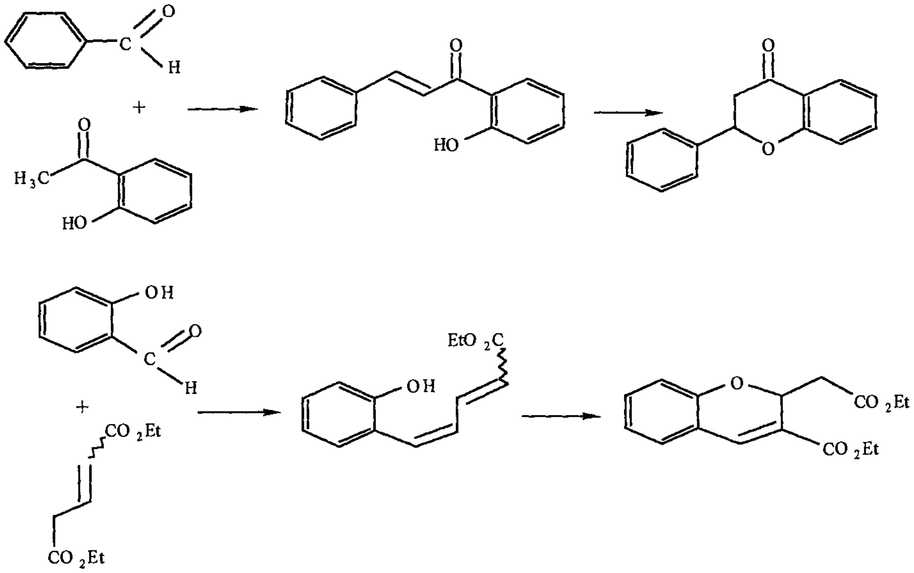


Figure 9. Synthesis of flavone and chromene.

Corma et al. have also tested MCM-41OH in the aldol condensation between benzaldehyde and 2′-hydroxyacetophenone. They showed that this material catalyzed successive aldol condensation and intramolecular Michael reaction addition to give flavone with good selectivity. Chromenes can be also produced by condensation of salicylaldehyde derivatives and diethylglucotaconate under mild conditions (Figure 9).

7.3.3.4 Monoglyceride Synthesis

The synthesis of monoglycerides is important in the fields of agrochemicals and pharmaceuticals. Esterification of glycerol does not furnish the required selectivity, and the base catalyzed ring opening of glycidol is the favored approach. Brunel et al. have studied the reaction of glycidol with lauric acid, using both primary and tertiary amines as catalysts [22] (Figure 10). Primary amines were relatively poor catalysts, presumably because of their conversion to aminodiol by reaction with glycidol. Tertiary amine sites were more effective, especially after the exposed silanols on the surface had been endcapped with trimethylsilyl groups. This end-capping treatment limits the undesirable polymerization reaction of glycidol. The catalyst can, moreover, be reused several times without loss of activity.

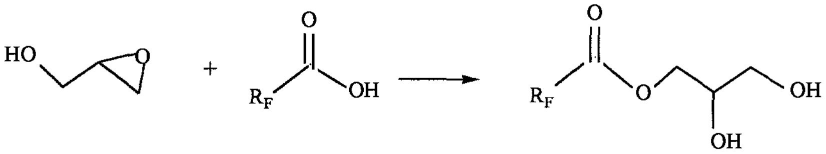


Figure 10. Preparation of monoglycerides.

7.3.4 Discussion of the Different Approaches

The possibility of attaching organic bases to inorganic supports either by grafting or by in-situ co-condensation enables the production of a large number of different types of base. In contrast with inorganic bases such as supported metal oxides, for which precise control over the nature of the basic site is difficult, a wide range of subtly different groups can be introduced directly. Although the bases available so far have, for the most part, been relatively simple, the possibility of incorporation of chiral bases capable of enantioselective basic catalysis is exciting. Chiral amines have been successfully introduced by grafting on to the surface of an MTS and used with some success as chiral ligands for organometallic C–C bond-forming reactions [49].

In addition to the attachment of a variety of different bases to the material structure, it is also possible to control the environment surrounding the basic center. Grafted MTS materials can be silylated to cap the silanols. This prevents the SiOH function hydrogen-bonding with the basic center, reducing its activity. and modifying the transport properties of the system to enable adsorption and desorption to occur more readily.

The MTS materials also result in higher loadings than the traditional silica supports. This, and the fact that grafting occurs on hydrophobic patches on the surface, means that relatively high local concentrations of basic sites are likely to be formed on these patches.

Possible limitations to this approach might include the relatively unstable nature of the surface under strongly basic and alkaline conditions. The silica structure can be hydrolyzed or solvolyzed under such conditions, leading to loss of structure and possible leaching of organics into solution, although attempts have been made to retard this phenomenon by covering the surface as completely as possible with organic groups, thus limiting the approach of possibly destructive species such as water and hydroxide.

The related HMS materials, prepared by the in-situ route, share many of the advantages and disadvantages of the MTS materials. Although synthesis is more direct and very simple to perform, the materials are less uniform than the MTS materials, a factor which might make them less attractive for certain applications. However, the possibility of recovering the template of varying the loading to very high levels (> 3 mmol g^{-1} of accessible sites has been achieved [50] by variation of the ratio of silanes in the preparation mixture), and the possibility of incorporating polarity-modifying groups during synthesis endows these materials with great potential as catalysts. It might well be true that the HMS materials (as for the MTS materials) suffer from instability under strongly basic systems, but similar methodology can be used to minimize this effect.

One intriguing difference might also lie in the distribution of the basic sites on the two classes of catalyst. Whereas the MTS materials develop hydrophobic and hydrophilic patches during calcination, leading to islands of high basic site density, this effect should not be seen for the HMS materials, because both the silicon-containing precursors are polymerized together (relative rates of polymerization and reorganization might, in fact, lead to high local concentrations of certain sites) and no calcination is used.

7.3.5 Conclusions

A series of supported-base catalysts has been prepared in recent years, by utilizing the rapid progress made in the construction of mesoporous silicas with unprecedented levels of structural control. These materials have been evaluated in a series of base-catalyzed reactions, with impressive results. The variety of different basic structures, and the number of support types and methods available to combine the two components will enable further progress to be made. The constant advances seen in materials chemistry, and continued efforts in synthetic applications, will no doubt lead to many more applications in future.

References

[1] (a) J S Beck, C T-W Chu, I D Johnson, C T Kresge, M E Leonowicz, W J Roth, J C Vartuli, WO 91/11390 (1991); (b) J S Beck, J C Vartuli, W J Roth, M E Leonowicz, C T Kresge, K D Schmitt, C T-W Chu, D H Olson, E W Sheppard, S B McCullen, J B Higgins and J L Schlenker, J. Am. Chem. Soc., 114 (1992) 10834.

[2] (a) A. Monnier, F. Shüth, Q. Huo, D. Kumar, D. Margolese, R.S. Maxwell, G.D. Stucky, M. Krishamurthy, P. Petroff, A. Firouzi, M. Janicke, B.F. Chmelka, Science, 261 (1993) 1299 ; Q. Huo, D.I. Margolese, G.D. Stucky, Chem. Mater., 8 (1996) 1147.

[3] A. Galarneau, F. Di Renzo, F. Fajula, L. Mollo, B. Fubini and M.F. Ottaviani, J. Colloid. Inter. Sci., 201 (1998) 105.

[4] F. Di Renzo, B. Chiche, F. Fajula, S. Viale and E. Garrone, Stud. Surf. Sci. Catal., 101 (1996) 851.

[5] Q.N. Le, R.T. Thomson and G.H. Yokomizo, US Pat., 5 134 241 (1992).

[6] G. Bellussi, C. Perego, A. Carati, S. Peratello, E.P. Massara and G. Perego, Stud. Surf. Sci. Catal., 84 (1995) 85.

[7] B. Chiche, E. Sauvage, F. Di Renzo, I.I. Ivanova and F. Fajula, J. Mol. Catal., A. Chem., 134 (1998) 145.

[8] E. Armengol, M. L Cano, A. Corma, H. Garcia and M.T. Navarro, J. Chem. Soc., Chem. Commun., (1995) 519.

[9] B. Chakroborty, A.C. Pulikottil and B. Viswanathan, Catal. Lett., 39 (1996) 63.

[10] S.B. Pu, J.B. Kim, M. Seno and T. Inui, Micropor. Mater., 10 (1997) 25.

[11] S. Hitz and R. Prins, J. Catal., 168 (1997) 194.

[12] E.A. Gunnewegh, S.S. Gopie and H. van Bekkum, J. Mol. Catal., 106 (1996) 151.

[13] K.R. Kloetstra and H. van Bekkum, J. Chem. Res., S (1995) 26.

[14] A. Tuel, Stud. Surf. Sci. Catal., 117 (1997) 159.

[15] X.M. Zhang, Z.R. Zhang, J.S. Suo and S.B. Li, Chem. Lett., (1998) 755.

[16] W.Z. Zhang, J.L. Wang, P.T. Tanev and T.J. Pinnavaia, Chem. Commun., (1996) 979.

[17] (a) D. Brunel, A. Cauvel, F. Fajula and F. Di Renzo, Stud. Surf. Sci. Catal., 97 (1995) 173; (b) A. Cauvel, D. Brunel, , F. Di Renzo and F. Fajula, Am. Inst. Phys., 354 (1996) 477.

[18] P. Sutra, F. Fajula, D. Brunel, P. Lentz, J.B. Nagy, Colloid. Surf., in press.

[19] D.J. Macquarrie, S.J. Taverner, G.W. Gray, P.A. Heath, J.S. Rafelt, S.I. Saulzet, J.J.E. Hardy, J.H. Clark, P. Sutra, D. Brunel, F. Di Renzo and F. Fajula, New J. Chem., 23 (1999) 725.

[20] D. Brunel, A. Cauvel, F. Di Renzo, F. Fajula, B. Fubini, B. Onida and E. Garrone, PCCP, submitted.

[21] (a) I. Rodriguez, S. Iborra, A. Corma, F. Rey and J.I. Jorda, Chem. Commun., 1999, 593; (b) I. Rodriguez, S. Iborra, F. Rey and A. Corma , Appl. Catal., in press.

[22] A. Cauvel, G. Renard and D. Brunel, J. Org. Chem., 62 (1997) 749.

[23] A. Derrien, G. Renard and D. Brunel, Stud. Surf. Sci. Catal., 117 (1998) 445.

[24] Y.V. Subba Rao, D.E. De Vos and P.A. Jacobs, Angew Chem., Int. Ed. Engl., 36 (1997) 2661.

[25] S.L. Burkitt, S.D. Sims and S. Mann, Chem. Commun., (1996) 1367.

[26] M.H. Lim, C.F. Blanford and A. Stein, J. Am. Chem. Soc., 119 (1997) 4090.

[27] P.T. Tanev and T.J. Pinnavaia, Science, 267 (1995) 835.

[28] D.J. Macquarrie, Chem. Commun, (1996) 1961.

[29] R. Richer and L. Mercier, Chem. Commun., (1998) 1775.

[30] D.J. Macquarrie, Green Chemistry, 1 (1999) 195.

[31] D.J. Macquarrie, D.B. Jackson, J.E.G. Mdoe and J.H. Clark, New. J. Chem., 23 (1999) 539.

[32] R.S.S. Murthy and D.E. Leyden, Anal. Chem., 58 (1986) 1228.

[33] G.S. Caravajal, D.E. Leyden, G.R. Quinting and G.E. Maciel, Anal. Chem., 60 (1998)1776.

[34] D.J. Macquarrie, unpublished results.

[35] D. J. Macquarrie, J. H. Clark, A. Lambert, J. E. G. Mdoe and A. Priest, React. Funct. Polym., 35 (1997) 153.
[36] E. K. Knoevenagel, Ber. 29 (1896) 172.
[37] G. Jones, Organic Reactions, 15 (1967) 204.
[38] G. Charles, Bull. Soc. Chim. Fr., (1966) 1559 and 1576.
[39] R. L. Reeves, in "The Chemistry of the Carbonyl Group", Pataï Eds, Interscience pubs, NY, 1966, 593.
[40] (a) A. Corma, V. Fornes, R. M. Martin-Aranda, H. Garcia and J. Primo, Appl. Catal., 59 (1990) 237; (b) M. J. Climent, A. Corma, S. Iborra and J. Primo, J. Catal;, 151 (1995) 60.
[41] (a) I. Rodriguez, H. Cambon, D. Brunel, M. Laspéras and P. Geneste, Stud. Surf. Sci. Catal., 78 (1993) 623; (b) M. Laspéras, I. Rodriguez, , D. Brunel, H. Cambon and P. Geneste, Stud. Surf. Sci. Catal., 97 (1995) 319; (c) I. Rodriguez, H. Cambon, D. Brunel and M. Laspéras, J. Mol. Catal. A: Chem., 130 (1998) 195.
[42] K. R. Kloetstra and H. van Bekkum, J. Chem. Soc., Chem. Commun., (1995) 1005.
[43] K. R. Kloetstra, M. van Laren and H. van Bekkum, J. Chem. Soc., Farad; Trans., 93 (1997) 1211.
[44] M. Lasperas, T. Lloret, L. Chaves, I. Rodriguez, A. Cauvel and D. Brunel, Stud., Surf. Sci., Catal., 108 (1997) 75.
[45] E. Angeletti, C. Canepa, G. Martinetti and P. Venturello, Tetrahedron Letters, 29 (1988) 2261; E. Angeletti, C. Canepa, G. Martinetti and P. Venturello, J. Chem. Soc., Perkin Trans 1, (1989) 105.
[46] D. J. Macquarrie and D. B. Jackson, Chem. Commun., (1997) 1785.
[47] B. M. Choudary, M. Lakshmi-Kantam, P. Sreekanth, T. Bandopadhyay, F. Figueras and A. Tuel, J. Mol. Cat., 142 (1999) 361.
[48] D. J. Macquarrie, J. E. G. Mdoe and J. H. Clark, Synlett (1998) 625.
[49] (a) M. Lasperas, N. Bellocq, D. Brunel and P. Moreau, Tetrahedron Asymm. *9 (1998) 3053*; (b) N. Bellocq, S. Abramson, M. Lasperas, D. Brunel and P. Moreau, Tetrahedron Asymm., 10 (1999) 3229.
[50] J. A. Elings, R. Ait-Meddour, D. J. Macquarrie and J. H. Clark, Chem. Commun., (1998) 2707.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

8 Catalytic Hydrogenation and Dehydrogenation

8.1 Alkynes

Steve Bailey, Frank King

8.1.1 General

The selective semi-hydrogenation of alkynes, is a particularly important reaction in the context of fine chemicals manufacture. The acetylenic group, $RC{\equiv}CR'$, readily participates in substitution reactions enabling the formation of new carbon–carbon bonds, for example, and selective hydrogenation, leading to alkene or alkane species, further enhances the synthetic utility of the alkynes and has been exploited in the synthesis of biologically active compounds, e. g. insect sex pheromones (pest control) and vitamins [1–3].

8.1.2 Structure and Bonding

Much of the catalytic activity and selectivity of alkyne hydrogenation can be attributed to the particular electronic and geometric features of the triple bond itself. The *sp*-hybridized carbon atomic orbitals combine in the form of a cylindrically symmetrical electron density distribution along the molecular axis, imparting the distinctive, rigid, linear alkyne geometry. High electron density coupled with restricted rotation of the carbon–carbon bond accounts for characteristically strong chemisorption on catalyst surfaces, plus the almost total *cis* (or *syn*) addition chemistry, of which hydrogenation is an example.

8.1.3 Hydrogenation, General Observations

Hydrogenation of an alkyne to an alkane occurs with the same general catalysts used for the reduction of alkenes (see later):

$$RC{\equiv}CR' + 2H_2 \xrightarrow{\text{Pt,Pd,Ni}} RCH_2CH_2R' \qquad (1)$$

The first step in the reduction is more exothermic than the second and the second step is so facile it can be very difficult to stop the reaction at the alkene stage:

$$HC{\equiv}CH + H_2 \rightarrow CH_2{=}CH_2 \qquad \Delta H^\circ = -41.9 \text{ kcal mol}^{-1} \qquad (2)$$

$$CH_2{=}CH_2 + H_2 \rightarrow CH_3CH_3 \qquad \Delta H^\circ = -32.7 \text{ kcal mol}^{-1} \qquad (3)$$

This, of course, presents enormous challenges to most catalyst formulations and provides commercial incentives for catalyst manufacturers to supply ever more selective hydrogenation catalysts. The order of reactivity for unsaturated hydrogenation is often quoted as [4]:

terminal alkyne > internal alkyne > terminal alkene > internal alkene

although more recent work suggests that this is a rather simplified generalization in respect of alkyne hydrogenation and that relative activity is influenced, quite markedly, by the nature of the substituent in related compounds. For example, although in one study phenylacetylene (terminal alkyne) was found to hydrogenate much faster than 1-phenyl-1-propyne (internal alkyne), in agreement with the above generality [5], in the same study, a selection of *alkyl*-substituted alkynes behaved in a manner contrary to expectation. Thus 2-pentyne (internal alkyne) was more reactive than 1-pentyne (terminal alkyne) and the same trend was observed for analogous hexynes. The higher molecular weight hexynes were, furthermore, shown to be more reactive than the lighter pentynes.

8.1.4 The Choice of Active Metal

For hydrogenation reactions generally, catalytic activity is considered to be a function of both electronic and geometric factors associated with the active sites [6], almost invariably fully reduced metal crystallites. The ready chemisorption of gases on a metallic surface requires vacant *d*-atomic orbitals (more strictly, vacancies within the *d*-band) capable of accepting electrons donated by the adsorbate. When the number of *d* vacancies is large, as in the Group IIIA and VIIA metals, gas is so strongly absorbed that removal is very difficult. In such cases, catalyst activity is heavily suppressed. Similarly, metals of Group IB, with no such vacancies, adsorb gases only weakly and, because catalytic surface reaction rates are directly related to surface coverage, overall activity is also correspondingly small. Maximum activity is expected for those metals with the smallest number of *d*-vacancies and these correspond to the metals of Group VIII. The foregoing description constitutes the so-called 'electronic factor' in catalytic activity.

The metal atoms of the surface exposed to the adsorbing medium should be spaced such that the transition-state complex formed has the lowest possible potential energy. It follows, therefore, that reaction activation energies will be reduced and progress under considerably milder reaction conditions than required for the equivalent non-catalyzed process, becomes possible. This constitutes the 'geometric factor' and both factors happen to be optimum for the Group VIII metals.

At first glance, there are numerous potential candidates present within the first to third transition metal series, although those which are reduced from the oxide only with difficulty can be excluded. This effectively precludes, Ti, V, Cr, Mn, Zr, Nb, Mo, Tc, Hf, W, and Re. Furthermore, Ag and Au have low hydrogenation activity (electronic factor) and Os can also be excluded on toxicity grounds. In terms of ethyne (C_2H_2) hydrogenation activity, the following trend is broadly true [7,8]:

Pd > Pt > Ni, Rh, > Co > Fe > Cu > Ir > Ru > Os > Au

Combination of Eqs (2) and (3), shows full alkyne hydrogenation to be a serial process and the ability to terminate at the alkene stage determines the selectivity. This may be quantified from:

Selectivity = Yield (alkene)/Yield (alkene + alkane)

Studies of the hydrogenation of 2-pentyne over various metals:

$$CH_3CH_2C{\equiv}CCH_3 \xrightarrow{H_2} cis\text{-}CH_3CH_2CH{=}CHCH_3 \xrightarrow{H_2} C_5H_{12} \tag{4}$$

led to the following sequence for comparative alkene selectivity [9]:

Pd > Rh > Pt > Ru > Os > Ir

The tendency for selectivity to decrease from the second to the third transition series is common for the platinum group metals. As a further example, the selectivity towards *cis*-but-2-ene formation from the hydrogenation of dimethylacetylene, increases from left to right across each series and decreases from the second to the third row [10]. The sequence of isomerization activity follows the order [10]:

Pd > Rh > Ru > Os >> Pt ≈ Ir

Chemisorptive bonding to the reduced metal surface is generally regarded as π-complex-formation involving charge transfer (d_π–d_π or d_π–π^*) between the metal and the alkyne (or alkene) [11–13]. The stability of π-complexes usually increases from Ru to Os, Rh to Ir, and Pd to Pt. Assuming the same order of stability is true for the catalytic adsorbed transition states, it follows that the greater capacity of the second row metals, compared with third row metals, to promote alkene selectivity can be attributed to the lower stability of the alkenic π-complexes formed; the less stable the complex, the more readily it will be desorbed before further hydrogenation can occur [10].

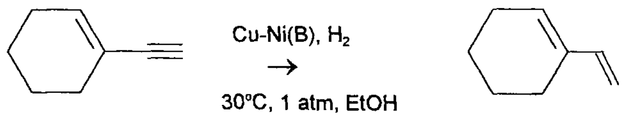
Selectivity is also influenced by the availability of hydrogen in the vicinity of the adsorbed alkyne. Clearly, a hydrogen-rich environment increases the risk of over-conversion to the alkane, whereas hydrogen-depleted conditions increase the likelihood of alkyne oligomerization, a major cause of catalyst deactivation [14].

On balance, palladium offers the best combination of activity and selectivity at reasonable cost, and for these reasons has become the basis of the most successful commercial alkyne hydrogenation catalysts to date. Because of their inherently high activity, these catalysts contain typically less than 0.5 % (by weight) of active metal–to preserve selectivity at high alkyne conversion. Despite the prominence of these catalysts, other active metals are used in fine chemicals applications. Of particular utility is the nickel boride formulation formed by the action of sodium borohydride on nickel(II) acetate (or chloride). Reaction in 95 % aqueous ethanol solution yields the P2-Ni(B) catalyst and selectivity in alkyne semi-hydrogenation has been demonstrated in the reaction of 3-hexyne to form *cis*-3-hexene in 98 % yield [15,16]:

$$CH_3CH_2C{\equiv}CCH_2CH_3 \xrightarrow[\text{RT, 1 atm}]{\text{P2-Ni(B), }H_2} cis\text{-}CH_3CH_2CH{=}CHCH_2CH_3 \tag{5}$$

This nickel catalyst can be further optimized by the addition of copper chloride before the hydride reduction step leading to improvements in alkene selectivity [17]:

$$CH{\equiv}CCH_2OH \xrightarrow[30^\circ\text{C, 1 atm, EtOH}]{\text{Cu-Ni(B), }H_2} CH_2{=}CHCH_2OH \tag{6}$$



(7)

Note the particularly mild reaction conditions and the fact that the reaction depicted by Eq. (6) progresses without cleavage of the allylic hydroxyl group. These copper-modified nickel catalysts were found to be more selective than the analogous Cu(B) formulations derived from borohydride reduction of copper chloride [17]. Copper modification of Raney nickel has also been shown to benefit the selectivity of phenylacetylene hydrogenation, but not to the same extent as the Cu–Ni(B) catalyst.

Arsenic, normally considered a notorious catalyst poison, actually promoted the selectivity of 1-bromo-11-hexadecyne hydrogenation over a catalyst formed by the action of borohydride on alumina-supported nickel arsenate [18]:

$$\begin{aligned} &BrCH_2(CH_2)_9C{\equiv}C(CH_2)_3CH_3 \xrightarrow{\text{Ni-As(B), }H_2} \\ &\qquad\qquad BrCH_2(CH_2)_9CH{=}CH(CH_2)_3CH_3 \end{aligned} \tag{8}$$

In this reaction hydrogenation proceeded without cleavage of the terminal C–Br bond.

8.1.5 Palladium-based Catalysts

Palladium, the preferred metal of choice for alkyne semi-hydrogenation, is normally used as a supported heterogeneous catalyst and frequently in the presence of some form of additive to promote selectivity. For heterogeneous systems in particular catalyst performance is strongly influenced by, firstly, the ability to get reactants to the active sites, then to establish the optimum hydrogen-to-hydrocarbon surface coverage, and, finally, the rapid removal of the hydrogenated products. These constitute the 'mass transfer limitations' and can have an overriding impact on the ability to achieve selective hydrogenation. In this respect, the nature of the support (inertness, surface area, pore size distribution) controls molecular access to the active sites and can also participate in unwanted side reactions through so-called 'spillover' effects. Detailed studies of mass transfer effects [19,20] have concluded that the best formulations are those in which the active sites are located close to the support pore mouths near the external surface of the catalyst particle. In practical terms, this equates to metal deposition within a tightly controlled band that has been termed 'egg-shell' distribution within the catalyst industry. Such a distribution gives rise to short residence times of the reacting molecules within the inner pore systems of the catalyst. The metal dispersion or crystallite size also requires consideration, particularly for those molecules that have active site structure sensitivity. Such effects have been demonstrated, for example, in the hydrogenation of a series of cycloalkenes over palladium [21]. In this work, the hydrogenation of C_5 to C_8 cycloalkenes revealed an activity (turnover frequency, TOF) maximum for a crystallite size of around 3.5 nm for all compounds in the series, apart from the C_7 alkene (cycloheptene). The authors attributed this apparent anomaly to particular structural features influencing the strength and mode of adsorption of this specific cycloalkene, although the role of the adsorbed state of hydrogen was also discussed (Figure 1).

The most common support materials exploited commercially have been silica and, particularly, low surface area α-alumina which combines high strength and

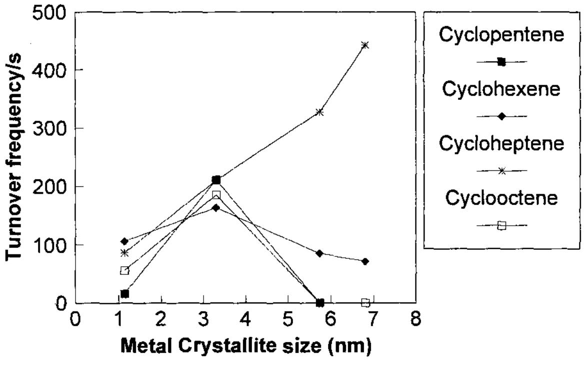


Figure 1. Variation of TOF with crystallite size.

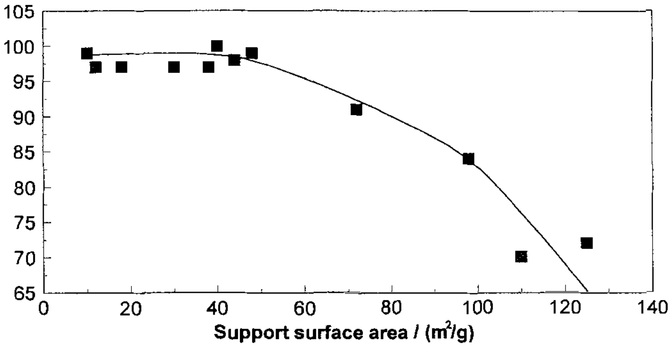


Figure 2. Ethylene yield at 90 % acetylene conversion.

low intrinsic chemical activity. As an example, the effect of surface area on the performance of an ethyne semi-hydrogenation catalyst is shown in Figure 2, above [22].

In this case high ethene selectivity is maintained up to a maximum support surface area of approximately 50 m^2 (g catalyst)$^{-1}$.

8.1.6 The Use of Promoters

Literature on the use of promoters is voluminous, and all claim enhancement of semi-hydrogenation selectivity. One of the more successful commercial catalysts for ethyne conversion to ethene, uses a silver promoted alumina-supported palladium catalyst [23]. Other promoting metals have been used, including rhodium and gold [24,25], copper [26–28], zinc (shown to inhibit oligomerization) [29–31], lead [32–34], chromium [35,36], vanadium [37], potassium [38–41], sodium [42], alkaline-earth metals [42,43] and even the lanthanides europium and ytterbium [44]. Attempts to rationalize promotional effects have focused upon the properties of alloys and effects on active site morphology, which then have an impact on the differential adsorption enthalpies of hydrogen, alkyne, and alkene [45–50]. Other explanations have invoked hydrogen spillover effects [47].

8.1.7 Illustrative Reactions

Perhaps the best known alkyne semi-hydrogenation catalyst is that developed by Lindlar which comprises calcium carbonate-supported palladium, modified by addition of lead acetate and, often, quinoline to improve selectivity [51]. Selective hydrogenation of 1-bromo-11-hexadecyne (Eq. 8) has been shown to occur in high yield and without hydrogenolysis of the carbon–bromine bond, over Lindlar's catalyst treated with aromatic amine oxides such as pyridine *N*-oxide

[52,53]. Other examples enabling the retention of carbon–chlorine or –fluorine bonds, have also been reported [54,55]:

$$\mathrm{Cl\text{-}(CH_2)_6{\equiv}CCH_2C(OCH_3)_2} \xrightarrow[\text{Room temp. 2 atm, 95\% yield}]{\text{Lindlar's catalyst, Pet ether}} cis\text{-}\mathrm{Cl\text{-}(CH_2)_6CH{=}CHCH_2C(OCH_3)_2} \qquad (9)$$

$$\mathrm{F_{15}C_7C{\equiv}CCO_2Et} \xrightarrow{\text{Lindlar's catalyst}} cis\text{-}\mathrm{F_{15}C_7CH{=}CHCO_2Et} \qquad (10)$$

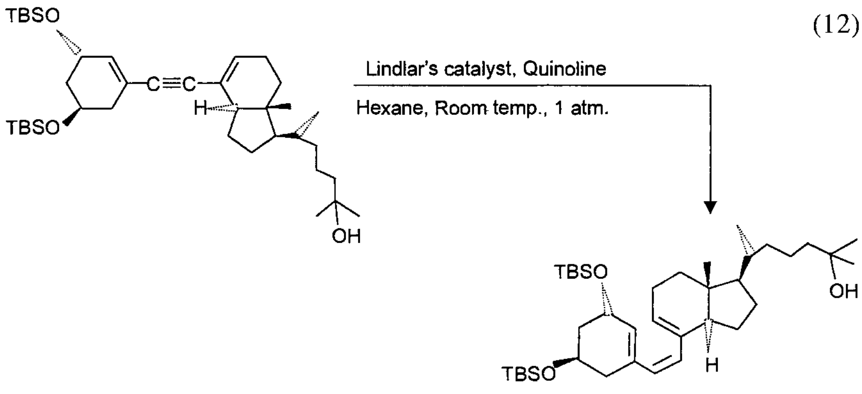
The semi-hydrogenation of the perfluoroacetylenic ester to the *cis*-acrylate (Eq. 10) was accomplished with 75–85 % yield [55].

Utilization of lead as a promoter has been developed further by the formulation of true Pd–Pb alloy catalysts; these have even higher selectivities than the Lindlar analogs, in the hydrogenation of 11-hexadecynyl acetate and 12-tetrahydropyranyloxy-3-tetradecyne (insect sex pheromones) [2]:

$$\mathrm{CH_3(CH_2)_3C{\equiv}C(CH_2)_9CH_2OAc} \xrightarrow[\text{Room temp. 1 atm, >99 yield}]{\mathrm{Pd\text{-}Pb/CaCO_3,\ MeOH}} cis\text{-}\mathrm{CH_3(CH_2)_3CH{=}CH(CH_2)_9CH_2OAc} \qquad (11)$$

The use of secondary modifiers, e. g. quinoline, and the choice of solvent also play important roles in directing semi-hydrogenation selectivity. For example, in the hydrogenation of 1-octyne over a series of Pd/Nylon-66 catalysts metal loading had no effect on selectivity when the reaction was performed in *n*-heptane as solvent. When the same experiment was conducted in *n*-propanol, however, an inverse relationship between selectivity and catalyst metal loading was observed [56]. This effect has been interpreted as a polar solvent-induced modification of the Pd active sites, which alters the relative adsorption behavior of the alkyne and alkene species [57]. Modification by addition of quinoline is reported to benefit the selective production of a *cis*-vitamin D precursor from the related disubstituted alkyne [58]:

(12)



Similarly, the effect of quinoline addition has been found to benefit the selectivity of other palladium formulations, as demonstrated in the semi-hydrogenation of an alkyne diester [59]:

$$\mathrm{CH_3O_2C(CH_2)_3C{\equiv}C(CH_2)_3CO_2CH_3} \xrightarrow[\text{Room temp. 1 atm.}]{\text{Pd/BaSO}_4\text{, MeOH, Quinoline}} \textit{cis}\text{-}\mathrm{CH_3O_2C(CH_2)_3CH{=}CH(CH_2)_3CO_2CH_3} \tag{13}$$

Zeolites have been successfully employed as catalyst supports for palladium. In one example of a disubstituted alkyne hydrogenation, additional treatment with diphenyldiethoxysilane increased the yield of 3-nonene from 3-nonyne by 57 % (40 to 97 %) [60]. The limited accessibility of zeolite A assumes only the extra-framework Pd sites are catalyzing the reaction:

$$\mathrm{CH_3(CH_2)_4C{\equiv}CCH_2CH_3} \xrightarrow[\text{Room temp. 1 atm.}]{\text{Pd/zeolite A, silanized}} \textit{cis}\text{-}\mathrm{CH_3(CH_2)_4CH{=}CHCH_2CH_3} \tag{14}$$

8.1.8 Acetylenic Alcohols (Carbinols)

The acetylenic alcohols are of particular synthetic utility because of their ease of formation via acetylide condensation with an aldehyde or ketone. Selective hydrogenation of such compounds affords convenient routes to more complex molecules, often with pharmaceutical or pesticidal activity [61,62]. The simplest member of this group is 2-propyn-1-ol or propargyl alcohol, $CH_2(OH)C{\equiv}CH$. It is evident from the basic structure of these molecules that selective hydrogenation to the allylic alcohol is a significant challenge to catalyst formulations, which must promote the rapid desorption of product before hydrogenolysis of the hydroxyl group can occur. This is especially significant for the preferred palladium-based catalysts as these are also very effective in facilitating hydrogenolysis.

A relatively simple way of suppressing hydroxyl bond cleavage while maintaining high alkene yield is to add small quantities of sodium or potassium hydroxide to the reaction mixture. This was used to good effect in the formation of an alkenic diol, for example [63]:

$$\mathrm{(CH_3)_2C(OH)C{\equiv}CC(OH)(CH_3)_2} \xrightarrow[\text{60°C, 2–4 atm}]{\text{Pd/carbon, KOH}} \textit{cis}\text{-}\mathrm{(CH_3)_2C(OH)CH{=}CHC(OH)(CH_3)_2} \tag{15}$$

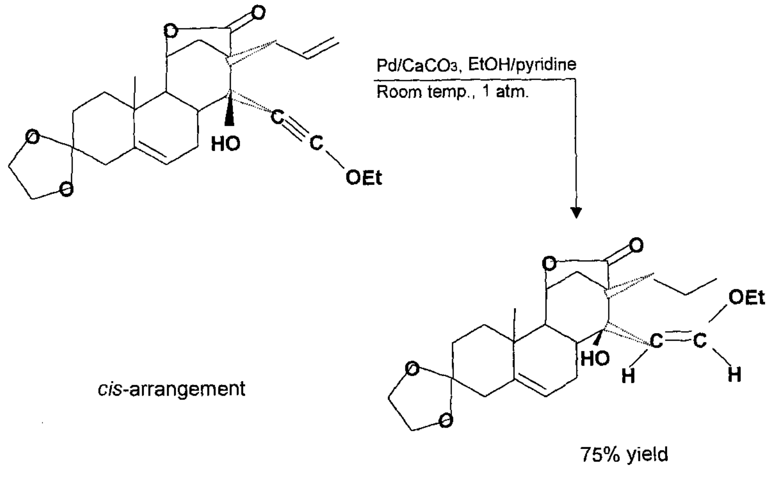
The beneficial action is thought to arise from the neutralization of acid sites on the catalyst support which may otherwise promote hydrogenolysis. In this context the alkaline-earth oxide supports $CaCO_3$ and $BaCO_3$ have been used with success to inhibit the hydrogenolysis of allylic alcohols and acetates [64,65].

The ubiquitous Lindlar catalyst has also been used for successful reduction of alkyne function alone in a compound with additional unsaturation in the form of a double bond [66]:

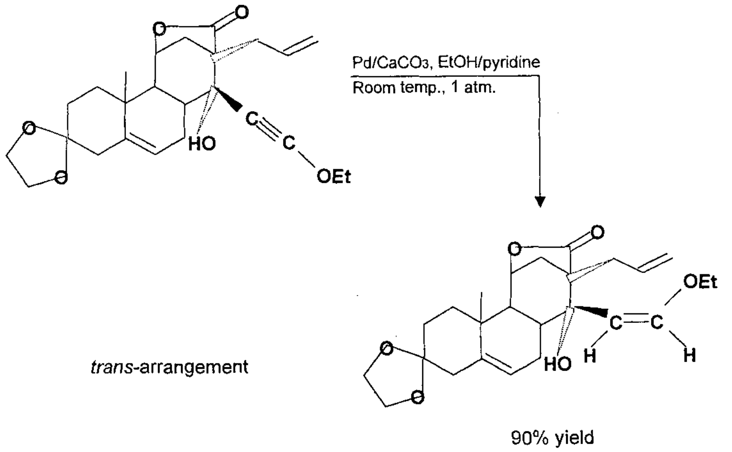
$$(CH_3)_2C{=}CH(CH_2)_3C(CH_3)(OH)C{\equiv}CH \xrightarrow[\text{30°C, 1 atm, 90\% yield}]{\text{Lindlar's catalyst, EtOH}} (CH_3)_2C{=}CH(CH_2)_3C(CH_3)(OH)CH{=}CH_2 \qquad (16)$$

8.1.9 Selectivity and Stereochemistry

As mentioned earlier, the particular geometric arrangement around the alkyne triple bond can also play a great part in controlling semi-hydrogenation selectivity. In molecules with both alkenic and alkynic functionality it is possible to preserve the original alkene group only if its approach to the catalyst surface can be restricted in some way. This effect was demonstrated in the reaction shown by Eqs (17) and (18) [67]:

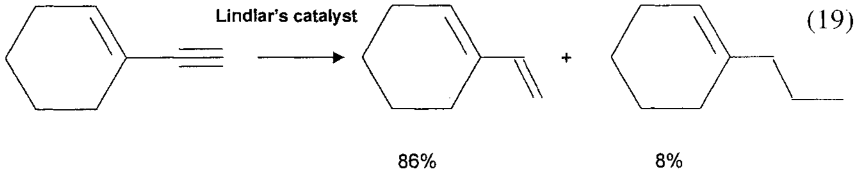


(17)



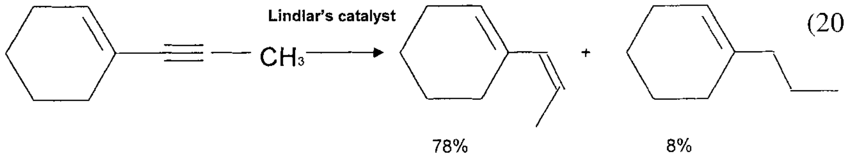
(18)

Conjugated alkynes are further challenges to the achievement of catalyst selectivity, and performance is very much dependent on the local environment of the enyne system. The hydrogenation of ethynylcyclohexene, for example, proceeded to 94 % conversion over Lindlar's catalyst with selectivities of 86 % for vinylcyclohexene and 8 % for ethylcyclohexene [68]:



(19)

If a substituent was present on the triple bond, reaction selectivity was found to degrade as evidenced by the following process [68]:



(20)

In this case, semi-hydrogenation proceeded to 86 % conversion with 78 % yield of the diene and 8 % of the propylcyclohexene over-hydrogenated product.

8.1.10 Alternative Metal Formulations

Although palladium occupies the dominant position in semi-hydrogenation catalysts, it is by no means the only metal suitable for formulation into a viable catalyst. Mention has already been made of the nickel boride alternatives, with or without copper promotion, for example. Other examples include the skeletal catalyst Raney nickel [69], alumina-supported nickel [70], and aluminum phosphate-supported nickel [71] (Eqs 21 and 22):

$$\mathrm{HOCH_2C{\equiv}CCH_2OH} \xrightarrow[\text{Room temp. 3 atm, 80\% yield}]{\text{Raney Ni, MeOH}} \mathit{cis}\text{-}\mathrm{HOCH_2CH{=}CHCH_2OH} \tag{21}$$

$$\mathrm{HOCH_2C{\equiv}CCH_2OH} \xrightarrow[\text{40°C, 4 atm, 92\% yield}]{\mathrm{NiAlPO_4}\text{, MeOH}} \mathrm{HOCH_2CH{=}CHCH_2OH} \tag{22}$$

References

[1] E N Marvell and T Li, *Synthesis*, **1973**, 457.
[2] J Sobczak, T Boleslawska, M Pawlowska and W Palczewska, in *Heterogeneous Catalysis and Fine Chemicals*, M Guisnet et al (eds), Elsevier Science Publishers, **1988**, pp 197–202.
[3] R A Raphael in, *Acetylenic Compounds in Organic Synthesis*, Butterworths Scientific Publications, **1955**, p 26.
[4] N A Dobson, G Eglinton, M Krishnamurti, R A Raphael and R G Willis, *Tetrahedron*, **1961**, *16*, 16.
[5] S D Jackson and G J Kelly, *Current Topics in Catalysis*, **1997**, *1*, 47.
[6] G C Bond, *Platinum Metals Rev.*, **1957**, *1*, 87.
[7] G C Bond and P B Wells, *Adv. Catal.*, **1964**, *15*, 171.
[8] G C Bond, D A Dowden and N Mackenzie, *Trans. Farad. Soc.*, **1958**, *54*, 1537.
[9] G C Bond and J S Rank, *Proc. 3rd Int. Congr. Catal.*, **1965**, *2*, 1225.
[10] G Webb, *Platinum Metals Reviews*, **1964**, *8*, 60.
[11] J Chatt and L A Duncanson, *J. Chem. Soc.*, **1953**, 2939.
[12] J J Rooney, *J. Catal.*, **1963**, *2*, 53.
[13] H Nakatsuji, M Hada and T Yonezawa, *Surface Science*, **1987**, *185*, 319.
[14] A Sarkany, A H Weiss, T Szilagyi, P Sandor and L Guczi, *Appl. Catal.*, **1984**, *12*, 373.
[15] C A Brown and V K Ahuja, *J. Chem. Soc., Chem. Commun.*, **1973**, 553.
[16] C A Brown and V K Ahuja, *J. Org. Chem.*. **1973**, *38*, 2226.
[17] Y Nitta, T Imanaka and S Teranishi, *Bull. Chem. Soc. Japan*, **1981**, *54*, 3579.
[18] T H Cymbaluk, *US Patent 4,659,687*, assigned to Phillips Petroleum Company (1987).
[19] A Wheeler, *Adv. Catal.*, **1951**, *3*, 249.
[20] A Wheeler, *Catalysis* (P H Emmett, ed), **2**, Rheinhold, New York, **1955**.
[21] S D Jackson, G J Kelly, S R Watson and R Gulickx, *Appl. Catal. A* in press.
[22] F E Hancock and J K Smith, *"The design and performance of acetylene hydrogenation catalysts"*, Paper presented at the 4th Ethylene Producers Conference, New Orleans, 31st March–1st April **1994**.
[23] M M Johnson, G A Nowack and D W Walker, *US Patent 4404124*, assigned to Phillips Petroleum Co., Sept. (1983).
[24] J G E Cohn, A J Haley and H A Shields, *US Patent 2927141*, assigned to Engelhard Industries Inc., March (1960).
[25] C Visser, J G P Zuidwijk and V Ponec, *J. Catal.*, **1974**, *35*, 407.
[26] A H Weiss, S Le Viness, V Nair, L Guczi, A Sarkany and Z Schay, *Proc. 8th. Int. Congr. Catal., Dechema, Berlin,* **1984**, *5*, 591.
[27] Z Schay, A Sarkany, L Guczi, A H Weiss and V Nair, *Geterog. Katal*, **1983**, *5*, 315.

[28] N R M Sassen, A J den Hartog, F Jongerius, J F M Aarts and V Ponec, *Farad. Disc. Chem. Soc.*, **1989**, *87*, 311.

[29] GB Patent *1,407,434*, assigned to BASF, Nov. (1972).

[30] D Sanfillipo and M Morelli, *German Patent DE 2622917*, assigned to Anic Sp.A, (1976).

[31] J C Rodriguez, A J Marchi, A Borgna and A Monzan, *J. Catal.* **1997**, *171*, 268.

[32] W Palczewska, I Szymerska and M Krawczyk, *Geterog. Katal.*, **1983**, *5*, 357.

[33] J Stachurski and J M Thomas, *Catal. Lett.*, **1988**, *1*, 67.

[34] S Karski, *Zesz. Nauk. Politech. Lodz. Chem*, **1991**, *616*, 128.

[35] A R Melvin, *GB Patent 954 203*, assigned to Chemetron Corp., (1960).

[36] H C Hudson, *US Patent, 84-675 175*, assigned to Shell Oil Co., (1988).

[37] P Bernusset, *GB Patent 1 302 269*, assigned to Produits Chimiques Pechiney-Saint-Gobain, July (1969).

[38] S Zisman, J Kimble and S H Brown, *European Patent application EP 0 738 540 A1*, assigned to Phillips Petroleum Co., Oct. (1996).

[39] Y H Park and G L Price, *J. Chem. Soc. Chem. Commun.*, **1991**, *17*, 1188.

[40] Y H Park and G L Price, *Ind. Eng. Chem. Res.*, **1992**, *31*, 469.

[41] G Gubitosa and A Cremona, *European Patent application, EP 0 567 198 B1*, assigned to Ministero dell' Universita' E Della Ricero Scientifica E Tecnologica, Rome, Jan (1996).

[42] G Nguyen Thanh, B Didillon, P Sarrazin and C Cameron, *European Patent application, EP 0 686 615 A1*, assigned to Institute Francais du Petrole, Dec. (1995).

[43] P J Lambert, E A Irvine and M V Twigg, *European Patent 29321*, assigned to ICI Ltd. Sept. (1983).

[44] H Imamura, K Igawa, Y Sakata and S Tsuchiya, *Bull. Chem. Soc. Japan*, **1996**, *69*, 325.

[45] *Chemical Market Reporter.* Oct. (1994), p 246.

[46] H Nagamoto and H Inoue, *J. Chem. Eng. Japan*, **1981**, *14*, 377.

[47] V M Gryaznov and M G Slin'ko, *Farad. Disc. Chem. Soc.*, **1982**, *72*, 73.

[48] D C Huang, K H Chang, W F Pong, K J Hung and W F Huang, *Catalysis Letters*, **1998**, *53*, 155.

[49] E W Shin, C H Choi, K S Chang, Y H Na, and S H Moon, *Catalysis Letters*, **1998**, *44*, 137.

[50] K Kili, L Hilaire and F Le Normand, *Phys. Chem. Chem. Phys*, **1999**, *1*, 1623.

[51] H Lindlar, *Helv. Chim. Acta*, **1952**, *35*, 446.

[52] C A Drake, *US Patent 4,596,783*, assigned to Phillips Petroleum Company (1986).

[53] C A Drake, *US Patent 4,605,797*, assigned to Phillips Petroleum Company (1986).

[54] A S Bailey, V G Kendall, P B Lumb, J C Smith and C H Walker, *J. Chem Soc.*, **1957**, 3027.

[55] M Lanier, M Haddach, R Pastor and J G Reiss, *Tetrahedron Letters*, **1993**, 2469.

[56] C Bowden, R J McLellan, R P MacDonald and J M Winterbottom, *J. Chem. Tech. Biotechnol.*, **1982**, *32*, 567.

[57] R L Augustine, *Adv. Catal.*, **1976**, *25*, 56.

[58] L A Sarandeses, J L Mascareñas, L Castedo and A Mouriño, *Tetrahedron Letters*, **1992**, *33*, 5445.

[59] D J Cram and N L Allinger, *J. Am. Chem. Soc.*, **1956**, *78*, 2518.

[60] H Kuno, M Shibagaki, K Takahashi, I Honda and H Matsushita, *Chem. Lett.*, **1992**, 1725.

[61] A W Johnson in *"The Chemistry of the Acetylenic Compounds, Volume 1, The Acetylenic Alcohols."*, Edward Arnold & Company Publishers, London, **1946**.

[62] T F Rutledge in *"Acetylenic Compounds, Preparation and Substitution Reactions."*, Reinhold Book Corporation, **1968**.

[63] R Tedeschi, *J. Org. Chem.*, **1962**, *27*, 2398.

[64] R A Raphael and F Sondheimer, *J. Am. Chem. Soc.*, **1951**, 2693.

[65] G F Hennion, W A Schroeder, R P Lu and W B Scanlon, *J. Org. Chem.*, **1956**, *21*, 1142.

[66] A M Pak, O I Kartonozhkina, A P Pogorelskii, E M Tsai and D V Sokolskii, *React. Kinet. Catal. Lett.*, **1981**, *16*, 265.

[67] A Lardon, O Schindler and T Reichstein, *Helv. Chim. Acta.*, **1957**, *40*, 666.

[68] E N Marvell and J Tashiro., *J. Org. Chem.*, **1965**, *30*, 3991.

[69] C S Marvel and C H Young, *J. Am. Chem. Soc.*, **1951**, *73*, 1066.

[70] Y Uemura and Y Hatate, *J. Chem. Eng. Japan*, **1989**, *22*, 287.

[71] F M Bautist, J M Campelo, A Garcia, R Guardeno, D Luna and J M Marinas, *Stud. Surf. Sci. Catal.*, *59*, (Heterog. Catal. Fine Chem II), 269, **1991**.

8.2 Aldehydes and Ketones

Keith Simons, Ken Griffin

8.2.1 Introduction

The catalytic hydrogenation of aldehydes and ketones is a widespread industrial practice and relatively straightforward. Aldehydes tend to be easier to reduce than ketones because the latter are more sterically hindered. The reaction is even more facile when an activating group is alpha to the carbonyl function. Reduction using supported platinum group metal (PGM) catalysts normally occurs at mild temperatures (20–80 °C) and under relatively low pressures ($<$ 10 bar) and is therefore ideally suited to batch operation in the fine chemical and pharmaceutical industries. Nickel catalysts are also in widespread use, but tend to require higher pressures and temperatures. They are also gradually being phased out because of their associated toxicity and their greater handling and disposal difficulties.

Because the choice of metal depends upon the exact nature of the functional group, this chapter has been separated, as far as possible, into different classes of reactant. Although the literature contains reference to many supports, activated charcoal is normally the preferred choice because of its low cost, high surface area (typically greater than 900 $m^2\ g^{-1}$), chemical inertness, strength, and ease of burning during metal recovery.

The specific example of sugar hydrogenation (e.g. glucose to sorbitol) has warranted an individual chapter in this book and so is excluded here. Reference to enantioselective hydrogenation of pro-chiral ketones is only included where appropriate, for the same reason.

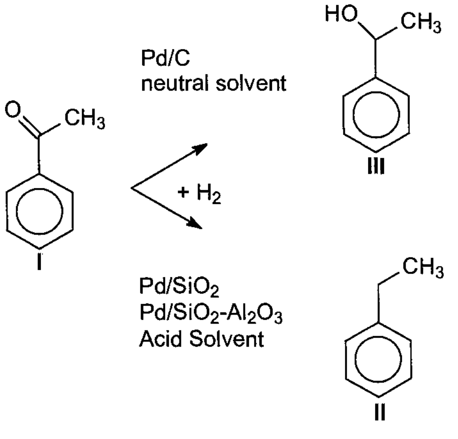
Excellent books by Augustine [1] and Rylander [2,3] are available to the interested reader for further reference.

Because of their versatile nature, specific mention will be made of the choice of PGM for a given reaction. The reader should, however, note that the ability of the catalyst manufacturer to change the nature of the metal's location, state of oxidation, method of preparation, and the specific support (carbon type, activation method, pH etc.) can all drastically affect performance in a given reaction. Consequently, specific advice from the supplier on the exact choice of 5 % Pd/C (for example) might well give improved selectivities and yields, rather than relying on a generic catalyst from a catalog.

8.2.2 Aromatic Aldehydes and Ketones

Palladium is usually the preferred metal of choice for aromatic aldehyde hydrogenation in neutral non-polar solvents such as hexane, DMF, or ethyl acetate (5–100 °C and 1–10 bar) although ruthenium, which is less active, can be considered and run in aqueous alcohol at similar temperatures and pressures. If higher pressures are accessible ruthenium may be preferable because of its lower (historical) cost. Its use has recently been reviewed [4]. Although platinum and rhodium could also be considered, there is the disadvantage of competitive ring hydrogenation, especially with increasing temperatures and pressures, when even ruthenium becomes non-selective. Ring hydrogenation can, however, be countered by addition of trace amounts of zinc, silver, or iron salts [5], typically < 1 mol% (*w/w*) relative to PGM. When platinum is used as the active metal trace quantities of iron as either ferrous sulfate [6] or ferric chloride [7] can be added in similar quantities to promote carbonyl hydrogenation. As stated in the introduction, nickel can also be used, although it is probably better suited to fixed-bed applications. In one such example nickel on alumina-wash-coated cordierite or α-alumina monolithic catalysts were used for the selective hydrogenation of benzaldehyde [8].

A further selectivity issue is the hydrogenolysis of the alcohol, which is promoted by the use of acidic media or supports. Attempts can be made to avoid this if the reaction is stopped after the addition of one equivalent of hydrogen. In some instances this is the desired reaction and although a few drops of concentrated hydrochloric, or perchloric acid may be added, the use of acetic acid will be less corrosive in the stainless steel autoclaves typically employed. An example is depicted in Scheme 1 for the hydrogenation of acetophenone **I** to either ethylbenzene **II** or 1-phenylethanol **III**.



Scheme 1.
Hydrogenation of acetophenone.

8.2.3 Aliphatic Ketones and Aldehydes

Hydrogenation of aliphatic ketones is normally performed over platinum or ruthenium (5–150 °C and 1–10 bar in alcohol, ethyl acetate, or water), although use of the more expensive rhodium and iridium is sometimes advantageous. Palladium tends to be an ineffective catalyst. As with aromatic aldehydes and ketones platinum is often used under less demanding pressures and temperatures than ruthenium. Once again ruthenium might require the use of aqueous solvents, otherwise (at low pressures) an induction period might be observed. Although very little work has been reported for iridium, it has been found to very effective for α-keto ester hydrogenation [9] and 1,4-cyclohexanedione hydrogenation [10], being much more active than Pt. Further hydrogenation of the corresponding alcohol to a methyl or methylene group does not normally occur.

8.2.4 Stereochemistry

The hydrogenation of a substituted cycloalkanone can result in either an equatorial or axial alcohol, depending on which face of the carbonyl function is adsorbed by the surface. In neutral media the least sterically hindered face will be adsorbed, giving the corresponding isomer. The stereochemistry can, however, also be influenced by the choice of the metal, support, solvent, and pH, with the last being the most important.

Generally, in basic media, the more stable equatorial isomer is the primary product; in acidic media the predominant product is axial. Consideration therefore needs to be given to whether the catalyst itself can be a source of base or acid. (e. g. residual base in Raney nickel).

Another consideration is other functionality on the molecule. Even if the groups do not direct the stereochemistry of the adsorption of the carbonyl functionality, if the functional group can itself be adsorbed by the surface, adsorption of the molecule obviously changes. This might be advantageous or disadvantageous to the desired outcome.

8.2.5 Amides

There are, unfortunately, few methods for amide hydrogenation under mild conditions; as a result metal hydrides are still used.

8.2.6 Anhydrides

Anhydrides can be either fully or partially hydrogenated. Most processes are for bulk chemicals and are hence used in fixed-bed applications under forcing conditions. When a slurry reactor is used, nickel catalysts, often promoted by molybdenum or palladium, are used. One example was a 16 % Ni, 2 % Pd/SiO_2 powder which gave 92 % conversion and 95 % selectivity in the hydrogenation of succinic anhydride to γ-butyrolactone (50–95 bar, 235 °C) [11].

8.2.7 Selective Hydrogenation of α,β-Unsaturated Aldehydes

Carbonyl hydrogenation is generally less facile than olefin hydrogenation, making selective hydrogenation of α,β-unsaturated aldehydes to the allyl alcohol a special challenge. Substitution of the carbon atom attached to the carbonyl (i. e. from the aldehyde to the ketone), substantially increases the steric hindrance to carbonyl adsorption, hence the lack of reports in the literature of selective unsaturated ketone hydrogenation. Selective hydrogenation of the olefin is readily promoted by the use of palladium catalysts under mild conditions.

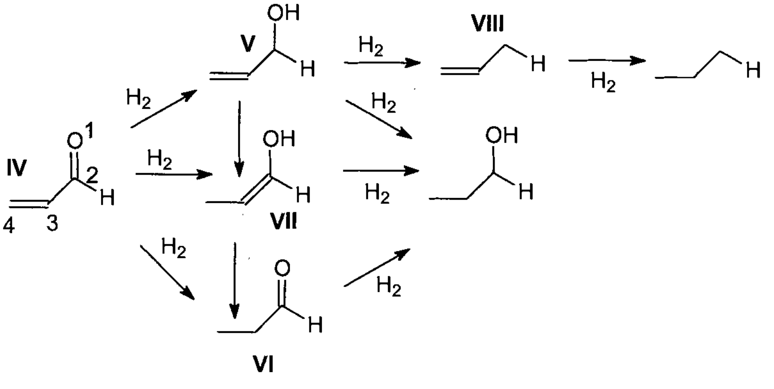
The subject has been reviewed by Gallezot and Richard, who give special attention to mechanism, steric, and electronic effects as investigated by surface-science techniques [5].

8.2.8 Reaction Pathway

The hydrogenation of unsaturated aldehydes **IV** can be a complex transformation, as depicted in Scheme 2. Although the desired reactions are normally either the formation of allylic alcohol **V**, or saturated aldehyde **VI**, by 1,2 addition of hydrogen across the functional group, 1,4-addition across the conjugated functions can provide the enol, **VII**. Over-hydrogenation can result either in further saturation or, for allylic alcohols, hydrogenolysis to the alkene **VIII** (which can, in turn, be further saturated).

Not only is full saturation a possible outcome, isomerization of the unsaturated alcohol **V** to the saturated aldehyde **VI** can also occur. This tends, however, to occur in the gas phase [12], although it has been reported when using a Rh/AlPO$_4$ catalyst in the liquid phase [13].

Although common examples in the literature mention acrolein and crotonaldehyde hydrogenation, it is probably best to consider research on cinnamaldehyde hydrogenation for determining the best conditions to apply to the hydrogenation of α,β-unsaturated aldehydes.



Scheme 2. Hydrogenation of α,β-unsaturated aldehydes.

8.2.9 Cinnamaldehyde Hydrogenation

The selective hydrogenation of cinnamaldehyde to produce cinnamyl alcohol is an important reaction. Because the major application of cinnamyl alcohol is as the base for perfumes (minor quantities of other molecules give a perfume its high added value), high selectivity and efficient conversions are vital to give a pure 'clean' smell.

Conjugation of the olefin function with the phenyl ring reduces the electron density in the olefin, thus increasing the likelihood of selective hydrogenation to the allyl alcohol. Moderate pressures (10+ bar) at 40–80 °C and alcohol–water solvents (e. g. ca 80 % isopropanol) should be preferred.

8.2.10 Unpromoted Catalysts

Several 'unpromoted' metals have been reported as being selective for the production of cinnamyl alcohol. Os/C [14], although mentioned in the literature as being highly selective (95 %), is not a practical catalyst for manufacture on an industrial scale because of the handling difficulties and bulk availability (and cost) of osmium salts. Iridium, supported on graphite or carbon, is probably a more realistic option; high selectivities ($\geq$ 80 %) have been reported [15] at 100 °C and 40 bar in isopropyl alcohol–water as solvent. This study also compared a number of PGMs on graphite and carbon and found that selectivity followed the trend Ir > Pt > Ru > Rh > Pd.

Although less selective, Pt is normally the metal of choice, especially when supported on graphite. Because selectivity has been found to be structure-sensitive, several catalysts, prepared by different methods, should be tested. In a study of graphite supported Pt catalysts [16], large faceted metal particles (3–6 nm) proved to be most selective (98 % selectivity at 50 % conversion).

8.2.11 Promoters

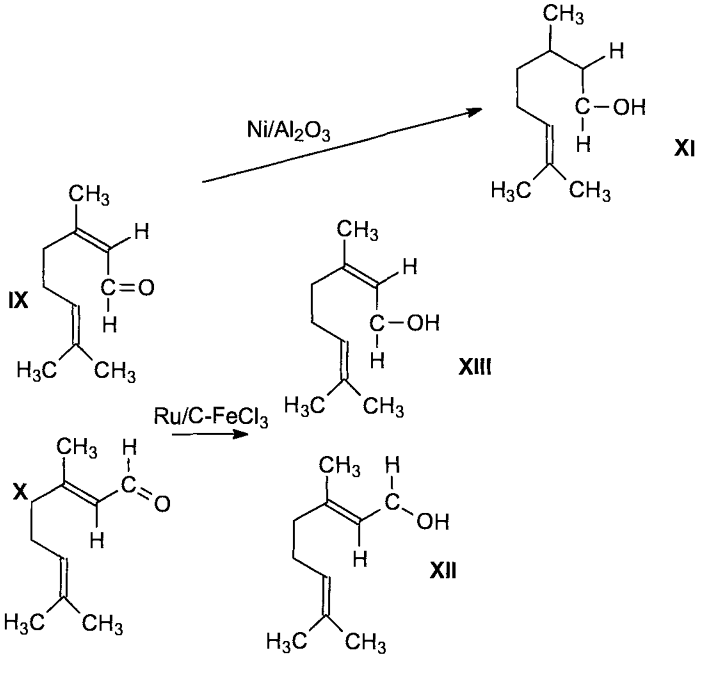
Promoters might be added to a PGM catalyst by the manufacturer, or directly to the reaction mixture. Each route has its benefits. In cinnamaldehyde hydrogenation the promoter is added to inhibit olefin hydrogenation during reduction of the carbonyl function. This has been achieved by addition of bases such as KOH or NaOH at 5–10 % concentration [17], or more often by addition of other electropositive metals that are reduced on the catalyst surface *in situ* upon admission of hydrogen into the reactor.

The promoter, whether increasing the electron density on the catalytic metal (and reducing the binding energy of the double bond [18]), or acting as a Lewis site for the lone pair of the carbonyl oxygen, significantly increases selectivity for the allyl alcohol. Iron chloride and zinc acetate were originally employed to promote the Adam's catalyst [19], and the same effects have been studied on conventional supported catalysts. The addition of zinc acts to inhibit olefin hydrogenation, as opposed to activating carbonyl reduction. Other electropositive metals, preferably germanium, tin, and cobalt, are also worthy of investigation.

It is important to optimize the amount of modifier metal added (too much will mask the catalytic metal) 0.005–0.03 mol% relative to the PGM is a reasonable place to start.

8.2.12 Citral Hydrogenation

The final example to mention is the hydrogenation of *E*- and *Z*-citral (**IX** and **X**, respectively), depicted in Scheme 3. The choice of catalyst depends upon the product desired. Citronellol **XI** has been prepared with 99 % selectivity over a Ni/Al_2O_3 catalyst [20] under mild conditions. In contrast, the isomers geraniol **XII** and nerol **XIII** were prepared with 97 % selectivity (the balance was citronellol) when Ru/C promoted by ferric chloride and trimethylamine was used at 100 °C and 50 bar.



Scheme 3. Hydrogenation of citral.

8.2.13 Pitfalls

Aldol condensation is a potential side reaction that can occur during aldehyde hydrogenation, especially at high or low pH. It leads to tar formation, which can deactivate the catalyst via a fouling mechanism.

If an amine functionality is present on another part of the molecule there is sometimes a risk of reductive amination when Pt or Pd is used as a catalyst.

Keto–enol tautomerization is also a potential reaction. It was because of this reaction that Pd was observed to be active for the hydrogenation of methyl pyruvate to methyl lactate [21].

It should be remembered that ruthenium might require activation at ca 125 °C, or higher, in hydrogen before use. Because ruthenium catalysts are readily oxidized by air, *in situ* reduction of the RuO_2 is required.

As with all catalytic systems, promoters (or poisons) can be introduced accidentally. This is increasingly likely when solvents are re-used. It has, for example, been known for Fe to be introduced from the mild steel drums used to store solvents.

References

[1] R. L. Augustine, *Heterogeneous Catalysts for the Synthetic Chemist*, Marcel Dekker Inc., New York (1996).
[2] P. N. Rylander, *Catalytic Hydrogenations over Platinum Metals*, Academic Press Inc., New York (1967).
[3] P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press Inc., New York (1979).
[4] L. Cerveny, Z. Belohlav and M. N. H. Hamed, *Research on Chemical Intermediates*, **22**, 15 (1996).
[5] P. Gallezot and D. Richard, *Catal. Rev. – Sci. Eng.* **40**, 81 (1998).
[6] L. Long and A. Burger, *J. Org. Chem.* **6**, 852 (1941).
[7] N. W. Campbell, W. Anderson and J. Gilmore, *J. Chem. Soc.*, 819 (1940).
[8] X. D. Xu, H. Vonk, A. C. J. M. Vanderiet, A. Cybulski, A. Stankiewicz, J. A. Moulijn, *Catal. Today* **30**, 91 (1996).
[9] K. E. Simons, A. Ibbotson, P. Johnston, H. Plum and P. B. Wells, *J. Catal.*, **150**, 321 (1994).
[10] M. Bonnet, P. Geneste and M. Rodriguez, *J. Org. Chem.* **45**, 40 (1980).
[11] UCB Patent EP339012 (1989).
[12] M. A. Vannice and B. Sen, *J. Catal.* **115**, 65 (1989).
[13] J. M. Campelo, A. Garcia, D. Luna and J. M. Marinas, *J. Catal.* **113**, 172 (1988).
[14] P. N. Rylander and D. R. Steele, *Tetrahedron Letters* 1579 (1969).
[15] A. Giroir-Fendler, D. Richard and P. Gallezot, *Stud. Surf. Sci. Catal.* **41**, 171 (1988).
[16] A. Giroir-Fendler, D. Richard and P. Gallezot. *Catal. Lett.* **5**, 175 (1990).
[17] V. Satagopan and S. B. Chandalia, *J. Chem. Tech. Biotechnol.* **60**, 17 (1994).
[18] F. Delbecq and P. Sautet. *J. Catal.* **164**, 152 (1996).
[19] W. F. Tuley and R. Adams, *J. Am. Chem. Soc.* **47**, 3061 (1925).
[20] D. V. Sokol'skii, A. M. Pak, M. A. Ginzburg and V. A. Zavorin, *Kinet. Catal.*, **20**, 531 (1979).
[21] T. J. Hall, P. Johnston, W. A. H. Vermeer, S. R. Watson, and P. B. Wells, *Stud. Surf. Sci. Catal.* **101**, 221 (1996).

8.3 Carboxylic Acids and Derivatives

T. Yokoyama, and T. Setoyama

The reduction of carboxylic acids and their derivatives to alcohols, diols, and lactones under high pressure is of considerable commercial importance. Aldehydes are widely used as intermediates in the production of organic fine chemicals such as pharmaceuticals, agrochemicals, and perfumes. These aldehydes are produced by conventional organic synthetic methods with concomitant production of large amounts of waste. Although the Rosenmund reduction of acid chlorides over a palladium catalyst is suitable for small-scale production of aldehydes, this method is not suitable for large-scale production because it needs a chloride such as $SOCl_2$ for the production of the acid chlorides, and HCl is formed upon reduction [1]. Hydrogenation of carboxylic acids by formic acid on titanium dioxide [2] is another method which is used in lab-scale production, but this method also is unsuitable for commercial production because it needs a large amount of reducing agent. Thus, the direct hydrogenation of carboxylic acids to the corresponding aldehydes (Eq. 1) seems to be an important industrial challenge, because water is the only by-product:

$$RCOOH + H_2 \rightarrow RCHO + H_2O \tag{1}$$

Selective hydrogenation of acids to aldehydes is very difficult under high pressure, because the product is, in general, more easily hydrogenated than the substrate over conventional catalysts. The key point of our research was how to fine-tune the properties of the catalyst in such a way that it becomes active and selective.

The current process for producing aromatic and aliphatic aldehydes by direct hydrogenation of the corresponding carboxylic acids over ZrO_2 and Cr_2O_3 has been developed by the Mitsubishi Chemical Corporation. It has successfully commercialized the production of *p-t*-butylbenzaldehyde, *m*-phenoxybenzaldehyde, *p*-methylbenzaldehyde, 10-undecenal, and dodecanal by reduction of the corresponding acids. By use of this technology, ca. 2000 t y^{-1} of aldehydes have been manufactured since 1988 [3].

8.3.1 Development of Hydrogenation Catalysts of Carboxylic acids and its Properties

Metal oxides such as iron oxide were first reported as catalysts for the hydrogenation of carboxylic acids to the corresponding aldehydes by GAF in 1935 [4]. A typical example was the production of benzaldehyde by hydrogenation of phthalic anhydride. After this discovery the success of this system, a variety of catalysts such as γ-alumina [5], vanadium oxide [6], manganese oxide [7], yttrium oxide [8], zinc oxide [9], and Ru based metal catalysts [10], have been reported as useful catalysts. However, their catalytic activity and stability under the reaction condi-

Table 1. Hydrogenation of benzoic acid over metal oxide catalysts.

Catalyst	Temperature (°C)	Conversion of acid (%)	Selectivity to aldehyde (%)
$20\%Y_2O_3$ α-Al_2O_3	440	100	87
γ-Al_2O_3	440	20	53
MgO	440	62	4
TiO_2	440	15	10
ZrO_2	400	53	97
ZnO	400	55	54

Reaction conditions: H2 GHSV = 625/h, benzoic acid = 2 vol%, P = 0.1 MPa.

tions seemed to be insufficient. Recently only modified ZrO_2 for production of aromatic aldehydes [3] and highly pure Cr_2O_3 [11] for the production of aliphatic aldehydes have been established as a commercial catalyst be MCC.

Here we show the brief summary of these catalysts. Results from catalytic hydrogenation of benzoic acid to benzaldehyde over different metal oxides is summarized in Table 1. ZrO_2 has excellent selectivity for benzaldehyde, but rather low activity. Y_2O_3/α-Al_2O_3 is also highly selective, but because of the high reaction temperature (400 °C), side reactions, e. g. decarboxylation, occur. Basic MgO has very low selectivity because the benzoate salt is formed during hydrogenation.

The catalytic performance of ZrO_2 is highly dependent on its method of preparation, suggesting that the surface properties of the ZrO_2 catalyst are essential for its performance. The correlation between surface acid–base strength of ZrO_2 and catalytic activity, expressed as the rate of aldehyde formation, is as follows. Non-acidic ZrO_2 with H_0 in the range +6.8 to +7.2, as measured by Hammet's indicator methods, has high activity and the activity increases with increasing surface area. Acidic ZrO_2 with $H_0 < +6.8$ has poor activity and a low selectivity, because of decarboxylation of the acid.

The acid–base characteristics of different ZrO_2 catalysts were determined by use of ammonia and carbon dioxide TPD (Temperature Programmed Desorption). With non-acidic ZrO_2 the temperatures of maximum desorption of ammonia and carbon dioxide are 160 and 150 °C, respectively. The molar ratio of desorbed ammonia to carbon dioxide is nearly equal and these peaks were assigned to weakly acidic or basic sites on the ZrO_2 surface. The amount of desorbed ammonia increases with increasing surface area. For acidic ZrO_2 with $H_0 \leqq -5.6$, a new peak from a strong acid site appears at 200 °C, and the total amount of desorbed ammonia increases. The amount of carbon dioxide desorbed from ZrO_2 decreases with increasing surface acidity, and becomes almost zero for ZrO_2 with $H_0 \leqq -5.6$.

The strongly acidic sites on the ZrO_2 surface would result in the polarization of the adsorbed carboxyl group of the carboxylic acid, leading to decarboxylation. Decarboxylation of aromatic carboxylic acids usually occurs on acidic catalysts [12] whereas in the presence of a strong base the acid forms the corresponding salts and further reaction does not occur under the hydrogenation conditions.

It has been reported that ZrO_2 with a moderate acid–base pair has very high catalytic activity in H–D exchange reactions between the methyl group of *iso*-propyl alcohol-d_8 and the surface OH groups. In contrast, acidic catalysts such as Al_2O_3, SiO_2–Al_2O_3 are inactive [13] in this exchange reaction. It is known that non-acidic ZrO_2 has specific catalytic activity in the hydrogenation of 1,3-butadiene by molecular hydrogen, or by hydrogen donors such as cyclohexadiene [14]. The surface of ZrO_2 is considered to have bifunctional acid–base catalytic properties. A pair of weakly acidic and basic sites on ZrO_2 might possibly be important for the catalytic properties, because the catalytic performance of non-acidic ZrO_2 is superior.

The activity of ZrO_2 is substantially enhanced by modification with metal ions such as Pb^{2+}, In^{3+}, Cr^{3+}, or Mn^{2+}, as shown in Table 2. The stability of the catalyst is, furthermore, also improved by this treatment. The addition of Ca^{2+}, generally well known as a topant of stabilized ZrO_2, has no effect.

Table 2. Hydrogenation of benzoic acid over modified ZrO_2.

Additives	Temperature (°C)	Conversion of acid (%)	Selectivity to aldehyde (%)
None	350	51	97
Pb	310	89	96
In	330	100	91
Cr	350	98	96
Mn	350	70	97
Ca	350	50	98

Reaction conditions: H2 GHSV = 625/h, benzoic acid = 2 vol%, P = 0.1 MPa.

The roles of added metal ions are summarized as follows.

(i) It is known that amorphous ZrO_2 crystallizes at ca 460 °C and that the specific surface area decreases upon crystallization. It has confirmed by X-ray diffraction (XRD) and differential thermal analysis (DTA) that added metal ions such as Cr^{3+} suppress the phase transition of ZrO_2. For example, the specific surface area of ZrO_2 increases from 31 $m^2\ g^{-1}$ to 88 $m^2\ g^{-1}$ on modification with Cr^{3+} and to 66 $m^2\ g^{-1}$ on modification with Mn^{2+}. The rate of formation of benzaldehyde (mol (kg cat)$^{-1}$ h^{-1}) at 350 °C increases from 0.28 for unmodified to 0.61 for the Cr^{3+} modification and to 0.42 for the Mn^{2+} modification.

(ii) The effects of Cr^{3+} on the acid–base properties of ZrO_2 were determined by TPD. The ammonia and carbon dioxide TPD profiles of Cr^{3+}-modified ZrO_2 were similar to those of unmodified ZrO_2 and there was no significant change in the amounts of desorbed ammonia and carbon dioxide per unit surface area. Thus, we concluded that the enhancement of catalytic activity is primarily a result of an increase in the specific surface area of the ZrO_2 catalyst.

(iii) Unmodified ZrO_2 is deactivated by coke formation during hydrogenation, but coke formation becomes less for modified ZrO_2; as a result degradation of catalyst performance is very low. This diminished coke formation on the modified ZrO_2 catalyst results in a higher specific surface area after hydrogenation of benzoic acid, compared with unmodified ZrO_2. For example, in Cr^{3+}-modified ZrO_2 the surface area was 88 $m^2\ g^{-1}$ for the fresh catalyst and 73 $m^2\ g^{-1}$ for the used catalyst after hydrogenation at 360 °C for 105 h. Thus coke formation on ZrO_2 seems to be reduced by addition of metal ions.

(iv) The addition of Cr^{3+} has an important role for the activation of molecular hydrogen [15].

8.3.2 Application of Cr-ZrO_2 Catalyst to Wide Variety of Carboxylic Acids

Cr^{3+}-modified ZrO_2 has been used for the hydrogenation of a variety of aromatic carboxylic acids; the results are given in Table 3. Alkyl- and phenoxy-substituted benzoic acids are hydrogenated to the corresponding aldehydes with selectivity up to 95 %. Terephthalaldehyde and 4-carbomethoxybenzaldehyde are formed by hydrogenation of dimethyl terephthalate.

Aliphatic aldehydes are also obtained with high selectivity. Selectivity is lower for primary aliphatic carboxylic acids because of a competing intermolecular decarboxylation reaction which results in ketone formation (Eq. 2) [16]. This ketonization activity of ZrO_2 was, substantially suppressed by addition of metal ions.

$$2RCOOH \rightarrow R_2C{=}O + CO_2 + H_2O \qquad (2)$$

Table 3. Hydrogenation of various carboxylic acids over the Cr-ZrO_2 catalysts.

Carboxylic acid or esters	Conv. of substrate (%)	Sel. to aldehyde (%)
Benzoic acid	98	97
o-Methylbenzoic acid	98	97
m-Phenoxybenzoic acid	97	96
Dimethyl terephthalate	64	73
m-Chlorobenzoic acid	82	77
Trimethylacetic acid	97	99
Methyl n-hexanoate	50	70
Cyclohexanecarboxylic acid	95	98
Methyl nicotinate	86	83
4-Methyl-5-carbomethoxythiazole	74	80
3-Furoic acid	62	52

Heterocyclic carboxylic acids containing nitrogen or sulfur atoms could also be hydrogenated to the corresponding aldehydes.

These results show that the modified ZrO_2 catalyst is applicable in the hydrogenation of various kinds of carboxylic acid.

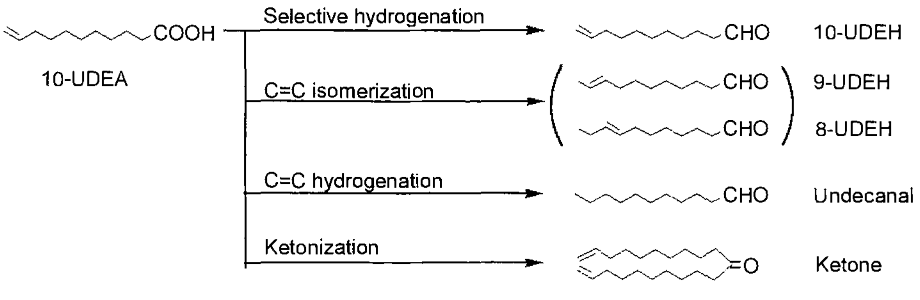
8.3.3 Hydrogenation of Aliphatic Carboxylic Acids

Aliphatic aldehydes are also important intermediates for fine chemical manufacture. The Cr^{3+}-modified catalyst, however, is not suitable for the preparation of these, because of its low selectivity [17].

As a substrate, we have chosen 10-undecylenic acid [10-UDEA]. Side-reactions in the hydrogenation of 10-undecylenic acid [10-UDEA] are illustrated in Scheme 1. Primary aliphatic carboxylic acids are liable to undergo ketonization, and the double bond readily migrates or hydrogenates when Cr^{3+}-modified ZrO_2 or other oxides are used as a catalyst. This double bond-migration must be suppressed, because the boiling points of isomers are so close that it is almost impossible to separate them by distillation. Thus, a new catalyst is required for this specific hydrogenation of aliphatic acids and it is expected to apply the catalysts to saturated aliphatic carboxylic acids with ease.

Results from the hydrogenation of 10-UDEA over different oxides are shown in Table 4. Acidic γ-Al_2O_3 has very poor activity and very high selectivity for the undesired ketone. Although the Cr^{3+}-modified ZrO_2 catalyst is suitable for aliphatic aldehyde production because of its higher selectivity toward undecenal (UDEH) formation, this catalyst also results in substantial double bond-migration, because the ratio of 10-UDEH to total aldehyde is just 0.38. Highly pure Cr_2O_3 has a remarkably high selectivity for 10-UDEH (10-UDEH/total aldehyde = 0.9).

Several commercially available Cr_2O_3 catalysts have been tested, affording quite different results for activity and selectivity (Table 4). Impurities in Cr_2O_3, especially alkali metals and alkaline earth metals, have a strong influence on catalytic performance. These contaminant impurities in Cr_2O_3 result in a drastic decrease in activity and selectivity, as has been reported elsewhere [17]. Selectivity is reduced mainly because of ketone formation.



Scheme 1. Hydrogenation of 10-Undecylenic acid over Cr_2O_3.

Table 4. Hydrogenation of 10-UDEA over various metal oxide catalysts.

Catalyst	Temperature (°C)	Conversion of acid (%)	Selectivity (%) Total-UDEH	Ketone	10-UDEH/ Total-UDEH
Cr_2O_3[a]	370	74	98	1	0.96
Cr_2O_3[b]	370	32	43	55	0.87
Cr/ZrO_2	330	87	83	16	0.38
ZrO_2	330	97	10	79	–
γ-Al_2O_3	330	8	3	96	–

Reaction conditions: H_2-GHSV = 1250/h, 10-UDEA/H_2 = 2/98 vol%, 0.1 MPA,
a) high purity Cr_2O_3, b) Cr_2O_3 including 1.4% of alkaline and alkaline earth metals as impurities.

The acid–base properties of the catalyst surface were characterized by ammonia and carbon dioxide TPD (Figure 1). Compared with other oxides, pure Cr_2O_3 contains fewer acidic sites and almost no basic sites. TPD shows that the acidic sites disappear, and new basic sites appear, when Cr_2O_3 is doped with alkali. TPD data from alkaline-doped Cr_2O_3 suggest that basic sites on the surface catalyze the ketonization. However the mechanism of double bond migration is not yet clear, interaction of the double bond with the oxide surface seems to be suppressed on Cr_2O_3, probably because of the character of its Lewis acid sites. The unique acid-base properties of pure Cr_2O_3 are easily destroyed by impurities, which is why the selectivity of commercially available Cr_2O_3 is usually poor. The uniformity of the acid sites on the surface of highly pure Cr_2O_3 seems to be important, and recent results show that the surface morphology of Cr_2O_3 is also important to catalytic performance. Well-crystallized Cr_2O_3 with a high concentration of crystalline Cr_2O_3 on the outer surface is more active than Cr_2O_3 with an amorphous phase on the outer surface, which is poorly active. It is believed that carboxylic acid is adsorbed on the highly crystalline Cr_2O_3 surface via a weak interaction, and this weakly adsorbed intermediate can be converted to the aldehyde.

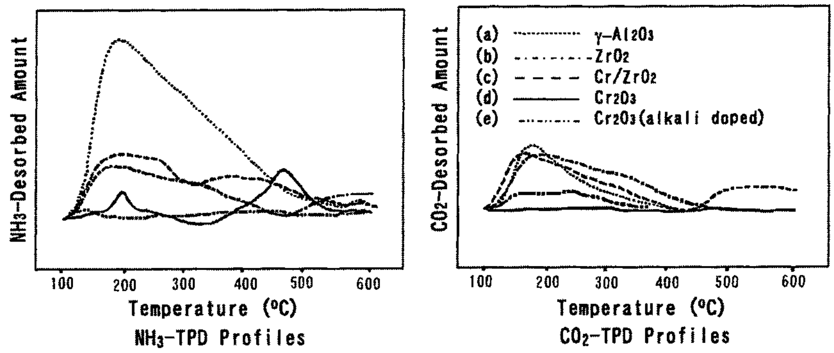


Figure 1. Acid and Base Properties of Metal Oxide Surfaces.

8.3.4 Application of Cr_2O_3 Catalysts to Different Aliphatic Carboxylic Acids

The Cr_2O_3 catalyst is also highly selective in the hydrogenation of other aliphatic carboxylic acids (Table 5). Selectivity is greater for the hydrogenation of saturated carboxylic acids than for the hydrogenation of 10-UDEA, and 9-octadecenoic acid, with an internal double bond, is hydrogenated to 9-octadecenal in excellent yield. Acyclic carboxylic acids can be hydrogenated with excellent selectivity. Aromatic carboxylic acids are also hydrogenated to the corresponding aldehydes over Cr_2O_3. The surface area of Cr_2O_3 is lower than that of the modified ZrO_2; this results in lower hydrogenation activity compared with the modified ZrO_2.

Table 5. Hydrogenation of various aliphatic carboxylic acids over high purity Cr_2O_3 catalysts[a].

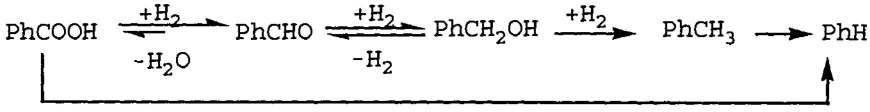
Carboxylic acids	Temperature (°C)	Conversion of acid (%)	Selectivity to aldehyde (%)
n-Octanoic acid	350	91	97
n-Decanoic acid	350	97	96
n-Octadecanoic acid	350	98	93
3-Methylpropionic acid	380	96	94
10-Undecylenic acid	370	74	98
	370[b]	95[b]	90[b]
7-Octadecenoid-acid	355	98	98
Cyclohexanecarboxylic acid	370	92	98

Reaction conditions: H2 GHSV = 1250/h, acid = 2 vol%, a) 0.1 MPa, b) 0.3 MPa.

8.3.5 Mechanistic Considerations

The by-products in the hydrogenation of benzoic acid to benzaldehyde are benzyl alcohol, toluene, and benzene. Their amounts increase with increasing conversion of benzoic acid or increasing reaction temperature. To elucidate the reaction pathway, these products were introduced over the catalyst under the hydrogenation conditions. Benzaldehyde is hydrogenated to benzyl alcohol with the formation of products having higher boiling point. The rate of formation of benzyl alcohol from benzaldehyde is small compared with that of benzaldehyde from benzoic acid. Benzyl alcohol is converted to toluene by hydrogenation and to benzaldehyde by dehydrogenation. Under the hydrogenation conditions, dehydrogenation is more rapid than hydrogenation. Benzene was formed by hydrogenolysis of toluene and by decarboxylation of benzoic acid [3].

In general, aldehydes are more easily reduced than carboxylic acids. A high yield of aldehyde over this catalyst is a result of, as mentioned above, the reaction equilibrium between benzaldehyde and benzyl alcohol is on the side of benzaldehyde. Strong interaction of benzoic acid with the catalyst surface is believed to suppress consecutive reaction of benzaldehyde, resulting in high aldehyde selectivity. There might also be an equilibrium between benzoic acid and benzaldehyde. The reverse reaction between benzaldehyde and water over ZrO_2 forms benzoic acid, but with a low rate of reaction [18]. The proposed reaction pathway for the hydrogenation of benzoic acid is shown in Eq. (3).

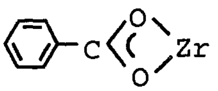


(3)

The rate of aldehyde formation is given by:

$$r = [k1(P_{H2})^{\alpha}(P_{CA})^{\beta}]/[(1+(k2P_{H2})^{1/2})]^{\gamma} \quad (4)$$

where r is the rate of aldehyde formation, $k1$ and $k2$ are reaction constants, P_{H2} and P_{CA} are the partial pressures of hydrogen and carboxylic acid, and α, β, and γ are reaction orders. Eq. (4) suggests that the rate-determining step is activation of a hydrogen molecule via dissociative adsorption. β is negligibly small and α and γ are nearly 1 and 2, respectively [19].



(5)

Onishi et al. [20] reported that molecular hydrogenation is activated on ZrO_2 by dissociative adsorption. This may show the validity of the current study.

It is well known that carboxylic acids are adsorbed by metal oxide surfaces such as γ-Al_2O_3 [21] and Y_2O_3 [22], to form surface carboxylate species. By use of FTIR a bidentate carboxylate (1540, 1440 cm^{-1}) has been detected on ZrO_2, after the hydrogenation of benzoic acid. This surface carboxylate is stable up to 350 °C under a nitrogen stream and decomposes to benzene above 450 °C. It is reduced under a hydrogen stream at 350 °C. Benzaldehyde is detected as the main desorbed product in the effluent. The strongly adsorbed benzoate species remains on the surface. Thus, it is suggested that benzaldehyde is formed from weakly adsorbed benzoate species. In the hydrogenation of 10-UDEA the surface carboxylate species is also detected on the Cr_2O_3 catalyst [11]. Interaction of the double bond with the catalyst surface is not evident.

Domen et al. reported that the surface carboxylate is formed by adsorption of acid via interaction of the acid group with ZrO_2 and Cr^{3+}-modified ZrO_2 [15,23]. Ponec et al. also reported this surface carboxylate species on their partially reduced iron oxide [24]. These results strongly suggest that the surface carboxylate species exists as an intermediate in the carboxylic acid hydrogenation.

Aldehyde is formed by reaction of the surface carboxylate and dissociated hydrogen atoms (Figure 2). On the other hand, acid is formed by the reaction of the surface carboxylate and water vapor, with the consequent formation of hydrogen; this is the reverse of the reaction of aldehyde formation. The activation mechanism of molecular hydrogen is not yet clear, however. Kondo et al. reported that the main role of the Cr^{3+} is considered to be related to the activation of hydrogen

[15]. It was suggested that the hydrogenation of the carboxylic acid proceeds via a redox mechanism on metal oxides. Further studies are required to clear the detail of the mechanism of activation of molecular hydrogen.

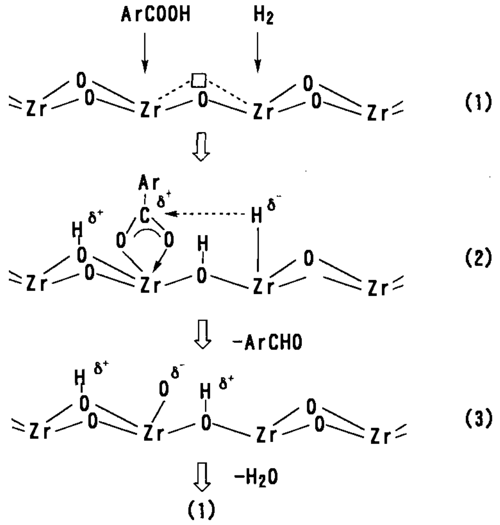


Figure 2. Proposed reaction mechanism.

8.3.6 The Commercial Process

A flow diagram for the commercial process is shown in Figure 3. Molten carboxylic acid is fed into the vaporizer where the acid is quickly mixed with hydrogen gas and evaporated. The reaction is slightly endothermic and the mixture is pre-heated and introduced on to the catalyst bed. The reaction is performed at 350–400 °C under a hydrogen pressure of 0.1–0.5 MPa. The effluents are condensed to separate the liquid products from hydrogen and the excess hydrogen is recycled to the reactor. Aldehydes are further purified by distillation.

This process is the first example of the direct hydrogenation of carboxylic acids to aldehydes on an industrial scale. It has several important advantages: (i) product yields are extremely high; (ii) the quality of the products is excellent and superior to that of other process; (iii) the process is simple; and (iv) waste formation is minimal.

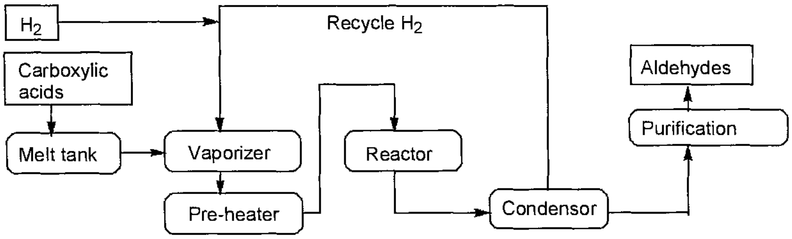


Figure 3. Process flow diagramm of multi-purpose plant.

8.3.7 Future Prospects for Hydrogenation of Carboxylic Acids

By using new technology, the amount of wastes is greatly reduced compared with current hydrogenation methods, and it is a typical example of the green chemistry to be developed in fine chemical industries. This novel process is applicable to the commercial production of a variety of aldehydes, except for the carboxylic acids which are thermally unstable or contain catalyst poisons such as halogen atoms. Yamamoto et al recently reported a one-pot synthesis of aldehydes by use of a Pd complex and pivalic anhydride reaction system in the liquid phase [25]. They comment that this new method could be applicable to the synthesis of dialdehydes and halogen- substituted aldehydes. In the near future it is expected that a new, efficient, and environmentally friendly catalytic system working even in liquid phase will be developed.

References

[1] T. Maki and T. Yokoyama, J. Synth. Org. Chem. Jpn., **49**, 195–204 (1991).
[2] R. D. Davies and H. H. Hudgson, J. Chem. Soc., 84–86 (1943).
[3] T. Yokoyama, T. Setoyama, N. Fujita, M. Nakajima, and T. Maki, Appl. Catal., **88**, 149–161 (1992).
[4] O. Drossbach and A. Johannsen, U. S. Patent 2018350 (1935).
[5] A. Feinstein and E. K. Field, U. S. Patent 3935265 (1976).
[6] D. C. Hargis, U. S. Patent 4950799 (1990).
[7] P. C. Van Geem and L. H. W. Janssen, EP Patent 290096 (1988).
[8] E. J. Strojny, U. S. Patent 4328373 (1982).
[9] W. Hölderich and J. Tjoe, D. E. Patent 19718742 (1999).
[10] R. M. Ferrero, EP Patent 539274 (1992).
[11] N. Yamagata, N. Fujita, T. Yokoyama, and T. Maki, Stud. Surf. Sci. Catal., **121**, 441–444 (1998), "Science and Technology in Catalysis 1998, Kodansya, Tokyo (1999)".
[12] G. A. Olah, K. Laali, and K. Mehrotra, J. Org. Chem., **48**, 3360–3362 (1983).
[13] T. Yamaguchi, Y. Nakano, T. Iizuka, and K. Tanabe, Chem. Lett., 677–678 (1976).
[14] H. Shima and T. Yamaguchi, J. Catal., **90**, 160–164 (1984).
[15] J. Kondo, N. Ding, K. Maruya, K Domen, T. Yokoyama, N. Naoko, and T. Maki, Bull. Chem. Soc. Jpn., **66**, 3085 (1993).
[16] W. Winkler, Chem. Ber., **81**, 258 (1948).
[17] T. Yokoyama, N. Fujita, and T. Maki, Stud. Surf. Sci. Catal., **92**, 331–334 (1994), "Science and Technology in Catalysis 1998, Kodansya, Tokyo(1995)".
[18] T. Yokoyama, N. Fujita, and T. Maki, Appl. Catal., **125**, 159–167 (1995).
[19] T. Yokoyama and K. Fujii, Petrotech (Tokyo), **14**, 633 (1991).
[20] T. Onishi, H. Abe, K. Maruya, and K. Domen, J. Chem. Soc., Chem. Commun., 617 (1985).
[21] S. T. King, Appl. Spectrosc., **34**, 632–636 (1980).
[22] S. T. King and E. J. Strojny, J. Catal., **76**, 274–284 (1982).
[23] N. Ding, J. Kondo, K. Maruya, K. Domen, T. Yokoyama, N. Fujita, and T. Maki, Catal. Lett., **17**, 309–317 (1993).
[24] R. Pestman, R. M. Koster, J. A. Z. Pieterse, and V. Ponec, J. Catal., **168**, 255–264 (1997).
[25] K. Nagayama, I. Shimizu, and A. Yamamoto, Chem. Lett., 1143–1144 (1998).

8.4 Carbohydrates

A. Abbadi, H. Van Bekkum

8.4.1 Introduction

The hydrogenation of the carbonyl group of carbohydrates is an important industrial process. Although a variety of catalytic and stoichiometric systems have been used to perform this reaction [1], the use of metal catalysts such as Pt, Pd, Ni, and Ru in conjunction with molecular hydrogen is the method of choice for industrial application. When the monosaccharide is brought into contact with such a metal catalyst under a hydrogen atmosphere polyols are formed. Polyol compounds are widely used in the food industry as low calorie, non-cariogenic sweeteners. They serve also as starting materials for further chemical and biochemical modifications such as the conversion of sorbitol to dianhydrosorbitol and to L-sorbose [2]. The additional presence of an amine in the reaction mixture during the hydrogenation of the carbonyl group leads to the formation of 1-(alkyl)amino-1-deoxy-polyols by reductive amination. Amines with long alkyl chain yield non-ionic surface-active compounds. When severe conditions are applied during hydrogenation, hydrogenolysis prevails and the carbohydrate molecule is broken down to smaller polyhydroxy compounds. Under alkaline conditions and in the presence of noble metal catalyst dehydrogenation of carbohydrates takes place to provide the corresponding aldonic acid.

In this contribution, we first review the hydrogenation of carbohydrates to polyols. Section 8.4.3 will focus on the reductive amination of carbohydrates and, finally (Section 8.4.4), the facile dehydrogenation of carbohydrates under alkaline conditions will be reported. The hydrogenolysis of carbohydrates is beyond the scope of this chapter. Readers interested in this subject should consult Ref. 3 and references cited therein.

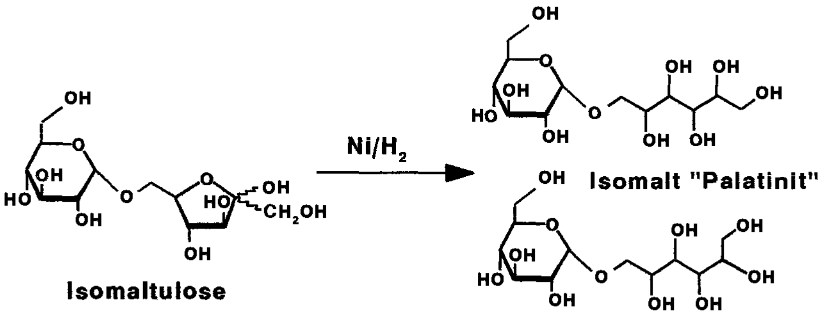
8.4.2 Hydrogenation of the Carbonyl Group

Industrially the most important carbohydrate hydrogenation product is sorbitol (D-glucitol), which is obtained by reduction of the carbonyl group of D-glucose [4–7]. Worldwide production is estimated to be 650 000 tons p. a. Sorbitol is used in numerous cosmetic, food and drinks formulations, and as a starting material e. g. in the manufacture of ascorbic acid (vitamin C).

Sorbitol was originally prepared by electrochemical reduction of D-glucose [8], but nowadays its manufacture is based almost completely on catalytic hydrogenation, with nickel as catalyst. Other metals such as platinum and, especially, ruthenium were reported to be effective catalysts for the hydrogenation of D-glucose to sorbitol [1]. Homogeneous ruthenium complexes have also been described as good catalysts for the hydrogenation of D-glucose [9,10].

In batch processes a 45–50 % (*w/v*) aqueous solution of D-glucose is hydrogenated in the presence of Raney nickel (3–6 % *w/w* relative to D-glucose) at pH 5–6 and 120–150 °C, under 30–70 bar of hydrogen. In continuous processes higher hydrogen pressures such as 170 bar with supported nickel, for example nickel on silica, are used.

When corn starch hydrolyzate, rather than D-glucose, is used as starting material C_{12} and C_{18} polyols are formed as by-products. Pure C_{12} polyols can also be prepared by catalytic hydrogenation of the corresponding disaccharide on a nickel catalyst [11]. According to this procedure lactitol and maltitol are obtained from lactose and maltose, respectively. Lactitol is currently produced on a commercial scale by PURAC in the Netherlands. Another industrially important C_{12} polyol is isomalt (palatinit) which is produced (Südzucker-Germany, ≈ 10 000 tons p. a.) by catalytic hydrogenation of isomaltulose (palatinose) on Raney nickel catalyst [12,13]. Isomalt is a mixture of two isomeric polyols which result from hydrogenation of the keto group of isomaltulose. The starting material, isomaltulose, is obtained by bacterial conversion of sucrose (Scheme 1).

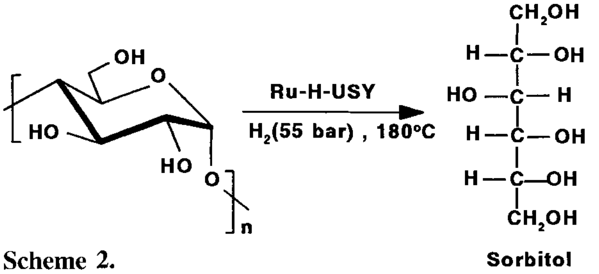


Scheme 1.

A mixture of high polyols has been prepared by the simultaneous action of α- or β-amylase and nickel catalyst on starch (maize) under hydrogen pressure [14]. A syrup with DE 11 and 82 % solubles was obtained. Higher DE-level syrups were not obtained by this combined hydrolysis–hydrogenation process because the enzyme was found to be inhibited by leached nickel from the catalyst.

An efficient single-step catalytic process was recently developed for the conversion of glucan-type polysaccharides, especially starch, to sorbitol [15]. This process is characterized by the simultaneous hydrolysis of the polysaccharide and hydrogenation of the liberated monosaccharide. The catalyst used is Ru-loaded H-USY zeolite (3 % *w/w* Ru) in which the zeolitic material fulfils the role of metal carrier (Ru) and solid-acid catalyst. The zeolite provides the Brønsted acidity required for the hydrolysis reaction either because of its outer surface or by introducing some homogeneous acidity, and the Ru catalyzes the hydrogenation of D-glucose to sorbitol (Scheme 2).

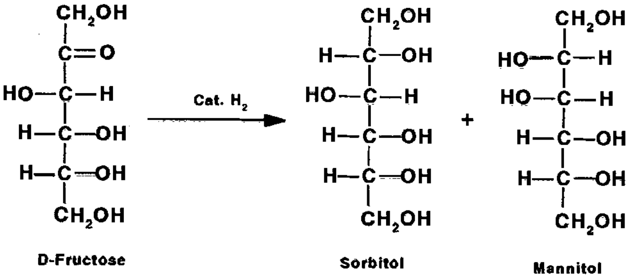
Typical reaction conditions for the conversion of starch are: batch autoclave, 180 °C, 55 bar H_2, starch concentration 30 % (*w/w*), Ru/starch *w/w* ratio 0.002. Under these conditions essentially quantitative conversion is reached within 1 h. Sorbitol selectivity is > 95 % and the catalyst can be re-used many times.



Scheme 2.

Similar results are obtained by combining a 5% Ru/C catalyst with a heterogeneous acidic zeolite catalyst (H-USY, H-mordenite or H-ZSM-5). It has been also reported in the literature that Ru/C was the catalyst of choice for hydrogenation in a combined process in the presence of a homogeneous inorganic acid [16]. The use of other metal catalysts, e. g. Pt/C, leads to degradation of the reaction products and, hence, moderate sorbitol selectivity.

The second most important polyol is mannitol. It is used, for example, in chewing gum and in pharmaceutical preparations [17]. Mannitol can be prepared by catalytic hydrogenation of the keto group of D-fructose followed by purification by crystallization, because sorbitol is also formed [1]. The aqueous solubility of mannitol is much lower than that of sorbitol, enabling selective crystallization (Scheme 3). Production methods for D-mannitol have been reviewed by Makkee [18].



Scheme 3.

The selectivity of the hydrogenation towards mannitol depends on the metal catalyst used and varies from 40% on Ru/C to 70% on Cu on silica [19]. When a small amount of borate is added to the reaction mixture in the presence of the Cu catalyst the selectivity towards mannitol is increased and reaches 90% [19–21].

Extensive studies have been performed to enable understanding of the mechanism of hydrogenation of D-fructose on copper catalysts. Experiments performed with deuterium showed clearly that the enediol form is not involved in hydrogenation and D-fructose is assumed to be preferentially hydrogenated via its furanose form by attack of a copper hydride-like species at the anomeric carbon, with inversion of configuration [22]. The proposed mechanism could explain the diastereoselectivity obtained in the hydrogenation of the other ketoses and its dependence on the ratios of the α and β forms of furanose present in solution. For instance, D-xylulose, which is present in solution as β-furanose/α-furanose/open form in the ratio 62.3:18.1:19.6, yields 65 % arabinitol under reductive conditions [23,24].

The hydrogenation of invert sugar (1:1 D-glucose/D-fructose mixture) as starting material for mannitol, over nickel catalyst yields a 7:3 sorbitol–mannitol mixture from which the mannitol is obtained by crystallization [25].

Mannitol can also be obtained from D-glucose when the hydrogenation is performed under conditions which enable its isomerization to D-fructose [26–29]. The use of calcium hydroxide or sodium bicarbonate–sodium hydroxide as alkaline agents for the isomerization of D-glucose, in the presence of Raney nickel as the hydrogenation catalyst, yielded 27 % mannitol [29].

Another approach for the preparation of mannitol from D-glucose is the use of a bi-catalytic system based on the cooperation of glucose isomerase and copper catalyst [19,20]. The role of glucose isomerase in this bio–chemo–catalytic system is to perform the isomerization of D-glucose to D-fructose while copper simultaneously catalyzes the hydrogenation step. The use of an enzyme to perform the isomerization step also has the advantage of eliminating alkaline degradation reactions, which occur when the isomerization is catalyzed by alkaline agents such as calcium hydroxide.

Typical operation conditions are: 60 g invert sugar in 200 mL water, 5 g 20 % copper on silica, 0.1 g $Na_2B_4O_7.10H_2O$ (as selectivity enhancer of the copper catalyst), 3 g Optisweet 22 (8 % glucose isomerase immobilized on silica), 0.3 g $MgSO_4$ (enzyme-stabilizing cation), 0.05 g EDTA (to protect the enzyme against traces of leached copper ions), 0.5 g $CaCO_3$ (as buffering agent), pH 7.1–7.6, 70 °C, and 50 bar hydrogen. Under these conditions, the yield of mannitol exceeds 60 % although long reaction times (60 to 80 h) are required, because of poisoning of the copper catalyst, probably by adsorption of mobile fragments originating from the immobilized enzyme system.

Ruddlesden and Stewart [30] reported the combination of glucose isomerase with Ru-loaded zeolite Y as bi-catalytic system for the preparation of mannitol from D-glucose. The advantage of using zeolite as carrier for the hydrogenation catalyst is the building of a barrier through the pore system of the zeolite to prevent access of the metal catalyst to inhibiting species, which are assumed to be large molecules. A yield of 29 % mannitol was realized with this system.

A multi-step process has also been developed for the preparation of mannitol from D-glucose [31,32]. D-Glucose is first epimerized to D-mannose by molybdate and D-glucose remaining in the mixture is then treated with glucose isomerase to establish equilibrium with D-fructose. Finally, the glucose–mannose–fructose mixture is hydrogenated to yield 40 % mannitol.

Inulin, which is glucose–$(\text{fructose})_n$, is nowadays available in large quantities. It seems to be a logical raw material for the preparation of mannitol. Combined hydrolysis and hydrogenation has recently been performed with homogeneous Ru-TPPTS catalyst at pH 2.3 [33], and by use of Ru on acidic carbon as a heterogeneous bifunctional catalyst [34].

Another polyol with promising applications is xylitol (3000 tons p. a.). It is prepared by hydrogenation of D-xylose [1]. An alternative economically valuable process for the preparation of xylitol from D-gluconic acid was recently developed by Cerestar [35]. D-gluconic acid is decarboxylated by treatment with hypochlorite or hydrogen peroxide to yield D-arabinose. The latter is hydrogenated to D-arabinitol which is subsequently isomerized to furnish a mixture of xylitol, ribitol and D,L-arabinitol. Xylitol is then isolated from this mixture by chromatography and the remaining pentitols are recycled to the isomerization step. Xylitol is as sweet as sucrose and is used in several food applications, including chewing gum.

The non-catalytic reduction of aldonolactones to the corresponding aldoses and/or alditols by sodium borohydride or lithium aluminum hydride has also been studied [1]. Because of the stoichiometric character of these procedures they are, however, limited to laboratory use.

8.4.3 Reductive Amination

The hydrogenation of carbohydrates over Raney nickel or platinum in the presence of amines leads to the formation of amino derivatives [36]. For instance, D-glucose and D-galactose in liquid ammonia are hydrogenated in the presence of Raney nickel at 40–120 °C under 50–100 bar hydrogen to yield glucitylamine and galactitylamine, respectively [37]. Initially the aldose reacts with ammonia (or alkylamine) to form (alkyl)-glycosylamine; this is hydrogenated in-situ to yield the corresponding 1-(alkyl)amino-1-deoxyalditol.

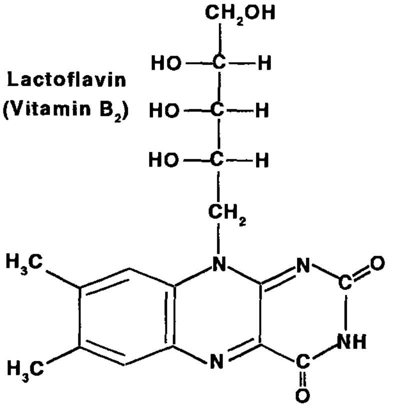
A process using a fixed-bed nickel catalyst for the preparation of 1-amino-1-deoxy-D-glucitol (glucitylamine) from D-glucose has recently been developed [38]. Catalytic reductive amination has also been applied to different disaccharides, e. g. lactose, maltose, and isomaltulose to yield (alkyl)-aminodeoxypolyols [39]. Other metal catalysts such as Pt and Pd have also been used to perform the reductive amination of carbohydrates [38–40].

N-methylglucamine is the most important reductive amination product of carbohydrates. It is further reacted with a fatty acid to provide *N*-methylglucamide, a new class of biodegradable surfactant produced by Hoechst and used by Procter and Gamble as surfactants in detergent formulations. Annual production of *N*-alkylglucamides is 5000 t.

1-Benzylamino-1-deoxypolyols have also been prepared; on removal of the benzyl group by hydrogenolysis these give the corresponding free 1-amino-1-deoxyalditols [41,42]. The addition of ammonium chloride to methanolic ammonia containing D-glucose, on the other hand, catalyzes the formation of diglucosylamine which upon hydrogenation gives bis(1-deoxy-D-glucit-1-yl)amine (dialditylamines) [43].

Hydrogenation of aldose oximes (aldoses: D-arabinose, D-mannose and D-galactose) at 50 °C over 5 % Pt/C catalyst, under 100 bar hydrogen, resulted in quantitative conversion of the oximes to a mixture of mono- and dialditylamines from which the latter were isolated in fairly good yield (26–80 %) [44].

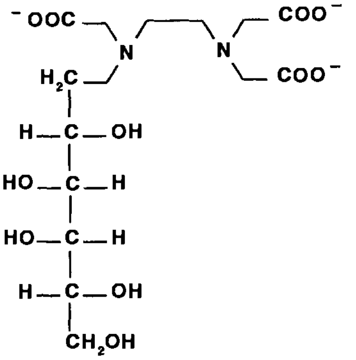
The preparation of *N*-(4,5-dimethyl-2-nitrophenyl)-D-ribosylamine followed by hydrogenation to yield 1-(2-amino-4,5-dimethylanilino)-1-deoxy-D-ribitol was also achieved. This compound is condensed with alloxan to form vitamin B_2 (lactoflavin) [45] (Fig. 1).



Lactoflavin (Vitamin B_2)

Figure 1.

The Delft group [46] recently reported the reductive amination of aldohexoses over Pt/C with mono- and bifunctional alkylamines. The chemical nature of the species present in solution was studied by ^1H and ^{13}C NMR. When the reductive amination was conducted in the presence of ethylenediamine, the resulting product was submitted to carboxymethylation to form an EDTA (ethylenediaminetetraacetate)-like complexing agent, with the aim of improved biodegradability (Fig. 2). The sequestering capacity of such compounds was also investigated.



N-(1-deoxy-D-galactitol-1-yl)ethylenediaminetriacetate

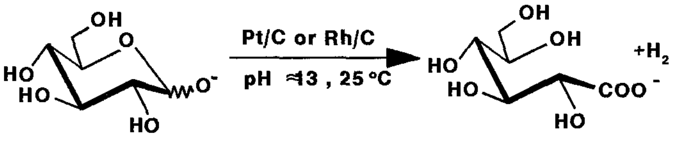
Figure 2.

Amino sugars obtained by reductive amination with alkylamine instead of ammonia have various applications. 1-Deoxy-1-methylamino-D-glucitol, for instance, is used as hydrophilic component, in particular to obtain water-soluble salts of

X-ray contrast materials such as 2,4,6-triiodobenzoic acid. Amino sugars with applications as surfactants, liquid crystalline materials, and in polymers, cosmetics, and pharmaceuticals have been prepared from long-chain alkylamines [47,48].

8.4.4 Dehydrogenation

The facile dehydrogenation of D-glucose and related mono- and disaccharides such as D-galactose and lactose on platinum or rhodium catalysts under alkaline conditions (pH ≈ 13.5) has been reported [49]. During this reaction, hydrogen was evolved whereas D-glucose was transformed into D-gluconic acid. Other metals, e. g. nickel, palladium, and ruthenium, were less active and much less selective (Scheme 4).



D-Glucose D-Gluconate

Scheme 4.

The dehydrogenation is first-order in catalyst, aldose, and hydroxide. Clearly, the reaction proceeds via the aldose anion (apparent pK_a 13.5 under these conditions [50,51]), whereas rupture of the 1C–H bond is the rate-determining step. The reaction is currently used on the industrial scale by Solvay (Germany) to prepare lactobionic acid from lactose.

The hydrogen-donor properties of reducing aldoses have, furthermore, been used in hydrogen-transfer reactions. Platinum (or rhodium)-catalyzed dehydrogenation (oxidation)/reduction of D-glucose/D-fructose under alkaline conditions (pH 13) was thereby achieved [52]. Essentially, all the hydrogen evolved from D-glucose dehydrogenation was used in the reduction of D-fructose.

8.4.5 Conclusion

Although (Ru) is a prominent alternative catalyst for the classical hydrogenation of D-glucose, it remains a challenge to hydrogenate fructose to mannitol with high diastereoselectivity. Combined hydrolysis/hydrogenation processes for the preparation of polyols are being developed for starch and inulin.

References

[1] J. W. Green in *The Carbohydrates* Vol. 1B, (Eds. W. Pigman, D. Horton), Academic Press, New York, **1980**, p. 989.
[2] P. Stoss, R. Hemmer, *Adv. Carbohydr. Chem. Biochem.*, **1991**, *49*, 93.
[3] A. Abbadi, H. van Bekkum in *Carbohydrate as Organic Raw Material III*, (Eds. H. van Bekkum, H. Röper, A. G. J. Voragen), VCH, Weinheim, **1996**, p. 37.
[4] L. W. Wright, *Chem Tech*, **1974**, 42.
[5] P. H. Brahme, L. K. Doraiswamy, *Ind. Eng. Chem. Process Des. Dev.*, **1975**, *15*, 130.
[6] J. Wisniak, R. Simon, *Ind. Eng. Chem. Prod. Res. Dev.*, **1979**, *18*, 50.
[7] R. Albert, A. Strätz, G. Vollheim, *Chem. Ing. Technol.*, **1980**, *52*, 582.
[8] M. Fedoronko, *Adv. Carbohydr. Chem. Biochem.*, **1974**, *29*, 107.
[9] ICI US 3935284 (1976).
[10] W. M. Kruse, L. W. Wright, *Carbohydr. Res.*, **1978**, *64*, 293.
[11] M. W. Kearsley, G. G. Birch, in *Sugar: Science and Technology*, (Eds. G. G. Birch, K. J. Parker), Applied Science Publishers, London, **1979**, p. 287.
[12] H. Schiweck, G. Steinle, H. Haberl, DE 2217628 (1972).
[13] G. Darsow, W. Biedermann, DE 3403973 (1984).
[14] M. W. Kearsley, S. H. Satti, I. Tregaskis, *Starch*, **1980**, *32*, 169.
[15] P. A. Jacobs, H. Hinnekens, EP 329923 (1989).
[16] A.A Balandin, N. A. Vasyunina, S. V. Chepigo, G. S. Barysheva, *Doklady Akad. Nauk. S. S. S. R.*, **1959**, *128*, 941, *Chem. Abstr.*, **1959**, *54*, 7140f.
[17] *Chem. Eng. News*, **1972**, *17*, 13.
[18] M. Makkee, A. P. G. Kieboom, H. van Bekkum, *Starch*, **1985**, *37*, 136.
[19] M. Makkee, *Thesis*, Delft University of Technology, **1984**.
[20] M. Makkee, A. P. G. Kieboom and H. van Bekkum, *Carbohydr. Res.*, **1985**, *138*, pp. 225, 237.
[21] J. Dewing, J. F. Ruddlesden, A. Stewart, D. J. Thomson, EP 6313 (1980).
[22] J. F. Ruddlesden, A. Stewart, D. J. Thomson, R. Whelan, *Faraday Discuss. Chem. Soc.*, **1981**, *72*, 397.
[23] J. Wu, T. Vuorinen, A. S. Serianni, *Carbohydr. Res.*, **1990**, *206*, 1.
[24] S. Angyal, *Adv. Carbohydr. Chem. Biochem.*, **1991**, *49*, 19.
[25] A. J. de Berardinis, US 3763246 (1973).
[26] A. J. de Berardinis, DE 2025314 (1971).
[27] L. W. Wright, J. D. Brander, DE 1268606 (1968).
[28] N. J. Gerharz, NL 6515786 (1966).
[29] H. C. M. Pijnenburg, B. F. M. Kuster, H. S. van der Baan, *Starch*, **1978**, *30*, 199.
[30] J. F. Ruddlesden, A. Stewart, *J. Chem. Res.*, **1981**, 378.
[31] T. Motohiro, I. Mochihiro, T. Yoshiaki, O. Yuji, M. Hiroyuki, US 4083881 (1977).
[32] W. M. Kruse, US 4173514 (1979).
[33] A. W. Heinen, G. Papadogianakis, R. A. Sheldon, J.A Peters, H. van Bekkum, *J. Mol. Catal.*, **1999**, *142*, 17.
[34] A. W. Heinen, J.A Peters, H. van Bekkum, to be published.
[35] Cerestar, US 5714602 (1996).
[36] H. Paulsen, K.-W. Pflughaupt, in *The Carbohydrates* Vol. 1B, (Eds. W. Pigman, D. Horton), Academic Press, New York, **1980**, p. 881.
[37] J. W. Long, G. N. Bollenback, in *Methods in Carbohydrate Chemistry*, Vol. II, (Eds. R. L. Whistler, M. L. Wolfrom), Academic Press, New York, **1963**, p. 79.
[38] *Kirk–Othmer Encyclopedia of Chemical Technology*, Vol. 4, 4th ed., Interscience, New York, **1992**, p. 925.
[39] H. Kelkenberg, *Tens. Surf. Det.*, **1988**, *25*, 8.
[40] J. Klein, W. Behrens, M. Kunz, EP 225033 (1987).
[41] R. B. Flint, P. L. Salzberg, US 2016962 (1974).
[42] J. M. J. Tronchet, B. Baehler, J.-B. Zumwald, *Helv. Chim. Acta*, **1977**, *60*, 1932.
[43] J. M. Larkin, E. L. Yeakey, Jr. L. W. Watts, US 4540821 (1985).

[44] F. Kagan, M. A. Rebenstorf, R. V. Heinzelmann, *J. Am. Chem. Soc.*, **1957**, *79*, 3541.

[45] I. Christiansen-Brams, M. Meldal, K. Bock, *J. Carbohydr. Chem.*, **1992**, *11*, 813.

[46] J. E. Hodge, B. F. Moy, *J. Org. Chem.*, **1963**, *28*, 2784.

[47] J. van Haveren, H. Lammers, J. A. Peters, H. van Bekkum, *Carbohydr. Res.*, **1993**, *243*, 259.

[48] R. Kuhn, R. Ströbele, *Ber.*, **1937**, *70*, 773.

[49] H. Lammers, J. A. Peters, H. van Bekkum, *Tetrahedron*, **1994**, *50*, 8103.

[50] H. Koch, R. Beck, H. Röper, *Starch*, **1993**, *45*, 2.

[51] G. A. Jeffrey, L. M. Wingert, *Liq. Crystals*, **1992**, *12*, 179.

[52] G. de Wit, J. J. de Vlieger, A. C. Kock-van Dalen, R. Heus, R. Laroy, A. J. van Hengstum, A. P. G. Kieboom, H. van Bekkum, *Carbohydr. Res.*, **1981**, *91*, 125.

[53] G. de Wit, A. P. G. Kieboom, H. van Bekkum, *Tetrahedron Lett.*, **1975**, 3943.

[54] G. de Wit, A. P. G. Kieboom, H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **1979**, *98*, 355.

[55] A. J. van Hengstum, A. P. G. Kieboom and H. van Bekkum, *Starch*, **1984**, *36*, 317.

8.5 Aromatic Nitro Compounds

H. U. Blaser, U. Siegrist, H. Steiner, M. Studer

8.5.1 Introduction

Hydrogenation of aromatic nitro compounds with heterogeneous catalysts is often the method of choice for the production of the corresponding anilines [1,2]. In contrast with reductions using metals such as iron (Béchamp) or sulfides, no stoichiometric by-products (except water) are formed. The purpose of this chapter is to familiarize practicing synthetic chemists both at university and in industry with the opportunities and problems of heterogeneous hydrogenation technology. The most important catalysts (and their suppliers) will be described; it will be shown how the reaction medium and the reaction conditions can affect catalyst activity and selectivity, and which equipment can be used. Other issues are the effect of pressure, impurities, and modifiers on rate and selectivity; the formation of desired or undesired intermediates (hydroxylamines, azo, azoxy, and hydrazo derivatives), and what is known about the mechanism of their formation. Safety and handling considerations will be emphasized because nitro arenes and some intermediates are metastable compounds with a very high energy content, and because some intermediates and products are carcinogenic. The selective reduction of nitro arenes containing reducible functional groups to the corresponding anilines, and strategies to suppress hydroxylamine formation when performing such transformations, will be described in some detail because of new results that have been obtained in the last few years.

8.5.2 The Reaction Network

To facilitate discussion, we first discuss the relatively complex set of reaction intermediates that can arise when reducing nitro arenes. As long as 100 years ago Haber [3] proposed a reaction network (Figure 1) to explain the results of the electrochemical reduction of nitrobenzene and substituted analogs. Since then the intermediates he suggested have all been verified and it has been shown that catalytic hydrogenation reactions proceed via the same routes.

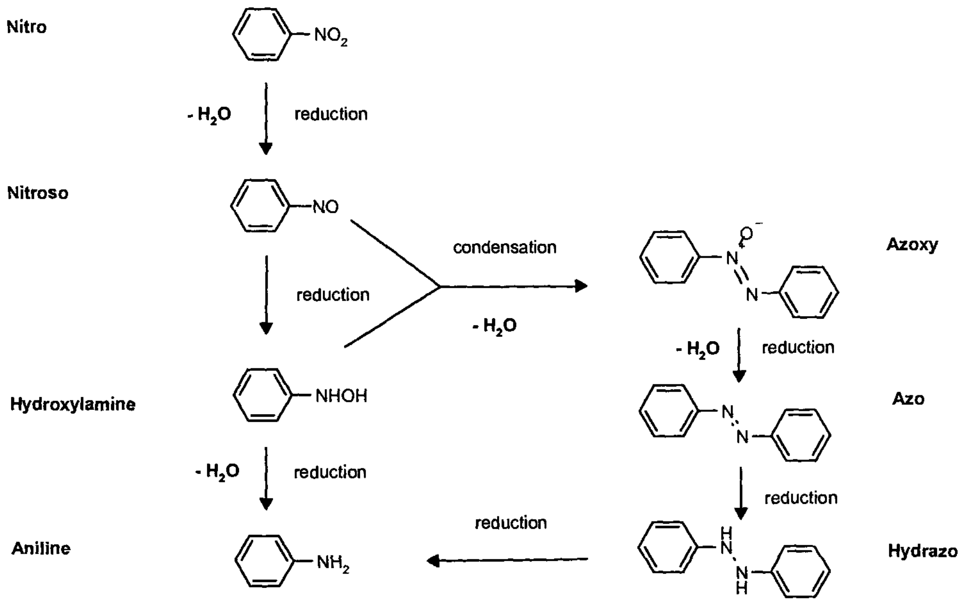


Figure 1. Reaction network proposed by Haber for the (electrochemical) reduction of a nitro arene.

8.5.3 Practical Aspects

8.5.3.1 Catalysts

Types of Catalyst

The 'classical' and most frequently used hydrogenation catalysts for the hydrogenation of nitro groups are the noble metals Pt and Pd supported on active carbon, Raney nickel, and Ni supported on kieselguhr [4]. A second metal is sometimes added to modify catalyst performance (see below). Because the active metal is present in the form of very small particles on a support or as a skeletal material, the specific metal surface area is usually very high. Many problems can be adequately solved by the use of standard catalysts; more demanding processes often require tailored catalysts. Typical examples are a 1 % Pt/C catalyst developed by Johnson Matthey [5] or a promoted 5 % Ir/C catalyst from Degussa-Huels [6] for the selective hydrogenation of halonitroarenes and/or the suppression of by-product formation.

Catalyst Suppliers

Several manufacturers supply a full range of hydrogenation catalysts (only European suppliers are listed): Degussa-Huels AG, Geschäftsbereich Anorganische Chemieprodukte, Postfach, D-63450 Hanau, Germany; Engelhard de Meern B. V., Catalysts and Chemical Division, PO Box 19, 3454 ZG De Meern, The Netherlands; Heraeus, Chemical Catalysts, Postfach 1553, D-63450 Hanau 1, Germany; Johnson Matthey, Process Catalysts, Orchard Road, Royston, Hertfordshire SG8 5HE, UK. They also have a substantial know-how about which type of catalyst is the most suitable for a specific problem. Our experience has shown that it is of advantage to search for or optimize a suitable catalyst in close collaboration with the catalyst suppliers. This is especially true for the development of technical processes and/or when the development team has little hydrogenation experience. Catalyst screening and development should always be performed with specified catalysts that can be supplied in technical quantities when needed. For laboratory use, Fluka and Aldrich Inorganics offer a wide variety of hydrogenation catalysts that are adequately suited for preparative purposes, although the catalyst manufacturer and the exact type of catalyst is not usually specified.

In recent years several lines of research have been directed at the preparation of catalysts with improved selectivity. Colloids [7–9] were reported to furnish remarkably selective catalyst systems for the hydrogenation of chloronitroarenes. Reusable Pd complexes on different supports have been described for the selective hydrogenation of nitroaromatic compounds in the presence of C=O [10] and C–Cl functionality [11]. Progress has also been reported in the use of chemoselective transfer hydrogenation systems, most notably with iron hydroxide catalysts in combination with hydrazine hydrate as reducing agent [12].

Spent Catalysts, Noble Metal Recovery

Precious metal catalysts are usually shipped back to the catalyst suppliers to recover the expensive metal from the spent catalysts. For hygiene and regulatory reasons the spent catalyst must be washed thoroughly to remove toxic organic products. To get the best results for metal recovery, spent catalysts should not contain inorganic products (e. g. materials to facilitate filtration such as Tonsil or Hyflo) or large amounts of water.

Catalyst Costs

The cost of using a catalyst is mainly determined by:

- The cost of fresh catalyst (catalyst price from the manufacturer, excluding the noble metal, which is treated as an investment).
- Metal losses during hydrogenation (e. g. metal corrosion, handling losses). Typical loss rates for Pd or Pt are in the range 2–10 %, depending on the specific substrate, reaction conditions, etc.
- Cost of recovery of the precious metal from the spent catalyst.

- Metal losses during the recovery process (recovery rates range from 80 % (for Ru) to 99 % (e. g. for Pd and Pt).
- Capital interest on the precious metal (catalyst manufacturers offer to open a precious metal account, the customer buys a certain amount of metal, the manufacturer takes the amount necessary to prepare the catalyst from the account, and will credit the recovered metal).

8.5.3.2 Reaction Medium and Modifiers

Catalytic hydrogenation of nitro groups is usually conducted in solution. The choice of the solvent affects not only the solubility of the reactants and products but can also have a very large effect on the activity and selectivity of a catalyst. Solvents should not be hydrogenated under the reaction conditions used. At the laboratory stage only high purity solvents should be used to minimize poisoning of the catalyst. Those used most often are alcohols (MeOH, EtOH, *i*PrOH, BuOH), ethyl acetate, aromatic and aliphatic hydrocarbons, ethers such as *t*BuOMe, THF, dioxane (care must be taken with Raney nickel at high temperatures), water, ketones and acetic acid. In special cases amides such as DMF, dimethylacetamide, or *N*-methylpyrrolidone, and dichloromethane, are also used.

The application of organic 'modifiers' is an important strategy for influencing the properties, mainly selectivity, of heterogeneous catalysts. Freifelder [13] has published a good overview of the effect of a wide variety of additives used in hydrogenation reactions. This approach will be discussed in more detail in Section 8.5.4.2.

8.5.3.3 Reaction Conditions

On the production scale, in particular, it is important to carefully optimize all aspects of the catalytic system: catalyst, reaction medium, and reaction conditions. The quality of the optimization will substantially affect the cost of hydrogenation! Conditions that can be varied and will affect process performance are hydrogen pressure (usually affects the rate of reaction, sometimes also the selectivity), temperature (because of the very high exothermicity of the reaction and to avoid accumulation of intermediates it is of advantage to conduct the hydrogenation at temperatures > 80 °C), substrate concentration (determines volume yield), catalyst/substrate ratio (depends on catalyst activity and determines reaction time and catalyst cost), agitation (affects gas–liquid diffusion and is especially important because many nitroarene hydrogenations are very fast and because, under hydrogen-starved conditions, metal leaching can be very pronounced), and catalyst pretreatment (e. g. pre-reduction is sometimes necessary to improve catalyst activity and to reduce corrosion of the precious metal). Occasionally the continuous addition of unstable or dangerous substrate(s) should be considered.

8.5.3.4 Safety Aspects

Problem Areas

The catalytic hydrogenation of aromatic nitro compounds is a potentially hazardous reaction. The safety of a specific operation depends both on the nature of the nitro arene and on the operating conditions [14].

Hazards Related to Hydrogen

Hydrogen–air mixtures are explosive over a wide range of concentrations (4–75 %, *v*/*v*) and have a very low ignition energy (0.02 mJ).

Hazards Related to the Catalyst

Dry hydrogenation catalysts such as Raney nickel and palladium or platinum on charcoal are pyrophoric. One safety measure is the use of wet catalysts; this is usually no problem because the hydrogenation reaction produces water.

Hazards from the Hydrogenation Reaction

The reduction of nitroaromatic compounds is a very exothermic reaction (560 kJ mol^{-1}). When reaction control is lost, decomposition of the aromatic nitro compound or of partially hydrogenated intermediates could be triggered easily.

Hazards Resulting from the High Decomposition Energy of Aromatic Nitro Compounds and Some Intermediates

Aromatic nitro compounds have a high decomposition energy (ca 2000 kJ mol^{-1}). Even though the activation energy is generally also high, the decomposition often follows a self-accelerating mechanism. In solution, in the presence of a metallic catalyst, and especially under basic conditions, decomposition can start at quite low temperatures. The catalytic hydrogenation of nitroarenes involves a series of intermediates, especially *N*-arylhydroxylamines, that can decompose exothermically and trigger the decomposition of the reaction mixture. This can be an acute safety problem under conditions when heat is accumulated, for example due to cooling failures or when the circulation pump fails in loop reactors, because these reactions do not consume hydrogen and therefore cannot be stopped by controlling hydrogen feed or stirring. Accumulation of hydroxylamines must, therefore, be kept to a minimum at all times during the reaction.

Tools for Risk Evaluation

Analytical Methods

The composition of the reaction mixture and especially the accumulation of hydroxylamines can be detected semi-quantitatively by TLC, and quantitatively by HPLC or by NMR; because of the thermal instability of many intermediates, GLC results are usually not reliable. More elegant is in situ monitoring (see below).

Differential Scanning Calorimetry (DSC) [14]

To assess the potential safety problem, isothermal DSC experiments at different temperatures and after different amounts of conversion (Figure 2), preferably in presence of the catalyst, can be used to predict the behavior of the reaction mass in the event of a cooling failure.

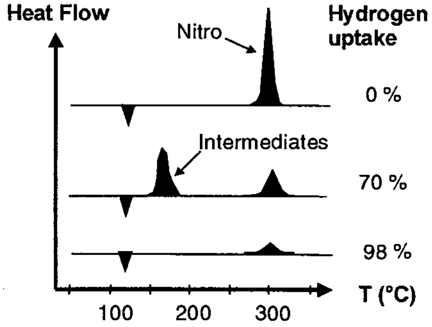


Figure 2. DSC thermograms after different amounts of conversion (adapted from Ref. 14).

Reaction Calorimetry [14,15]

Because reduction of a nitroarene is a multistep process, hydrogen uptake and heat evolution need not occur in parallel, as would be observed for a one-step reaction. Because most of the heat of reaction arises from the formation of the two water molecules (Figure 1), at the hydroxylamine stage two thirds of the total hydrogen have been taken up, whereas only about half of the total reaction heat has been produced. This means that comparing conversions measured via heat flow and hydrogen uptake can provide information about hydroxylamine accumulation. Reaction calorimetry also enables the simulation of the effects of a cooling failure, as illustrated in Figure 3.

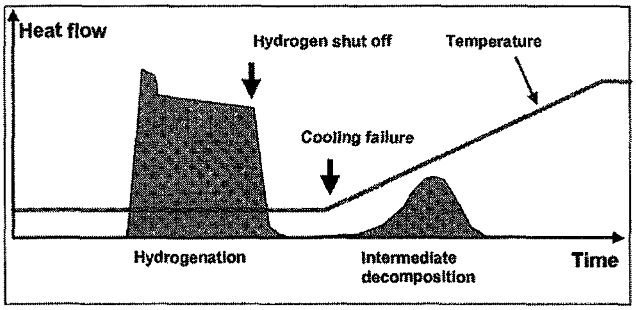


Figure 3. Simulation of a cooling failure (adapted from Ref. 14).

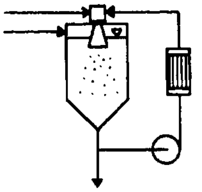
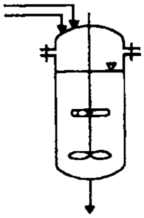
In Situ Monitoring

In situ monitoring of the reaction rate and/or of the intermediate concentration can be useful. Besides calorimetry, other in situ methods suitable for such investigation are measurement of the catalyst potential [16,17] and the use of optical probes [18].

8.5.3.5 Hydrogenation Equipment

As pointed out above, the catalytic hydrogenation of nitro arenes in the fine chemicals industry is usually conducted in the liquid phase. For successful implementation three demands must be met: very good dispersion of the hydrogen gas and the suspended solid catalyst in the reaction solution (efficient gas–liquid mixing and stirring), very effective heat removal (reaction control), and safe handling of the sometimes pyrophoric catalyst and of sometimes toxic starting materials and products. In practice, two reactor types have proven to be capable of meeting these requirements as well as the need for high reliability in operation and ease of control: the stirred autoclave and the loop reactor (Table 1). The loop-reactor enables very efficient hydrogen dispersion and the heat exchanger surface is almost unlimited; it is especially useful when the space–time yield is very high (rapid reaction, high substrate concentration) or when a low reaction temperature is required. The stirred autoclave is probably more versatile; it is more suitable when substrate slurries or viscous media must be used, or when the starting material are added continuously. It is, in addition, usually easier to clean, and space requirements and investment costs are lower.

Table 1. Comparison of the loop reactor and the stirred autoclave.

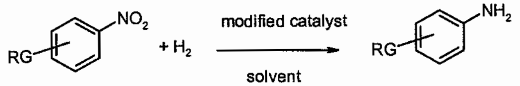
Reactor type	Loop reactor	Stirred autoclave
		
Gas-dispersion	Mixing nozzle (Venturi principle)	Mechanical agitator (hollow-shaft turbine)
Efficiency	High	Medium to high
Heat removal	$> 1300\ \mathrm{W\ m^{-2}\ K^{-1}}$, very high exchange area	$\sim 900\ \mathrm{W\ m^{-2}\ K^{-1}}$, limited exchange area
Problem areas	Circulating pump (viscous slurries), continuous feed addition	Heat-exchange capacity
Recommended for	High performance, dedicated plant	Multi purpose plant

8.5.4 Chemoselective Hydrogenation of Functionalized Nitro Arenes

8.5.4.1 Main Problems, and Overview of the State of the Art

The hydrogenation of simple nitro arenes poses few selectivity problems because the hydrogenation of the aromatic ring is usually much slower with conventional catalysts. The situation is different if other reducible functional groups are present in the molecule. Table 2 gives a very condensed overview of the compatibility of different important functional groups with the hydrogenation of a nitro group. It is apparent that the nature of the catalytic metal and very often the presence of modifiers determine the solution of a particular chemoselectivity problem. Because the selectivity of the unwanted reduction of the second function is usually better at low temperatures and/or with low-activity catalysts, the accumulation of reaction intermediates can become a dominant issue. Here we will not review the literature on this topic in detail but will, on the one hand, refer to the references cited in Table 2 and, on the other hand, summarize results described in two recent publications by the Catalysis Group of Novartis/Ciba–Geigy on new catalysts for the chemoselective hydrogenation functionalized nitro arenes [19] and on suppressing the accumulation of hydroxylamine [20].

Table 2. Selectivity profiles for the hydrogenation of aromatic nitro groups.



RG: Reducible Group

-C≡N, -C≡CH, -CH=NOH
-C=C bonds, .C=O
-Y-benzyl
-Cl, -Br, -I etc.

Metal	Function to be retained Ar–Hal^a		C≡C		C=C^b		C=O		C=N		Y^c-Benzyl	
Pd	$+^{d,e}$	[22] p. 520	–	[21] p. 109	±	[13] p. 193	+	[22] p. 528	+	[22] p. 531	±	[13] p. 200
	–	[22] p. 520				[22] p. 519		[13] p. 194		[13] p. 198		
Pt	$+^{d,e}$	[21] p. 108	+	Section 8.5.4.2.	+	[13] p. 193	+	[22] p. 528	±	[21] p. 110	+	[13] p. 198
		[22] p. 520	$+^f$	[19]				[13] p. 193	+	[13] p. 196		
Ru	$\pm^d$	[22] p. 521	+	[21] p. 109					+	[22] p. 531		
	$\pm^g$	[22] p. 522										
Rh	+	[22] p. 520										
Ni	+	[22] p. 522			+	[13] p. 193	+	[22] p. 528	+	[22] p. 531	+	[13] p. 199
	$+^d$	[18]			±	[22] p. 518		[13] p. 194		[13] p. 196		[22] p. 531

+ = selective, ± = partially selective, – = unselective.

[a] Rate of dehalogenation I > Br > Cl > F.

[b] Rate of double bond hydrogenation: mono > di > tri > tetra substituted.

[c] Y = N, O.

[d] Non-metallic modifier.

[e] Metal sulfides or sulfided metal on support.

[f] Modified with second metal.

[g] Hydrogen transfer process.

8.5.4.2 New Catalyst Systems for the Hydrogenation of a Nitro Group in the Presence of Reducible Functional Groups

As is apparent from Table 2, the chemoselective reduction of nitro groups often requires a modified catalyst system. This approach has a long history which is documented in the reference books cited and is also well described in reviews [1,2] and in a text book by Augustine [24]. Two approaches can be distinguished: modification of the catalyst (ex-situ modification) and addition of modifiers to the reaction mixture (process modifiers). Here, we do not try do give an overview but rather demonstrate the potential of the two approaches with two recent examples from our own laboratories.

Lead-modified Platinum Catalysts: The 'Lindlar Approach' [19]

The idea behind this approach was influenced by the success of the Lindlar catalyst, i. e. modification of the selectivity of a catalyst by addition of a second metal. The catalyst was developed for a herbicide intermediate in collaboration with Degussa AG. In summary, the studies showed that:

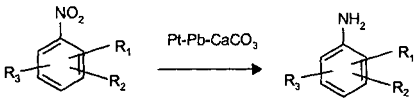
- $CaCO_3$ is the best carrier material, other supports (e. g. charcoal or alumina) led to catalysts with low selectivity;
- the lead content is very important; the optimum lead content is 1 %;
- to obtain reasonable catalytic activity, a reaction temperature $\geq$ 120 °C is necessary;
- the catalysts can be prepared according to the Lindlar procedure [9,10], but reproducibility can sometimes be a problem;
- the polarity of the solvent has a strong influence on both catalyst activity and yield, the best results are obtained with polar solvents;
- addition of small amounts of $FeCl_2$ and tetramethylammonium chloride (TMAC) has a beneficial influence on the rate of hydrogenation, and to a lesser extent on the yield as well.

The preparative scope of the catalytic system is shown in Table 3. Functionalities other than the C=C bond are not reduced. The occasionally low yield is due to the formation of side-products and intermediates. Noteworthy is the high yield of 2,4-diamino-3-chlorobenzonitrile without ring formation with the cyano group (entry 8).

H_3PO_2-modified Pt Catalysts in Presence of Vanadium Promoters

The second catalyst system that evolved during the development work already mentioned was based on the results of a long running research project. Here, the basic idea was to change catalyst selectivity by addition of organic or inorganic compounds to the reaction solution. Process modifiers to enhance catalyst selectivity for the hydrogenation of a variety of substituted nitro compounds had previously been used successfully [23]. The starting point for the novel cata-

Table 3. Scope of the new 'Pt–Lindlar catalyst'.



Entry	R_1	R_2	R_3	Solv.[a]	Temp. [°C]	Time [h]	Yield [%]
3'1	3-$CH{=}CH_2$	H	H	A	120	21	75
3'2	3-$CONHCH_2CH{=}CH_2$	4-Cl	H	B	140	38	70
3'3[b]	3-$COOCH_2C{\equiv}CH$	H	H	A	140	14	65[e]
3'4	4-$CH{=}NOH$	H	H	C	120	8.5	51
3'5[c]	2-NH_2	3-J	5-Cl	B	140	6	>90
3'6[c,d]	2-CH_2CN	5-F	H	B	140	4	75
3'7	2-Br	5-$COCH_3$	H	C	120	37	83
3'8	2-Cl	3-NO_2	5-CN	A	120	19	88[f]

Reaction conditions: $pH_2 = 20$ bar; [5 % Pt-1 % Pb-$CaCO_3$]: 2 % w/w to nitro, [$FeCl_2$: 0.5 mol % to nitro

[a] A = MEK, B = THF/n-PrOH 5:1, C = THF.

[b] 5 % w/w 5 % Pt-1 % Pb-$CaCO_3$.

[c] 20 % w/w 5 % Pt-1 % Pb-$CaCO_3$.

[d] 1.5 mol% $FeCl_2$.

[e] Propargyl/allyl 4:1 (after purification by chromatography).

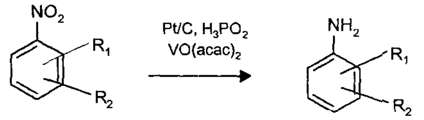
[f] Isolated 2,4-diamino-3-chlorobenzonitrile.

lyst was a paper by Kosak [25], who described Pt/C modified with H_3PO_3 for the selective hydrogenation of iodonitrobenzenes, albeit with substantial accumulation of hydroxylamines. In summary, our studies showed that:

- the best modifier is H_3PO_2; excellent selectivity is also obtained with other additives, e.g. H_3PO_3, $(PhO)_2P(O)H$ and $HPPh_2$; $P(OPh)_3$ and, especially, PPh_3 are less efficient;
- the H_3PO_2 concentration has a substantial effect on rate and selectivity; the critical level was 2.5 %, optimum results were obtained with 5 % relative to the Pt catalyst;
- addition of V-promoters is essential for low hydroxylamine accumulation;
- toluene or toluene–water mixtures are suitable reaction media; in contrast to Pt–Pb–$CaCO_3$, polar and protic solvents were less suitable for Pt–C modified with H_3PO_2.

Table 4 shows selected results for the reduction of a variety of functionalized nitro compounds to the corresponding anilines with this new catalyst system. No reduction of the second function was ever detected; even a C≡C bond remained completely unreduced!

Table 4. Scope of the Pt/C-H_3PO_2 catalyst.



Entry	R_1	R_2	Yield [%]
1	3-$CH=CH_2$	H	95
2	3-COO-$C(CH_3)_2COOCH_2CH=CH_2$	4-Cl	98
3	3-$CH=CH$-$COOH$	H	95
4	3-$COOCH_2C\equiv CH$	H	99
5	Br	$COCH_3$	93
6	4-$CH=NOH$	H	> 50

Reaction conditions: [5 % Pt/C]: 1 % *w/w* of substrate; [H_3PO_2]: 10 % *w/w* of catalyst; [$VO(acac)_2$]: 16 % *w/w* of catalyst; solvent: toluene; *T*: 100 °C; *p*: 5 bar H_2.

8.5.4.3 Accumulation of Hydroxylamine

As remarked above, hydroxylamines are problematic, because of their potential strongly exothermic decomposition [26]. They are also known to be highly carcinogenic and are therefore hazardous after interrupted or incomplete hydrogenation [27]. Hydroxylamine accumulation can also lead to low product quality because reaction with the nitroso compound gives colored azo or azoxy condensation products (as mentioned above). The maximum concentration of hydroxylamines can vary and is notoriously difficult to predict; product quality can, therefore, differ from batch to batch. The suppression of hydroxylamine accumulation is therefore a topic of industrial importance. In a recent publication we reported that the addition of vanadate and other metal salts can drastically reduce accumulation of hydroxylamines in the hydrogenation of nitroarenes catalyzed by commercial Pt and Pd catalysts [20].

The results can be summarized as follows:

- The addition of promoters, especially vanadium salts, had a dramatic effect on the course of the hydrogenation of several nitroarenes. Occasionally the maximum level of hydroxylamine accumulation was reduced from > 40 % to < 1 % with NH_4VO_3 or V/Pd/C. Salts of Fe, Co, Cu, and Tl also reduced the hydroxylamine level but were less effective. Other metals salts had no effect.
- The over-all reaction with vanadium promoter was usually faster than without, whereas other successful promoters led to a somewhat slower reaction. Products obtained with efficient promoters were whiter (cleaner) than those without.

- Significant effects were achieved merely by adding small amounts of vanadium salts to the hydrogenation mixture. Deactivation of the Pt or Pd catalysts by vanadium salts was sometimes observed. By depositing the promoter on charcoal, the problem could be partially solved. It is also possible to impregnate the Pd/C or Pt/C catalyst with a vanadium salt.

8.5.4.4 Partial Hydrogenation of Nitroarenes

The accumulation of intermediates, described above as a serious problem, can be turned to advantage if partially hydrogenated products such as hydroxylamines, *p*-aminophenols (the respective Bamberger rearrangement products), azoxy arenes, or hydrazo arenes are needed. Again similar strategies of catalyst modification turned out to be successful, for details we recommend the overviews by Augustine [24a] and Strätz [1]. Ir catalysts that produce hydroxylamines in good yields have recently been described [28].

8.5.5 Mechanistic Concepts in the Hydrogenation of Nitroarenes

8.5.5.1 General

The reduction sequence depicted in Figure 1 can be formulated as a series of electron- and proton- transfer reactions. For reduction at heterogeneous surfaces there is strong evidence that the dissolved reactants and intermediates and the corresponding species adsorbed on the metal surface are in dynamic equilibrium. The specific reaction pathway of a transformation depends on many factors, e. g. the nature of the nitro arene, the catalyst and the solvent, the presence of a base, etc.

During a typical hydrogenation reaction, only the starting nitro arene, the hydroxylamine and the aniline product are usually detected in solution. The maximum concentration observed for the hydroxylamine intermediate depends on substrate structure, reaction temperature, hydrogen pressure, solvents, catalysts, and pH, etc. High accumulation is observed with electron-deficient aromatic systems, at low temperature and high hydrogen pressure. The nitroso intermediate is only present at very low concentrations because it adsorbs strongly and further reaction is very fast. The same is true for the azo and azoxy condensation products, except when a strong base is present and sometimes for very slow reactions. Once formed, their reduction to the aniline is not easy, because the last step, hydrogenolysis of the N–N bond of the hydrazo compound is slow and requires elevated temperatures and pressures. Because condensation compounds are often colored, they strongly affect the quality of the products.

Kinetic investigations have been reported for the hydrogenation of a variety of substrates [29,30]. Typically, the reaction is between zero- and first-order for hydrogen and, especially at higher concentrations of nitro arene, zero-order in substrate. A Langmuir–Hinshelwood approach (reversible adsorption of reactants and intermediates on the metal surface) is usually chosen for kinetic analysis, quite often with good agreement.

8.5.5.2 Mode of Action of Modifiers

As described below, modifiers and promoters can play an important role in achieving highly selective hydrogenation of nitro arenes. For this reason, some ideas relating to their mode of action will briefly be discussed here.

Promoters that Reduce the Accumulation of Hydroxylamine [20]

Catalytic hydrogenations of aromatic nitro compounds with a stable hydroxylamine intermediate often have two different kinetic phases: hydrogen uptake is rapid up to ca 60 %, then distinctly slower in the second phase. This means that reduction of the hydroxylamine to the aniline, formally a hydrogenolysis, is difficult in these cases. In the presence of the promoters discussed in Section 8.5.4.3, the second phase is less pronounced or disappears. This suggests a mechanism which could be called ‘catalytic by-pass’ (see Figure 4). Experiments in the absence of hydrogen indicated that the vanadium promoters catalyze the disproportionation to give aniline and the nitroso intermediates that re-enter the catalytic cycle. As a consequence, the hydroxylamine does not accumulate and aniline formation is accelerated.

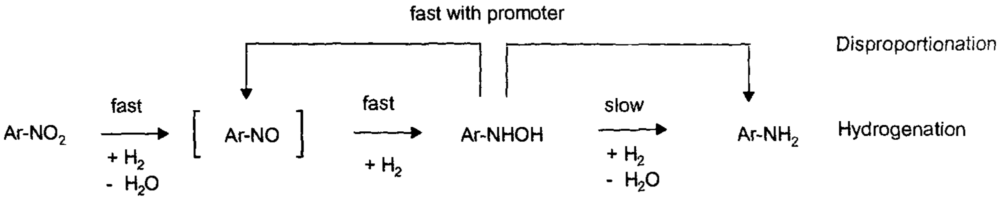


Figure 4. Effect of promoters on the reaction of hydroxylamines.

Modifiers that Increase Chemoselectivity [19]

Although nitro groups are very electropositive and easy to reduce, classical hydrogenation catalysts reduce most other functional groups as well (see Section 8.5.4). Because nitro arenes are adsorbed rather strongly by the catalyst surface, reduction of the other reducible groups normally starts only when all nitro groups have been consumed. Parallel competing reactions have, however, also been observed. The addition of sulfur-, phosphorus-, nitrogen-, or halogen-containing modifiers often furnishes more selective catalysts, although very often with lower activity. A common viewpoint is that such compounds are preferentially adsorbed reversibly or irreversibly by the most reactive sites (which are also thought to be the most unselective), thereby hindering adsorption and unselective hydrogenation. Other possible consequences of adsorption are the formation of isolated (smaller ensembles) or electronically altered sites. Needless to say, these explanations are not easy to confirm experimentally and are therefore more of a heuristic nature.

For very irreversibly adsorbed species or inactive metals which can form a compact over-layer on the active metal, another mode of action can be discussed. We will use Pt/Pb/$CaCO_3$ [19] as an example. There are many indications that the best effects are observed when a thin but complete layer of lead is deposited on top of the platinum. This prevents the adsorption of nitro and other reducible groups on active sites of Pt whereas the smaller hydrogen molecule can still reach the Pt and dissociate. Because the nitro group is a very strong oxidant, it can be reduced in the double layer without adsorption on the active surface (electrochemical mechanism) [31]. The hydrogenation of most other reducible functions however, can only proceed via a classical mechanism that requires adsorption on the active site on Pt. This hypothesis is in agreement with the effect of the Pt/Pb ratio, promotion by Cl^- anions, and the fact that polar solvents are needed for high activity.

8.5.6 Alternative Commercial Methods of Reduction

8.5.6.1 Béchamp Reduction

The Béchamp reduction, i. e. the use of stoichiometric amounts of finely divided iron metal, is the most important and established alternative to catalytic hydrogenation. It is a simple and robust reduction system and the technology is well established for the large-scale production of a variety of aromatic amines. The selectivity profile is somewhat broader than for catalytic hydrogenation. In contrast with catalytic hydrogenation, inhibition of the reaction by impurities and accumulation of thermally unstable intermediates seldom occur. A distinct disadvantage is the formation of environmentally problematic iron oxide sludges (250–500 g mol^{-1} nitro) that are difficult to filter, always contain adsorbed reaction product, and are therefore a disposal problem. In addition, the Béchamp reduction must be conducted in aqueous media which limits its applicability because of solubility problems or because of hydrolysis of other functional groups.

8.5.6.2 Sulfide Reduction

Sulfide reduction has an even broader selectivity profile than catalytic hydrogenation or the Béchamp reduction and enables the chemoselective reduction of nitro compounds in presence of C=C, azo, or other nitro groups. The method is insensitive to by-products and high levels of impurities. Depending on pH, different reduction agents with the following stoichiometries are applicable:

$$\begin{array}{ll} pH \sim 7: & 3H_2S + ArNO_2 \rightarrow ArNH_2 + 2H_2O + 3S^0 \\ pH < 7: & 6NaHS + 4ArNO_2 + H_2O \rightarrow 4ArNH_2 + 3Na_2SO_3 \\ pH > 7: & 6Na_2S + ArNO_2 + H_2O \rightarrow 4ArNH_2 + 6NaOH + 3Na_2SO_3 \end{array}$$

The major disadvantages (and the reason it is very seldom used today) are the toxicity and odor of most reducing agents and sulfur-containing organic side-products, and the formation of elemental sulfur.

8.5.6.3 Comparison of Reduction Methods

Reduction methods are compared in Table 5.

Table 5. Comparison of several properties of catalytic hydrogenation, and Béchamp and sulfide reduction.

	Catalytic hydrogenation	Béchamp reduction	Sulfide reduction
Selectivity	Broad scope with special catalytic systems	Restricted scope	Broad scope
Synthetic potential	Broad	Broad	Narrow
Combination with other reactions	Possible	Not possible	Not possible
Starting material	Sensitive to catalyst poisons	Robust	Very robust
Reaction medium	Organic solvents and aqueous media	Aqueous media	Aqueous media
Reaction conditions	10–100 % *v/v* 20–150 °C	10–25 % *v/v* 80–100 °C	20–40 % *v/v* 30–160 °C
Development effort	Complex; high development costs	Relatively simple	Not problematic
Logistics	Transport and storage of hydrogen	Not critical	Not critical
Reaction characteristics	Heat removal 560 kJ mol^{-1} Catalyst separation	Heat removal ca 280 kJ mol^{-1} Separation of large amounts of solids	Separation of (soluble) oxidized sulfur compounds
Reactors	High pressure reactors and equipment	Standard stirred tank (acid resistant)	Standard stirred tank
Safety	Handling of hydrogen and pyrophoric catalysts Accumulation of thermally unstable intermediates	Formation of hydrogen possible	Formation of H_2S
Ecology	Environmentally friendly No critical wastes	Disposal of Fe sludge Large amounts of critical waste water	Large amounts of critical waste water

8.5.7 Conclusions and Recommendations

As can be seen from the comparison in Table 5, the catalytic hydrogenation of nitroarenes is the most versatile, effective, economical, and ecological method for producing a variety of substituted anilines. As a general rule, commercial heterogeneous catalysts are well suited to the reduction of simple nitro arenes. Recent progress with modified catalyst systems has greatly expanded the scope of the hydrogenation methodology and most chemoselectivity problems have been solved.

The catalytic hydrogenation of nitro arenes nevertheless has some peculiarities, especially process safety, that require thorough understanding of the technology. We strongly recommend that the development of production processes is performed by teams with good experience of catalysis or by service companies that offer the development of such catalytic reactions [32].

References

[1] A. M. Strätz, Catalysis of Organic Reactions, Chem. Ind. (Dekker) 18 (1984) 335.
[2] R. S. Downing, P. J. Kunkeler, H. van Bekkum, Catalysis Today 37 (1997) 121.
[3] F. Haber, Z. Elektrochemie 22 (1898) 506.
[4] H. U. Blaser, Modern Synthetic Methods, B. Ernst, Ch. Leumann (eds.), Verlag Helvetica Chimica Acta, Basel, 1995, p. 179.
[5] G. G. Ferrier, F. King, Platinum Metal Reviews 27 (1983) 72.
[6] E. Auer, A. Freund, M. Gross, R. Hartung, P. Panster, Chem. Ind. (Dekker) 75 (1999) 551.
[7] H. Bönnemann, W. Wittholt, J. D. Jentsch, A. Schulze Tilling, New J. Chem. (1998) 713
[8] W. Yu, M. Liu, H. Liu, X, An, Z. Liu, X. Ma, J. Mol. Cat. A: Chemical 142 (1999) 201.
[9] X. Yang, Z. Deng, H. Liu, J. Mol. Cat. A: Chemical 144 (1999) 123.
[10] S. Cao, S. Xu, S. Xu, Polym. Adv. Tech. 10 (1999) 43.
[11] M. Islam, A. Bose, D. Mal, C. R. Saha, J. Chem. Res. (S) (1998) 44.
[12] M. Lauwiner, P. Rys, J. Wissmann, Applied Catalysis A: General 172 (1998) 141.
[13] M. Freifelder, Practical Catalytic Hydrogenation, Wiley–Interscience, New York, 1971.
[14] F. Stoessel, J. Loss Prev. Process Ind. 6 (1993) 79.
[15] C. LeBlond, J. Wang, R. Larsen, C. J. Orella, A. L. Forman, F. P. Gortsema, T. R. Verhoeven, Y.-K. Sun, Stud. Surf. Sci. Catal. 108 (1997) 247.
[16] T. Mallat, A. Baiker, Topics in Catalysis 8 (1999) 115.
[17] A. Kretschmer, H. Ehwald, G. Alscher, Chem. Tech. 48 (1996) 163.
[18] M. Studer, A. Zilian, Novartis Services AG, unpublished results.
[19] P. Baumeister, H. U. Blaser, U. Siegrist, M. Studer, Chem. Ind. (Dekker) 75 (1998) 207.
[20] P. Baumeister, H.-U. Blaser, M. Studer, Catal. Lett. 49 (1997) 219.
[21] P. N. Rylander, Hydrogenation Methods, Academic Press, Bench top Edition, New York, 1990.
[22] Houben–Weyl, Methoden der Organischen Chemie, Reduktionen I, Vierte Auflage, Band IV/1c, Georg Thieme Verlag, Stuttgart, 1980.
[23] P. Baumeister, H. U. Blaser, W. Scherrer, Stud. Surf. Sci. Catal. 59 (1991) 321.
[24] R. L. Augustine, Heterogeneous Catalysis for the Synthetic Chemist, Marcel Dekker, Inc., New York, Basel and Hong Kong, 1996. (a) p. 408.
[25] J. R. Kosak, Catalysis in Organic Synthesis, W. H. Jones (ed.), Academic Press, New York, 1980, p. 107.
[26] W. R. Tong, R. L. Seagrave, R. Wiederhorn, AICHE Loss Prev. 11 (1977) 71.
[27] J. A. Miller, Cancer Res. 3 (1970) 559.
[28] V. I. Savchenko, I. A. Makaryan, V. G. Dorokhov, Platinum Metal Reviews 41 (1997) 176.

[29] For a typical example see V. R. Choudary, M. G. Sane, S. V. Tambe, Ind. Eng. Chem. Res. 37 (1998) 3879.
[30] G. Neri, M. G. Musolino, L. Bonaccorsi, A. Donato, L. Mercadante, S. Galvagno, Ind. Eng. Chem. Res. 36 (1997) 3619.
[31] M. Heyrovsky, S. Vavricka, J. Electroanal. Chem. 28 (1970) 411.
[32] H. U. Blaser, M. Studer, Chimia 53 (1999) 261.

8.6 Catalytic Hydrogenation of Aromatic Rings

J. G. Donkervoort, E. G. M. Kuijpers

8.6.1 Introduction

The field of arene hydrogenation chemistry will soon enter its second century. The initial work of Sabatier on the interaction of finely divided nickel with ethylene and hydrogen gas led to the development of the first active catalyst for the hydrogenation of benzene. Sabatier was awarded the Nobel prize for his work in 1912 [1]. After Sabatier's work, a variety of non-supported heterogeneous catalysts for arene hydrogenation was developed, of which Adam's [2] and Raney's catalysts [3] are of great historical significance. Nowadays, more efficient utilization of expensive metals calls for the deposition of the metal or its precursor on to suitable supports.

Traditionally, the area of hydrogenation catalysis has been attracting much attention because of its technological importance in petroleum refining and reforming processes [4]. Over the past two decades, hydrogenation catalysts have also become increasingly important in the industrial production of fine chemicals. The last area will be the main focus of this chapter.

It is not an objective of this paper to provide an elaborate literature survey on heterogeneous aromatic hydrogenation. For that, reference is made to a book by Augustine [5]. Rather it is intended to present several typical examples of arene hydrogenation with some recent literature and industrially relevant developments.

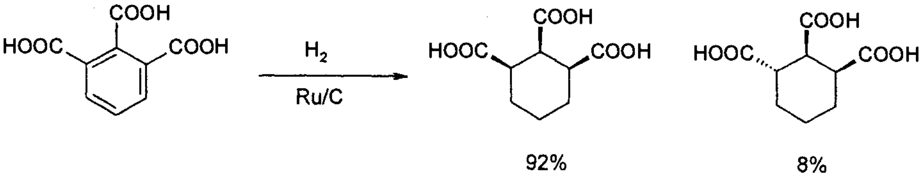
8.6.2 Intermediates and Mechanism

The mechanism of aromatic hydrogenation is still the subject of extensive research. Most of the work presented describes hydrogenation as proceeding through parallel adsorption of the aromatic ring on the metallic surface, by interaction of the π-electrons of the aromatic ring with empty d-orbitals of the metal [6]. The successive transfer of hydrogen atoms from the metal surface to the adsorbed aromatic ring and subsequently adsorbed intermediates, i. e. cyclohexadiene and cyclohexene, finally results in the fully saturated ring system [7]. Although cyclohexene formation has been observed (cf. Section 8.6.3), no cyclohexadienes have yet been detected as intermediates [8]. Several explanations have been proposed to explain why formation of a diene on the metal is by-passed, e. g. the concept of kinetic coupling between the elementary steps [8c,9] or the hypothesis of an aromaticity rule as an expansion of Baladin's multiplet theory [8d,e].

8.6.3 Hydrogenation of Benzene Derivatives

In general, the hydrogenation of arenes is accomplished by use of a Group VIII metal, the rate of hydrogenation depending on the metal used, i. e. Rh > Ru > Pt > Ni > Pd > Co [10]. Not only does the type of metal influence activity in aromatic hydrogenation, but the nature of the support also. For example, the specific rate observed in the hydrogenation of benzene and toluene with Pt and Pd is higher on acidic supports than on neutral or basic supports. Several models have been proposed which ascribe this enhanced activity to a metal–support interaction which alters the electronic and chemical properties of the dispersed metal [11], and several materials obtained by attaching organometallic compounds to oxide surfaces have recently been shown to be highly active arene hydrogenation catalysts [12].

Hydrogenation of multiply substituted aromatic rings can lead to the formation of a variety of stereoisomers. The nature of the carrier, type of metal, solvent, temperature, and pressure influence the amount of stereochemical induction. Hydrogenation of such functionalized arenes usually leads to predominantly the *cis*-substituted product. This is readily explained in terms of the mechanism proposed for aromatic hydrogenation (vide supra). For example, the use of Ru/C enables hydrogenation of a trisubstituted benzoic acid into the corresponding *cis* product with high stereoselectivity (Scheme 1) [13]. It is supposed that the other isomer shown is formed by desorption and re-adsorption of 1-cyclohexene-1,2,3-tricarboxylic acid. In general, stereochemical control is reduced as the substituents on the arene are positioned further apart [4,14].



Scheme 1.

The synthesis of enantiopure cyclohexane derivatives has been investigated by hydrogenating arenes by use of chiral auxiliaries bound either to the support of the catalyst or to the substrate, or by use of chiral phase-transfer reagents [15]. Although significant progress has been reported, enantioselectivity is still moderate (maximum 68 % e. e.).

The partial hydrogenation of an arene to its cyclohexene derivative is difficult to achieve, because complete hydrogenation to cyclohexane tends to occur. Often the use of a Ru/C catalyst can solve this problem, because Ru is not very effective at hydrogenating olefinic double bonds. In other reactions selectivity of Pt/C and Rh/C has also been high [16]. In general, reducing the availability of hydrogen increases the selectivity towards the formation of cyclohexene. The presence of water has been shown to be essential for obtaining cyclohexene in reasonable yield [17], and other modifiers have also been reported to result in improved selectivity [18].

In recent years the Asahi Corporation has developed a benzene-to-cyclohexene process involving a liquid–liquid two-phase system (benzene–water) with a solid ruthenium catalyst dispersed in the aqueous phase. The low solubility of cyclohexene in water promotes rapid transfer towards the organic phase. An 80 000 t annum^{-1} plant using this process is in operation. Another way to scavenge the intermediate cyclohexene is to support the metal hydrogenation catalyst on an acidic carrier (e. g. silica–alumina). On such a bifunctional catalyst the cyclohexene enters catalytic alkylation of the benzene (present in excess) to yield cyclohexylbenzene [19], which can be converted, by oxidation and rearrangement reactions, into phenol and cyclohexanone.

8.6.4 Hydrogenation of Polycyclic Aromatic Ring Systems

Raney nickel and platinum, palladium, and rhodium catalysts have been used to accomplish the hydrogenation of polycyclic aromatics. Hydrogenation of fused polycyclic arenes leads to the *cis*- or *trans*-substituted cyclohexane derivatives. The *cis* product is usually obtained; again this can be understood in terms of the mechanism proposed for aromatic hydrogenation (vide supra).

cis-Decalin is used for the industrial production of sebacic acid, a starting material for Nylon-6,10 and softeners [20]. By use of Pt supported on zeolites, *cis*-decalin is produced from naphthalene with over 80 % selectivity under mild reaction conditions [21]. This high selectivity is not just a simple function of zeolite pore structure–the presence of acidic sites and the type of metal used were also found to be important. Control of the selectivity by the nature of the metal used is evidenced by the high selectivity of alumina-supported Pt catalysts (ESCAT 24) [22]. With other than Pt catalysts, e. g. Ru/C, more severe reaction conditions are required, although even higher stereoselectivities (> 95 %) are achievable [23].

Solvent effects are sometimes important in the hydrogenation of substituted naphthalenes, e. g. 2-naphthol [24]. Use of Rh-on-alumina catalysts in acetic acid results in a mixture of decalone and *cis*-decalol, whereas changing the solvent to methanol or ethanol gives *cis*-decalol as the predominant product.

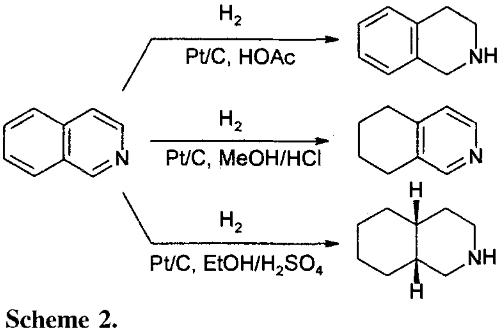
Polycyclic aromatic rings are, in general, sequentially hydrogenated, enabling hydrogenation of just one of the rings present. For example, tetralin is selectively prepared from naphthalene by use of platinum catalysts [5] or sulfur-passivated noble metals supported on zeolites [25]. Interestingly, 100 % selectivity is obtained when Cu catalysts are used [26]. Several reports have been published on the subject of directing partial hydrogenation toward one of the aromatic rings. Many factors influencing this selectivity have been reported; these include steric effects of the substituents [27], solvent pH [28], and other reaction conditions [29].

8.6.5 Hydrogenation of Nitrogen-containing Aromatic Ring Systems

Platinum catalysts are usually used in the hydrogenation of nitrogen-containing aromatic rings. Mild reaction conditions can be used, but an acidic medium is necessary. Acidification results in the formation of the corresponding protonated nitrogen complex, which is more readily hydrogenated than the free base [30]. In addition, basic amine functionality is removed; this would otherwise coordinate to the metal, thereby poisoning the active sites. Under the appropriate experimental conditions, the hydrogenation of a pyridine ring can be accomplished selectively, even in the presence of carbonyl, cyano, benzene, and indole groups. If hydrogenolysis or N-alkylation can occur as an undesirable side-reaction, ruthenium catalysts should be used [31], and palladium catalysts also have been reported to give good results.

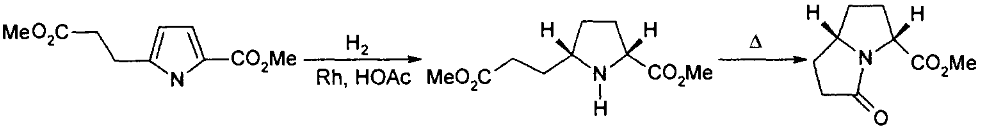
Multiply substituted pyridines can be hydrogenated under a variety of reaction conditions with high levels of stereocontrol, to give mainly the *cis* product [32]. This is illustrated by the preparation of enantiomerically pure sedrine and conhydrine by use of platinum catalysts [33].

Quinoline and isoquinoline ring saturation can be directed towards any of the two rings. For example (Scheme 2), when a platinum catalyst is used in acetic acid the hydrogenation of isoquinoline results in saturation of the nitrogen-containing aromatic ring. Changing the solvent to methanolic hydrogen chloride results in hydrogenation of the other aromatic ring and use of ethanol in combination with sulfuric acid results in saturation of both aromatic rings. Under the latter reaction conditions, especially when using Ru catalysts, the *cis* product is formed preferentially. In contrast, the *trans* product is predominantly formed when nickel catalysts are used.



Scheme 2.

For the hydrogenation of pyrroles, palladium and rhodium catalysts can be used besides platinum, under 3 to 4 atm of hydrogen. Electron-deficient pyrroles can even be hydrogenated at atmospheric pressure. Multiply-substituted pyrroles are hydrogenated by use of platinum or rhodium catalysts to give the *cis* product only [34]. This method has, for example, been used in the synthesis of a pyrrolidizine carboxylic acid derivative (Scheme 3), a possible agent of the angiotensin-converting enzyme [35], and in the synthesis of Anatoxin *a* [36].



Scheme 3.

The hydrogenation of indoles is rather difficult and is normally achieved by use of Raney nickel at high temperatures and pressures. Either of the two rings may be saturated, depending on the conditions employed, and on the substitution pattern of the indole. The presence of a substituent on one of the two rings promotes reduction of the other ring. Stereochemical control of this type of reaction is not observed except for tricyclic systems [37].

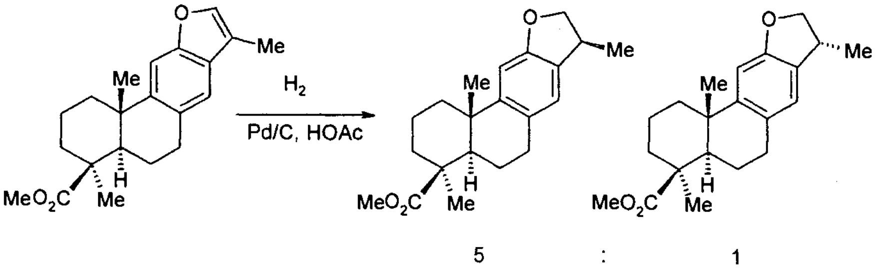
The presence of a stereogenic center influences the stereochemical outcome of the hydrogenation. This effect has been used to prepare a series of enantiomerically pure, naturally occurring pyrrolidizine and indolidizine alkaloids [38]. It seems that a substituent on the non-aromatic ring affects the adsorption side of the pyrrole ring thereby directing the stereochemical outcome of the hydrogenation.

8.6.6 Hydrogenation of Oxygen- and Sulfur-containing Aromatic Ring Systems

In general, Raney nickel at ambient temperature and 3 to 4 atm hydrogen are used for hydrogenation of unsubstituted furans. For substituted furans higher temperatures and pressures are needed, but ring-opening can occur concomitantly [39]. To prevent ring-opening side reactions, rhodium [40] or ruthenium [41] catalysts can be used; with multiply-substituted furans these catalysts have the additional advantage that predominantly the *cis* product is formed upon hydrogenation [40]. Rhodium catalysts have, for example, been used to prepare enantiomerically pure 1,4-disubstituted tetrahydrofurans and nonactin [41c–f].

Benzofuran is completely hydrogenated by use of rhodium catalysts to give mainly the *cis* stereoisomer [42]. If Pd/C in acetic acid is used, partial hydrogenation of the oxygen-containing ring can be accomplished.

Scheme 4 shows an example of the partial, stereospecific hydrogenation of a tetracyclic system containing several chiral centers [43].



Scheme 4.

Because of the strong coordination of sulfur to metal surfaces, sulfur-containing molecules are very effective catalyst poisons. Nevertheless, a few examples of the hydrogenation of such molecules have been reported. Thiophene can be hydrogenated to tetrahydrothiophene by use of rhenium heptasulfide [44] under harsh conditions (250 °C and 300 atm hydrogen) or with a large excess of palladium in methanolic sulfuric acid [45]. In the synthesis of biotin, stereoselective *cis*-hydrogenation of a tri-substituted thiophene was achieved with Pd/C in acetic acid [46].

8.6.7 Concluding Remarks

Several methods have been presented for the selective hydrogenation of aromatic rings. As industrial products become more complex, however, further methods are needed for the selective organic transformations required in the production of chemical intermediates and fine chemicals. Of special interest are sulfur-tolerant catalysts and catalysts for the synthesis of chiral complexes. Future research should focus on either of these areas. Much is expected from novel catalysts obtained by immobilizing homogeneous complexes.

Acknowledgments

The authors would like to thank Dr K. van Gorp and Dr J. A. M. Brandts for their contributions to the manuscript. Dr M. Vaarkamp and Ing. W. Dijkstra performed the experimental work leading to unpublished results obtained at the Engelhard De Meern laboratories.

References

[1] P. Sabatier, *Ind. Eng. Chem.* **1926**, *18*, 1004.
[2] (a) R. Adams, J. R. Marshall, *J. Am. Chem. Soc.* **1928**, *50*, 1970; (b) V. Voorhees, R. Adams, *J. Am. Chem. Soc.* **1922**, *44*, 1397.
[3] M. Raney, *Ind. Eng. Chem.* **1940**, *32*, 1199.
[4] P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, **1985**.
[5] R. L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist*, Marcel Dekker Inc., New York, **1996**.
[6] (a) R. Gomez, G. Del Angel, C. Damion, G. Corro, *React. Kinet. Catal. Lett.* **1979**, *11*, 137; (b) T. T. Phuong, J. Massardier, P. Gallezot, *Bull. Soc. Chim. Fr.* **1985**, 456; (c) J. Bandiera, P. Meriavdeau, *React. Kinet. Catal. Lett.* **1988**, *37*, 373.
[7] (a) J. A. Don, J. J. F. Scholten, *Faraday Discuss. Chem. Soc.* **1981**, *72*, 145; (b) S. Siegel, J. F. Outlaw Jr., N. Garti, *J. Catal.* **1979**, *58*, 370.
[8] (a) S. T. Lin, D. L. Wharry, R. L. Yates, N. Garti, S. Siegel, *Abstracts, 192nd ACS Chem. Meeting*, **1986**; (b) J. F. Outlaw Jr., J. R. Cozort, N. Garti, S. Siegel, *J. Org. Chem.* **1983**, *48*, 4186; (c) M. C. Schoenmaker-Stolk, J. W. Verwijs, J. A. Don, J. J. F. Scholten, *Appl. Catal.* **1987**, *29*, 73; (d) M. I. Temkin, D.Yu. Murzin, N. V. Kul'kova, *Kinet. Catal.* **1989**, *30*, 637; (e) S. Smeds, T. Salmi, D. Yu. Murzin, *React. Kinet. Catal. Lett.* **1998**, *63*, 47.
[9] M. Boudart, *J. Phys. Chem.* **1983**, *87*, 2786.
[10] P. N. Rylander, D. R. Steel, *Engelhard Ind. Tech. Bull.* **1962**, *3*, 19.

[11] (a) G. Larsen, G. H. Haller, *Catal. Lett.* **1989**, *3*, 103; (b) B. L. Mojet, M. J. Kappers, J. C. Muijsers, J. W. Niemantsverdriet, J. T. Miller, F. S. Modica, D. C. Koningsberger, *Studies in Surface Science and Catalysis, 84B, Zeolites and Related Microporous Materials: State of the Art 1994*, (Eds. J. Weitkamp, H. G. Karge, H. Pfeifer, W. Hölderich), Elsevier, Amsterdam, **1994**, 909; (c) W. M. H. Sachtler, A. Y. Stakheev, *Catal. Today* **1992**, *12*, 283; (d) A. P. J. Jansen, R. van Santen, *J. Phys. Chem.* **1990**, *94*, 6764.

[12] (a) M. S. Eisen, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 10358; (b) R. D. Profilet, A. P. Rothwell, I. P. Rothwell, *J. Chem. Soc., Chem. Commun.* **1993**, 42.

[13] S. N. Balasubrahmanyam, N. Balasubrahmanyam, *Tetrahedron* **1973**, *29*, 683.

[14] R. D. Schuetz, L. R. Caswell, *J. Org. Chem.* **1962**, *27*, 486.

[15] (a) M. Besson, P. Gallezot, C. Pinet, S. Neto, *Heterogeneous Catalysis and Fine Chemicals IV*, (Eds. H. U. Blaser, A. Baiker, R. Prins), Elsevier, **1997**, p. 215; (b) C. Exl, E. Ferstl, H. Hoenig, R. Ragi-Kohlenprath, *Chirality* **1995**, *7*, 211.

[16] H. van Bekkum, H. M. A. Buurmans, G. van Minnen-Pathuis, B. M. Wepster, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 779.

[17] C. U. I. Odenbrand, S. T. Lundin, *J. Chem. Technol. Biotechnol.* **1981**, *31*, 660.

[18] (a) S. Niwa, F. Mizukami, M. Kuno, K. Takeshita, H. Nakamura, T. Tsuchiya, K. Shimizu, J. Imamura, *J. Mol. Catal.* **1986**, *34*, 247; (b) O. Mitsui, Y. Fukuoka, US 4.678.861 (**1987**); (c) *Chem. Abstr.* **1987**, *107*, 77344; (d) M. Soede, E. J. A. X. van de Sandt, M. Makkee, J. J. F. Scholten, *Stud. Surf. Sci. Catal.* **1993**, *78*, 345.

[19] L. H. Slaugh, J. A. Leonard, *J. Catal.* **1969**, *13*, 385.

[20] K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, VCH, Weinheim, **1997**, p. 239.

[21] A. W. Weitkamp, *Adv. Catal.* **1968**, *18*, 41.

[22] A. S. Schmitz, G. Bowers, C. Song, *Catal. Today* **1996**, *31*, 45.

[23] Engelhard internal report.

[24] A. I. Meyers, W. Bevering, G. Garcia-Munoz, *J. Org. Chem.* **1964**, *29*, 3427.

[25] C. Song, A. D. Schmitz, *Energy & Fuels* **1997**, *11*, 656.

[26] Engelhard internal report.

[27] T. J. Nieuwstad, P. Klapwijk, H. van Bekkum, *J. Catal.* **1973**, *29*, 404.

[28] (a) G. Stork, *J. Am. Chem. Soc.* **1947**, *69*, 576; (b) H. A. Arbit, *J. Am. Chem. Soc.* **1946**, *68*, 1662; (c) D. M. Musser, H. Adkins, *J. Am. Chem. Soc.* **1938**, *60*, 664.

[29] (a) H. Adkins, H. Krsek, *J. Am. Chem. Soc.* **1948**, *70*, 412; (b) H. J. Dauben, B. C. McKusick, G. B. Mueller, *J. Am. Chem. Soc.* **1948**, *70*, 4179; (c) W. E. Bachmann, J. Contoulis, *J. Am Chem. Soc.* **1951**, *73*, 2636; (d) L. F. Fieser, R. N. Jones, *J. Am. Chem. Soc.* **1938**, *60*, 1940; (e) W. G. Dauben, C. F. Hiskey, A. H. Markhart Jr., *J. Am. Chem. Soc.* **1951**, *73*, 1393; (f) S. Nishimura, S. Ohbuchi, K. Ikeno, Y. Okada, *Bull. Chem. Soc., Jpn.* **1984**, *57*, 2557.

[30] R. R. Burtner, J. M. Brown, *J. Am. Chem. Soc.* **1947**, *69*, 630.

[31] M. Friefelder, G. R. Stone, *J. Org. Chem.* **1961**, *26*, 3805.

[32] (a) G. G. Ayerst, K. Schofield, *J. Chem. Soc.* **1958**, 4097; (b) Y. Sato, T. Iwashigo, T. Miyadera, *Chem. Pharm. Bull.* **1960**, *8*, 427; (c) G. Lunn, E. B. Sansone, *J. Org. Chem.* **1986**, *51*, 513.

[33] (a) G. A. Cooke, G. Fodor, *Can. J. Chem.* **1968**, *46*, 1105; (b) G. Fodor, E. Bauerschmidt, J. Cymerman Craig, *Can. J. Chem.* **1969**, *47*, 4393.

[34] H. P. Kaiser, J. M. Muchowski, *J. Org. Chem.* **1984**, *49*, 4202.

[35] W. W. Turner, *J. Heterocycl. Chem.* **1986**, *23*, 327.

[36] H. A. Bates, H. Rapoport, *J. Am. Chem. Soc.* **1979**, *101*, 1259.

[37] (a) I. Butula, R. Kuhn, *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 208; (b) S. A. Montie, R. R. Schmidt III, *Tetrahedron* **1971**, *27*, 3331; (c) Y. Nagai, A. Irie, Y. Masuda, M. Oka, H. Uno, *J. Med. Chem.* **1979**, *22*, 677.

[38] (a) H. Kato, E. Koshinaka, N. Ogawa, K. Yamagishi, K. Mitani, S. Kubo, M. Hanaoka, *Chem. Pharm. Bull.* **1980**, *28*, 2194; (b) C. W. Jefford, K. Sienkiewicz, S. R. Thornton, *Helv. Chim. Acta* **1995**, *78*, 1511.

[39] (a) R. Paul, G. Hilly, *Compt. Rend.* **1939**, *208*, 359; (b) W. N. Haworth, W. G. M. Jones, L. F. Wiggins, *J. Chem. Soc.* **1945**, 1.

[40] J. A. Moore, J. E. Kelly, *Org. Prep. Proc. Int.* **1972**, *4*, 289; (b) J. E. Semple, M. M. Loullie, *Heterocycles* **1980**, *14*, 1825; (c) H. Gerlach, H. Wettler, *Helv. Chim. Acta* **1974**, *57*, 2306; (d) M. J. Arco, M. H. Trammel, J. D. White, *J. Org. Chem.* **1976**, *41*, 2075; (e) U. Schmidt, J. Gombos, E. Hashinger, H. Zak, *Chem. Ber.* **1976**, *109*, 2628; (f) U. Schmidt, J. Werner, *J. Chem. Soc., Chem. Commun.* **1986**, 996.

[41] I. D. Webb, G. T. Borcherdt, *J. Am. Chem. Soc.* **1951**, *73*, 752.

[42] A. G. Anastassiou, R. P. Cellura, *J. Chem. Soc., Chem. Commun.* **1969**, 1521.

[43] T. Matsumoto, S. Imai, T. Yoshinori, K. Tsuruta, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2401.

[44] H. S. Broadbent, C. W. Whittle, *J. Am. Chem. Soc.* **1959**, *81*, 3587.

[45] R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine Jr., N. R. Easton, K. Folkers, *J. Am. Chem. Soc.* **1945**, *67*, 2092.

[46] P. N. Confalone, G. Pizzolato, M. R. Uskokovi'c, *J. Org. Chem.* **1977**, *42*, 135.

8.7 Hydrogenolysis of C–O, C–N and C–X Bonds

Ferenc Notheisz, Mihály Bartók

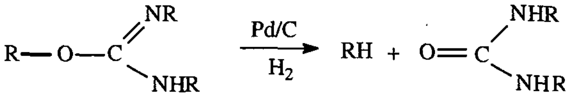
Reductive cleavage of sigma bonds during catalytic hydrogenation is usually described as hydrogenolysis. Hydrogenolysis of C–O, C–N, and C–halogen bonds has been surveyed in different reviews [1–10].

8.7.1 Hydrogenolysis of C–O Bonds

Pd and Ni are the most widely used catalysts for the hydrogenolysis of C–O bonds. The rates of hydrogenolysis increase in the order: OH < OR << OAr < OCOR. This order corresponds to the leaving-group properties of these moieties, which is characteristic of S_N-type reactions. The stereochemistry of the reaction depends mainly on the metal. Inversion of the configuration of carbon is characteristic of Pd whereas retention is usually observed with Ni [2,11].

8.7.1.1 Alcohols

Elevated temperature is usually needed for the hydrogenolysis of C–O bonds in alcohols [12]. Hydrogenolysis of primary alcohols can be described as an S_N2-like reaction involving hydride attack on the carbon, whereas transformation of a tertiary alcohol is closer to an S_N1-type reaction [2,13]. Tertiary alcohols can be hydrogenolyzed much faster than secondary. Alcohols are readily converted to the corresponding *O*-alkylisoureas. Hydrogenolysis of these compounds leads to hydrocarbons (Scheme 1) [14].



Scheme 1.

Zeolites have also been used for the hydrogenolysis of alcohols. For example, hydrogenolysis of 2-phenylethanol was achieved over Cs-exchanged zeolite X catalyst [15].

Glycerol and other polyols can be converted into propane-1,2-diol with high selectivity on sulfur-modified Ru on carbon; the reaction is not simple hydrogenolysis but rather dehydrogenation, then dehydroxylation and hydrogenation of the enol produced [16–18].

8.7.1.2 Phenols

Hydrogenolytic cleavage of aryl carbon–oxygen bonds is difficult without the transformation of the OH group to a better leaving group. Aryl tosylates or mesylates are, however, readily hydrogenolyzed [2]. At relatively low hydrogen pressure dibenzofuran was selectively hydrogenolyzed to 2-phenylphenol on Pd/C catalyst [19].

8.7.1.3 Ethers

Hydrogenolysis of open-chain ethers is also difficult whereas cyclic ethers are much more reactive. Cyclic ethers can be classified into two groups–strained three- and four-membered rings (oxiranes and oxetanes) are sufficiently reactive to be transformed even at room temperature whereas the five- and six-membered rings (oxolanes and oxanes) undergo transformation at higher temperatures only.

8.7.1.4 Oxiranes

Oxiranes can be hydrogenolyzed easily; alcohols and oxo compounds are formed as the result of primary processes [11,20,21]. The less sterically hindered bond is cleaved on Pt and Pd whereas the more hindered bond is broken on Ni and Cu. The rates of transformation of dimethyloxirane stereoisomers were also different on these metals. *cis*-2,3-Dimethyloxirane is transformed much more rapidly than the *trans* isomer on Pt and Pd catalysts, whereas on Ni the two isomers are converted at almost the same rate [22]. Solid-phase hydrogenolysis of oxiranes on supported palladium catalysts has also been reported [23].

8.7.1.5 Oxolanes

Platinum, palladium, and nickel catalysts cleave the oxolanes in the sterically less hindered position; Cu is inactive toward these molecules. On supported Pt the rupture of the secondary C–O bond was also observed [24]. Ring-opening is much easier than the hydrogenolysis of open chain ethers, presumably because of the presence of specially bonded $\alpha\beta\gamma$-intermediates [25]. Neither on Pt nor on Ni is any difference observed between the rates of transformation of the isomers among the dimethyl derivatives of oxolanes [26].

8.7.1.6 Acetals

Acetals can also be hydrogenolyzed to ethers in acidic media. Vinyl ethers are assumed to be intermediates in this reaction [27].

8.7.1.7 Acid Anhydrides

Maleic anhydride can be hydrogenated to the industrially important compounds γ-butyrolactone and tetrahydrofuran. Hydrogenolytic cleavage of the C–O bond on Cu-based multicomponent catalysts is much easier in γ-butyrolactone than in tetrahydrofuran [28].

8.7.1.8 Esters

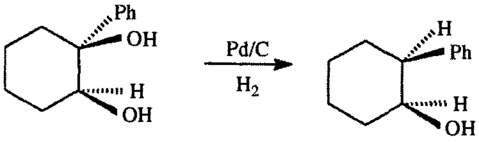
The preparation of fatty alcohols by hydrogenolysis of fatty acid esters is a well known process. Other promising fields of ester hydrogenolysis are the transformations of acetates to ethanol and of the esters of dicarboxylic acids to diols. Hydrogenolysis of esters and the industrial application of this reaction have been reviewed in detail in the literature [29,30]. Copper-based catalysts are used in the majority of applications [31–37], although rhodium-based catalysts have recently attracted interest, because they are more reactive than copper. A Rh–Sn bimetallic catalyst, prepared via an organometallic route, was very selective in the hydrogenolysis of ethyl acetate to ethanol [38]. These catalysts could also be used for the hydrogenolysis of fatty esters to fatty alcohols.

8.7.1.9 Benzyl Compounds

Hydrogenolysis of C–O bonds occurs readily if the oxygen is connected to a carbon which can produce stable carbocations. Benzylic carbocations are known to be very stable intermediates, and benzylic compounds are, accordingly, among the best molecules for hydrogenolysis. The benzyl group is one of the most popular protecting groups in synthetic organic chemistry, primarily because cleavage of the benzylic bond occurs under very mild conditions [39]. Pd is widely used for the hydrogenolysis of benzyl–oxygen bonds; the reaction combines high hydrogenolysis activity with low activity toward the saturation of aromatic rings [1,3,40]. Because of the ready removal of benzyl groups, selective catalytic debenzylations are often possible [9].

Benzyl Alcohols

Benzyl alcohols can be hydrogenolyzed at a reasonable rate even at room temperature. The reaction is usually conducted in ethanol. Because hydroxyl is a poor leaving group, a catalytic amount of a strong acid is usually added to the mixture. Palladium is the most widely used catalyst for the cleavage of benzylic C–O bonds, and 10% Pd/C is the most popular form of Pd for the hydrogenolysis of benzyl alcohols. This catalyst usually contains residual acids which increase reaction rates. Stereoselective hydrogenolysis (with inversion of configuration) of (1*S*,2*S*)-1-phenylcyclohexane-1,2-diol on Pd/C in the presence of HCl afforded (1*S*,2*S*)-2-phenylcyclohexanol (Scheme 2) [41].



Scheme 2.

Benzyl Ethers

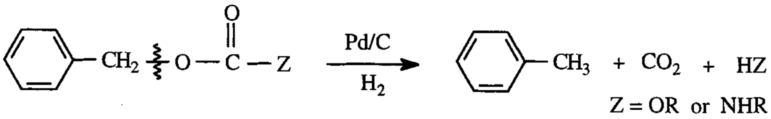
Benzyl ethers are among the most widely used *O*-protecting groups in organic chemistry. Removal of benzyl ether protecting groups is usually performed over Pd/C in ethanol, methanol, or ethyl acetate. Pearlman's catalyst ($Pd(OH)_2/C$) is also widely used for removing benzyl ether protecting groups [42,43].

Benzyl Esters

Benzyl esters of carboxylic acids are frequently used in organic synthesis for the protection of carboxyl groups. The C–O bond in benzyl esters can be cleaved more readily than the corresponding benzyl ether bond, because esters contain the best leaving group in this series.

Benzyl Carbonates and Carbamates

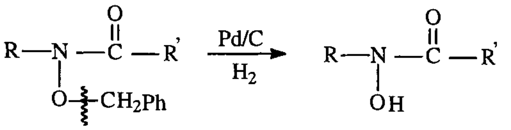
Benzyl carbonates and carbamates also have reactive benzylic C–O bonds, and consequently can be hydrogenolyzed easily. They are frequently used as protecting groups (*O*- or *N*-benzyloxycarbonyl groups) [39]. The extent of hydrogenolysis can be followed by measuring the amount of carbon dioxide produced (Scheme 3).



Scheme 3.

8.7.1.10 *N*-Benzyloxy Compounds

Both benzyl–oxygen and nitrogen–oxygen bonds are present in *N*-benzyloxy compounds and can be hydrogenolyzed. Because of the greater reactivity of benzylic compounds, the benzyl–oxygen bond can usually be made to cleave selectively on Pd/C in MeOH (Scheme 4) [44].



Scheme 4.

8.7.1.11 Transfer Hydrogenolysis

During hydrogenolysis the hydrogen source is usually hydrogen gas, but occasionally hydrogen donor molecules are also used as hydrogen sources [45–47]. This is called 'transfer hydrogenolysis' (or, sometimes, 'transfer hydrogenation'). In this method no special apparatus is required for handling gaseous hydrogen and rapid and selective removal of protecting groups under moderate conditions is occasionally possible by use of this method. Several hydrogen donors, e. g. cyclohexene, formic acid, and ammonium formate have been successfully used in the presence of different heterogeneous Pd catalysts [48–51].

N-benzyloxycarbonyl protecting groups have also been removed by transfer hydrogenolysis. Cyclohexene as hydrogen donor is not practical for the removal of benzyl-type protecting groups in peptide synthesis, because the reaction must be performed in boiling solvent and certain protecting groups suffer from undesirable decomposition at the boiling temperature. Cyclohexa-1,4-diene is a much more effective hydrogen donor and is used to perform catalytic transfer hydrogenolysis at room temperature on Pd/C [52].

The Mechanism of the Reaction

Despite of the popularity of benzyl as a protective group there is a lack of fundamental studies on the mechanism of hydrogenolysis [9]. It is probable that hydrogenolysis occurs via two reaction routes. The first mechanism is characteristic of Pd and Pt and proceeds mainly with inversion of configuration at the carbon atom, whereas the second occurs with Ni and Cu and configuration is retained [11]. With unsymmetrically substituted oxiranes the two mechanisms have different regioselectivity–the sterically less hindered bond is cleaved on Pt and Pd, whereas the more hindered bond is ruptured on Ni and Cu [11]. At the same time *cis*-1,2-dimethyloxirane reacts much more rapidly than the *trans* isomer on Pd and Pt, whereas on Ni there is no difference between the rates [22]. The first mechanism is probably an S_N2-like reaction involving hydride attack on the carbon (hydrogenolytic cleavage, cf. Scheme 3) whereas the second is insertion of the metal into the C–O bond.

It is thought that unreduced metal ions might play an important role in the insertion mechanism (electrophilic catalysis). The type of metal, the method of preparation, and additives present can influence the concentration and stability of these ions. Oxygen-containing compounds can oxidize metal surfaces and so produce electrophilic sites [53].

An S_N2-like mechanism is likely on primary carbon atoms whereas the reaction probably has high S_N1 character for compounds containing tertiary or benzylic carbon atoms. For this S_N1 mechanism, however, inversion of configuration is also expected, because rotation around the sigma bond is difficult because of steric interaction of the large groups with the catalyst surface.

8.7.2 Hydrogenolysis of C–N Bonds

Palladium catalysts, usually Pearlman's catalyst [42] and Pd/C are used for the hydrogenolysis of benzyl–nitrogen bonds. Acetic acid, ethyl acetate, ethanol, or methanol are frequently used as solvents. Sometimes a small amount of a strong acid is added to the reaction mixture [54–56]. The bond rupture needs the adsorption of carbon [57]. The hydrogenolysis of C–N bonds occurs with inversion on both Pd and Ni [2,58].

8.7.2.1 Amines

Hydrogenolysis of methylamine was studied on Pd and Pt catalysts. Exchange occurs at lower temperature than is required for rupture of C–N bond. The kinetics of hydrogenolysis of methylamine were also studied. It was found that at higher hydrogen pressures the limiting step is scission of the C–N bond in a partially dehydrogenated intermediate, with no direct participation of hydrogen, whereas at lower pressure chemisorbed hydrogen participates directly in the rate-limiting step as reactant [59]. On Pt catalyst it was assumed that metal sites are important for supplying the hydrogen atoms for the reaction, whereas the more ionic oxide sites facilitate the adsorption of the amine [57]. The hydrogenolysis of aniline was faster on a Ni(100) surface than on a Ni(111) surface and much less external hydrogen was required for the Ni(100) surface to achieve the same hydrogenolysis [60].

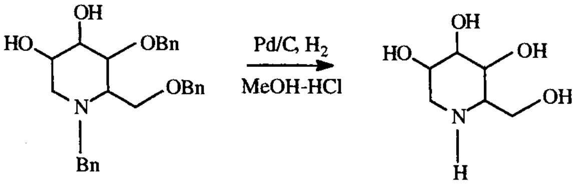
8.7.2.2 Aziridines

Ring opening of aziridines occurs readily, because of strain in the three-membered ring [58]. Pt, Pd, Rh, and Ni are used as catalysts. Usually the sterically less hindered C–N bond is ruptured. Catalytic hydrogenolysis of aziridines occurs with inversion on Pd; on Pt and Ni substantial racemization was observed.

8.7.2.3 Benzylic C–N Bonds

Hydrogenolytic debenzylation of *N*-benzyl derivatives is also great importance in synthetic organic chemistry, e. g. the synthesis of peptides [8]. Hydrogenolytic cleavage of the carbon–nitrogen bond is thought to be a slightly more difficult than that of the carbon–oxygen bond.

This means that during cleavage of *N*-benzyl groups, *O*-benzyl groups are usually also ruptured (Scheme 5) [61].

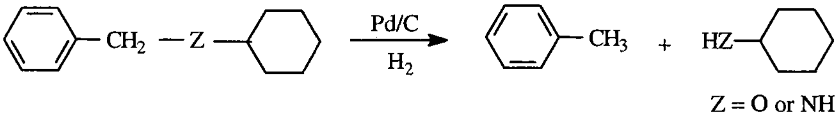


Scheme 5.

8.7.2.4 Selective Hydrogenolysis of Benzylic C–O and C–N Bonds

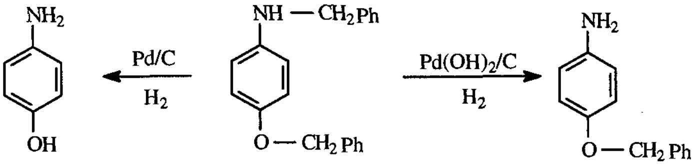
It is widely accepted that a benzyl–nitrogen bond is not as readily cleaved as a benzyl–oxygen bond. The presence of nitrogen can, however, influence the hydrogenolysis of C–O bonds. It has been reported that butylamine completely prevented the hydrogenolysis of the benzylic C–O bond [62]. The same effect was observed for molecules containing both benzylic C–O and C–N bonds [62,63]. In a mixture of *N*-benzylcyclohexylamine and benzyl cyclohexyl ether only the C–N bond was hydrogenolyzed on Pd/C, whereas in the presence of HCl the

C–O bond was ruptured exclusively (Scheme 6) [64]. Different strengths of adsorption might govern selectivity here.



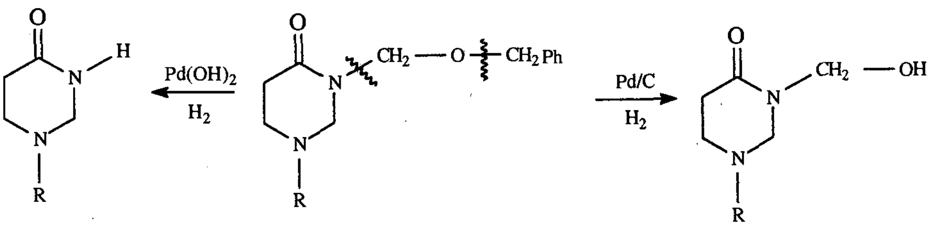
Scheme 6.

Both benzyl groups were removed from *N*,*O*-dibenzyl-*p*-aminophenol over Pd/C, whereas only the C–N bond was cleaved on $Pd(OH)_2/C$ (Scheme 7) [64]. Finally, in the presence of butylamine the C–O bond was ruptured selectively on Pd/C in methanol. Thus under appropriate conditions selective cleavage of either *N*-benzyl or *O*-benzyl groups is possible.



Scheme 7.

The same was found for nitrogen-containing compounds protected by benzyloxymethyl groups. These compounds have two reactive bonds. The regioselectivity of the hydrogenolysis depends on the catalyst used. The carbon–oxygen bond was ruptured by use of Pd/C as catalyst whereas the rupture of the C–N bond occurred when hydrogenolysis was performed with $Pd(OH)_2$ in MeOH (Scheme 8) [65].



Scheme 8.

It is possible that adsorption of *N*-containing compounds reduces the electrophilic character of the catalyst (by removing traces of acids or poisoning metal ions). For this reason hydrogenolysis occurs via an S_N2-like mechanism instead of the faster S_N1. Additional evidence is that oxidic or unreduced catalysts give the best selectivity in debenzylation [9]. It has also been found that for *O*-benzyl systems palladium oxide was much more effective than palladium metal whereas no such effect was observed with *N*-benzyl systems [66].

8.7.2.5 Transfer Hydrogenolysis

Transfer hydrogenolysis using Pd/C and cyclohexene has been used for *N*-debenzylation in peptide synthesis. The process is not, however, suitable for *tert*-butyl-derived protecting groups because they can undergo undesirable decomposition at the temperature of boiling ethanol. Cyclohexa-1,4-diene would be a much more effective hydrogen donor because it can be used at room temperature [52]. Peptides are, however, usually immiscible with apolar hydrogen donors. Fortunately formic acid is a good solvent for most peptides and can also be used as hydrogen donor for transfer hydrogenolysis of peptides.

Occasionally transfer hydrogenolysis can cleave bonds resistant to classical methods. For example, the hydrogenolysis of the oxazoline moiety on Pd/C, $Pd(OH)_2/C$, or Pd black in MeOH proved unsuccessful but transfer hydrogenolysis using Pd black and ammonium formate in AcOH afforded γ-lactam ester [67].

8.7.3 Hydrogenolysis of C–X Bonds

Hydrogenolysis of carbon–halogen bonds is very important because halogenated hydrocarbons are well known environmental pollutants [6,68]. The ease of hydrogenolysis of halides is dependent on the type of halide [69]. Alkyl halides are much less readily hydrogenolyzed than vinyl, aryl, and, especially, benzyl or allyl halides. The order of ease of dehalogenation is $I > Br \approx Cl >> F$. According to this sequence alkyl fluorides are very difficult to remove by catalytic hydrogenolysis.

The mechanism of the reaction has not been irrefutably established. It has been found that exchange was not observed over different metals [70,71]. The reaction was considered both as nucleophilic [72,73] or electrophilic [74] attack. Retention of configuration was found on Pd whereas racemization was almost complete on Ni [2,75].

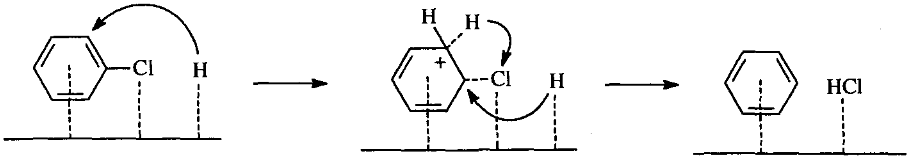
8.7.3.1 Alkyl Halides

Halogen removal from aliphatic compounds over supported nickel catalysts occurs predominantly via E1 elimination (dehydrohalogenation) [76]. The desulfurization and dehydrochlorination activity of the catalysts is similar [77]. The hydrogenolysis of alkyl halides to alkanes can be achieved in the presence of Pd/C or Raney Ni [78]. The reactivity of alkyl halides follows the sequence: tertiary > secondary > primary. Hydrogen halides produced during the reaction can deactivate the catalysts. Raney Ni is an active catalyst for dehalogenations but is readily deactivated by the reaction products, whereas Pd/C is less susceptible to this poisoning effect. Different bases, especially sodium hydroxide, are frequently used to react with hydrogen halides, whereas amines are used for base-labile compounds. 1,1,2-Trichlorotrifluoroethane was dechlorinated over an alumina-supported palladium/zinc oxide catalyst [79]. Zn–Cu catalysts were also active in this reaction [80]. CCl_2F_2 was hydrogenolyzed selectively to

CH_2F_2 over Pd/C [81]. Hydrogenolysis of neopentyl iodide on Pt/MgO catalyst takes place via a π-complexed half-reaction state [82].

8.7.3.2 Aromatic Halides

Hydrogenolysis of these compounds is important because it enables hydrogenolysis of polyhalogenated aromatic compounds to the parent hydrocarbons without the production of waste. Supported Pd catalysts are active in the hydrodehalogenation of aromatic compounds [83]. Halobenzenes interact with the metal surfaces to form surface halides and benzene, whereas hydrogen reduces the covered surfaces [84–86]. Selective hydrogenolysis of the C–I bond was observed on Pd/C in MeOH in the presence of AcONa and traces of quinoline [87]. Hydrodehalogenation of polyhalogenated aromatic compounds with Pd/C as catalyst can also be performed in the presence of ammonium or phosphonium salts [88]. The hydrocarbon solvent and the strongly alkaline solution constitute a two-phase system, and the onium salt, insoluble in both phases, is located at the interface. The onium salt coats the catalyst particles and constitutes the phase in which the reaction occurs. This system enables rapid displacement of chlorine from polychlorinated benzenes. Transfer hydrogenolysis with formate salts has also been used for dehalogenation of aromatic compounds [89,90]. Many publications have appeared on the application of platinum-loaded zeolites [91,92]. Pt/H-BEA zeolite had high activity in the hydrogenolysis of the C–Cl bond. Deactivation of this catalyst was ascribed to acid-catalyzed oligomerization reactions. Replacement of acid sites by sodium ions resulted in improved stability [93]. Halogen removal from aromatic compounds over a supported nickel catalyst was assumed to occur predominantly by an electrophilic route (hydrodehalogenation; Scheme 9) [76].



Scheme 9.

Acid halides are among the most reactive carboxylic acid derivatives and can be converted into many kinds of substance, for example, to aldehydes by hydrogenolysis on Pd/$BaSO_4$ (Rosenmund reduction)[94–96]. The catalysts usually contain additives to moderate their activity and prevent over-reduction [97]. Tetramethylthiourea was the most effective additive [98]. These additives probably do not block active sites but rearrange the surface structure of the catalysts [99]. Undec-10-enoyl chloride was hydrogenolyzed, however, to undec-10-enal on Pd/C without any inhibitor [100].

References

[1] M. Freifelder, *Practical Catalytic Hydrogenation,* Wiley, New York, **1971**.

[2] A. P. G. Kieboom, F. van Rantwijk, *Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry,* Delft University Press, **1977**.

[3] P. N. Rylander, *Hydrogenation Methods,* Acad. Press, New York, **1985**.

[4] J. H. Sinfelt, *Catal. Lett.* **1991**, *9,* 159.

[5] *Comprehensive Organic Synthesis,* (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8.

[6] M. Wilde, K. Anders, *Chem. Tech. (Leipzig)* **1994**, *46*, 316.

[7] R. L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist,* Dekker, New York, **1995**.

[8] V. Slavinska, G. Cipens, A. Strautina, E. Korcagova, D. Sile, E. Liepina, M. Katkevics, R. Vegners, *Latv. Khim. Zhur.* **1996**, 3.

[9] P. Baumeister, M. Studer, F. Roessler, *Handbook of Heterogeneous Catalysis,* Wiley–VCH, Weinheim, Vol. 5., **1997**, p. 2204.

[10] G. V. Smith, F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry,* Acad. Press, San Diego, **1999**.

[11] F. Notheisz, M. Bartók, in *Stereochemistry of Heterogeneous Metal Catalysis,* (ed. M. Bartók), Wiley, Chichester, **1985**, pp. 309, 435.

[12] S. W. McCombie, in *Comprehensive Organic Synthesis,* (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8., p. 811.

[13] M. Kraus, *Adv. Catal.* **1980**, *29*, 151.

[14] E. Vowinkel, I. Büthe, *Chem. Ber.* **1974**, *107*, 1353.

[15] T. Sooknoi, J. Dwyer, *Stud. Surf. Sci. Catal.* **1995**, *97*, 423.

[16] C. Montassier, J. C. Ménézo, L. C. Hoang, C. Reanaud, J. Barbier, *J. Mol. Catal.* **1991**, *70*, 99.

[17] P. Müller, P. Rimmelin, J. P. Hindermann, R. Kieffer, A. Kiennemann, J. Carré, *Stud. Surf. Sci. Catal.* **1991**, *59*, 237.

[18] K. Wang, M. C. Hawley, T. D. Furney, *Ind. Eng. Chem. Res.* **1995**, *34*, 3766.

[19] H. Sakashita, K. Ohara, T. Tatsumi, H. Tominaga, *Nippon Kagaku Kaishi* **1992**, 673.

[20] M. Bartók, in *Hydrogen Effects in Catalysis,* (ed. Z. Paál, P. G. Mennon), Marcel Dekker, **1988**, p. 521.

[21] S. Murai, T. Murai, S. Kato, in *Comprehensive Organic Synthesis,* (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8., p. 871.

[22] M. Bartók, F. Notheisz, Á. G. Zsigmond, *J. Catal.* **1980**, *63*, 364.

[23] T. Kitamura, T. Harada, T. Osawa, *Stud. Surf. Sci. Catal.* **1997**, *112*, 491.

[24] U. Gennari, R. Kramer, H. L. Gruber, *Appl. Catal.* **1984**, *11*, 341; **1988**, *44*, 239.

[25] H. Zimmer, M. Dobrovolsky, P. Tétényi, P., Z. Paál, Z., *J. Phys. Chem.* **1986**, *90*, 4758.

[26] F. Notheisz, Á. G. Zsigmond, M. Bartók, G. V. Smith, *J. Mol. Catal.* **1988**, *44*, 337.

[27] J. H. Brewster, in *Comprehensive Organic Synthesis,* (ed. B. M. Trost, I. Fleming, I.), Pergamon Press, Oxford, **1991**, Vol. 8., p. 211.

[28] M. Messori, A. Vascari, *J. Catal.* **1994**, *150*, 177.

[29] H. Adkins, *Org. React.* **1954**, *8*, 1.

[30] T. Turek, D. L. Trimm, N. W. Cant, *Catal. Rev.-Sci. Eng.* **1994**, *36*, 645.

[31] M. S. Wainwright, in *Chemical Industries (Catalysis of Organic Reactions),* **1996**, *68*, 213, (ed. R. E. Malz, Jr), Marcel Dekker, New York.

[32] K. Klier, *Adv. Catal.* **1982**, *31*, 243.

[33] A. M. Pollard, M. S. Spenzer, R. G. Thomas, P. A. Williams, *Appl. Catal. A* **1992**, *85*, 1.

[34] G. C. Shen, S. J. Fujita, N. Takezawa, *J. Catal.* **1992**, *138*, 754.

[35] F.Th. van de Scheur, D. S. Brands, B. van der Linden, C. Oude Luttikhuis, E. K. Poels, L. H. Staal, *Appl. Catal. A.* **1994**, *116*, 237.

[36] T. Turek, D. L. Trimm, D.StC. Black, N.W. Cant, *Appl. Catal. A* **1994,** *116*, 137.

[37] F.Th. van de Scheur, G. U. A. Sai, A. Bliek, L.H. Staal, *J. Am. Oil. Chem. Soc.* **1995**, *72*, 1027.

[38] O. A. Ferretti, J. P. Bournonville, G. Mabilon, G. Martino, J. P. Candy, J. M. Basset, *J. Mol. Catal.* **1991**, *67*, 283.

[39] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, **1991**.

[40] I. D. Entwistle, W. W. Wood, in *Comprehensive Organic Synthesis*, (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8., pp. 955.

[41] S.H Zhao, U. S. US 5,420,366 (1995), *Chem Abstr.* **1995**, *123*, 11659z.

[42] W. M. Pearlman, *Tetrahedron Lett.* **1967**, 1663.

[43] K. Yoshida, S. Nakajima, T. Wakamatsu, Y. Ban, M. Shibasaki, *Heterocycles* **1988**, 27, 1167.

[44] R. J. Bergeron, J. S. McManis, O. Phanstiel, R. J. T. Vinson, *J. Org. Chem.* **1995**, *60*, 109.

[45] G. Brieger, T. J. Nestrick, *Chem. Rev.* **1974**, *74*, 567.

[46] I. D. Entwistle, R. A. W. Johnstone, A. H. Wilby, *Chem. Rev.* **1985**, *85*, 129.

[47] Z. Dobrovolná, L. Cerven'y, *Chem. Listy* **1996**, *90*, 350.

[48] S. Hanessian, T. J. Liak, B. Vanasse, *Synthesis* **1981**, 396.

[49] Y. Araki, E. Mokubo, N. Kobayashi, J. Nagasawa, Y. Ishido, *Tetrahedron Lett.* **1989**, *30*, 115.

[50] M. K. Anwer, A. F. Spatola, *Synthesis* **1980**, 929.

[51] S. Rajagopal, A. F. Spatola, *Appl. Catal. A* **1997**, *152*, 69.

[52] A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, J. Meienhofer, *J. Org. Chem.* **1978**, *43*, 4194.

[53] F. Notheisz, Á. Molnár, Á. G. Zsigmond, M. Bartók, *J. Catal.* **1986**, *98*, 131.

[54] J. Zhu, J-C. Quirion, H-P. Husson, *J. Org. Chem.* **1993**, *58*, 6451.

[55] S. F. Martin, S. Liras, *J. Am. Chem. Soc.* **1993**, *115*, 10450.

[56] W. Deng, L. E. Overman, *J. Am. Chem. Soc.* **1994**, *116*, 11241.

[57] Triyono, R. Kramer, *Appl. Catal. A* **1993**, *100*, 145.

[58] Gy. Göndös, L. Gera, M. Bartók, in *Stereochemistry of Heterogeneous Metal Catalysis*, (ed. M. Bartók), Wiley, Chichester, **1985**, pp. 414, 497

[59] G. Meitzner, W. J. Mykytka, J. H. Sinfelt, *Catal. Lett.* **1995**, *32*, 335; **1996**, *37*, 137.

[60] S. X. Huang, D. A. Fischer, J. L. Gland, *Catal. Lett.* **1995**, *34*, 365.

[61] G. R. Cook, L. G. Beholz, J. R. Stille, *J. Org. Chem.* **1994**, *59*, 3575.

[62] B. P. Czech, R. A. Bartsch, *J. Org. Chem.* **1984**, *49*, 4076.

[63] R. C. Bernotas, R. V. Cube, *Synth. Commun.* **1990**, *20*, 1209.

[64] L. S. Seif, K. M. Partyka, J. E. Hengeveld, in *Chemical Industries (Catalysis of Organic Reactions)*, **1990**, *40*, 197, (ed. D. W. Blackburn), Marcel Dekker, New York.

[65] S. Ichikawa, S. Shuto, N. Minakawa, A. Matsuda, *J. Org. Chem.* **1997**, *62*, 1368.

[66] K. G. Griffin, S. Hawker, M. A. Bhatti, in *Chemical Industries (Catalysis of Organic Reactions)*, **1996**, *68*, 325, (ed. R. E. Malz, Jr.), Marcel Dekker, New York.

[67] T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P. A. Sprengler, A. B. Smith, *J. Am. Chem. Soc.* **1996**, *118*, 3584.

[68] A. Converti, M. Zilli, D. M. De Faveri, G. Ferraiolo, *J. Hazard. Mater.* **1991**, *27*, 127.

[69] A. R. Pinder, *Synthesis* **1980**, 425.

[70] J. S. Campbell, C. Kemball, *Trans. Faraday Soc.* **1961**, *57*, 809.

[71] J. R. Anderson, B. H. McConkey, *J. Catal.* **1968**, *11*, 54.

[72] P. Dini, J. C. Bart, N. Giordano, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1479.

[73] M. Kraus, V. Bazant, *Proc. 5th Int. Congr. Catal. (Miami 1972)* **1973**, 1073.

[74] B. Hagh, D. Allen, *Chem. Eng. Sci.* **1990**, *45*, 2695.

[75] K. Felföldi, M. Bartók, in *Stereochemistry of Heterogeneous Metal Catalysis*, (ed. M Bartók), Wiley, Chichester, **1985**, p. 525.

[76] G. Tavoularis, M. A. Keane, *J. Mol. Catal. A: Chem.* **1999**, *142*, 187.

[77] J. Frimmel, *Chem. Listy* **1997**, *91*, 840.

[78] T. Imamoto, in *Comprehensive Organic Synthesis*, (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8., p. 793.

[79] S. P. Scott, M. Sweetman, J. Thomson, A. G. Fitzgerald, E. J. Sturrock, *J. Catal.* **1997**, *168*, 501.

[80] B. E. Platonov, V. I. Krasnov, *Zhur. Org. Khim.* **1994**, *30*, 1271.

[81] E. J. A. X. van de Sandt, A. Wiersma, M. Makkee, H. van Bekkum, J. A. Moulijn, *Rec. Trav. Chim.* **1996**, *115*, 505.
[82] V. Amir-Ebrahimi, J. J. Rooney, *J. Mol. Catal. A: Chem.* **1997**, *120*, 89.
[83] M. Hudlick'y, in *Comprehensive Organic Synthesis*, (ed. B. M. Trost, I. Fleming,), Pergamon Press, Oxford, **1991**, Vol. 8., p. 895.
[84] B. Coq, G. Ferrat, F. Figueras, *React. Kinet. Catal. Lett.*, **1985**, *27*, 157.
[85] B. Coq, G. Ferrat, F. Figueras, *J. Catal.*, **1986**, *101*, 434.
[86] P. Bodnariuk, B. Coq, G. Ferrat, F. Figueras, *J. Catal.*, **1989**, *116*, 459.
[87] D. R. Boyd, N. D. Sharma, S. A. Barr, H. Dalton, J. Chima, G. Whited, R. Seemayer, *J. Am. Chem. Soc.* **1994**, *116*, 1147.
[88] C. A. Margues, M. Selva, P. Tundo, *J. Org. Chem.* **1993**, *58*, 5256; **1994**, *59*, 3830.
[89] M. K. Anwer, D. B. Sherman, J. G. Roney, A. F. Spatola, *J. Org. Chem.* **1989**, *54*, 1284.
[90] G. Shapiro, B. Gomez-Lor, *J. Org. Chem.* **1994**, 59, 5524.
[91] H. W. Kouwenhoven, B. de Kroes, *Stud. Surf. Sci. Catal.* **1991**, *58*, 524.
[92] W. F. Hölderich, H. van Bekkum, *Stud. Surf. Sci. Catal.* **1991**, *58*, 638.
[93] E. J. Creyghton, M. H. W. Burgers, J. C. Hansen, H. van Bekkum, *Appl. Catal. A: General.* **1995**, *128*, 275.
[94] K. W. Rosenmund, *Chem. Ber.* **1918**, *51*, 585.
[95] E. Mosettig, R. Mozingo, *Org. React.* **1948**, *4*, 362.
[96] O. H. Wheeler, in *The Chemistry of Acyl Halides*, (ed. S. Patai), Interscience, London, **1972**, p. 231.
[97] A. P. Davies, in *Comprehensive Organic Synthesis*, (ed. B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8., p. 283.
[98] S. Affrossman, S. J. Thomson, *J. Chem. Soc.* **1962**, 2024.
[99] A. B. McEwen, M. J. Guttieri, W. F. Maier, R. M. Laine, Y. Shvo, *J. Org. Chem.* **1983**, *48*, 4436.
[100] V. G. Yadav, S. B. Chandalia, *Org. Process Res. Dev.* **1997**, *1*, 226.

8.8 Dehydrogenation

Wolfgang F. Hölderich, Dominique M. Roberge

Dehydrogenation is a key reaction in the production of commodity chemicals such as butadiene, styrene and formaldehyde and in the catalytic reforming of petroleum naphtha [1–3]. In the fine chemical industry, however, dehydrogenation is used less than the numerous hydrogenation reactions which are available. Dehydrogenation is usually an endothermic reaction which requires high temperatures. For such conditions the chemical stability of many fine chemicals is often insufficient. Most of the dehydrogenation reactions used in fine chemistry yield aromatic or heteroaromatic compounds and aldehydes or ketones.

8.8.1 Thermodynamics

The dehydrogenation of organic molecules producing molecular hydrogen can be classified into different families of reactions. The dehydrogenation may form isolated double bonds, aromatic compounds, heteroaromatic compounds, aldehydes, or ketones. In all these the product yield is limited by thermodynamics. Figure 1 shows the thermodynamic equilibrium attained for different dehydrogenation reactions. It is illustrated that the formation of isolated double bonds requires a higher temperature even though the enthalpy of reaction is lower than for aromatic com-

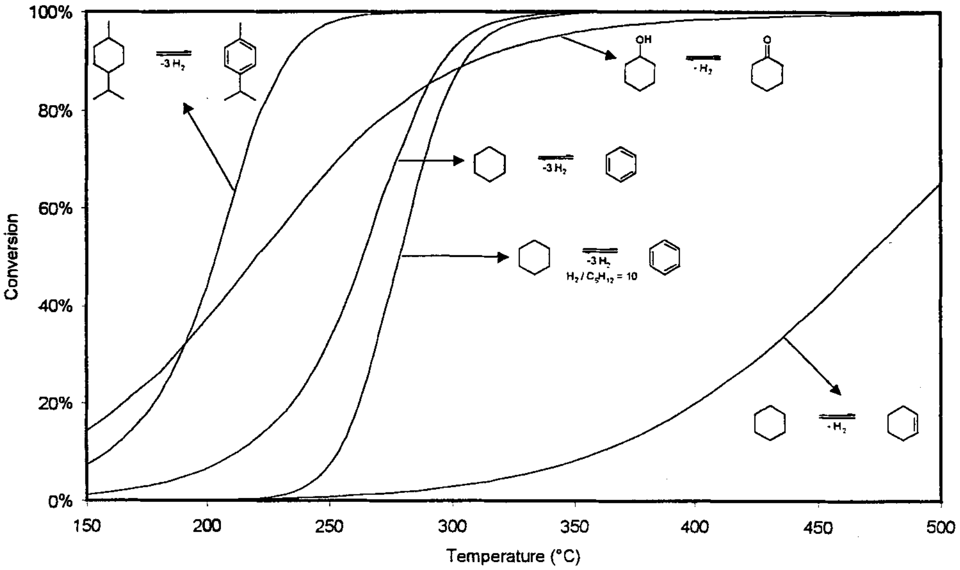


Figure 1. Thermodynamic equilibrium conversion for different dehydrogenation reactions. Conditions: $P = 1$ bar, H_2/saturated hydrocarbon = 0 (calculations based on the software HSC Chemistry from Outokumpu Research Oy).

Table 1. Selected dehydrogenation reactions.

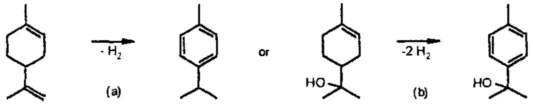
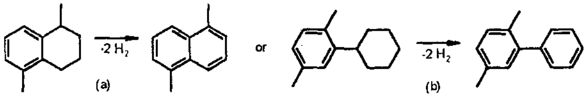
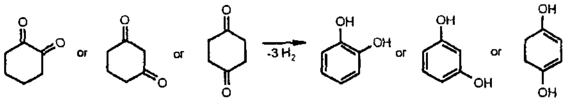
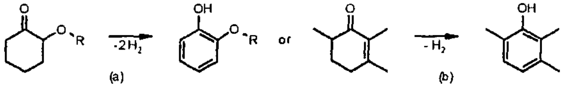
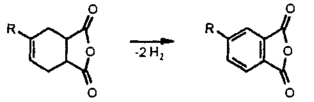
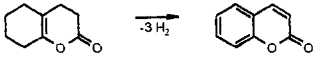
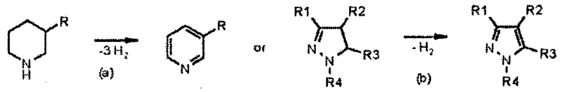
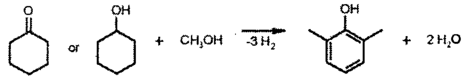
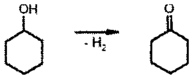
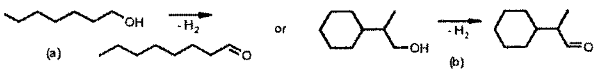
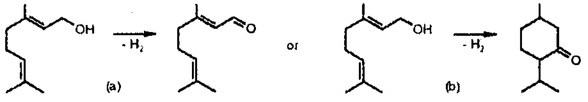
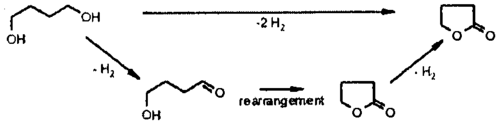
No.	Reaction scheme	Conditions	Catalysts	Refs
Dehydrogenation to aromatic or heteroaromatic compounds				
1		(a) $T \approx 300$ °C, $P_{H2} \approx 1$ bar, H_2/terpenes ≈ 3, WHSV ≈ 3 for Pd/SiO_2; (b) reactive distillation, $T \approx 140$ °C, $P < 0.01$ bar, triethylamine as base.	(a) Pd/SiO_2 (low-acidic) or $Cr_2O_3/\gamma\text{-}Al_2O_3$ or Pd-Ce/ZSM-5 (acidic); (b) Pd/carbon, SiO_2 or Al_2O_3, acidity on the catalyst must be minimal.	[5,9, 17–23]
2		$T \approx 400$ °C, P_{H2} up to 10 bar, H_2/Hydrocarbon ≈ 10, WHSV ≈ 2, conditions for the Amoco process.	Pt/$\gamma\text{-}Al_2O_3$, catalyst washed with Na_2CO_3, Na also as promoter.	[24–28]
3		$T \approx 210$ °C, aliphatic ethers as solvent (polyglycol ether), solvent dilution > 70 % *w/w*.	Pd/carbon, catalyst is added to the reaction mixture with a low molecular weight alcohol.	[29–33]
4		(a) $T \approx 150$–250 °C at reflux, esters as solvent (trimethylene glycol diacetate); (b) $T \approx 300$ °C, P = 1 bar, H_2 as carrier gas, contact time = 2–10 s.	(a) Pd/charcoal, no deactivation; (b) Pd/$\alpha\text{-}Al_2O_3$, low surface area catalyst, pore sizes 40–400 nm, very selective.	[34,35]
5		$T \approx 200$ °C, ramp of 1 °min^{-1}, P ≈ 1–3 bar, H_2 acceptors (dimethyl maleate → dimethyl succinate).	Pd/charcoal or Pd/Al_2O_3, selective at high conversion but very sensitive to impurities.	[6]
6		$T \approx 220$ °C, liquid phase with H_2 acceptors (diethyl maleate or fumarate).	Pd/charcoal, yield > 90 %	[7]

Table 1. Continued.

No.	Reaction scheme	Conditions	Catalysts	Refs
7		(a) $T \approx 320$ °C, 5 bar, WHSV ≈ 0.6, N_2 or H_2 as carrier gas; (b) $T \approx 100$ °C, liquid phase with solvent and H_2 acceptors (S or Se).	(a) Pd/Al_2O_3 or $Pd/SiO_2–Al_2O_3$ treated with NH_3. Yield > 97 %; (b) no catalyst is used.	[4,36]
8		$T \approx 400$ °C, 1 bar, WHSV ≈ 0.4, N_2 as carrier gas, MeOH in excess.	Bi-functional catalyst, base-catalyzed alkylation with dehydrogenation, TiO_2/V_2O_5 or Cr_2O_3/MgO.	[37–39]
Dehydrogenation of alcohols to aldehydes or ketones				
9		$T \approx 360$ °C, $P \approx 2$ bar, H_2/cyclohexanol ≈ 3, LHSV ≈ 0.4, H_2 and CH_4 (1:1 mol) as carrier gas + H_2O.	Bulk ZnO with Al_2O_3 and sulfates and promoters such as CaO and K_2O.	[42]
10		(a) $T \approx 265–329$ °C, ↑ 0.25–3 °/day, P ≈ 1 bar, H_2/N_2/octanol = 1:9:1, LHSV ≈ 0.8; (b) $T \approx 250$ °C, $P \approx 1$ bar, liquid paraffin as solvent, N_2 as purging gas.	(a) Cu/MgO, °C ≈ 58 %, S ≈ 99 %, stable catalyst; (b) Cu–Cr mixed oxide, C ≈ 67 %, S ≈ 91 %.	[44,45]
11		(a) Oxidative dehydrogenation, T ≈ 350 °C; (b) $T \approx 230$ °C, $P_{H2} \approx 2$ bar, liquid phase reaction without solvent.	(a) Group IB metal coated on stainless steel powder (Propak®); (b) CuO/Cr_2O_3 = 1:1 or Raney Cu, Yield ≈ 90 %.	[11,46]
12		Gas phase: T ≈ 250 °C, P ≈ 4 bar, H_2/butanediol ≈ 4, WHSV ≈ 3; Liquid phase: T ≈ 195 °C (reflux), P ≈ 1 bar, catalyst/butanediol ≈ 5 w/w.	Cu–Cr catalyst promoted with Mn or Ba, Na or K can also be added. Pure Cu–Cr catalyst has bad abrasion properties in the liquid phase.	[49–52]

pounds. The aromatic stability and the high entropy gain resulting from the loss of three hydrogen molecules are the reasons for the formation of aromatic compounds in a narrow range of lower temperatures (200–300 °C). In comparison, the dehydrogenation of secondary alcohols to ketones occurs over a wider range of temperatures. The presence of substituent groups (alkyl, aryl) attached to the aromatic ring further favors the formation of aromatic compounds at lower temperatures.

The use of hydrogen acceptors enables reaction of unstable molecules at lower temperatures. Examples of hydrogen acceptors are sulfur or selenium [4], α-olefins [5], dimethyl maleate [6], diethyl maleate or fumarate [7], and chloranil [8]. Table 1 lists some reactions which employ hydrogen acceptors.

8.8.2 Reaction Conditions

Reaction conditions for the dehydrogenation of single saturated bonds to isolated double bonds are severe. High temperatures (> 500 °C) and low pressures (≤ 1 bar) are essential if reasonable conversions are to be achieved. Under such conditions coke is formed in a matter of minutes and regeneration via oxidation is a process combined with the dehydrogenation. The thermal stability of the catalyst is, therefore, of major concern. Nobel metal carriers such as alumina are preferred because of their improved sintering stability when compared with silica. Alumina induces a good metal support interaction (MSI) especially when the metal has an oxidation state of 2+ under oxidizing conditions.

The presence of hydrogen is usually not detrimental when aromatic compounds are formed. It has even been reported to be a promoter [9]. The benefit of using hydrogen is probably related to the better desorption rate of the aromatic molecule. It has been suggested that this desorption step is the rate limiting factor [10]. Hydrogen also prevents rapid accumulation of carbon on the metal surface. Figure 1 shows that introduction of hydrogen slightly increases the optimum temperature for high-equilibrium conversions, as shown for the dehydrogenation of cyclohexane to benzene. Dehydrogenation at higher temperatures also means a faster reaction rate and a higher space–time yield.

The dehydrogenation can also be performed in the liquid phase, when lower temperatures are required. High pressure of an inert gas is sometimes required to maintain the reactants in the liquid state. The hydrogen gas evolving from the reaction can be stripped out of the reaction mixture by means of circulating an inert gas such as nitrogen. The constraints imposed by the equilibrium conversion are thereby reduced. Small amounts of oxygen can also be added to react slowly with the hydrogen formed [11].

Gas-phase reactions are usually performed with a series of fixed bed adiabatic reactors with re-heating between each catalytic bed. Liquid-phase reactions are usually performed in a slurry reactor with a circulating inert gas. The new trends in dehydrogenation reactors and conditions are membrane reactors [12], wall reactors [13], reactions performed in supercritical water [14], and oxidative dehydrogenation [11].

8.8.3 Catalysts

Hydrogenation/dehydrogenation reactions are reversible processes. Hence, a catalyst, which is good for hydrogenation, is also suitable for dehydrogenation. Problems arise because dehydrogenation is performed at higher temperatures. Indeed, it is more difficult to favor the cleavage of the C–H bond over the cleavage of the C–C bond at high temperatures, and hydrogenolysis is usually followed by carbonization and coke formation as side reactions.

Catalysts for dehydrogenation are either metallic, oxidic, or basic. Metallic catalysts based on Pd and Pt are usually used for the dehydrogenation of cyclic compounds to aromatic compounds. The dehydrogenation of alcohols to aldehydes or ketones is usually performed on oxides such as ZnO, CuO, Cr_2O_3, and Fe_2O_3, because the OH group of an alcohol can undergo an ionic interaction with an oxidic material. This interaction has a significant influence on selectivity. Each type of catalyst is now discussed in more detail:

Metallic catalysts are usually based on Pt and Pd because these metals have by far the lowest hydrogenolysis activity of group VIII metals while sustaining good hydrogenation/dehydrogenation activity [10]. The cleavage of C–H, O–H, and H–H bonds is, moreover, usually regarded as structure-insensitive whereas the cleavage of C–C bonds requires a large ensemble of metal atoms and is therefore considered structure sensitive. Thus, the dilution of a noble metal with a group IB metal is one of the most efficient means of reducing hydrogenolysis. The effect can be interpreted in terms of a geometric or an electronic factor. The geometric factor supposes that the large ensembles of atoms are heterogenized because of an alloying effect. The electronic effect supposes that different metal–adsorbate bond strengths are modified so that hydrogenolysis is significantly reduced. The alloying effect is not only limited to group IB metals. It is, for example, common to alloy Pt with Ge, In, Ga, and Sn. The dehydrogenating activity of Pd is increased when alloyed with Ni, Ru, and Pt. Sulfidation of Ni is another method of using a good hydrogenation catalyst for dehydrogenation.

The most active oxides for dehydrogenation under reductive conditions are usually metal oxides such as Fe_2O_3 and metal oxides of group VIA (Cr, Mo, W). They have a variable oxidation state and can be supported on high surface-area carriers. Cr_2O_3 is used as such or supported on γ- or θ-Al_2O_3, or ZrO_2. The latter support has intrinsically lower acidity than Al_2O_3. When Al_2O_3 is used, an alkali or a rare earth metal is necessary to suppress the acidity and to avoid dehydration. CuO, ZnO, Cr_2O_3, Fe_2O_3, and a combination thereof are frequently used for the dehydrogenation of alcohols. Cu, which can also be employed as a metal, is prepared in high percentage by co-precipitation with another metal as in copper chromite. The resulting material has better stability against sintering. This is also true for Zn and when combined with Cr or Fe forms a spinel which has a large surface area.

Purely basic oxide catalysts have, to some extent, a dehydrogenation function. An example is CaO in the dehydrocyclodimerization of conjugated dienes [15]. Hattori has published a review on the multi-functionality of basic catalysts in fine chemistry [16].

The next sections will discuss in more detail different dehydrogenation reactions performed in organic synthesis (see Table 1 for a summary). These reactions have been chosen to exemplify the complex reaction conditions and catalyst formulation associated with different reactants.

8.8.4 Dehydrogenation to Aromatic or Heteroaromatic Compounds

The use of renewable feedstocks from natural sources is probably a field where heterogeneous catalysis can bring considerable improvements. The dehydrogenation of cheaply available mono-terpenes from citrus production or the pulp and paper industry to furnish the more commercially valuable *p*-cymene is a good example (Table 1, Scheme 1). This reaction has been studied in detail over metallic [9,17,18], oxidic [19,20], and basic [21] catalysts.

Figure 2 shows two different reaction pathways for converting limonene to *p*-cymene (reaction 1a). It was first believed that acid centers are required to isomerize the double bonds into the cyclohexene ring. Once these ring conjugated bonds are formed aromatization can proceed rapidly over the dehydrogenation function of the catalyst. The function can be either based on Cr_2O_3 [19] or Pd [9]. The major problem is careful control of acid strength to avoid polymerization and isomerization of *p*-cymene to *m*-cymene. Krishnasamy and Yeddanapalli have shown that an optimum amount of potassium is favorable over a $Cr_2O_3/\gamma\text{-}Al_2O_3$ catalyst [20]. The strong acid sites are neutralized leaving the weak sites unaffected. Weyrich et al. [22], on the other hand, used a catalyst based on Pd/ZSM-5 promoted with Ce. They were able to increase the selectivity to *p*-cymene because of the shape-selectivity effect of the MFI structure.

The second approach to the conversion of limonene to *p*-cymene is the use of a purely hydrogenation/dehydrogenation catalyst under reducing conditions. For this process Pd supported on a low-acidic silica carrier turned out to be the most appropriate catalyst [18]. Figure 2 illustrates the possible reaction pathway.

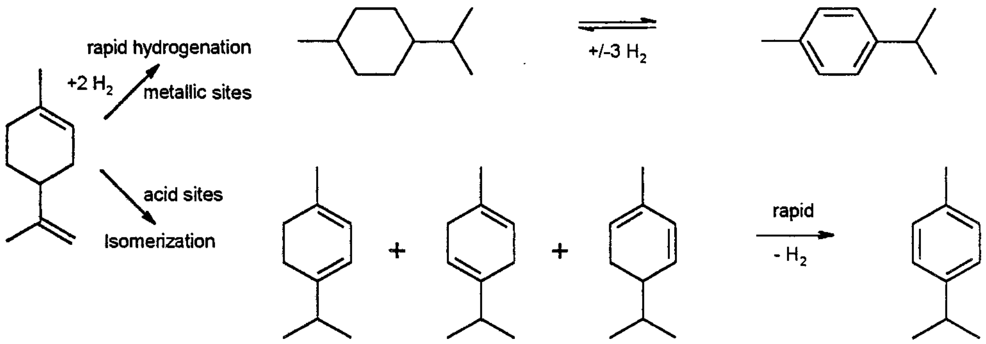


Figure 2. Two different reaction pathways for the synthesis of *p*-cymene from limonene.

In the presence of hydrogen, the isolated double bonds can be hydrogenated very rapidly. An equilibrium is established between *p*-menthane and *p*-cymene that is a function of the temperature and the hydrogen pressure (Figure 1). At temperatures of ca 300 °C the yield of *p*-cymene is > 99 %. The use of hydrogen makes the conditions milder for dehydrogenation (less coke formation) and no deactivation is observed after more than 100 h on-stream. The reaction is, moreover, slightly exothermic, which is convenient for industrial application. The catalyst has been tested with commercial mixtures of terpenes (dipentene) and the yield remained high (> 95 %). The process is now being tested in a scale-up unit and preliminary results have been published [17].

The role of acidity is emphasized when an OH group is present in the limonene structure (reaction 1b) [23]. The acidity of the carrier must then be strongly reduced to avoid dehydration. Carriers such as carbon, silica, and alumina are appropriate, although other forms than γ-Al_2O_3 are usually used. The introduction of a base such as triethylamine directly into the reaction mixture is also imperative. Considering these restrictions, the temperature of the reaction must not exceed 150 °C. Thus, it is essential to reduce the pressure (< 0.01 bar) to increase the yield.

An interesting use of dehydrogenation is the formation of specific alkylpolynuclear aromatic compounds, specifically dimethylnaphthalene (DMN) and dimethylbiphenyl (DMB). They are usually synthesized by alkylation of the corresponding non-alkylated aromatic compound with methanol, and a mixture of compounds is produced which is difficult to separate by distillation. Amoco has developed a four-step commercial process (Figure 3) based on the side-chain base-catalyzed alkylation of *o*-xylene with butadiene to form 2,6-DMN [24]. The third step of this process is the dehydrogenation to 1,5-DMN (reaction 2a) [25]. The advantage of first synthesizing 1,5-DMN is that it can be selectively isomerized to 2,6-DMN [26]. The same idea is also used to form DMB derivatives, i. e. *p*-xylene is alkylated with cyclohexene or cyclohexanol to form an intermediate that can be further dehydrogenated to 2,5-DMB [27]. A similar method can be used to produce 2,4-DMB from *m*-xylene [28].

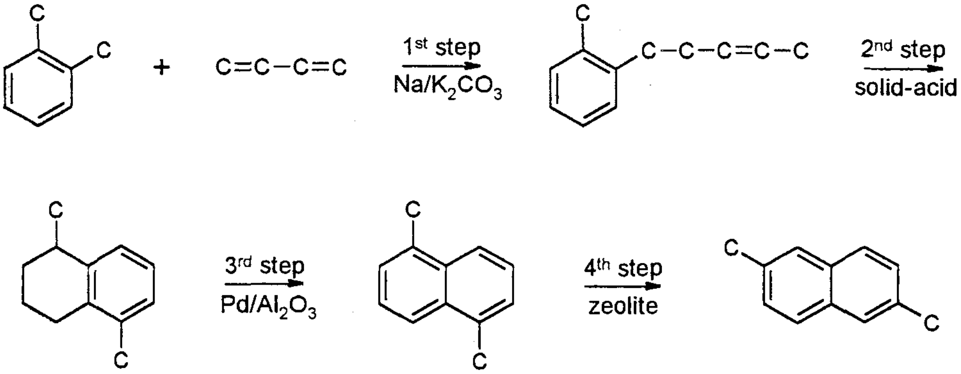


Figure 3. Amoco process for the synthesis of 2,6-dimethylnaphthalene.

Dehydrogenation to these polynuclear aromatic compounds is quite straightforward. The reaction conditions are similar to catalytic reforming. The reaction is performed in the presence of 10 bar hydrogen with a hydrogen to reactant ratio of 10. The temperature is relatively high (400 °C) and the reaction is fast and selective (> 95 %). The catalyst is Pt supported on γ-Al_2O_3. The carrier was previously treated with a base (Na_2CO_3) to remove residual chlorine. Excess of Na is maintained on the support to eliminate potential acid centers, which might cause undesired isomerization and cracking of the hydrogenated starting material [25].

The dehydrogenation to aromatic compounds becomes more complex when groups such as hydroxy, carbonyl, and acid anhydride are attached to the ring (Table 1, Schemes 3–5) [6,29–35]. The reaction is then usually performed under milder conditions in the liquid phase by the use of a solvent. Common solvents are high boiling-point aliphatic ethers or esters and the typical catalyst is Pd on activated charcoal. When the conditions are optimized conversion and selectivity can be very high (> 95 %). Reaction 5 is an example of the use of a hydrogen-acceptor molecule (dimethyl maleate). The conditions for reaction 4(b) deserve a closer look. The reaction is performed in the gas phase with a low surface-area catalyst (α-Al_2O_3, 5 m^2 g^{-1}). The low surface area probably hinders rapid consecutive reactions of the phenol derivative. These rapid reactions (probably condensation) would inevitably occur in the pores of high surface-area supports such as γ-Al_2O_3. Thus the use of a low surface-area catalyst has the same effect as adding a solvent to the liquid phase.

The same logic also applies for the dehydrogenation to heteroaromatic compounds. The dehydrogenation is usually simple and straightforward with relatively uncomplicated molecules such as 3-methylpiperidine (reaction 7a). In this case, β-picoline can be produced in high yield over a classical Pd supported catalyst with conditions similar to the Amoco process [36]. When, however, the reactants become more complex (reaction 7b or 6) hydrogen acceptors, solvents and milder conditions are more practical [4,7]. In the pharmaceutical industry the synthesis of hormones, alkaloids, and vitamins via dehydrogenation is almost exclusively based upon hydrogen acceptors. Chloranil often finds application in the selective dehydrogenation of corticosteroids [8].

An interesting approach to dehydrogenation is combination with a second reaction, e. g. alkylation. Such so-called ‘one pot reactions’ are performed on a bifunctional catalyst. For example, the dehydrogenation of dimethyltetralin can be accomplished with the ring closure to form the cyclohexyl group (Figure 3). The catalyst, which has dehydrogenation activity due to Pd or Pt, must be combined with acid functionality [26]. The selectivity is increased when both functionalities are physically separated, i. e. an acid catalyst (USY) is well mixed with a noble metal supported on its own non-acidic support (activated carbon). The noble metal is not directly impregnated on the acidic catalyst. An example of base-catalyzed ‘one pot reactions’ is the alkylation of methanol with cyclohexanol or cyclohexanone to form 2,6-dimethylphenol (reaction 8) [37–39]. For this reaction MgO is impregnated with Cr_2O_3. MgO has base functionality to alkylate methanol and Cr_2O_3 is probably the dehydrogenation functionality. Synergy between both metals cannot be excluded. Cr_2O_3 on MgO can be reduced more easily and the Cr^{3+} ion might have some Lewis acidic character [38,39].

8.8.5 Dehydrogenation of Alcohols to Aldehydes or Ketones

The synthesis of aldehydes or ketones by dehydrogenation of alcohols is one chemical route of many possible alternatives. The hydroformylation of olefins is the most utilized synthetic route, although dehydrogenation has found a place in the production of fragrance aldehydes. From the Ullmann Encyclopedia [40] it is apparent that dehydrogenation becomes predominant when the carbon number is C_8 or more for straight-chain aldehydes. The unsaturated C_{10} aldehydes from the transformation of essential oils are a second important field where dehydrogenation is often employed (Table 1).

The formation of cyclohexanone from cyclohexanol (Table 1, Scheme 9) is a commercially important reaction and also a good test reaction for many catalysts. The dehydrogenation of cyclohexanol can give three main products, cyclohexanone, cyclohexene, and phenol. The product obtained depends on catalyst functionality and the reaction has often been used to characterize the properties of bimetallic catalysts. A recent example is found in Ref. 41, where many other references are cited. The commercial catalyst is usually based on ZnO (79 %) with promoters such as CaO (6.6 %), K_2O (3.3 %), Al_2O_3 (4.5 %), and sulfates (2.5 %, all in % *w/w*) [42]. The reaction is performed at temperatures within the range 340–380 °C and under a pressure of 2 bar. For maximum dehydrogenation efficiency it is preferable to use a one-to-one mixture of hydrogen and inert gas (methane) with a hydrogen-to-cyclohexanol ratio of 3. The key element is water, which is introduced in small amounts (1–2 % *w/w* cyclohexanol) to act as a promoter. The optimal LHSV in this reaction varies between 0.2 and 0.6. The conversion is thermodynamically limited to values up to 80 % but the total yield after recycling of the product can be as high as 97 %, because of the good reaction selectivity.

The dehydrogenation of long-chain alcohols or unsaturated terpenols is conducted under similar conditions (Table 1, Schemes 10 and 11). It is usually accepted that dehydrogenation is advantageous with primary alcohols to prevent overoxidation to carboxylic acids when oxidation is a competitive method [43]. De Graaf and Delahaye [44] reported that the introduction of water is not always an advantage especially when an azeotrope can be formed. An appropriate gaseous mixture of hydrogen and inert gas can compensate for the lack of water, and hydrogen is introduced only when the reaction has started. When the reactants become more complex the reaction can also be performed in the liquid phase. Addition of a solvent such as liquid paraffin is useful for diluting the system and increasing the thermodynamic yield [45]. Occasionally hydrogenation/dehydrogenation are both applied in the same process as, for example, in the hydrogenation of phenol to cyclohexanol and its consecutive dehydrogenation to cyclohexanone [42]. In a continuous process it is then convenient to use the same flue gas composition to perform the reaction in one pass. In a batch process, it is convenient to find appropriate conditions to perform the process in the same reactor [46].

The presence of functional groups other than alkyl in addition to the OH group makes the dehydrogenation more sensitive to side reactions. The $-CH_2OCH_3$, $-CH_2OC_6H_5$, $-CH_2N(CH_3)_2$, and $-CF_3$ groups sustain the action of the catalysts at higher temperatures whereas cyano, chloro, bromo, tertiary OH, and COOH groups undergo decomposition [47]. A way to partially circumvent the problem is to reduce the temperature and to work under reduced pressure [48]. Substituents also influence the reaction rate. Electron-withdrawing substituents usually reduce the rate [47].

Finally, The dehydrogenation of butanediols to γ-butyrolactone is an important commercial reaction that was developed by BASF and named the Reppe process. The most probable reaction mechanism via the γ-hydroxybutyraldehyde intermediate clearly shows that the reaction proceeds via two separate alcohol dehydrogenation steps with a rearrangement step taking place in-between (Table 1, Scheme 12) [49]. The reaction is usually performed in the gas phase with hydrogen as carrier gas, to reduce catalyst deactivation, which is a characteristic problem. Thus, extensive research is now being conducted in the liquid phase [50,51]. In addition to a lower catalyst deactivation rate, liquid phase reaction also reduces the number of side-products. The drawbacks are, of course, lower activity but also abrasion problems with the catalyst. The catalyst is preferably stabilized as a powder in a silica matrix (Ludox®R) [51]. The catalyst most often encountered in the patent literature is a Cu–Cr with a promoter such as Ba or Mn. The catalyst is also preferably doped with Na or K and pretreated very carefully in a reducing atmosphere [52].

8.8.6 Conclusion

Dehydrogenation is normally performed at high temperatures and low pressures, preferably with hydrogen as carrier gas. This is acceptable as long as the chemical stability of the molecules tolerates such severe conditions. When this is not so, different alternatives must be considered. Such alternatives are reactions in liquid phase at the appropriate temperature and pressure by use of: (i) solvent, (ii) a purging inert gas; (iii) hydrogen acceptors; or (iv) even low surface-area catalysts. The conditions are a function of the type of reaction and must be adjusted in consequence.

References

[1] R. J. Farrauto, C. H. Bartholomew, Fundamentals of Industrial Catalytic Processes, Chapman and Hall, New York, 1997, p. 630.

[2] M. Kraus, in G. Ertl, H. Knözinger, J. Weitkamp (eds.), Handbook of Heterogeneous Catalysis, Vol. 5, Wiley-VCH, Weinheim, 1996, p. 2159.

[3] C. N. Satterfield, Heterogeneous Catalysis in Industrial Practice, McGraw–Hill, New York, 1991, p. 554.

[4] N. Goetz, D. Mangold, J. Wahl, US Patent 4424364 (1984), to BASF AG.

[5] P. Lesage, J. P. Candy, C. Hirigoyen, F. Humblot, J. M. Basset, J. Mol. Catal. A 112 (1996) 431.

[6] J. Käsbauer, H. Fiege, US Patent 5672719 (1997), to Bayer AG.
[7] S. Alini, L. Cotarca, P. Delogu, US Patent 5872265 (1999), to Industrie Chimiche Caffaro S.P.A.
[8] E.J. Agnello, G.D. Laubach, J. Am. Chem. Soc. 82 (1960) 4293.
[9] P.A. Weyrich, W.F. Hölderich, Appl. Catal. A 158 (1997) 145.
[10] J.H. Sinfelt, Catal. Rev.-Sci. Eng. 9 (1974) 147.
[11] J.B. Woell, J.W. Catino, US Patent 5241122 (1993), to Union Camp Corporation.
[12] J.N. Armor, Catal. Today 25 (1995) 199.
[13] S. Tschudin, T. Shido, R. Prins, A. Wokaun, J. Catal. 181 (1999) 113.
[14] P.E. Savage, Chem. Rev. 99 (1999) 603.
[15] H. Suzuka, H. Hattori, J. Mol. Catal. A 63 (1990) 371.
[16] H. Hattori, Stud. Surf. Sci. Catal. 78 (1993) 35.
[17] D. Buhl, D.M. Roberge, W.F. Hölderich, Appl. Catal. A, accepted for publication (1999).
[18] D. Buhl, P.A. Weyrich, W.M.H. Sachtler, W.F. Hölderich, Appl. Catal. A 171 (1998) 1.
[19] V. Krishnasamy, Aust. J. Chem. 33 (1980) 1313.
[20] V. Krishnasamy, L.M. Yeddanapalli, Can, J. Chem. 54 (1976) 3458.
[21] Y. Tanaka, H. Hattori, K. Tanabe, Bull. Chem. Soc. Jpn 51 (1978) 3641.
[22] P.A. Weyrich, W.F. Hölderich, M.A. van Daelen, A.M. Gorman, Chem. Lett. 52 (1998) 7.
[23] C.P. Newman, US Patent 5082979 (1992), to Unilever Patent Holdings B.V.
[24] K. Tanabe, W.F. Hölderich, Appl. Catal. A 181 (1999) 399.
[25] J.A. Amelse, US Patent 5189234 (1993), to Amoco Corporation.
[26] S. Ozawa, M. Takagawa, T. Fujimori, US Patent 5446226 (1995), to Mitsubishi Gas Chemical Company Inc.
[27] B.L. Gustafson, C.E. Summer, M. Bellas, G.J. Irick, D.W.J. Fuller, E.W. Arnold, E.J. Fugate, US Patent 5359134 (1994), to Eastman Chemical Company.
[28] S.G. Koshel, N.V. Lebedeva, E.K. Rudkovskii, T.B. Krestinina, G.N. Koshel, A.S. Danilova, Russ. J. Org. Chem. 33 (1997) 55.
[29] W.H. Müller, K. Riedel, H. Krekeler, US Patent 4160113 (1979), to Hoechst AG.
[30] H. Krekeler, W.H. Müller, US Patent 4024196 (1977), to Hoechst AG.
[31] K. Maki, K. Murayama, JP Patent 5855439 (1981), to Mitsubishi Kasei Company.
[32] J.D. Fellmann, R.J. Saxton, P. Tung, US Patent 5233095 (1993), to Catalytica Inc.
[33] P.J.N. Meijer, A.M.F. Vanholsaet, E.T.M. Wolters, US Patent 4154965 (1979), to Stamicarbon, B.V.
[34] A.B. McKague, W. deWaal, C.E. Van Winckel, US Patent Re. 29201 (1977), to CPC International Inc.
[35] F.J. Bröcker, P. Trübenbach, M. Baumann, J. Schubert, US Patent 5817891 (1998), to BASF AG.
[36] J. Heveling, E. Armbruster, W. Siegrist, US Patent 5714610 (1998), to Lonza, Ltd.
[37] F.-L. Wang, K. Yu, W.-S. Lee, W.-F. Yang, Chem. Comm. (1994) 811.
[38] F.-l. Wang, T.-f. Tsai, Y.-h. Tsai, Y.-k. Cheng, Appl. Catal. A 126 (1995) L229.
[39] F.-l. Wang, T.-f. Tsai, Catal. Today 44 (1998) 259.
[40] J. Falbe, P. Lappe, J. Weber, in Ullmann's Encyclopedia of Industrial Chemistry, Vol. A 1, Wiley–VCH, Weinheim, 1985, p. 321.
[41] D.V. Cesar, C.A. Peréz, V.M.M. Salim, M. Schmal, Appl. Catal. A 176 (1999) 205.
[42] C.A. Gibson, US Patent 3998884 (1976), to Union Carbide Corporation.
[43] S. Nikola, S. Rakovsky, Oxid. Commun. 18 (1995) 358.
[44] T.F.M. de Graaf, H.J.A. Delahaye, US Patent 4383124 (1983), to Stamicarbon, B.V.
[45] J. Koshino, Y. Fujikura, US Patent 4918052 (1990), to Kao Corporation.
[46] T. Yamanaka, M. Yagi, US Patent 4134919 (1979), to Takasago Perfumery Co., Ltd.
[47] D. Gulkova, M. Kraus, J. Mol. Catal. A 87 (1994) 47.
[48] S. Kahn, US Patent 3940446 (1976), to Universal Oil Products Company.
[49] S. Oka, Bull. Chem. Soc. Jpn 35 (1962) 986.
[50] R. Sigg, H. Regner, US Patent (1995), to Huels AG.
[51] H.E. Bellis, US Patent 5110954 (1992), to E.I. Dupont de Nemours and Company.
[52] T. Ichiki, K. Mori, S. Suzuki, H. Ueno, K. Kobayashi, US Patent 5210229 (1993), to Tonen Chemical Corporation.

8.9 Meerwein–Ponndorf–Verley Reduction, Oppenauer Oxidation, and Related Reactions

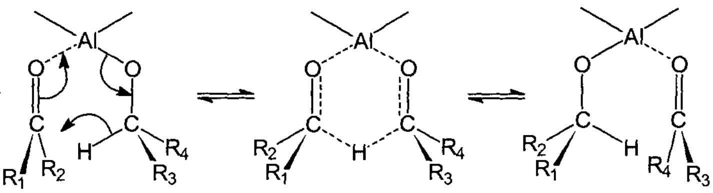
E. J. Creyghton, J. C. van der Waal

8.9.1 Introduction

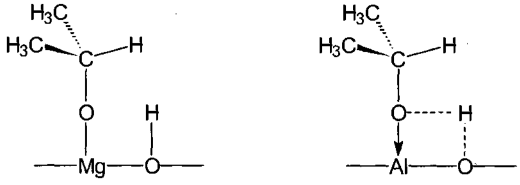
The Meerwein–Ponndorf–Verley reduction of aldehydes and ketones and its reverse, the Oppenauer oxidation of alcohols, are hydrogen-transfer reactions that can be performed under mild conditions and without the risk of reducing or oxidizing other functional groups [1]. The hydrogen donors are easily oxidizable secondary alcohols (e. g. *i*-PrOH) and the oxidants are simple ketones (e. g. cyclohexanone). Industrial applications of the MPVO reactions are found in the fragrance and pharmaceutical industries, for example.

Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reactions are usually mediated by metal alkoxides such as Al(O*i*-Pr)$_3$. The activity of these catalysts is related to their Lewis-acidic character in combination with ligand exchangeability. The mechanism of these homogeneous MPVO reactions proceeds via a cyclic six-membered transition state in which both the reductant and the oxidant are co-ordinated to the metal center of the metal alkoxide catalyst (Scheme 1). The alcohol reactant is co-ordinated as alkoxide. Activation of the carbonyl by co-ordination to Al(III)-alkoxide initiates the hydride-transfer reaction from the alcoholate to the carbonyl. The alkoxide formed leaves the catalyst via an alcoholysis reaction with another alcohol molecule, usually present in excess [1].

The major advantage of heterogeneously catalyzed MPVO reactions over the homogeneous variant is that the solid catalysts can easily be separated from the liquid reaction mixture. Many examples of heterogeneously catalyzed MPVO reactions have nowadays been reported. The catalysts comprise (modified) metal oxides which have either Lewis acid or base properties. Several reaction mechanisms have been proposed; in all of these the first step is formation of an alkoxide-like species, and the reactions proceed via cyclic six-membered transition states, comparable with those in homogeneous systems. From infrared studies, Ivanov et al. proposed two mechanistic variants for Lewis-acid and -base catalysis [2]. They suggested that with basic catalysts the *sec*-alcohol becomes dissociated on weak Lewis-acid/strong-base pairs, resulting in the metal alkoxide and surface



Scheme 1. Reaction mechanism for the homogeneously catalyzed MPVO reaction.



Scheme 2. Formation of an alkoxide-type species on a basic catalyst (left) and on a Lewis-acid catalyst (right), as proposed by Ivanov et al. [2].

OH groups. With Lewis-acid catalysts alkoxide formation occurs on co-ordinatively unsaturated metal sites, probably assisted by neighboring oxygen sites (Scheme 2).

This chapter presents a comprehensive overview of heterogeneously catalyzed MPVO reactions. It includes, apart from the use of various metal oxides, the more recent application of chemically anchored co-ordination compounds, hydrotalcites, mesoporous materials, and zeolites as recyclable solid catalysts. Some remarkable examples of shape-selective conversions resulting in high stereoselectivities illustrate the progress made in this field.

8.9.2 MPVO Reactions Catalyzed by Metal Oxides

8.9.2.1 Alumina

Posner et al. have used γ-Al_2O_3 in the reduction of unsaturated carbonyl compounds by *i*-PrOH [3]. Dehydrated alumina deprotonated *i*-PrOH forming the alkoxide in situ. High temperatures were needed (up to 300 °C) and only low yields of alcohol were obtained, because of the occurrence of several side-reactions which are catalyzed by weak Brønsted acid sites present on the alumina surface.

Horner and Kaps have used chlorinated γ-Al_2O_3 in combination with a small amount of $Al(Oi\text{-}Pr)_3$ as the catalyst for the reduction of benzaldehyde, cyclohexanone, and acetophenone by *i*-PrOH [4]. In the absence of $Al(Oi\text{-}Pr)_3$, no reaction occurred. The addition of a small amount of strong base was found to enhance the reaction rate. Analogous phenomena have been observed in the Oppenauer oxidation of several secondary alcohols. Strong bases presumably assist the deprotonation of alumina-surface co-ordinated *i*-PrOH, thereby forming the required alkoxide surface species. The modified alumina, which contained ca 85 mmol chloride/100 g alumina, was obtained by heating dry alumina in thionyl chloride for 24 h. The chloride at the surface increases the Lewis acidity of the aluminum ions and the addition of the base facilitates the deprotonation of *i*-PrOH.

Wismeijer et al. studied the liquid-phase transfer-hydrogenation of 4-*tert*-butylcyclohexanone by *i*-PrOH at 83 °C over activated γ-Al_2O_3 as the catalyst [5]. The activity of the catalyst was found to increase with increasing activation temperature. Selective poisoning experiments indicated that co-ordinatively unsaturated Al^{3+} surface ions (Lewis acid sites), formed upon dehydroxylation, were essential for catalyst activity. During reaction the catalyst was found to become conditioned by irreversible alcoholysis of the initial active sites, producing less active sites. The reaction mechanism, however, remained essentially the same as indicated by the constant ratio of *cis*- to *trans*-4-*tert*-butylcyclohexanol (9:91).

Gargano et al. investigated the pretreatment of the alumina catalyst with hydrogen at 270 °C [6]. This enabled the use of much lower reaction temperatures, thus increasing the selectivity towards the alcohols required. Several other metal oxides have been tested and La_2O_3 proved to be the best catalyst, with regard to both conversion and selectivity.

Ravasio et al. investigated hydrogen transfer from different secondary alcohols to a steroidal conjugated enone and a saturated ketone over a Cu/Al_2O_3 catalyst at 90 °C [7]. The stereoselectivity of the transfer reaction was found to depend on the secondary alcohol used as hydrogen donor. Selectivity for the 5β isomer ranged from 48 to 85 %. A large effect of the donor alcohol on stereoselectivity was also found in the reduction of the 3-keto group. In all cases excess of the thermodynamically favored equatorial alcohol was obtained.

8.9.2.2 Zirconia and Immobilized Zirconium Complexes

Kuno et al. used hydrous ZrO_2 as solid catalyst in the oxidation of both secondary and primary alcohols [8]. The catalyst was prepared via precipitation of an aqueous solution of $ZrCl_2O.8H_2O$ with sodium hydroxide at room temperature. The resulting hydroxide was calcined at 300 °C. Batch oxidations were performed at 80 °C in benzene or toluene with 60 equiv. acetone as the oxidant. Alumina, aluminum silicate, and zeolite NaA were also tested. These catalysts were shown to give lower yields in the oxidation of 2-octanol, whereas SiO_2, hydrous TiO_2, and hydrous SnO_2 were not active. A continuous liquid-phase system with a fixed catalyst bed in a tube reactor was used, and the reaction temperature was optimized for several secondary alcohol substrates. Primary alcohols were oxidized by *p*-benzoquinone or benzophenone with ZrO_2 as the catalyst at 140 °C in xylene as the solvent. The same zirconium catalyst also reduced carboxylic acids and even esters with *i*-PrOH [9].

The chemoselective reduction of nitro and carbonyl functions with *i*-PrOH/KOH over nickel-stabilized zirconia has recently been reported by Upadhya et al. [10]. This catalytic system selectively reduced 4-nitroacetophenone and 4-nitrobenzophenone to 4-aminoacetophenone and 4-aminobenzophenone, respectively, without reduction of the carbonyl function. It was assumed that Ni^{2+} both stabilizes the cubic zirconia structure and actively participates in the reaction by promoting the dehydrogenation of *i*-PrOH. It was proposed that the Ni^0 species formed, still incorporated in the ZrO_2 bulk structure, had only moderate activity, thus enabling chemoselective reduction.

Leyrit et al. reported the synthesis of silica-anchored mononuclear (tris)isopropoxyzirconium, $(\equiv SiO)Zr(Oi\text{-}Pr)_3$, as a true heterogeneous catalyst in MPVO reactions [11,12]. It is worthy of note that dissolved tetraisopropoxyzirconium is not active in MPVO reactions. The solid catalyst was prepared by reacting partially dehydroxylated silica with tetra(neopentyl)zirconium ($Zr(Np)_4$) to form a mononuclear and covalently bonded (siloxy)tris(neopentyl)zirconium complex. Controlled alcoholysis with *i*-PrOH gave the final alkoxy complex. The catalyst proved to be active in the reduction of both aromatic and cyclic ketones. Diphenyl ketone, however, could not be reduced as a result of steric repulsion preventing proper co-ordination to Zr, neither was the aliphatic 2-methyl-4-pentanone reduced. In this reaction *i*-PrOH seems to be unable to substitute the 2-methyl-4-pentanolate product rapidly. In the reverse reaction, 4-methyl-2-pentanol was readily oxidized to the corresponding alcohol by employing acetophenone as hydrogen acceptor. The catalyst proved to be fully recyclable and stable against leaching. Activity in successive runs was essentially identical and no Zr was found in solution. Apparently, the ≡SiO–Zr bond is stable against alcoholysis.

8.9.2.3 Magnesium Oxide, Magnesium Phosphates, and Mg-Al Hydrotalcites

Kaspar et al. demonstrated the reduction of α,β-unsaturated ketones to allylic alcohols with *i*-PrOH in the gas phase, over MgO as fixed bed catalyst at 250 °C [13]. The MgO was formed in situ by heating $Mg(OH)_2$ at 350 °C in an air current for 4 h. Regeneration of the catalyst was achieved similarly. In a subsequent paper the chemoselective reduction of the carbonyl group of 4-hexen-3-one over a variety of solid catalysts was reported [14]. MgO was found to have the highest chemoselectivity, although, as a result of its high basicity, several side reactions were also observed. Doping of the MgO catalysts with HCl afforded solid catalysts with improved selectivity.

Kijenski et al. studied hydrogen-transfer reactions of a variety reactants with different functional groups [15]. The reactions were performed in the gas phase over MgO in a fixed bed, activated at either 550 or 750 °C, at reaction temperatures in the range of 350–450 °C. Donor molecules included alcohols and hydrocarbons. All the (de)hydrogenation reactions studied were important for the preparation of perfumery flavors and fragrances. They included the reduction of carbonyl groups and the dehydrogenation of long-chain aliphatic alcohols. Other related reactions that were screened included the hydrogenation of epoxy compounds, the hydrogenation of styrene, and the reduction of aromatic nitro compounds. The successful hydrogenation of nitrobenzene to aniline with ethanol initiated further research in this field, leading to a separate communication [16]. Kijenski et al. extended their research in the field of hydrogen-transfer reactions to a series of main group and transition metal oxides, supported on silica [17]. The reductions of ethyl methyl ketone, methyl isopropyl ketone and 4-methylacetophenone with *i*-PrOH were chosen as model reactions. Most of the metal oxides tested had catalytic activity. Catalytic titration, using poisons suppressing different types of surface site, was used for identification of the active centers of the catalysts. The results indicated the participation of basic and/or one-electron donor sites of the MgO surface. Acidic centers were mainly responsible for undesired consecutive dehydration. Acidity could also be introduced deliberately by modifying MgO with mineral acids such as H_3PO_4 and H_2SO_4 [18]. The bifunctional catalysts thus obtained proved active in the reduction of arylalkyl ketones and in the dehydration of the corresponding alcohols. In this way, acetophenone, 4-isopropylacetophenone, and propiophenone were quantitatively transformed into their styrene derivatives.

Szöllösi et al. have studied MgO as a catalyst for the hydrogen-transfer reaction between methyl ketones and *i*-PrOH in the vapor phase [19]. It was shown that deactivation occurred as a result of condensation products formed from methyl ketones and acetone. This deactivation could be prevented by pretreatment of the catalyst with carbon tetrachloride. It was proposed that Cl^- ions block the irreversible adsorption of ketones at Lewis-acid sites.

Aramendía et al. have prepared different magnesium phosphates and tested them in the vapor-phase MPVO reaction between 2-hexanol and cyclohexanone [20]. The activity and selectivity of magnesium orthophosphates was found to depend largely on their preparation and activation procedure which determines their (surface) structure and chemical properties. Depending on the Lewis-base and (Brønsted) acid surface density and the balance between the two, the reaction is directed to hydrogen transfer or dehydration, the latter resulting in the formation of olefins. Only some of the magnesium orthophosphates had the same high activity and selectivity in the MPVO reaction as MgO, suggesting similar active sites. Magnesium pyrophosphate, however, mainly dehydrated 2-hexanol into olefins which is explained by its high surface acidity and low basicity. The reaction of acetophenone with methanol or dimethyl carbonate over magnesium phosphate and MgO catalysts was reported in a separate paper [21].

Kumbhar et al. have used hydrotalcites in the MPV reduction of carbonyl compounds [22]. Mg-Al hydrotalcites with Mg/Al molar ratios varying between 2 and 5, activated at temperatures ranging from 350 up to 550 °C, were both active and selective in the reduction of 4-*tert*-butylcyclohexanone with *i*-PrOH. The highest activity was found for a hydrotalcite with an Mg/Al ratio of 3, calcined at 450 °C. This catalyst, which proved recyclable, was also suitable for the reduction of citronellal, cinnamaldehyde, and citral to the corresponding unsaturated alcohols, which are valuable perfumery compounds. The activity was explained by the synergistic effect of both strong Lewis basicity and mild acidity.

8.9.3 MPVO Reactions Catalyzed by Mesoporous Materials

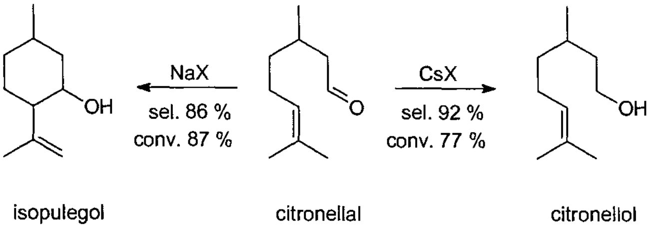
Mesoporous materials of the MCM-41 type have also been used in MPVO reactions. Creyghton et al. reported the use of both H- and Na-exchanged activated MCM-41 (Si/Al = 15) in the reduction of 4-*tert*-butylcyclohexanone in *i*-PrOH under reflux [23,24]. After 6 h, conversion to the alcohols was only 10 %; the thermodynamically favored *trans* compound was obtained with 90 % selectivity. It was proposed that the activity resides in co-ordinatively unsaturated Al atoms which can react with the alcohol to form an activated alkoxide species.

Increased activity was found by Anwander et al. who grafted aluminum alkoxide moieties on siliceous mesoporous MCM-41 [25]. These materials were first prepared by a one-step solution impregnation by treating Al(O*i*-Pr)$_3$ with partially dehydroxylated MCM-41 in hexane. In a second approach, MCM-41 was reacted with 4-coordinate $Al[N(SiHMe_2)_2]_3.THF$, a method which produces surface species with lower co-ordination. Treatment of this material with excess *i*-PrOH gave the final catalyst. It was confirmed by ^{27}Al NMR that the second approach resulted in the highest amount of 4- and 5-coordinated aluminum species. Both materials had similar activity in the reduction of 4-*tert*-butylcyclohexanone with *i*-PrOH, however, and the *cis*/*trans* ratio of the alcohols produced approached that of thermodynamic equilibrium. The catalysts could be readily recycled without loss of activity. Furthermore, after separation of the catalyst no further reaction occurred upon addition of fresh substrate to the reaction solution. Apparently, no homogeneous $Al(Oi\text{-}Pr)_3$ had leached from the solid catalyst, indicating its stability. Comparable synthesis routes were also used to graft neodymium alkoxide species on siliceous MCM-41 [26]. They proved to be efficient solid catalysts in MPV reduction. As for homogeneous rare-earth alkoxide complexes, this is explained by their high ligand exchangeability.

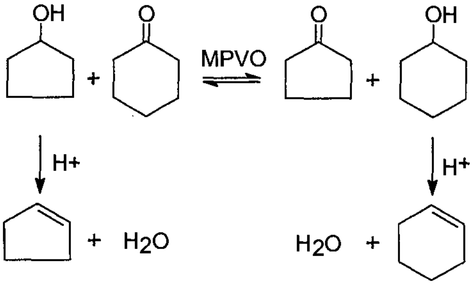
8.9.4 MPVO Reactions Catalyzed by Zeolites

Shabtai et al. studied the potential of alkali and alkaline-earth exchanged X-type zeolites in the gas-phase (100–180 °C) MPV reduction of a variety of saturated and unsaturated aldehydes and ketones, with *i*-PrOH as reducing agent [27]. In the reduction of linear aldehydes over NaX a gradual decrease in the reduction rate was observed with increasing chain length; this was attributed to increasing diffusional limitations in the micropores. Selectivity to the corresponding 1-alcohols was generally high ($> 95\,\%$). Application of Lewis-acidic CaX resulted in acetalization of the aldehydes as an important side-reaction. This could be prevented, however, by use of higher reaction temperatures. Unfortunately, the X-type zeolite/isopropanol system was not capable of reducing α,β-unsaturated aldehydes. Shape-selectivity was found in the selective conversion of citronellal under MPV conditions. In NaX there was enough space for the substrate to undergo intramolecular ring closure to isopulegol, whereas over CsX reduction to the linear citronellol was observed (Scheme 3). In the reduction of methylcyclohexanone isomers at 100 °C it was observed that the 4-isomer reacted relatively fast and gave the thermodynamically determined product distribution (*cis*/*trans* = 24:76). 2- and 3-Methylcyclohexanone reacted more slowly and gave a kinetically determined product distribution (*cis*/*trans* = 62.5:37.5 and 23.5:76.5 for the 2- and 3-isomers, respectively). It was proposed that the mechanism involved the formation of a surface isopropoxide group attached to a cationic site (basic mechanism). It could not be excluded, however, that incompletely co-ordinated Si or Al sites contributed to the catalytic activity (Lewis-acid mechanism).

The reaction of cyclopentanol in the presence of cyclohexanone at 350 °C over amorphous metal oxides and zeolites was studied by Berkani et al. (Scheme 4) [28]. MgO was found to be the most active catalyst for the hydrogen transfer reaction, then potassium impregnated gamma alumina (γ-Al_2O_3-K), γ-Al_2O_3, and CsNaX zeolites. With the zeolites MPVO activity decreased with decreasing cesium content. The opposite trend was observed for the acid-catalyzed dehydra-



Scheme 3. Shape-selective conversion of citronellal to isopulegol or citronellol under MPV conditions [27].



Scheme 4. Reaction of a mixture of cyclopentanol and cyclohexanone at 350 °C over different metal oxide catalysts [28].

tion activity. Addition of CO_2 poisoned only the hydrogen-transfer reaction–the amount of cyclopentene remained constant. It was, therefore, concluded that hydrogen transfer occurred only on the basic sites of the catalysts and dehydration only on their acid sites.

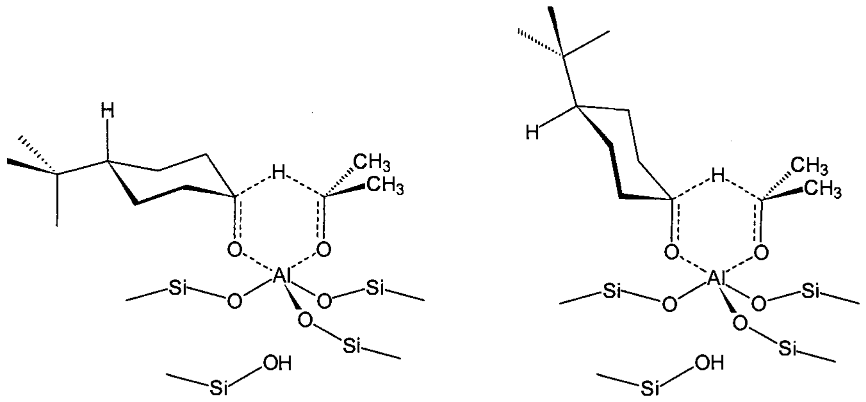
Creyghton et al. recently reported the application of zeolite Beta (BEA topology) in the stereoselective ($>$ 95 %) reduction of 4-*tert*-butylcyclohexanone to *cis*-4-*tert*-butylcyclohexanol in the liquid phase [23,24]. This zeolite-based catalyst proved to be fully regenerable without loss of activity or stereoselectivity. This is of industrial relevance, because the *cis* isomer is a fragrance-chemical intermediate. Other active solid catalysts, including zeolites, invariably gave the thermodynamically more stable *trans* isomer in excess.

The activity of the zeolite Beta catalyst was found to increase upon increasing activation temperature and deep-bed calcination conditions resulted in higher catalytic activity than a shallow-bed procedure, implying a relationship between the catalytic activity and the extent of framework dealumination, because the former method results in more auto-steaming. Infrared results indicated, moreover, a relationship between catalytic activity and the amount of partially hydrolyzed framework aluminum. This was further supported by a detailed ^{29}Si and ^{27}Al MAS NMR and FTIR study [29]. In the proposed mechanism, the first step is chemisorption of *i*-PrOH on a Lewis-acid site, consisting of co-ordinatively unsaturated framework-attached Al. This results in the formation of a surface alkoxide considered to be the H-donor. Co-ordinative interaction of the ketone to the same Al atom enables the formation of a six-membered transition state (analogous to that of the homogeneous reaction) enabling hydride transfer to occur.

The transition states leading to the *cis* and *trans* alcohols differ substantially in size and the way in which they can be accommodated in the pores of zeolite Beta. That for the *cis* isomer is more or less linearly aligned with the pore axis and can easily be accommodated within the straight channels of the zeolite. The transition state for the formation of the *trans* isomer is more or less perpendicular to the channel wall and cannot be well accommodated within the micropores (Scheme 5). As required by this mechanism, the *cis* alcohol was found to undergo Oppenauer oxidation over zeolite Beta whereas activity for the *trans* isomer being negligible.

In addition to the stereoselective MPV reaction presented above, van der Waal et al. reported the catalytic activity of aluminum-free titanium Beta (Ti-Beta) zeolite in the same MPV reaction [30]. Again, selectivity was very high for the *cis* isomer, indicating a similar reaction mechanism. Kinetically determined product distributions were also obtained in the MPV reduction of 2-, 3-, and 4-methylcyclohexanone; the *cis*, *trans* and *cis* alcohols, respectively, being the major products. It was suggested that in this reaction tetrahedrally incorporated Ti atoms with Lewis-acid properties were involved in the alkoxide formation. The Lewis-acid properties of tetrahedrally incorporated titanium in zeolite Ti-Beta had already been observed during catalytic studies on the epoxidation of olefins with aqueous hydrogen peroxide in alcoholic solvents. Recently, quantum-chemical calculations on zeolites TS-1 and Ti-Beta confirmed the higher Lewis acidity of the latter [31].

The catalytic activity of Ti-Beta was found to be much lower than that of its aluminum analog, although its tolerance of water was much higher. The latter property, which is related to its hydrophobic character, and especially the absence of acid sites, enables its use in the gas phase at higher reaction temperatures when acid-catalyzed side reactions become significant [32]. In a typical gas-phase

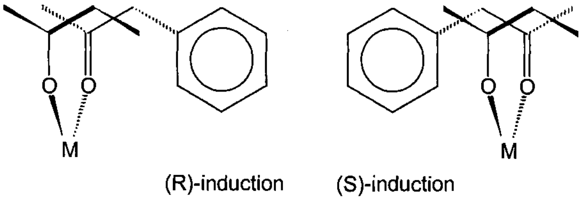


Scheme 5. Transition states for the formation of *cis*-4-*tert*-butylcyclohexanol (left) and *trans*-4-*tert*-butylcyclohexanol (right) by the MPV reduction of 4-*tert*-butylcyclohexanone with *i*-PrOH catalyzed by zeolite Beta [24].

experiment with 4-methylcyclohexanone and *i*-PrOH at 100 °C it was observed that the aluminum-containing zeolite Beta (Al-Beta) catalyst was deactivated within hours whereas deactivation of its titanium analog occurred much more slowly. 4-Methylcyclohexene, formed by acid-catalyzed dehydration of the product alcohols, was the main product for Al-Beta whereas Ti-Beta was found to be selective for the *cis* and *trans* alcohols.

Further evidence for the proposed mechanism in which both the alcohol and ketone are co-ordinated to the same Lewis-acid metal site came from the liquid-phase reaction of prochiral phenylacetone with (*S*)-2-butanol [33]. Both the aluminum- and titanium-containing zeolite Beta catalysts gave the corresponding alcohol in an enantiomeric excess (e. e.) of 34 %. The positive rotation of the reaction mixture after removal of the excess alcohol proved the preferred formation of the (*S*)-(+)-1-phenyl-2-propanol enantiomer. The formation of the (*S*) enantiomer can be explained by the preferential orientation of the bulky benzyl group of phenylacetone relative to the spatially smaller methyl group of (*S*)-2-butanol in the transition state (Scheme 6).

When zeolite MCM-22 is employed as catalyst for the reaction between substituted cyclohexanones and *sec*-alcohols, instead of the MPV reduction obtained with Beta, a novel reductive etherification occurs to give, for example, from 4-*tert*-butylcyclohexanone and *i*-PrOH the isopropyl ether of 4-*tert*-butylcyclohexanol with a *cis/trans* isomer ratio of 60:40 [34]. It is considered that in this reaction the higher Brønsted-acid site population relative to MPV sites favors the formation of the ether via an intermediate hemiacetal.



Scheme 6. Transition states for the chiral MPV reduction of phenylacetone on zeolite Beta, via optical induction, with (*S*)-2-butanol as the reductant [33].

8.9.5 Conclusions

Solid catalysts active in MPVO reactions have surface basicity or Lewis acidity. They include, amongst others, alumina, zirconia, magnesium oxide, and magnesium phosphates. More recent developments include the chemical anchoring of catalytically active co-ordination complexes, and the application of hydrotalcites, mesoporous materials (MCM-41), and zeolites. Anchoring of co-ordination compounds might open the route to true heterogeneous enantioselective MPVO reactions. As a result of their inherent shape-selectivity zeolites uniquely afford remarkable stereoselectivity in MPVO reactions.

Acknowledgment

The authors would like to thank Dr R. S. Downing for critically reviewing the manuscript.

References

[1] For a review see: C.F. de Graauw, J. A. Peters, H. van Bekkum and J. Huskens, *Synthesis*, **10** (1994) 1007.
[2] V. A. Ivanov, J. Bachelier, F. Audry and J.C. Lavalley, *J. Mol. Catal.*, **91** (1994) 45 and references therein.
[3] G.H. Posner, A.W. Runquist and M.J. Chapdelaine, *J. Org. Chem.*, **42** (1977) 1202.
[4] L. Horner and U.B. Kaps, *Ann. Chem.*, (1980) 192.
[5] A.A. Wismeijer, A.P.G. Kieboom and H. van Bekkum, *Appl. Catal.*, **34** (1987) 189.
[6] M. Gargano, V. D'Oranzio, N. Ravasio and M.J. Rossi, *J. Mol. Catal.*, **58** (1990) L5.
[7] N. Ravasio, M. Gargano, V.P. Quatraro and M. Rossi, *Stud. Surf. Sci. Catal.*, **59** (1991) 161.
[8] H. Kuno, M. Shibagaki, K. Takahashi and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **64** (1991) 312.
[9] K. Takahashi, M. Shibagaki, H. Kuno and H. Matsushita, *Shokubai*, **37** (1995) 23.
[10] T.T. Upadhya, S.P. Katdare, D.P. Sabde, V. Ramaswamy and A. Sudalai, *J. Chem. Soc., Chem. Commun.*, (1997) 1119.
[11] P. Leyrit, C. McGill, F. Quignard and A. Choplin, *J. Mol. Catal. A: Chemical*, **112** (1996) 395.
[12] A. Choplin, B. Coutant, C. Dubuisson, P. Leyrit, C. McGill, F. Quignard and R. Teissier, *Stud. Surf. Sci. Catal.*, **108** (1997) 353.
[13] J. Kaspar, A. Trovarelli, M. Lenarda and M. Graziani, *Tetrahedron Lett.*, **30** (1989) 2705.
[14] J. Kaspar, A. Trovarelli, F. Zamoner, E. Farnetti and M. Graziani, *Stud. Surf. Sci. Catal.*, **59** (1991) 253.
[15] J. Kijenski, M. Glinski and J. Reinhercs, *Stud. Surf. Sci. Catal.*, **41** (1988) 231.
[16] J. Kijenski, M. Glinski, R. Wisniewski and S. Murghani, *Stud. Surf. Sci. Catal.*, **59** (1991) 169.
[17] J. Kijenski, M. Glinski, J. Czarnecki, R. Derlacka and V. Jarzyna, *Stud. Surf. Sci. Catal.*, **78** (1993) 631.
[18] J. Kijenski, M. Glinski and C.W. Aquilar Quiroz, *Appl. Catal. A: General*, **150** (1997) 77.
[19] Gy. Szöllösi and M. Bartók, *Appl. Catal. A: General*, **169** (1998) 263.
[20] M.A. Aramendía, V. Borau, C. Jiménez, J.M. Marinas and F.J. Romero, *Catal. Lett.*, **58** (1999) 53.
[21] M.A. Aramendía, V. Borau, C. Jiménez, J.M. Marinas and F.J. Romero, *J. Catal.*, **183** (1999) 119.
[22] P.S. Kumbhar, J. Sanchez-Valente, J. Lopez and F. Figuras, *J. Chem. Soc., Chem. Commun.*, (1998) 535.
[23] E.J. Creyghton, S.D. Ganeshie, R.S. Downing and H. van Bekkum, *J. Chem. Soc., Chem. Commun.*, (1995) 1859.
[24] E.J. Creyghton, S.D. Ganeshie, R.S. Downing and H. van Bekkum, *J. Mol. Catal. A: Chemical*, **115** (1997) 457.
[25] R. Anwander, C. Palm, G. Gerstberger, O. Groeger and G. Engelhardt, *J. Chem. Soc., Chem. Commun.*, (1998) 1811.
[26] R. Anwander and C. Palm, *Stud. Surf. Sci. Catal.*, **117** (1998) 413.
[27] J. Shabtai, R. Lazar and E. Biron, *J. Catal.*, **27** (1984) 35.
[28] M. Berkani, J.L. Lemberton, M. Marczewski and G. Perot, *Catal. Lett.*, **31** (1995) 405.
[29] P.J. Kunkeler, B.J. Zuurdeeg, J.C. van der Waal, J.A. van Bokhoven, D.C. Koningsberger and H. van Bekkum, *J. Catal.*, **180** (1998) 234.
[30] J.C. van der Waal, K. Tan and H. van Bekkum, *Catal. Lett.*, **41** (1996) 63.

[31] G. Sastre and A. Corma, *Chem. Phys. Lett.*, **302** (1999) 447.
[32] J. C. van der Waal, P. J. Kunkeler, K. Tan and H. van Bekkum, *J. Catal.*, **173** (1998) 74.
[33] J.C. van der Waal, E. J. Creyghton, P. J. Kunkeler, K. Tan and H. van Bekkum, *Topics Catal.*, **4** (1997) 261.
[34] M. J. Verhoef, E. J. Creyghton, J. A. Peters and H. van Bekkum, J. Chem. Soc., *Chem. Commun.*, (1997) 1989.

8.10 Enantioselective Hydrogenation with Solid Catalysts

T. Mallat, A. Baiker

8.10.1 Introduction and Scope

Synthesis of pure enantiomers of chiral compounds is the biggest challenge in the field of solid-catalyzed hydrogenation reactions. Though heterogeneous catalysts have several inherent technical advantages connected with the ease of separation, handling, and re-use, their enantioselectivity and range of application cannot yet match those of homogeneous asymmetric catalysts. Enantioselective hydrogenation over solid catalysts has been known since the early thirties but major progress indicating its potential is confined to the past two decades. The most promising synthetic approach is use of a metal hydrogenation catalyst in the presence of a soluble chiral modifier. Chirally modified metals are a technically simple and inexpensive solution to asymmetric hydrogenation. If the scope of these catalysts systems can be considerably broadened and their efficiency increased, they might be an economic alternative to proven homogeneous transition metal catalysts or conventional hydrogenation–resolution processes.

The topic of this chapter is enantioselective hydrogenation over chiral or chirally modified solid catalysts. Diastereoselective hydrogenation of chiral compounds and asymmetric hydrogenation with heterogenized (supported, embedded) homogeneous transition metal complexes will not be discussed.

8.10.2 Strategies for Developing Solid Enantioselective Catalysts

Several approaches can be used to design solid enantioselective catalysts [1–5]. In general, the solid material must combine catalytic activity with stereochemical control. The active site should be regarded as an ensemble of surface metal atoms which adsorb and activate the reactant and hydrogen and can also accommodate a soluble chiral modifier. For example, in the hydrogenation of ethyl pyruvate over cinchona-modified Pt an ensemble of about 15–20 metal atoms is required to accommodate the bulky modifier, substrate, and hydrogen [6].

8.10.2.1 Metal on a Chiral Support

This is the earliest strategy for preparing a chiral solid hydrogenation–dehydrogenation catalyst (for reviews see [1–3,5,7,8]). Quartz, silk fibroin, cyclodextrin, and cellulose were applied as chiral supports of natural origin. With a Pd/silk catalyst up to 66 % optical yield was obtained in C=C bond hydrogenation, but subsequently the results proved irreproducible.

A drawback of this approach is that the chiral support can provide the necessary chiral environment only for the neighboring metal atoms (metal-support interface). Note that the chiral environment induced by a chiral support is much more rigid than that created by an adsorbed soluble chiral modifier (see below). The stability of the chiral support might also be critical. A feasible explanation for the unexpectedly high enantioselectivity and poor reproducibility of Pd/silk fibroin is the degradation of the natural polymer during metal deposition – the actual catalyst might be Pd chirally modified by dissolved amino acids or oligomeric residue.

8.10.2.2 Metal Modified by a Soluble Chiral Compound

Modification of a metal hydrogenation catalyst by addition of a naturally occurring chiral compound is another classical method: the first successful attempts were published about 60 years ago (for reviews see [1–3,7,8]). Continuous progress led to efficient chiral solid catalysts affording up 97–98 % enantiomeric excess (ee).

The Raney Ni–tartaric acid–NaBr catalyst system affords good to high enantioselectivity in the hydrogenation of β-functionalized and unfunctionalized ketones [9–13]. The technique of preparing an effective modified Ni catalyst has been improved remarkably during recent decades. It has been shown that Ni powder or supported Ni are almost as good precursors as Raney Ni. Large Ni crystallites are most favorable for enantio-differentiation, whereas the Al-enriched disordered Ni domains should be removed from Raney Ni by chemical or physical treatment [13]. The latest technique is not only highly efficient but also relatively simple. Crucial steps are ultrasonication of Raney Ni in water then modification with tartaric acid and NaBr at 100 °C and pH 3.2. The modification procedure is highly corrosive and produces large amounts of nickel- and bromide-containing waste – a major drawback for industrial application. The activity of modified Ni is also rather low. For example, full conversion of β-ketoesters at 100 bar and 60–100 °C (typical conditions) required up to 48 h even at a catalyst/substrate ratio of 23 % *w/w* [14]. For comparison, hydrogenation of ethyl pyruvate or ketopantolactone over the Pt-cinchonidine system is faster by orders of magnitude.

Another class of natural compounds, namely cinchona alkaloids, is used for stereochemical control in the Pt-catalyzed hydrogenation of α-functionalized, activated ketones [6,15–17]. Chiral modification of (supported) Pt is very simple: a small amount of the chiral compound is added to the reaction mixture before hydrogenation. The modifier is adsorbed by the metal surface – with hydrogen and substrate – and its interaction with the substrate during hydrogen uptake induces enantio-differentiation. In the hydrogenation of some activated ketones, high temperature (200–400 °C) reductive pretreatment of Pt in hydrogen doubled the enantioselectivity [8,17]. A typical feature of the Pt-catalyzed hydrogenation of activated ketones is the remarkable 'ligand acceleration' effect of the modifier by a factor of 5–100. The highest substrate/modifier molar ratio of 237 000 and lowest modifier/surface Pt atom ratio of 0.019 were reported for the hydrogenation of ketopantolactone to (*R*)-pantolactone (91.6 % ee [18]). Note that cinchona alkaloids are cheap and that separation of the modifier is not necessary because of the low concentration in the product. The extremely high substrate/modifier ratio enables hydrogenation in a continuous fixed bed reactor with minute quantities of modifier added to the feed [19].

Pd modified by cinchona, vinca, or ephedra alkaloids is a moderately efficient catalyst but Pd is still the catalyst of choice for the enantioselective hydrogenation of olefins with a functional group in the *α* position [8,20]. Modification of Pd with cinchonidine is as simple as for Pt, but Pd requires a considerably lower substrate/modifier ratio than Pt, probably because of weaker adsorption and/or partial degradation (hydrogenation) of the modifier during reaction. Another drawback is that the reactions are not accelerated but decelerated by the chiral modifier (by a factor of up to 140 [21]). This phenomenon can rationalize the moderate performance of chirally modified Pd.

8.10.2.3 Chiral Metal Surface

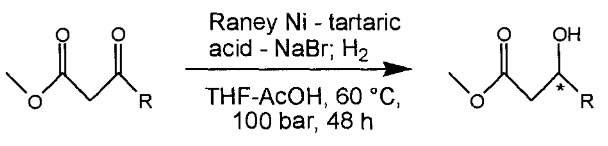
It has recently been proposed that kink sites of high Miller index metal surfaces should be considered as chiral when the step lengths on either side of the kink are unequal [22]. Two such surfaces, which are not superimposable, can be defined – by analogy with the Cahn–Ingold–Prelog rules – as, e.g., Ag(643)^R and Ag(643)^S. Theoretical calculations predicted that adsorption of chiral molecules should be stereospecific on such surfaces, but the only experimental evidence yet available is the electro-oxidation of D- and L-glucose on Pt(643) and Pt(531) surfaces [23]. It was speculated that with the polycrystalline metal catalyst, which contains equal numbers of (*R*)- and (*S*)-type kink sites, preferential adsorption of a chiral modifier on one type of kink site would leave the other type of site free for catalysis.

Although this approach is the only example in which catalytic activity and stereochemical control are not separated, no synthetic application can yet be foreseen because the concentration of such chiral sites in practically useful polycrystalline metal catalysts is very low and surface restructuring is likely to occur under reaction conditions. A similar conclusion can be drawn about the importance of other chiral metal structures, such as a screw dislocation or a chiral surface produced by asymmetric corrosion. Interestingly, asymmetric leaching of Ni in the presence of tartaric acid has already been proposed as an explanation for the enantio-differentiation by the tartaric acid-modified Ni catalyst [5].

8.10.3 Hydrogenation of Ketones

8.10.3.1 *β*-Functionalized Ketones

Hydrogenation of *β*-ketoesters is highly efficient over the Ni–tartaric acid–NaBr system [11,12]. Fine tuning of catalyst modification conditions resulted in quantitative yield of the corresponding *β*-hydroxy esters and good to excellent ee. Variation of the alkyl chain length next to the keto-carbonyl or in the ester group had only a minor effect on ee. The influence of substrate structure is illustrated by the best examples in Scheme 1 [24]). The outstanding ee with the cyclopropyl function was explained by steric and kinetic effects.

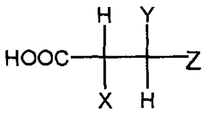


R	ee, %
Methyl	86
Ethyl	94
Isopropyl	96
Cyclopropyl	>98

Scheme 1.

In general, addition of weak acids increases the ee but the presence of water is detrimental. The modified catalyst has higher activity and a lower activation energy than unmodified Ni [10]. It is not clear yet, however, whether the enhanced rate is because of higher dispersion of the modified (corroded) Ni particles or because of a ligand acceleration effect. Note that Ni is thermodynamically unstable under ambient conditions in the presence of oxygen, a feature which complicates not only the application but also the reliable characterization of Ni catalysts.

Variation of the structure of (*R*,*R*)-tartaric acid revealed that two carboxyl groups and only one OH group are crucial for enantio-differentiation (Fig.1) [11].



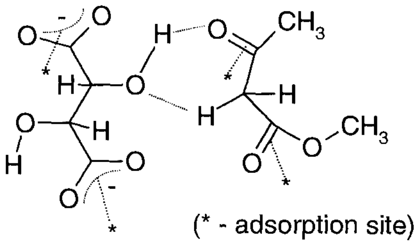
X	Y	Z	ee, %
HO	HO	COOH	83 (R)
HO	MeO	COOH	68 (R)
MeO	MeO	COOH	0
HO	HO	H	0

Figure 1.

The application range of modified Raney Ni has been extended to the enantioselective hydrogenation of other β-functionalized ketones such as β-diketones (e. g. acetylacetone, 74 % ee), 4-hydroxy-2-butanone and its methyl ether (68–70 % ee), and β-ketosulfones (67–71 % ee) [11].

There is no agreement yet about the mechanism of enantio-differentiation over the Ni-tartrate system. According to the model suggested by Japanese scientists [11], both OH groups of chemisorbed tartaric acid would be involved in H-bonding interactions with the chemisorbed β-ketoester. This model is presently under revision because it cannot explain the enantio-differentiation induced by monohydroxy acids (e. g. lactic or malic acid) and amino acids (e. g. alanine).

Another proposal [25] assumes the formation of a six-membered ring intermediate via H-bonding interactions (Fig. 2). It is important that the substrate is present in the keto form on the metal surface as the enol form affords the opposite enantiomer in excess. Ni-tartrate, which is believed to interact with the substrate on the metal surface, is a poor modifier; it is more probable that the sodium salt provides the high ee [13].

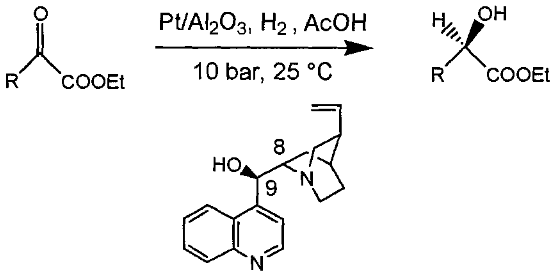


(* - adsorption site)

Figure 2.

8.10.3.2 α-Functionalized Ketones

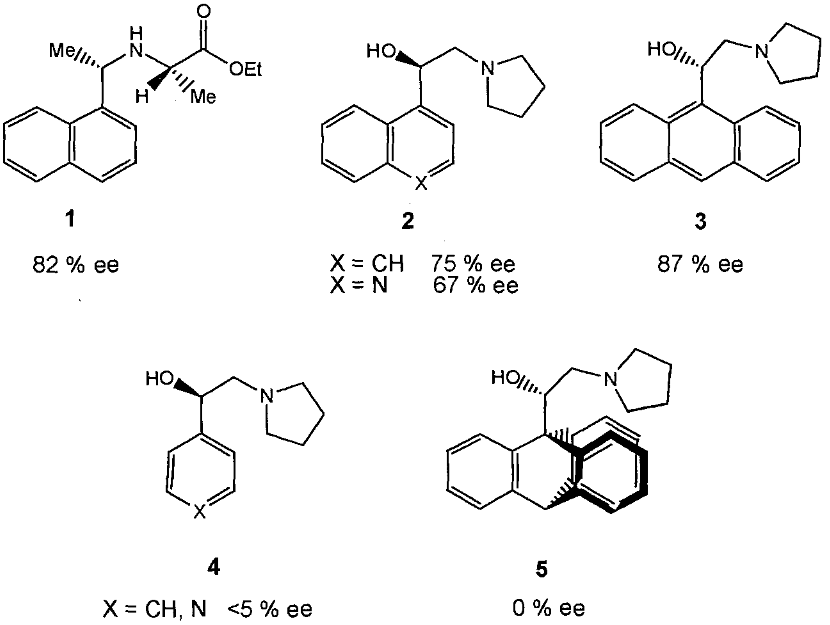
The first, and still the most studied, reaction of this class is the hydrogenation of α-ketoesters to the corresponding α-hydroxy esters (for recent reviews, see [6,15–17]). The best catalyst system is Pt/Al_2O_3 modified with cinchonidine or its simple derivative 10,11-dihydro-*O*-methyl-cinchonidine. Acetic acid or toluene as solvents, close to ambient temperature and medium to high pressure (10–70 bar) enhance enantioselectivity. The highest ee has been obtained after reductive heat treatment of Pt/Al_2O_3 and subsequent sonochemical pretreatment at room temperature (Scheme 2) [26]. The same high ee was achieved in the hydrogenation of methyl pyruvate with polyvinylpyrrolidone-stabilized small Pt clusters (1.4 nm), modified with cinchonidine [27].



R	ee, %
Me	97.5
Ph	92
$Ph(CH_2)_2$	95

Scheme 2.

Concerning the role of the modifier, crucial structural parts of cinchonidine are the stereogenic center at C8, the flat aromatic ring system for anchoring the modifier to the metal surface, and the basic quinuclidine N for interacting with the activated carbonyl group of the substrate [6,15,17]. It is now generally accepted that the C9 OH group of cinchonidine is not involved in the modifier–substrate interaction. Although methylation, acetylation, or complete removal of the C9 OH changes the ee, the effect probably results from a change in the conformation of cinchonidine. Discovery of 1-(1-naphthyl)ethylamine derivatives as chiral modifiers (e. g. **1** in Figure 3) confirmed this conclusion: some of these N-alkylated derivatives did not contain an O atom but they still induced up to 40 % ee in ethyl pyruvate hydrogenation [28].



1

82 % ee

2

X = CH 75 % ee
X = N 67 % ee

3

87 % ee

4

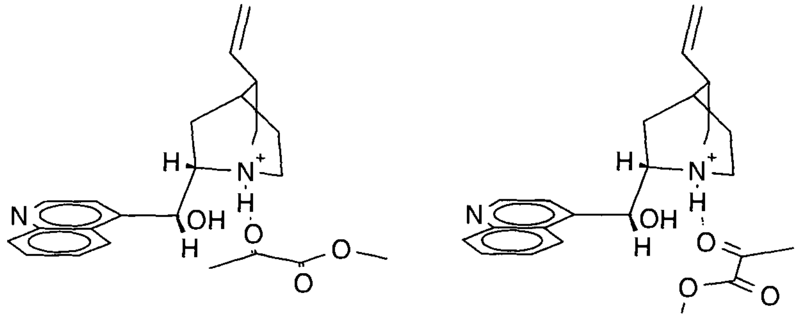
X = CH, N <5 % ee

5

0 % ee

Figure 3.

Several models have been proposed to interpret enantio-differentiation in the hydrogenation of α-ketoesters over the Pt-cinchonidine system. A feasible approach [6] assumes that the quinoline ring system and the two carbonyl groups in *trans* position are adsorbed parallel to the Pt surface. The quinuclidine N is not in direct contact with the metal surface but interacts with the keto-carbonyl O atom via H-bonding. Ab initio and force-field calculations indicated that the complex leading to (*R*)-lactate is energetically favored compared to the pro-(*S*)-complex. In apolar media the transition complex corresponds to the (stabilized) half-hydrogenated state of the substrate. Protonation of cinchonidine favors modifier–substrate interaction, in agreement with the enhancement in ee achieved by use of acetic acid as solvent or cinchonidine hydrochloride as modifier (Fig. 4).

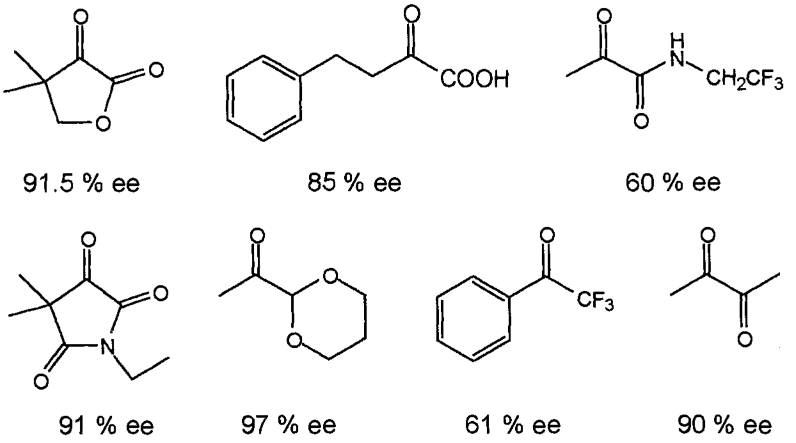


pro-(*R*) complex pro-(*S*) complex

Figure 4.

On the basis of the structural requirements for an efficient modifier, and using the above model as a working hypothesis, several new modifiers have been developed (Fig. 3) [6,29,30]. These studies revealed that (i) only extended flat aromatic ring systems (the naphthyl, quinolyl, anthracenyl groups in **1**–**3**) are efficient anchoring moieties, whereas phenyl or pyridyl rings in **4** or the non-flat triptycenyl moiety in **5** are not suitable for adsorption parallel to the metal surface, and (ii) the N-heteroatom in the aromatic ring system (**2**) is not a necessary requirement for adsorption of the modifier and enantio-differentiation.

In recent years the application range of cinchona-modified Pt has been extended to the hydrogenation of several other activated ketones, including ketopantolactone [18], α-keto acids [31], linear and cyclic α-keto amides [32,33], α-keto acetals [34,35], and trifluoroacetophenone [36]. In the hydrogenation of α-diketones the ee is moderate but a combination of enantioselective reaction and kinetic resolution afforded up to 90% ee at yields below 30% [37,38]. Examples of suitable substrates with the best ee are shown in Figure 5.



91.5 % ee 85 % ee 60 % ee

91 % ee 97 % ee 61 % ee 90 % ee (< 30 % yield)

Figure 5.

Hydrogenation of most of the activated ketones requires a sufficiently high rate of hydrogen supply to the Pt surface. Low surface hydrogen concentration because of diffusion limitations in the reactor can substantially suppress enantioselectivity [39,40]. An exception is the hydrogenation of trifluoroacetophenone [36], for which the best ee was achieved under mass transport-limited conditions (low pressure, inefficient stirring). Impurities in the system can also have a negative impact on ee; this is understandable when considering that the modifier, present at a very low concentration, has to compete with the impurities for the adsorption sites.

8.10.3.3 Simple Ketones

For hydrogenation of unfunctionalized ketones the only efficient solid catalyst is Ni [13]. Catalyst pretreatment conditions are similar to those used for catalysts in the hydrogenation of β-ketoesters. A major difference is the application of pivalic acid in greater than stoichiometric amounts during the hydrogenation reaction. This additive, with sufficient Na^+ ions, enhanced the ee from 2 to 80–85 % in the reduction of a variety of 2-alkanones.

The proposed model assumes that one of the carboxylate anions and the neighboring OH group of tartaric acid form a complex with pivalic acid (Fig. 6). The position of 2-alkanone over the Ni surface is fixed by an H-bond with the other OH group of tartaric acid and by the steric effect of the *t*-butyl group of pivalic acid. In the reverse orientation, where the 2-alkanone and pivalic acid change place, the carbonyl group is far from the metal surface and hydrogenation does not occur.

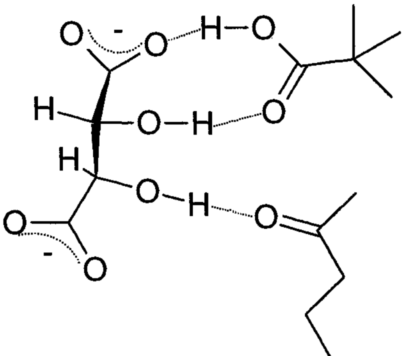


Figure 6.

Hydrogenation of 3-alkanones requires slightly different conditions; e. g. the best catalyst was obtained by modification of a Ni powder. Discrimination between the ethyl and another alkyl group is considerably more difficult than differentiation between a methyl and a longer chain alkyl group, which explains why the best ee is only 44 % in the hydrogenation of 3-octanone, compared with 80 % for 2-octanone [13]. Interestingly, in the presence of pivalic acid δ- and ε-ketoesters could also be hydrogenated with ca 60 % ee [13].

8.10.4 Hydrogenation of Functionalized Olefins

Chirally modified Pd is the best catalyst for the enantioselective hydrogenation of olefins. ee > 50 % has been achieved in two types of reaction; in both the reactant has an interacting functional group in the α-position.

8.10.4.1 α,β-Unsaturated Carboxylic Acids

Up to 72 % ee has been achieved in the hydrogenation of a diphenyl-substituted reactant, (*E*)-α-phenylcinnamic acid, with a Pd/TiO_2 catalyst and cinchonidine [41]. For aliphatic α,β-unsaturated acids the ee varied between 20 and 53 %, depending on the structure of the acid [42]. Interestingly, the two types of reaction require strikingly different conditions – the best ee was obtained at 1 bar in a strongly polar solvent mixture in the former reaction, whereas apolar solvents and high hydrogen pressure (30–60 bar) are favorable for aliphatic alkenoic acids. A possible explanation of this difference is the isomerization of the C=C bond as a competing side reaction during hydrogenation [43]. The rate of double bond migration depends on the solvent and on hydrogen pressure, and the subsequent hydrogenation of the isomeric alkenoic acids reduces the enantioselectivity because of the formation of the opposite enantiomers. Hence, chirally modified Pd can afford good ee only if double-bond migration is slow (internal double bond in the substrate), or this side reaction can be completely ruled out (e. g. α-phenylcinnamic acid).

Variation of the structure of cinchonidine at the quinuclidine N and C9 OH group revealed that both functional groups are involved in interactions with the substrate during enantio-differentiation [44]. On the basis of spectroscopic analysis and ab initio calculations [42,45] an empirical model has been suggested which can predict the configuration of the major product in the hydrogenation of aliphatic alkenoic acids in apolar media (Fig. 7). In this adsorption arrangement the *trans* acid dimer and the quinoline ring system of cinchonidine are adsorbed parallel to the Pd surface. It is important that one of the C=C bonds points toward the quinoline ring system. In this position, bottom side *syn* addition of two hydrogen atoms results in the major enantiomer.

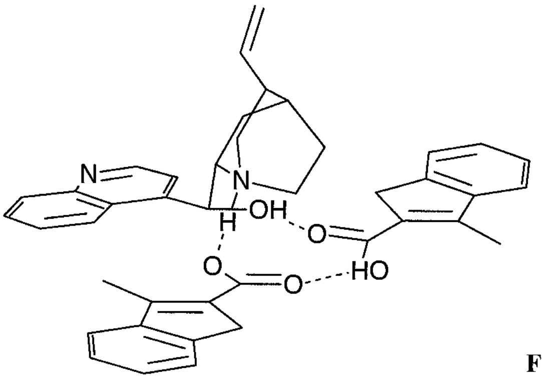


Figure 7.

In another model, cinchonidine is assumed to interact with a phenylcinnamic acid monomer via two H-bonds [44]. Note that in a strongly polar medium, which favors enantio-differentiation in this reaction, carboxylic acids are present predominantly as monomers.

8.10.4.2 *α,β*-Unsaturated Ketones

A vinca-type alkaloid, (–)-dihydroapovincaminic acid ethyl ester (Fig. 8) afforded up to 55 % ee in the hydrogenation of isophorone to the corresponding cyclic ketone [46]. The authors assumed that a H-bond between the protonated N atom of the alkaloid and the carbonyl O atom of isophorone was responsible for the enantioselectivity [47].

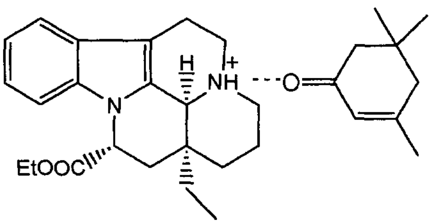


Figure 8.

Ephedrine was used as chiral modifier of Pd in the hydrogenation of some cyclic *α,β*-unsaturated ketones, tetralone and indanone derivatives, affording 50–93 % chemoselectivity for the saturated ketones and up to 36 % ee [48]. Hydrogenation of the (*E*) isomer was much faster and afforded higher ee than that of the (*Z*) isomer, though both reactions provided the same major enantiomer.

8.10.5 Hydrogenation of C=N Bonds

Despite the importance of this reaction for the synthesis of chiral amines and amino acids, no effective solid catalyst is yet available [3]. There are two instances where 26 % ee was achieved (Fig. 9), but results with silk-supported Pd are difficult to reproduce, and in the hydrogenation of acetophenone oxime and pyruvic acid oxime stoichiometric amounts of chiral auxiliary were used [21,49]. The latter reaction was also extremely slow – only 15 % yield of alanine was obtained in 45 h. Efficient enantioselective hydrogenation of imines and oximes apparently remains a challenge for future development.

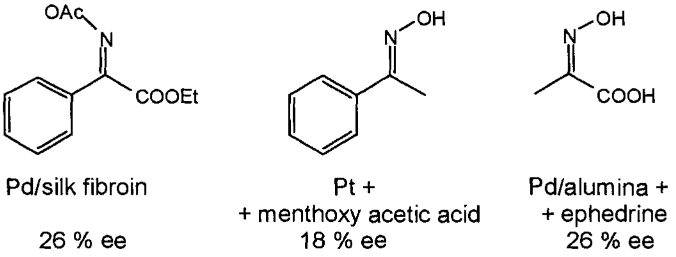


Figure 9.

References

[1] Izumi, Y., *Adv. Catal.* **32**, 215 (1983).
[2] Bartok, M., Czombos, J., Felföldi, K., Gera, L., Göndös, G., Molnàr, À., Notheisz, F., Pàlinko, I., Wittman, G. and Zsigmond, À. G., in: Stereochemistry of Heterogeneous Metal Catalysts, Wiley, Chichester 1985, p. 511.
[3] Blaser, H. U., *Tetrahedron: Asym.* **2**, 843 (1991).
[4] Baiker, A., *Current Opinion Solid State Mater. Sci.* **3**, 86 (1998).
[5] Smith, G. V. and Notheisz, F., Heterogeneous Catalysis in Organic Chemistry, Academic Press, San Diego, 1999.
[6] Baiker, A., *J. Mol. Catal. A: Chem.* **115**, 473 (1997).
[7] Klabunovskii, E. I., *Russ. Chem. Rev.* **60**, 980 (1991).
[8] Baiker, A. and Blaser, H. U., in: Handbook of Heterogeneous Catalysis, Vol. 5, eds. G. Ertl, H. Knözinger and J. Weitkamp (VCH, Weinheim 1997) p. 2422.
[9] Harada, T., Imachi, Y., Tai, A. and Izumi, Y., *Stud. Surf. Sci. Catal.* **11**, 377 (1982).
[10] Sachtler, W. M. H., in: Catalysis of Organic Reactions, eds. R. L. Augustine (M. Dekker, New York 1985) p. 189.
[11] Tai, A. and Harada, T., in: Tailored Metal Catalysts, ed. Y. Iwasawa (D. Reidel, Dordrecht 1986) p. 265.
[12] Webb, G. and Wells, P. B., *Catal. Today* **12**, 319 (1992).
[13] Osawa, T., Harada, T. and Tai, A., *Catal. Today* **37**, 465 (1997).
[14] Nakagawa, S., Sugimura, T. and Tai, A., *Chem. Lett.* 859 (1997).
[15] Baiker, A., in: Supported Reagents and Catalysts in Chemistry, Vol. 216, eds. B. K. Hodnett, A. P. Kybett, J. H. Clark and K. Smith (Royal Soc. Chem., Cambridge 1998) p. 142.
[16] Wells, P. B. and Wilkinson, A. G., *Topics in Catal.* **5**, 39 (1998).
[17] Blaser, H. U., Jalett, H. P., Müller, M. and Studer, M., *Catal. Today* **37**, 441 (1997).
[18] Schürch, M., Künzle, N., Mallat, T. and Baiker, A., *J. Catal.* **176**, 569 (1998).
[19] Künzle, N., Hess, R., Mallat, T. and Baiker, A., *J. Catal.* **186**, 239 (1999).
[20] Tungler, A., Tarnai, T., Hegedüs, L., Fodor, K. and Màthé, T., *Plat. Met. Rev.* **42**, 108 (1998).
[21] Borszeky, K., Mallat, T., Aeschimann, R., Schweizer, W. B. and Baiker, A., *J. Catal.* **161**, 451 (1996).
[22] McFadden, C. F., Cremer, P. C. and Gelman, A. J., *Langmuir* **12**, 2483 (1996).
[23] Ahmadi, A., Attard, G., Feliu, J. and Rodes, A., *Langmuir* **15**, 1420 (1999).
[24] Nakagawa, S., Sugimura, T. and Tai, A., *Chem. Lett.* 1257 (1998).
[25] Leclerq, E., Rives, A., Payen, E. and Hubaut, R., *Appl. Catal. A.* **168**, 279 (1998).
[26] Török, B., Balàzsik, K., Szöllösi, G., Felföldi, K. and Bartók, M., *Chirality* **11**, 470 (1999).
[27] Zuo, X., Liu, H. and Liu, M., *Tetrahedron Lett.* **39**, 1941 (1998).
[28] Minder, B., Schürch, M., Mallat, T., Baiker, A., Heinz, T. and Pfaltz, A., *J. Catal.* **160**, 261 (1996).
[29] Simons, K. E., Wang, G., Heinz, T., Giger, T., Mallat, T., Pfaltz, A. and Baiker, A., *Tetrahedron: Asym.* **6**, 505 (1995).
[30] Schürch, M., Heinz, T., Aeschimann, R., Mallat, T., Pfaltz, A. and Baiker, A., *J. Catal.* **173**, 187 (1998).
[31] Blaser, H. U. and Jalett, H. P., *Stud. Surf. Sci. Catal.* **78**, 139 (1993).
[32] Wang, G.-Z., Mallat, T. and Baiker, A., *Tetrahedron: Asym.* **8**, 2133 (1997).
[33] Künzle, N., Szabo, A., Schürch, M., Wang, G., Mallat, T. and Baiker, A., *Chem. Commun.* 1377 (1998).
[34] Török, B., Felföldi, K., Balàzsik, K. and Bartók, M., *Chem. Commun.* 1725 (1999).
[35] Studer, M., Burkhardt, S. and Blaser, H. U., *Chem. Commun.* 1727 (1999).
[36] Bodmer, M., Mallat, T. and Baiker, A., in: Catalysis of Organic Reactions, ed. F. E. Herkes (M. Dekker, New York 1998) p. 75.
[37] Slipszenko, J. A., Griffiths, S. P., Johnston, P., Simons, K. E., Vermeer, W. A. H. and Wells, P. B., *J. Catal.* **179**, 267 (1998).
[38] Studer, M., Okafor, V. and Blaser, H. U., *Chem. Commun.* 1053 (1998).

[39] Sun, Y., Wang, J., LeBlond, C., Landau, R. N. and Blackmond, D. G., *J. Catal.* **161**, 759 (1996).

[40] Mallat, T., Bodnar, Z., Minder, B., Borszéky, K. and Baiker, A., *J. Catal.* **168**, 183 (1997).

[41] Nitta, Y. and Kobiro, K., *Chem. Lett.* 897 (1996).

[42] Borszeky, K., Mallat, T. and Baiker, A., *Tetrahedron: Asym.* **8**, 3745 (1997).

[43] Borszeky, K., Mallat, T. and Baiker, A., *Catal. Lett.* **59**, 95 (1999).

[44] Nitta, Y. and Shibata, A., *Chem. Lett.* 161 (1998).

[45] Bürgi, T. and Baiker, A., *J. Am. Chem. Soc.* **120**, 12920 (1998).

[46] Farkas, G., Fodor, K., Tungler, A., Màthé, T., Tòth, G. and Sheldon, R. A., *J. Mol. Catal. A.* **138**, 123 (1999).

[47] Tungler, A., Fodor, K., Máthé, T. and Sheldon, R. A., *Stud. Surf. Sci. Catal.* **108**, 157 (1997).

[48] Thorey, C., Hénin, F. and Muzart, J., *Tetrahedron: Asym.* **7**, 975 (1996).

[49] Nakamura, Y., *Bull. Chem. Soc. Jpn.* **16**, 367 (1941).

8.11 Selective N-Alkylation of Amines with Alcohols over γ-Alumina

Fabienne Fache, Frédéric Valot, Marc Lemaire

8.11.1 Introduction

The amine function is present in numerous industrial products such as drugs, herbicides, and dyes. Amines can also be used as oxidation and corrosion inhibitors, dispersants, or stabilizers. Much research has, therefore, been devoted to amine synthesis and to N-alkylation in particular. This transformation, called the Hofmann reaction [1] is generally achieved by nucleophilic substitution with chloro or bromo compounds as alkylating agents. It can be applied to almost all type of amine, but has several drawbacks. Thus, selective monoalkylation is difficult to control and mixtures of polyalkylated amines must often be separated to obtain the desired product. The use of halides or other good leaving groups can also induce the stoichiometric formation of salts as by-products [2]. Indeed, Hofmann-type reactions do not meet the modern criteria of efficiency for organic synthesis [3] and their applications are more or less limited to very small-scale production. Although other alkylating agents such as R_3Bi [4], ethylene [5], or cyclic ethers [6] have also been used with success, they often require harsh conditions or are limited in their application. Alcohols and carbonyl compounds (aldehydes or ketones) have also been widely used in the presence of a catalyst. These last methods include reductive amination, dehydroamination, and dehydrative amination [7].

8.11.1.1 Reductive Amination

In reductive amination the alkylation is performed under hydrogen in the presence of a transition metal catalyst and an aldehyde or ketone as the alkylating agent. Reductive alkylation is a general reaction which can be extended to several other nucleophiles. We have developed this method for anilines in particular [8] and extended it [9] to amide N-alkylation [10] and ether synthesis [11]. We have shown that nitro derivatives can be used as aniline precursors in a one-pot reduction of the nitro group and subsequent reductive alkylation of the resulting aniline (Figure 1).

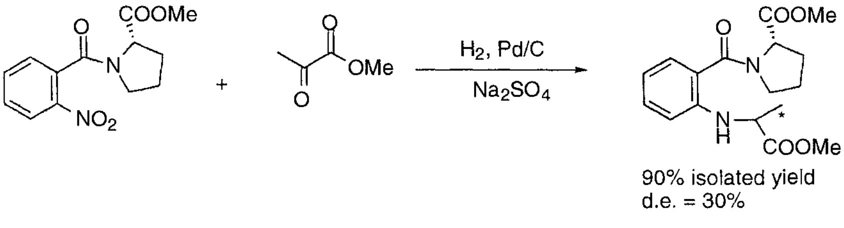


Figure 1. Reductive amination of nitro derivatives–synthesis of non-natural amino acid precursors.

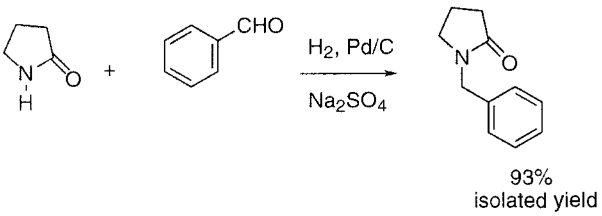


Figure 2. Extension of the reductive alkylation to amides.

Extension of the reductive amination to amides has required modification of the catalyst by addition of sodium sulfate (Figure 2).

The effect of sodium sulfate is not fully understood: it can either act as a dehydrating agent to increase the formation of the hemiaminal intermediate or as a catalyst poison to limit carbonyl reduction.

8.11.1.2 Dehydroamination [12]

Dehydroamination is performed in the presence of a hydrogenation–dehydrogenation catalyst and an alcohol. It has been proven that an aldehyde is formed as an intermediate. Formally, this transformation is obtained by three successive reactions–dehydrogenation of the alcohol (Oppenauer type oxidation), formation of an imine by nucleophilic attack then dehydration, and, finally, reduction of the imine (MPV-type reduction). In the last reaction step, it can be assumed that the dehydroamination pathway is similar to that of reductive amination.

8.11.1.3 Dehydrative Amination

Dehydrative amination is amination of the alcohol in the presence of dehydration catalysts. This method is similar to the previous process if we consider only the reagents (amine and alcohol) and the final products (alkylamine and water) but the chemical pathway involving acidic activation of the hydroxyl group of the alcohol is different. It is, nevertheless, sometimes difficult to definitively exclude one of the two pathways, especially when a transition metal oxide is used as a catalyst. Whatever the mechanism, the two methods lead only to water as a by-product and meet the efficiency criteria.

Suitable catalysts for dehydrative amination are alumina, silica–alumina, alumina–magnesia [13], aluminum phosphate [14], binary transition metal oxides [15], and zeolites [13]. All these reactions are performed under gas-phase conditions at temperatures between 300 and 500 °C under 1–200 bar pressure. Aliphatic (C_1–C_8) and aromatic amines (e. g. aniline) are the most studied, with methanol as the alkylating agent. Although gas-phase dehydrative amination is well-documented and is applied on an industrial scale, the reaction is almost unknown by organic chemists because it requires conditions which seem incompatible with almost every functionalized substrate. The aim of this article is to demonstrate that the scope of dehydrative alkylation of amines is much larger than expected. Indeed, even the chiral α-methylbenzylamine could be alkylated by methanol with good selectivity and total retention of chirality.

8.11.2 Experimental

In a typical procedure, the amine/alcohol mixture is introduced via a syringe on top of a vertical continuous-flow reactor (2 mL h^{-1}) with nitrogen as carrier gas (20 mL min^{-1}). The reagents pass through the catalyst (2 g γ-Al_2O_3 [16]), the reactor being operated in an oven, by means of which the temperature is regulated. The reaction products are condensed for 1 h in an ice bath at the bottom of the reactor (Figure 3). N-alkylamines are isolated by removal of the alcohol under reduced pressure. When the boiling point of the product is low, the crude mixture is treated with HCl to obtain the non-volatile hydrochloride of the amine.

A variety of amines has been N-alkylated under gas-phase conditions with γ-Al_2O_3 as catalyst and different alcohols as alkylating agents (Figure 4).

Irrespective of the amine and the alcohol chosen, conversion increases with temperature.

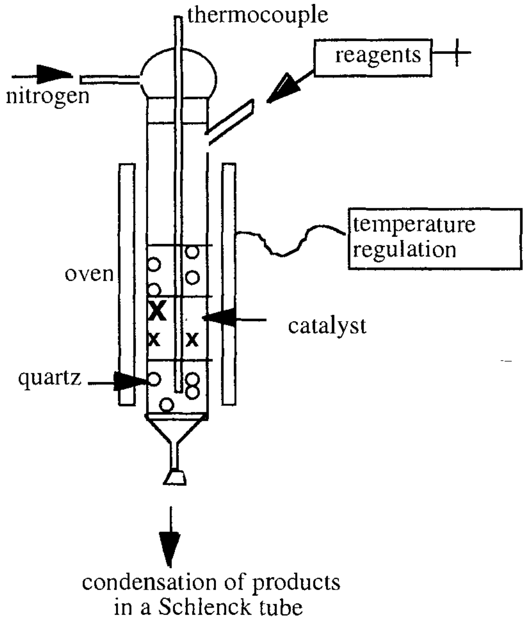
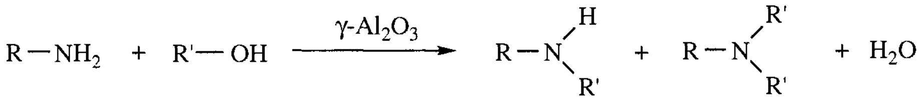


Figure 3. Gas-phase reactor.



$$R{-}NH_2 + R'{-}OH \xrightarrow{\gamma\text{-}Al_2O_3} R{-}N(H)R' + R{-}NR'_2 + H_2O$$

Figure 4. General reaction scheme of dehydrative amine alkylation.

8.11.3 Methanol as Alkylating Agent

The alkylation of different amines has been performed with methanol. Table 1 shows the results obtained with *n*-octylamine.

With a primary amine such as *n*-octylamine, we observe at low conversion (8 %) high selectivity for the N-monoalkylated product whereas 90 % N,N-dimethylated amine are formed at high conversion (94 %). In reductive alkylation, it is even more difficult to obtain the monomethylated product selectively. For example, in the Eschweiler Clarke procedure [17], only the dimethylated amine is formed, even with an amine-to-formaldehyde ratio of 1. In the Hofmann-type reaction, a mixture of mono- and dimethylamine with the corresponding trimethylammonium salt is generally produced.

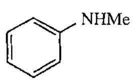
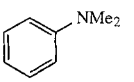
With a primary aromatic amine such as aniline and under the same conditions as with *n*-octylamine, conversion and selectivity evolve similarly–from N-methylated aniline at low conversion to N,N-dimethylated aniline at high conversion [18]. Selectivity is, moreover, better because 90 % *N*-monomethylaniline is produced at 45 % conversion and 85 % dimethylated product at total conversion. By-products resulting from C-alkylation of the aromatic ring are also formed at high conversion (Table 2), although they never exceed 10 %.

Table 1. Alkylation of *n*-octylamine by methanol.

T (°C)	*n*-Octylamine conversion (%)	Selectivity (%)	
			
195	8	74	26
250	60	43	57
280	94	10	90

Conditions: methanol/*n*-octylamine molar ratio = 300.

Table 2. Alkylation of aniline by methanol.

T (°C)	Aniline conversion (%)	Selectivity (%)		
				C-alkylated products
200	45	90	10	0
240	77	52	47	1
280	94	23	72	5
320	99.5	5	85	10

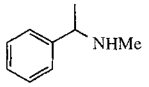
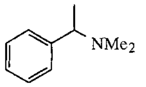
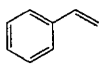
Conditions: methanol/aniline molar ratio = 300.

Among the different C-alkylated products, *N,N*-dimethyltoluidine is by far the most abundant. It can be concluded that aniline methylation on γ-Al_2O_3 follows a sequential reaction path of formation of *N*-methylaniline, then *N,N*-dimethylaniline, then C-alkylated products. This is typical of acid catalysts [2].

α-Methylbenzylamine has also been tested (Table 3).

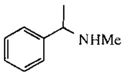
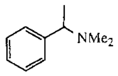
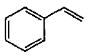
Above 250 °C, deamination of the reagent is observed and styrene is formed. Below this temperature, however, it is possible to obtain *N*-methyl-*α*-methylbenzylamine with good selectivity (90 % selectivity at 20 % conversion, 220 °C). The selectivity towards the N,N-dimethylated product is lower at the same conversion than with the other primary amine already tested, i. e. the *n*-octylamine (38 % at 84 % conversion for *α*-benzylamine and 57 % at 60 % conversion for *n*-octylamine). The NH group is bound to a secondary carbon in *α*-methylbenzylamine, whereas it is linked to a primary carbon in *n*-octylamine. This steric factor explains the different reactivity. This relatively good selectivity for monomethylation can be regarded as an advantage compared with reductive alkylation.

Table 3. Alkylation of *α*-methylbenzylamine by methanol.

T (°C)	*α*-Methylbenzylamine conversion (%)	Selectivity (%)		
				
175	3	100	0	0
200	11	94	6	0
225	20	90	9	ε
250	37	84	14	2
275	84	55	38	7

Conditions: methanol/*α*-methylbenzylamine molar ratio = 300.

Table 4. Influence of the methanol/*α*-methylbenzylamine ratio on both activity and selectivity of methylation.

T (°C)	Methanol/ amine (mol)	*α*-Methylbenzylamine conversion (%)	Selectivity (%)		
					
200	300	11	94	6	0
225	20	6	99	1	0
225	300	20	90	9	ε
250	20	20	89	9	2
250	300	37	84	14	2
275	20	44	80	15	5
275	300	84	55	38	7
300	20	84	51	36	13

We have also studied the influence of the alcohol/amine ratio on both activity and selectivity (Table 4).

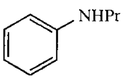
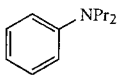
When the alcohol/amine ratio is 20, a temperature 25 degrees higher is necessary to obtain the same results, both in terms of activity and selectivity, as with a ratio of 300. Activation of the alcohol seems to be the limiting step of the reaction.

8.11.4 Influence of the Structure of the Alkylating Agent

To evaluate the scope of this reaction, several primary and secondary alcohols were also tested. With aniline and *n*-propanol (Table 5), at the same temperature, conversion was lower than with methanol.

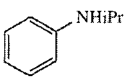
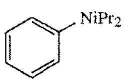
With *n*-propanol good selectivity for the monoalkylated product is observed even at high conversion (90 % selectivity for 83 % conversion instead of 52 % selectivity at 77 % conversion with methanol). Dehydrative alkylation of the amine seems to be very sensitive to steric hindrance of both the amine and the alcohol. This phenomenon is much more evident when a secondary alcohol is used, and thus with isopropanol the conversion is low (Table 6).

Table 5. Alkylation of aniline by *n*-propanol.

T (°C)	Aniline conversion (%)	Selectivity (%)	
			
200	23	98	2
250	59	97	3
300	83	90	10

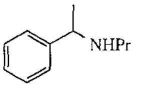
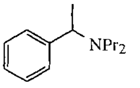
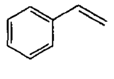
Conditions: propanol/aniline molar ratio = 300.

Table 6. Alkylation of aniline by isopropanol.

T (°C)	Aniline conversion (%)	Selectivity (%)	
			
200	0.5	–	–
230	8	96	1

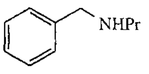
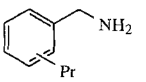
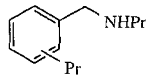
Conditions: isopropanol/aniline molar ratio = 300.

Table 7. Alkylation of α-methylbenzylamine by *n*-propanol.

T (°C)	α-Methyl-benzylamine conversion (%)	Selectivity (%)		
				
200	16	100	0	0
250	42	97	0	3
300	84	73	0	27

Conditions: *n*-propanol/aniline molar ratio = 300.

Table 8. Alkylation of benzylamine by *n*-propanol.

T (°C)	Benzylamine conversion (%)	Selectivity (%)		
				
200	14	96	4	0
250	71	86	10	4
290	94	71	18	11

Conditions: *n*-propanol/benzylamine molar ratio = 300.

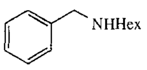
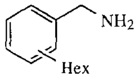
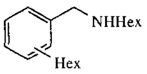
In both reactions, with *n*- or *iso*-propanol, no C-alkylated products are formed. Propene formation was not detected.

With α-methylbenzylamine and *n*-propanol, no dialkylated product is formed and thus at 42 % conversion, 97 % selectivity in monopropylated amine is obtained (Table 7). Styrene is, nevertheless, produced in relatively high yields until the temperature reaches 300 °C (27 % styrene at 84 % conversion).

It should be noted that with benzylamine, C-alkylated products are formed (Table 8) whereas with aniline (Table 5) only N-alkylation is reported. This is surprising, given that aniline is a weaker nucleophile than benzylamine and its aromatic ring is richer in electrons, and thus more suitable for alkylation. The latter situation might change, however, when the nitrogen is coordinated to surface Al or interacting with surface OH.

At the same temperature, conversion is higher with benzylamine than with α-methylbenzylamine probably because of the steric bulkiness of the methyl group. This confirms the importance of steric hindrance in this reaction. Even at high conversion, monopropylated product selectivity is high (94 % conversion, 70 % selectivity). With *n*-hexanol (Table 9), the same tendencies are observed as with *n*-propanol.

Table 9. Alkylation of benzylamine by *n*-hexanol.

T (°C)	Benzylamine conversion (%)	Selectivity (%)		
				
200	5	100	0	0
250	25	84	14	2
290	92	71	14	14

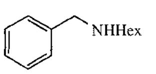
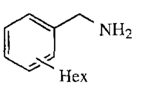
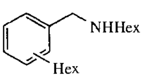
Conditions: *n*-hexanol/benzylamine molar ratio = 300.

8.11.5 Ether as Alkylating Agent

During the alkylation of benzylamine with *n*-hexanol, the simultaneous formation of dihexyl ether is detected by gas chromatography. With methanol or propanol the corresponding ethers might be formed but they coelute with the solvent in gas chromatography and so cannot be detected. Because it is, therefore, unclear whether the alkylating agent is the alcohol or the corresponding ether, we have tested the N-alkylation of benzylamine with dihexyl ether (Table 10). Alkylation with dimethyl, diethyl, dipropyl and dibutyl ether has already been claimed in a patent [19].

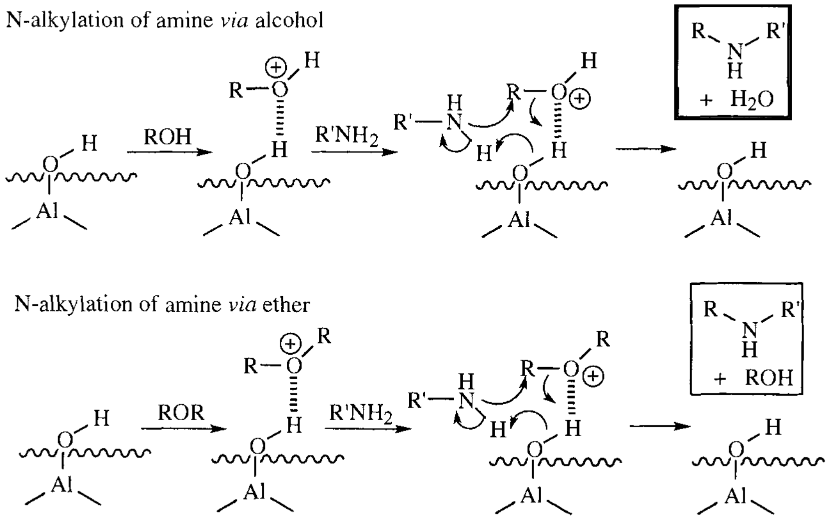
The same products and selectivities are obtained with hexanol or dihexyl ether as the alkylating agent, although reactivity seems higher with the ether. Different hypotheses can be proposed to explain this. Firstly, we could assume that the real alkylating agent is the ether. Secondly, the ether could react faster than the alcohol (acidic activation). Finally, water, the by-product of reaction of the alcohol could have a negative effect on catalyst efficiency. We therefore propose a general mechanism which could explain both the N-alkylation reaction and the ether synthesis (Figure 5). A molecule of alcohol is adsorbed at the alumina surface via a surface hydroxyl which increases the electrophilicity of the alkyl part of the alcohol. The alcohol can then react further either with the oxygen of another alcohol molecule, leading to an ether or with the nitrogen of an amine leading to an N-alkylated

Table 10. Alkylation of benzylamine by dihexyl ether.

T (°C)	Benzylamine conversion (%)	Selectivity (%)		
				
200	17	100	0	0
250	63	77	16	7
290	99	42	32	26

Conditions: dihexyl ether/benzylamine molar ratio = 10.

amine. By the same mechanism, the secondary amine thus formed can be alkylated further. When the alcohol is replaced by an ether the same mechanism is possible. When a C-alkylation product is obtained we can assume that the amine, via its nitrogen atom, is adsorbed by the alumina surface on an aluminum hydroxyl group (Brönsted acid site) and thus undergoes C-alkylation with an adsorbed alcohol molecule.


N-alkylation of amine *via* alcohol

N-alkylation of amine *via* ether

Figure 5. Proposed mechanism for the N-alkylation with alcohols and ethers.

8.11.6 Chirality

The chemical transformation of chiral molecules without racemization is of high interest in organic synthesis and is usually difficult to perform. Thus, the N-alkylation of α-methylbenzylamine without loss of chirality is realized in *N,N'*-dimethylpropylurea as solvent with stoichiometric quantities of sodium carbonate and different alkyl halides [20]. Homogeneous palladium catalysis with phosphine ligands and bases is also described for intra- or inter-molecular N-alkylation of chiral amines [21]. We have tested our method with optically pure α-methylbenzylamine with an alcohol/amine ratio of 20. As expected, the same results in terms of conversion and chemioselectivity have been obtained as with the racemic mixture. The reaction mixture is analyzed on a Cydex-B chiral capillary gas chromatography column. No racemization occurs during the reaction, even at 300 °C (Figure 6).

On the left of the chromatogram is depicted the analysis of the reaction mixture obtained with racemic α-methylbenzylamine: two groups of two peaks corresponding to the two enantiomeric forms of both the starting material and the reaction product are observed. The right of the chromatogram shows the results

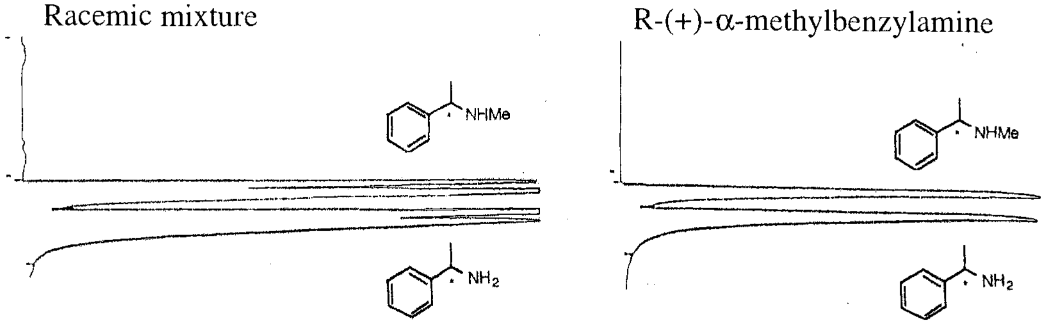


Figure 6. Comparative gas-phase N-alkylation of a chiral amine and its corresponding racemic mixture.

obtained with the pure *R*-(+)-*α*-methylbenzylamine. Only one peak for each amine, the starting *R*-(+)-*α*-methylbenzylamine and the *N*-methyl-*α*-methylbenzylamine, are observed. This suggests direct nucleophilic attack of the amine on to the alcohol without formation of an imine intermediate, which would lead to racemization. This important result shows that gas-phase reactions can be successfully applied to chiral molecules. In this particular example, the result is all the more interesting because it is difficult to monomethylate primary amines selectively by most known methods [22].

8.11.7 Conclusion

We have shown that N-alkylation of amines by alcohols in the gas-phase over *γ*-alumina is possible for a wide range of amines (aliphatic or aromatic) and alcohols (from methanol to hexanol). We have also proved that ethers can be used as alkylating agents. This last point is of practical interest because separation of the polar amine from the non-polar ether solvent is easier than from the polar alcohol. Above all, we have clearly demonstrated that chirality is compatible with gas-phase conditions and thus proposed a selective new method for mono-N-alkylation and, in particular, for methylation of chiral amines. This opens new perspectives for gas-phase heterogeneous catalysis.

References

[1] March J (1985, New York) 3rd ed. John Wiley & Sons (Ed.) 798.
[2] Onaka M, Umezono A, Kawai M, Izumi Y J Chem Soc Chem Commun (1985) 17: 1202.
[3] Sheldon RA Chemistry and Industry (1992): 903.
[4] Barton DHR, Ozbalik N, Ramesh M Tetrahedron Lett (1988) 29(8): 857.
[5] Diamond SE, Szalkiewicz A, Mares F J Am Chem Soc (1979) 101(2): 490.
[6] Hargis DC CA 106:156270f, US 4643762 (17 Feb. 1987).
[7] Baiker A, Kijenski J Catal Rev Sci Eng (1985) 27(4): 653.
[8] Fache F, Valot F, Milenkovic A, Lemaire M Tetrahedron (1996) 52(29): 9777.
[9] Fache F, Bethmont V, Jacquot L, Lemaire M Recl Trav Chim Pays-Bas (1996) 115: 231.
[10] Fache F, Jacquot L, Lemaire M Tetrahedron Lett (1994) 35(20): 3313.
[11] Bethmont V, Fache F, Lemaire M Tetrahedron Lett (1995) 36(24): 4235.
[12] Pouilloux Y, Doidy V, Hub S, Kervennal J, Barrault J (1997, Elsevier) Stud. Surf. Sc. Cat., Blaser HU, Baiker A, Prins R (Ed.) 108: 139–147.
[13] Li KT, Peng YC Applied Catal A: General (1994) 109: 225.
[14] Bautista F, Campelo JM, Garcia A, Luna D, Marinas JM, Romero A (1997, Elsevier) Stud. Surf. Sc. Cat., Blaser HU, Baiker A, Prins R (Ed.) 108: 123–130.
[15] Takita Y, Nishida Y, Seiyama T Bull Soc Chem Jpn (1976) 49: 3699.
[16] Valot F, Fache F, Jacquot R, Spagnol M, Lemaire M Tetrahedron Lett (1999) 40: 3689; γ-Al_2O_3 was purchased from Degussa (oxid. C (g), 100 m^2 g^{-1}, d = 60 g L^{-1})
[17] March J (1985, New York) 3rd ed. John Wiley & Sons (Ed.) 899.
[18] Matsuhashi H, Arata K Bull Soc Chem Jpn (1991) 64: 2605.
[19] Bayer A.-G. US Patent 5,055,617 (1991).
[20] Juaristi E, Murer P, Seebach D Synthesis (1993) 1243.
[21] Wagaw S, Rennels' RA, Buchwald SL J Am Chem Soc (1997) 119: 8451.
[22] Grieco PA, Bahsas A J Org Chem (1987) 52(26): 5746.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

9 Oxidation

9.1 Epoxidation

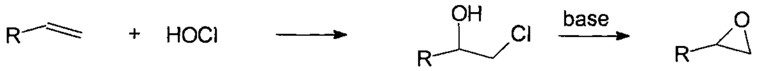
R. A. Sheldon, M. C. A. van Vliet

9.1.1 Introduction

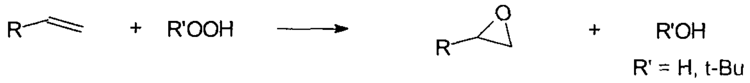
Olefin epoxidation is not only important in the manufacture of bulk chemicals, e. g. ethylene and propylene oxides, but is also a widely used transformation in the fine-chemicals industry [1]. Ethylene oxide is manufactured by vapor-phase oxidation of ethylene, with air or oxygen, over a supported silver catalyst [2]. This method is not generally applicable as olefins containing allylic or other reactive C–H bonds give complex mixtures of products with low epoxide selectivity. The method has recently been extended to some other olefins that do not contain reactive allylic C–H bonds, e. g. butadiene, styrene, norbornene, and *tert*-butyl ethylene [3]. Some of these products, e. g. butadiene monoepoxide and styrene oxide, have potential applications as fine chemicals/intermediates.

Traditionally the main method for performing epoxidations in organic synthesis has been oxidation with organic peracids (Eq. 1) or, to a lesser extent, the chlorohydrin route (Eq. 2). The latter method is, however, under considerable environmental pressure to be replaced and the use of many organic peracids, e. g. peracetic acid, is problematical owing to restrictions on their transport, storage, and handling. These shortcomings have focused attention on the development of methods using hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP) as the oxidant (Eq. 3).

(1)



(2)



(3)

In this review we shall focus on the use of heterogeneous catalysts for the liquid phase epoxidation of olefins with alkyl hydroperoxides or hydrogen peroxide. The latter is generally the oxidant of choice for fine-chemicals production owing to a better availability and lower price. Emphasis is placed on methods with a broad scope in organic synthesis.

9.1.2 Mechanistic Considerations

Metal catalyzed epoxidations with H_2O_2 or RO_2H are examples of oxygen transfer processes in which the active oxidant can be an oxometal or a peroxometal species (Figure 1) [4]. Early transition elements (Ti, Zr, Mo, W) react via peroxometal intermediates whereas catalysis by late and/or many first-row transition elements (Cr, Mn, Fe) involves high-valent oxometal intermediates. Some elements react via oxometal or peroxometal intermediates depending on the substrate, e. g. vanadium(V) catalyzes epoxidations via a peroxometal pathway and alcohol oxidations via oxometal intermediates. It is also worth noting that an oxometal intermediate can be formed via heterolysis of the O–O bond of an initially formed peroxometal species. A major difference between the two pathways is that in the peroxometal pathway there is no change in the oxidation state of the metal center during reaction. The metal ion increases the oxidizing power (electrophilicity) of the peroxo moiety by withdrawing electrons, i. e. by acting as a Lewis acid. Hence, the peroxometal pathway is not limited to variable-valence elements. In the oxometal pathway, in contrast, the metal center undergoes a two-electron reduction and is subsequently reoxidized by the oxygen donor.

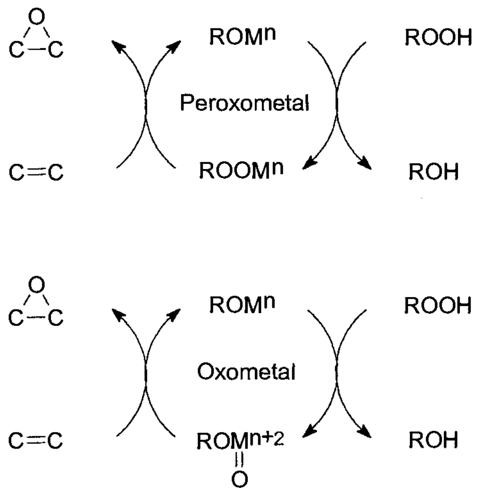


Figure 1. Peroxometal and oxometal pathways in olefin epoxidation.

9.1.3 Historical Development and Overview of Catalysts

In the sixties Halcon [5] and Atlantic Richfield (ARCO) [6] independently developed processes for the production of epoxides using an alkyl hydroperoxide in the presence of homogeneous catalysts based on, inter alia, Mo, W, V, Ti, and Zr. Rates and selectivity were highest for molybdenum catalysts. Halcon and ARCO subsequently formed a joint venture, the Oxirane Corporation, to exploit this technology for the manufacture of propylene oxide. The Oxirane process currently accounts for roughly half of the 3 million tons of propylene oxide produced annually on a worldwide basis. The reaction proceeds via a peroxometal pathway (see above) and the active catalyst contains the metal in its highest oxidation state. Metals with low oxidation potentials and high Lewis acidity in their highest oxidation states are superior catalysts and have the order of reactivity: Mo(VI) > W(VI) > V(V) > Ti(IV) [7,8].

Reactions are usually performed in the temperature range 80–120 °C, although highly reactive substrates, such as allylic alcohols, react at room temperature. Strongly coordinating solvents, particularly alcohols and water, severely retard the reaction by competing for coordination sites on the catalyst [9]. Consequently, autoretardation by the co-product alcohol (Michaelis–Menten kinetics) is observed, the extent of which increases in the order W < Mo < Ti < V. The preferred solvents are hydrocarbons, although chlorinated hydrocarbons result in higher rates [9]. The epoxidation is stereospecific, i. e. *cis* olefins give only *cis* epoxides, and the rate increases with increasing substitution of the double bond by electron-donating alkyl groups, consistent with a heterolytic mechanism involving an electrophilic oxidant (see above). The structure of RO_2H generally has only a minor effect on the rate with the exception of highly sterically hindered hydroperoxides, such as pinane hydroperoxide, which are unreactive [10].

Shell subsequently developed a heterogeneous, silica-supported titania catalyst [11,12] which forms the basis of the commercial process for the epoxidation of propylene with ethylbenzene hydroperoxide. The co-product alcohol is dehydrated, in a separate step, to styrene. Ti(IV)SiO_2 was the first truly heterogeneous epoxidation catalyst useful for continuous operation in the liquid phase.

In contrast with soluble Ti(IV) compounds, which are rather mediocre catalysts, Ti(IV)/SiO_2 has selectivity comparable with that of homogeneous molybdenum and (for a heterogeneous catalyst) high activity. The superior catalytic activity of Ti(IV)/SiO_2 was attributed [11] to both an increase in Lewis acidity of the Ti(IV), owing to electron withdrawal by silanoxy ligands, and to site isolation of discrete Ti(IV) centers on the silica surface preventing oligomerization to unreactive μ-oxo species (which occurs readily with soluble Ti(IV) compounds). It was further demonstrated that only the combination of titanium(IV) with silica affords a stable heterogeneous catalyst; all other combinations, e. g. Mo(VI), W(VI), V(V) on silica, suffered from rapid leaching of the metal, affording a homogeneous catalyst [13]. Indeed, despite extensive research efforts a stable, truly heterogeneous analog of the homogeneous molybdenum catalyst has, as far as we are aware, not yet attained commercial status.

One property which Ti(IV)/SiO_2 shares with the homogeneous catalysts is a marked sensitivity towards deactivation by strongly coordinating ligands, especially water [9]. For this reason Ti(IV)/SiO_2 is an ineffective catalyst for epoxidations with aqueous hydrogen peroxide. Hence the discovery, by Enichem scientists [14–17] in the mid-eighties, of the remarkable activity of titanium silicalite-1 (TS-1) in, inter alia, selective epoxidations with 30% aqueous hydrogen peroxide under very mild conditions, constituted a new milestone in oxidation catalysis. It was subsequently shown, by use of a variety of spectroscopic techniques [18], that TS-1 contains titanium(IV) isomorphously substituted for silicon in the framework of silicalite-1, a hydrophobic molecular sieve with a three-dimensional system of intersecting elliptical pores with diameters of 5.3 × 5.5 Å and 5.1 × 5.5 Å. Its remarkable activity in (ep)oxidations with aqueous H_2O_2 is attributed to site isolation of Ti(IV) centers in the hydrophobic pores of silicalite, which enables the simultaneous adsorption of the oxidant and the hydrophobic substrate in the presence of water. In contrast, Ti(IV)/SiO_2 is hydrophilic and this difference is reflected in the hydrophobicity index (*HI*) [19]: 3.4 and 0.1 for TS-1 and Ti(IV)/SiO_2, respectively.

TS-1 catalyzes the smooth epoxidation of relatively unreactive olefins, e. g. propylene and even allyl chloride, with 60% aqueous H_2O_2 at 40–50 °C in methanol [20]. A serious shortcoming of TS-1 is, however, its restriction to substrates with kinetic diameters < 5.5 Å. For example, 1-hexene is readily epoxidized at 50 °C whereas cyclohexene is essentially unreactive. By the same token TS-1 does not catalyze epoxidations with the more bulky *tert*-butyl hydroperoxide (TBHP), i. e. TS-1 has catalytic properties complementary to those of the Shell catalyst.

The success of TS-1 sparked a flourish of activity, which still continues today, on the synthesis and application of other redox molecular sieves [21]. This was driven by the expectation that TS-1 was the progenitor of a new class of novel catalytic materials. For example, titanium has been incorporated in the framework of wide variety of molecular sieves including mesoporous silicas, such as MCM-41, with pore diameters ranging from 20 to 50 Å (see below).

An alternative approach to new epoxidation catalysts involves the synthesis of amorphous mixed titania–silica oxides, containing up to 20% *w/w* TiO_2, by the sol–gel technique [22]. These materials resemble the Shell catalyst more closely than TS-1, i.e. they are active with TBHP in anhydrous media but not with H_2O_2. An advantage of the Shell catalyst is the much higher titanium loading which translates to higher catalyst productivity. In an attempt to mimic TS-1 more closely, hydrophobic mixed titania–silica oxides were prepared containing Si–C bonds by the sol–gel method [23,24] or subsequent trimethylsilylation of the surface [25], although this has not yet resulted in catalysts with sufficient activity and scope with aqueous hydrogen peroxide. Hence the search continues, as is reflected in the number of novel materials reported in the literature [25–27].

At the same time progress continues to be made in the development of homogeneous catalysts for epoxidation with aqueous H_2O_2. Notable examples are tungstate under phase-transfer conditions [28], methyltrioxorhenium [29] and manganese triazacyclononane complexes [30]. Different strategies can be envisaged for the immobilization of such promising homogeneous catalysts (see below).

Finally, we note that caution should be exercised, because many of the solid catalysts reported in the literature have not been subjected to rigorous proof of heterogeneity under oxidizing conditions [31]. Both alkyl hydroperoxides and, especially, hydrogen peroxide can readily leach metal ions from solid catalysts.

9.1.4 Titanium(IV)-on-silica

The TiO_2-on-SiO_2 catalyst, consisting of ca 2% *w/w* TiO_2, discovered by Shell, was the first truly heterogeneous catalyst for liquid-phase epoxidations [11,12]. The catalyst is prepared by impregnating silica with a Ti(IV) precursor, e. g. $TiCl_4$ or an organotitanium compound, then steam treatment and calcination. The amount of TiO_2 which can be incorporated is limited by the number of silanol groups on the silica surface. The resulting hydrophilic material is an active and selective catalyst for the epoxidation of a broad range of olefins with alkyl hydroperoxides such as TBHP [7,11]. The catalyst is rapidly deactivated by water which renders it unsuitable for epoxidations with hydrogen peroxide. It is now generally believed [32] that the titanium is attached to the silica surface by (at least) three silanoxy groups, consistent with the original proposal that reaction of $TiCl_4$ with silica gel involves attachment to three Si–OH groups [33].

More recently, Mayoral and coworkers [34] prepared Ti(IV)/SiO_2 catalysts by impregnating silica with $Ti(O\text{-}i\text{-}Pr)_4$ then heating at 140 °C in vacuo. Under these conditions the catalyst retained (presumably one per titanium) isopropoxy groups. It was shown to be an excellent catalyst for epoxidations with TBHP, giving smooth conversions with a variety of olefins at room temperature (Table 1).

The same group subsequently showed that the activity of the catalyst could be tuned by exchanging the surface isopropoxy groups with *vic* diols such as ethylene glycol [35]. The best catalyst was obtained by treating the original Si-Ti(O-*i*-Pr) with tartaric acid. This catalyst was active in epoxidations with 30% H_2O_2 at

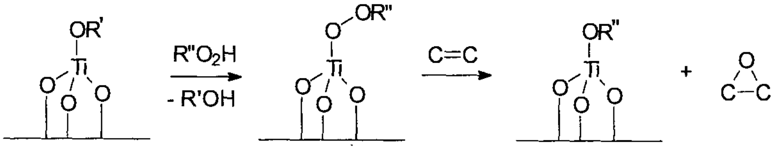
Table 1. Catalytic epoxidations with $Ti(OPr^i)_4$-modified SiO_2.

Olefin	Olefin/TBHP	Time (h)	TBHP conv. %	Selectivity (%) TBHP	Olefin
1-Hexene	8:1	24	73	62	96
Styrene	8:1	3	95	65	80
cis-2-Heptene	2:1	7	83	96	97
(*R*)-Limonene	3:1	4	93	90	98
(*R*)-Citronellol	3:1	24	89	100	100
Cinnamyl alcohol	3:2	24	33	68	68
Nerol	3:2	3.5	95	70	96
Cyclohexenol	3:2	24	100	0	0
1-Penten-3-ol	3:2	24	87	0	0

Conditions: 1 g catalyst (ca 1 mmol Ti g^{-1}) with 36 or 96 mmol olefin and 12 mmol TBHP (TBHP/Ti = 12:1) in CH_2Cl_2 at room temperature.

80 °C albeit with reactive olefins (cyclooctene and cyclohexene). Cyclohexene afforded mixtures of epoxide, cyclohexane-1,2-diol, and allylic oxidation products.

In view of the requirement for attachment to three surface silanoxy groups (see above) it would seem likely that an isopropoxy group is exchanged for a *tert*-butylperoxy group. The resulting alkylperoxotitanium(IV) species then transfers an oxygen atom to the olefin (Eq. 4). It is, however, difficult to accommodate the rate-enhancing effect of substitution of isopropoxy groups by *vic* diols in this mechanism.



(4)

9.1.5 Mixed Oxides by the Sol–Gel Method

After earlier work by Neumann and coworkers [36] the synthesis of amorphous titania–silica mixed oxides by the solution sol–gel procedure has been extensively studied by the Baiker group [22,36]. Acid-catalyzed hydrolysis and polycondensation of a mixture of Ti- and Si-alkoxides affords mixed oxides with significantly higher Ti content (up to 20% *w/w*) than conventional supported titania catalysts (see Section 9.1.4). The drying procedure is of crucial importance [22,36]. Conventional drying by evaporation produces microporous xerogels whereas drying by extraction with supercritical CO_2 retains the delicate mesoporous structure of the solid (aerogel). The resulting aerogels have high surface areas (up to ca 700 m^2 g^{-1}) with well dispersed titania, i.e. a high proportion of site-isolated $Ti(OSi)_4$ species, a key feature commensurate with high activity as an epoxidation catalyst (see earlier).

These mesoporous mixed titania–silica oxides are hydrophilic materials and are excellent catalysts for epoxidations of olefins, allylic alcohols and α,β-unsaturated ketones with alkyl hydroperoxides in non-aqueous media [37]. Their performance can be improved even further by adding organic or inorganic bases to neutralize acid sites present on the surface [38,39]. The latter cause side-reactions, especially with acid sensitive epoxides. Amine addition was particularly effective and led to the development of a mesoporous Ti–Si mixed oxide containing surface-tethered tertiary amino groups as an active, selective, and recyclable catalyst for the epoxidation of allylic alcohols [38].

A shortcoming of these materials is their hydrophilicity, which means they are ineffective catalysts for epoxidations with hydrogen peroxide; strong adsorption of water on the hydrophilic surface severely limits access of hydrophobic substrates to the active site. Hence, much effort has been devoted to the synthesis of hydrophobic analogs by polycondensation of a titanium(IV) alkoxide with $RSi(OEt)_3$ (R = alkyl, aryl) instead of $Si(OEt)_4$ [23,24,40].

Both microporous [23] and mesoporous [24] hydrophobic Ti–Si mixed oxides have been synthesized but their activities as epoxidation catalysts with aqueous hydrogen peroxide are, as yet, disappointingly low compared with the corresponding reactions with TBHP in organic media or with TS-1 (Section 9.1.6).

9.1.6 Framework-substituted Molecular Sieves

As mentioned above the discovery of the remarkable activity of titanium silicalite-1 (TS-1) as a catalyst for a variety of synthetically useful oxidations, including epoxidation, with aqueous hydrogen peroxide constituted a major breakthrough in oxidation catalysis [14–20]. The success of TS-1 stimulated the search for related materials [21]. Titanium silicalite-2, with the MEL structure, was discovered by Ratnasamy and coworkers in 1990 [41] and had properties similar to those of TS-1.

To circumvent the size restrictions associated with titanium silicalites (both TS-1 and TS-2) the incorporation of titanium in large-pore molecular sieves was investigated by several groups. For example, Corma and coworkers [42] incorporated Ti in the framework of zeolite beta (pore dimensions 7.6 × 6.4 Å). The resulting Ti,Al-beta is a bifunctional catalyst containing Ti(IV) sites for peroxide activation and Brønsted acid (Al) sites. Hence, Ti,Al-beta catalyzes epoxidations with aqueous H_2O_2 but the resulting epoxides undergo acid-catalyzed ring opening to afford *vic* diols and/or rearrangement products [42–45]. This could be circumvented by neutralizing the Brønsted acid sites, by treatment with alkali metal acetates and recalcination, or by performing the reaction in acetonitrile (a Lewis base) as solvent [45]. Subsequently, several groups succeeded in synthesizing aluminum-free Ti-beta and showed that it catalyzes epoxidations with aqueous hydrogen peroxide, albeit with activity lower than that of TS-1 and, depending on the conditions, with accompanying ring opening of the epoxide product [46–48]. Titanium-substituted beta also, as would be expected, catalyzes epoxidations with TBHP [49].

Titanium was also incorporated into mesoporous silicas such as MCM-41 [50] and MCM-48 [51]. The resulting materials catalyze epoxidations with both H_2O_2 and TBHP. They are not, however, stable towards leaching under reaction conditions, particularly with H_2O_2 [52]. Different strategies have been employed [53] to enhance the hydrophobicity and, hence, the stability and overall performance of these materials as catalysts for epoxidations with H_2O_2, albeit with only moderate success.

In an alternative approach, Maschmeyer et al. [26] grafted titanium(IV) species on to the internal surface of MCM-41, by reaction with $(Cp)_2TiCl_2$ and subsequent calcination. Because all the Ti(IV) sites are at the surface one would expect this material to be more active than Ti-MCM-41 prepared by hydrothermal synthesis, and this proved to be the case [26]. Here again, this material was effective only in epoxidations with TBHP, not with H_2O_2, and its stability towards leaching was not rigorously established.

In yet another novel approach titanium(IV) silsesquioxanes (see Figure 2 for structure) were prepared and shown to be excellent homogeneous catalysts for

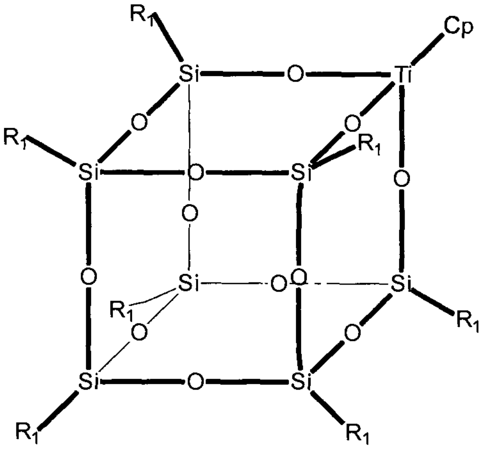


Figure 2. Titanium silsesquioxane

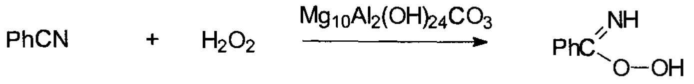
epoxidations with TBHP [32]. A heterogeneous variant was prepared by adsorbing the titanium(IV) silsesquioxane in the pores of MCM-41 that had been silylated with Ph_2SiCl_2 to passivate the external surface. The resulting material was claimed to be a stable recyclable catalyst for epoxidations with TBHP [54].

Other transition metal-substituted molecular sieves have been synthesized and tested as epoxidation catalysts [21]. The stability of many of these materials towards leaching is, however, seriously in doubt [31]. Catalysis by vanadium-substituted molecular sieves has, in all cases studied, been shown to be homogeneous in nature, i. e. because of leached vanadium [31,55]. A priori, one would expect zirconium- [56] and tin- [57] substituted molecular sieves to be more stable but more rigorous proof is needed.

9.1.7 Hydrotalcites

Hydrotalcites are synthetic basic clays, so-called layered double hydroxides (LDHs) of magnesium and aluminum consisting of Brucite-like layers with an overall positive charge with anions (usually OH^- or CO_3^{2-}) in the interlamellar space [58]. A typical composition is $Mg_{10}Al_2(OH)_{24}CO_3$. Hydrotalcites have been used as solid-base catalysts in several organic reactions [58] including the epoxidation of electron-deficient olefins with H_2O_2 or RO_2H [59].

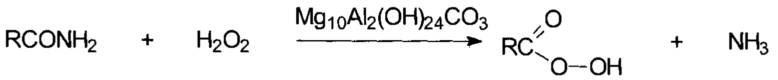
In a variation on this theme $Mg_{10}Al_2(OH)_{24}CO_3$ has been shown to catalyze the oxidation of a variety of olefins–linear and cyclic–and unsaturated alcohols and ketones with H_2O_2 in the presence of benzonitrile [60]. The reaction involves in situ formation of the Payne reagent [61], PhC(OOH)=NH, by base-catalyzed reaction of H_2O_2 with benzonitrile (Eq. 5). Reaction with the olefin then affords the epoxide and one equivalent of benzamide (Eq. 6).



(5)

(6)

More recently, the same group [62] showed that hydrotalcite catalyzes the epoxidation of olefins with 30 % H_2O_2 in the presence of an amide, e. g. isobutyramide was most effective, in 1,2-dichloroethane at 70 °C. Addition of an anionic surfactant, e.g. sodium dodecyl sulfate, further enhanced the rate. With less reactive terminal olefins, e. g. 1-octene, a large excess of the amide (10 equiv.) was necessary to attain a high yield of epoxide. A mechanism was proposed (Eqs 7 and 8) which involved reaction of HO_2^-, formed on the hydrotalcite surface, with the amide generating a peracid and NH_3:



(7)

(8)

The interlamellar anions of hydrotalcites can be exchanged, and anion-exchange capacities are in the range 2–4 meq g^{-1} [63]. This property was exploited by Jacobs and coworkers [63,64] to prepare tungstate-exchanged hydrotalcite. The resulting WO_4^{2-}-LDH was an effective heterogeneous catalyst for the epoxidation of allylic alcohols [64] with 35 % H_2O_2. Further tuning of the hydrophobicity of the active site, by exchange of *p*-toluenesulfonate ions and WO_4^{2-}, afforded a catalyst for epoxidations of unfunctionalized olefins.

9.1.8 Immobilization of Homogeneous Complexes

As noted above, homogeneous catalysts based on W, Re, and Mn have been shown to be effective for epoxidations with H_2O_2. Several immobilization strategies have been employed to prepare heterogeneous analogs of these systems, e.g. ion exchange, grafting, or tethering to surfaces, encapsulation in zeolite supercages, and occlusion in polydimethylsiloxane membranes [63,65].

For example, tungstate and heteropolytungstates have been immobilized by anion exchange with quaternary ammonium-modified silica [66] and polysiloxane [67] or Amberlite IRA-900 [68] resins. The latter catalyst was shown to be effective, and recyclable, in the epoxidation of relatively reactive olefins with 50 % aq. H_2O_2 in CH_3CN as solvent.

Methyltrioxorhenium (MTO) supported on silica functionalized with polyether tethers (prepared by a sol–gel procedure) was shown to catalyze epoxidations with 30 % H_2O_2 in the absence of solvent [69]. The silica-attached polyether phase is assumed to act as a 'solvent' for the MTO (see Figure 3). The hydropho-

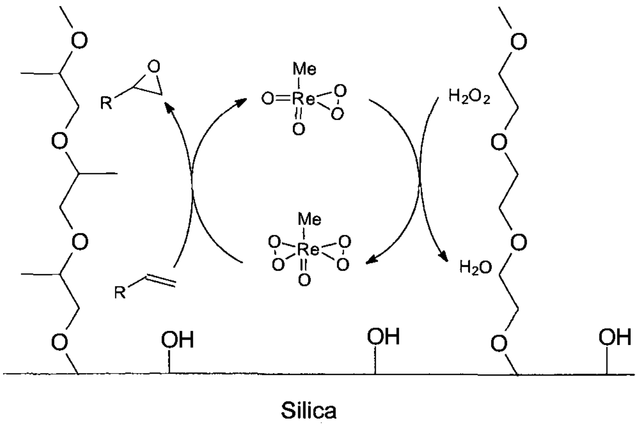
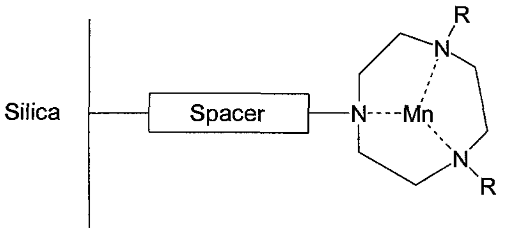


Figure 3. MTO on silica tethered with polyethers.

bic–hydrophilic balance of this polyether phase can be tuned by adjusting the ratio of polypropylene oxide (PPO) to polyethylene oxide (PEO) units attached to the surface. For example, in the epoxidation of cyclohexene an optimum result (86% yield) was obtained with a catalyst containing 10% *m*/*m* PPO and 10% *m*/*m* PEO. In recycling experiments conversion and selectivity dropped considerably from the fifth cycle onwards.

Two strategies have been followed to immobilize manganese triazacyclononane complexes, which are good homogeneous epoxidation catalysts [30]. In one approach a manganese trimethyltriazacyclononane (tmtacn) complex was assembled in the supercages of zeolite Y [70]. This leads, however, to the formation of less reactive dinuclear complexes in the supercages. A more promising approach involved the tethering of triazacyclononane (tacn) ligands to silica surfaces (Figure 4) [71].

Molybdenum(VI) complexes of thermally and oxidatively stable polybenzamidazoles were shown to be recyclable catalysts for epoxidations with TBHP although stability towards slow leaching of molybdenum was not rigorously demonstrated [72].



Spacer = $-(CH_2)_3-$ or $-(CH_2)_3OCH_2CH(OH)CH$

R = H or $-CH_2CH(OH)R'$

Figure 4. Covalent attachment of tacn ligands to silica.

9.1.9 Heterogeneous Catalysts for Asymmetric Epoxidation

A heterogeneous version of the Sharpless [73] epoxidation of allylic alcohols has been described [74]. A complex formed between $Ti(OPr^i)_4$ and a linear poly-L-tartrate, in combination with zeolite 4A as a drying agent, catalyzed the enantioselective epoxidation of *trans*-2-hexen-1-ol with TBHP (92 % yield and 79 % ee), although not all of the titanium remained complexed to the polymer on recycling and was uncomplexed or complexed with tartrate monomer/oligomer in solution.

Several oxide-supported titanium systems for enantioselective epoxidation have been reported [75] but their stability is questionable. A basic problem is that the titanium must be coordinated to two tartrate oxygens, allylic alkoxide, and *tert*-butylperoxo in addition to being bonded to the surface by, e. g., silanoxy groups. As was recently pointed out by Basset and coworkers [76], pentavalent tantalum is in a better position to accommodate all these ligands. They demonstrated that silica grafted tantalum ethoxides were effective as heterogeneous catalysts for enantioselective epoxidation of allylic alcohols with TBHP, e. g. *trans*-2-hexen-1-ol gave the corresponding epoxide in 85–94 % ee.

Another interesting system for asymmetric epoxidation involves the use of synthetic poly-amino acids as catalysts, often referred to as the Julia epoxidation [77]. The reaction is usually performed in a triphasic system consisting of alkaline hydrogen peroxide, an organic solvent, and the (insoluble) polymer. The method is limited to the epoxidation of electron-deficient olefins such as α,β-unsaturated ketones [78,79]. Inherent disadvantages are long reaction times and swelling of the polymer in the reaction medium but these could be overcome by using the poly-amino acid supported on a cross-linked polystyrene resin [80].

9.1.10 Comparison of the Different Catalytic Systems

A meaningful comparison of the variety of catalysts reported in the literature for epoxidation with TBHP or H_2O_2 is difficult. Reactions are often performed under markedly different conditions using olefin substrates with dramatically different reactivity. Authors often claim high activity but on closer inspection highly reactive olefins producing stable epoxides, e. g. cyclooctene, were used. To have real synthetic utility a catalyst should be effective with a broad range of olefins, including less reactive ones, e. g. terminal olefins, and those producing (acid-) sensitive epoxides, e. g. terpenes. To have real utility, moreover, a heterogeneous catalyst should be stable and recyclable, i. e. the metal should not be leached from the surface during reaction, and many authors fail to address this aspect [31].

A useful criterion for comparing catalysts is the turnover frequency (TOF; mol product per mol catalyst per unit time, usually expressed as h^{-1}). For heterogeneous catalysts, where the active species may constitute only a small fraction of the total weight, productivity (g product per g catalyst per unit time) can be more useful.

We have attempted to compare the activities of different catalysts in epoxidations with TBHP and H_2O_2 in Tables 2 and 3, respectively. A meaningful com-

Table 2. Comparison of the different catalyst for epoxidation of cyclohexene with organic hydroperoxides.

Catalyst	S/C[a]	RO_2H/C[b]	S/RO_2H[c]	Conv. alkene (%)	TOF (h^{-1})	Productivity[d] ($g\ g^{-1}h^{-1}$)	Ref.
Ti → MCM-41	750	187	4	3	5	0.12	34
Ti ↑ MCM-41	173	207	0.83	50	87	11	26
Ti-Beta	202	50	4	8.5	3.4	0.14	34
Ti-aerogel	308	52	5.9	17	35	8.3	37
Ti-Si mixed oxide	596	149	4	24	29	3.0	34
id, mesoporous	1500	373	4	19	570	7.0	53
Ti ↑ SiO_2	100	100	1	66	3.7	0.09	8
Homogeneous Mo^{VI}	100	100	1	92	92	27	8

[a] Substrate to catalyst ratio.

[b] Hydroperoxide to catalyst ratio.

[c] Alkene to hydroperoxide ratio.

[d] Based on amount of catalyst charged.

Table 3. Comparison of the different catalysts for cyclohexene epoxidation with aqueous hydrogen peroxide.

Catalyst	S/C[a]	H_2O_2/C[b]	S/H_2O_2[c]	Conv. alkene (%)	TOF (h^{-1})	Sel.[d]	Ref.
Ti-Beta Hydrophobic	1470	740	2	26	130	86 %	47
Ti–Si mixed oxide	640	1280	0.5	16	20	66 %	23
id.	1220	60	20	11	–	low	24
Homogeneous Re^{VII}	1000	2000	0.5	99	> 1000	> 99 %	29

[a] Substrate to catalyst ratio.
[b] Hydrogen peroxide to catalyst ratio.
[c] Alkene to hydrogen peroxide ratio.
[d] Selectivity towards epoxide, based on converted alkene.

parison of different catalysts is complicated because TOFs and productivities are often highly dependent on conversion, and authors report data at different conversions. Initial rates are (much) higher than final rates and for most catalytic systems incomplete data are presented. One conclusion is clear, however, from the vast literature–catalytic epoxidations with TBHP are much easier than those with aqueous H_2O_2, for reasons outlined above.

The only successful heterogeneous catalyst for epoxidations with H_2O_2, TS-1, is compared with state-of-the-art homogeneous systems in Table 4.

Table 4. Comparison of TS-1 with state-of-the-art homogeneous catalysts for 1-hexene epoxidation with aqueous hydrogen peroxide.

Catalyst	S/C[a]	H_2O_2/C[b]	S/H_2O_2[c]	*t* (h)	*T* (°C)	Conv. alkene (%)	TOF (h^{-1})	Sel.[d]	Productivity[e] ($g\ g^{-1}h^{-1}$)	Ref.
TS-1	83	83	1	1.2	25	68	49	90 %	1.5	20
Re^{VII}	1000	2000	0.5	6	25	95	158	> 99 %	63	29
W^{VI}	81	48	1.7	0.75	70	53	70	88 %	10	28
Mn^{III}	666	1000	0.67	0.3	5	99	2000	99 %	620	30

[a] Substrate to catalyst ratio.

[b] Hydrogen peroxide to catalyst ratio.

[c] Alkene to hydrogen peroxide ratio.

[d] Selectivity towards epoxide, based on converted alkene.

[e] Based on amount of catalyst charged.

9.1.11 Concluding Remarks

The development of effective methods for catalytic epoxidation, particularly using aqueous hydrogen peroxide as the primary oxidant, remains an important goal in industrial organic synthesis. Many heterogeneous catalysts, largely based on titanium, have been described in the literature but they are mostly only effective with alkyl hydroperoxides as the oxidant. The development of TS-1 was a major breakthrough in catalysis of oxidations with aqueous H_2O_2 but its scope is limited to relatively small substrates which can be accommodated in the micropores of the catalyst. Hence, the quest for heterogeneous catalysts that are both effective and broad in scope continues.

References

[1] R. A. Sheldon in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils and W. A. Herrmann). VCH, Weinheim, **1996**, p. 411.
[2] R. A. van Santen and H. P. C. E. Kuipers, *Adv. Catal.* 1987, *35*, 265; R. A. van Santen in *Handbook of Heterogeneous Catalysis* (Eds.: G. Ertl, H. Knözinger and J. Weitkamp), Wiley–VCH, Weinheim, **1997**, Vol. 5, p. 2244.
[3] J. R. Monnier, *Stud. Surf. Sci. Catal.* **1997**, *110*, 123; Eastman Chemical (J. R. Monnier and P. J. Muehlbauer), US 5.145.968 (1992).
[4] R. A. Sheldon, *Top. Curr. Chem.* **1993**, *164*, 21.
[5] Halcon (J. Kollar), US 3350422 and 3351635 (1967).
[6] M. N. Sheng and J. G. Zajacek, *ACS Adv. Chem. Ser.* **1968**, *76*, 418; Atlantic Richfield (M. N. Sheng and J. G. Zajacek), GB 1136923 (1968).
[7] R. A. Sheldon in *Aspects of Homogeneous Catalysis* (Ed.: R. Ugo), Reidel, Dordrecht, **1981**, Vol. 4, pp. 3–70.
[8] R. A. Sheldon and J. A. van Doorn, *J. Catal.* **1973**, *31*, 427.
[9] R. A. Sheldon, J. A. van Doorn, C. W. A. Schram and A. J. de Jong, *J. Catal.* **1973**, *31*, 438.
[10] H. E. B. Lempers, A. Ripollès i Garcia and R. A. Sheldon, *J. Org. Chem.* **1998**, *63*, 1408; H. E. B. Lempers, M. J. van Crey and R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 542; H. E. B. Lempers and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1997**, *110*, 557.
[11] R. A. Sheldon, *J. Mol. Catal.* **1980**, *7*, 107.
[12] Shell Oil (H. P. Wulff), GP 1249079 (1971).
[13] A ZrO_2–SiO_2 catalyst was also claimed to be active in epoxidation: Shell Oil (F. Wattimena and H. P. Wulff), US 1249082 (1971).
[14] Enichem (M. Taramasso, G. Perego and B. Notari), US 4410501 (1983).
[15] B. Notari, *Adv. Catal.* **1996**, *41*, 253; B. Notari, *Catal. Today* **1993**, *18*, 163; B. Notari, *Stud. Surf. Sci. Catal.* **1988**, *37*, 413.
[16] U. Romano, A. Esposito, F. Maspero, C. Neri and M. G. Clerici, *Chim. Ind. (Milan)* **1990**, *72*, 610.
[17] P. Ingallina, M. G. Clerici, L. Rossi and G. Bellussi, *Stud. Surf. Sci. Catal.* **1994**, *92*, 31.
[18] G. Bellussi and M. S. Rigutto, *Stud. Surf. Sci. Catal.* **1994**, *85*, 177.
[19] The hydrophobicity index, HI $= x_{\text{octene}}/x_{\text{water}}$ is defined as the ratio of the final loadings of the molecular sieve with *n*-octane and water, determined from the breakthrough curves in the gas phase at 308 K.
[20] M. G. Clerici and P. Ingallina, *Catal. Today* **1998**, *41*, 351; M. G. Clerici and P. Ingallina, *J. Catal.* **1993**, *140*, 71.
[21] I. W. C. E. Arends, R. A. Sheldon, M. Wallau and U. Schuchardt, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1144.
[22] M. Schneider and A. Baiker, *Catal. Rev. Sci. Eng.* **1995**, *37*, 515.

[23] S. Klein and W. F. Maier, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2230.

[24] H. Kochkar and F. Figueras, *J. Catal.* **1997**, *171*, 420.

[25] M. B. D'Amore and S. Schwarz, *Chem. Commun.* **1999**, 121.

[26] T. Maschmeyer, F. Rey, G. Sankar and J. M. Thomas, *Nature* **1995**. 159.

[27] S. Krijnen, H. C. L. Abbenhuis, R. W. J. M. Hanssen, J. H. C. van Hooff and R. A. van Santen, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 356.

[28] K. Sato, M. Aoki, M. Ogawa, T. Hashimoto and R. Noyori, *J. Org. Chem.* **1996**, *61*, 8310; K. Sato, M. Aoki, M. Ogawa, T. Hashimoto, D. Panyella and R. Noyori, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905; C. Venturello, E. Alneri and M. Ricci, *J. Org. Chem.* **1983**, *48*, 3831; C. Venturello and R. D'Aloisio, *J. Org. Chem.* **1988**, *53*, 1553; Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida and M. J. Ogawa, *J. Org. Chem.* **1988**, *53*, 3587.

[29] W. Herrmann, R. W. Fischer and D. W. Marz, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1638; W. A. Herrmann, R. W. Fischer, M. U. Rauch and W. Scherer, *J. Mol. Catal.* **1994**, *86*, 243; J. Rudolph, K. Laxma Reddy, J. P. Chiang and K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 6189; C. Copéret, H. Adolfsson and K. B. Sharpless, *Chem. Commun.* **1997**, 1565; W. A. Herrmann, R. M. Kratzer, H. Ding, W. R. Thiel and H. Glas, *J. Organomet. Chem.* **1998**, *555*, 293; A. L. Villa, D. E. De Vos, C. Montes de C. and P. A. Jacobs, *Tetrahedron* **1998**, *39*, 8521; M. C. A. van Vliet, I. W. C. E. Arends and R. A. Sheldon, *Chem. Commun.* **1999**, 821.

[30] D. E. De Vos, B. F. Sells, M. Reynaers, Y. V. S. Rao and P. A. Jacobs, *Tetrahedron Lett.* **1998**, *39*, 3221; D. De Vos and T. E. Bein, *Chem. Commun.* **1996**, 917; R. Hage et al., *Nature* **1994**, *369*, 637; R. Hage, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 385.

[31] R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485; R. A. Sheldon, I. W. C. E. Arends and H. E. B. Lempers, *Coll. Czech. Chem. Commun.* **1998**, *63*, 1724.

[32] H. C. L. Abbenhuis, S. Krijnen and R. A. van Santen, *Chem. Commun.* **1997**, 331.

[33] S. I. Kol'tsov and V. B. Aleskovskii, *J. Appl. Chem. USSR* **1967**, *40*, 907.

[34] C. Cativiela, J. M. Fraile, J. I. Garcia and J. A. Mayoral, *J. Mol. Catal. A: Chemical* **1996**, *112*, 259; J. M. Fraile, J. I. Garcia, J. A. Mayoral, L. C. de Ménorval and F. Rachdi, *J. Chem. Soc., Chem. Commun.* **1995**, 539; J. M. Fraile, J. Garcia, J. A. Mayoral, M. G. Proietti and M. C. Sanchez, *J. Phys. Chem.* **1996**, *100*, 19484.

[35] J. M. Fraile, J. I. Garcia, J. A. Mayoral and E. Vispe, *J. Catal.* **2000**, *189*, 40.

[36] D. C. M. Dutoit, M. Schneider and A. Baiker, *J. Catal.* **1995**, *153*, 165; D. C. M. Dutoit, M. Schneider, R. Hutter and A. Baiker, *J. Catal.* **1996**, *161*. 651; D. C. M. Dutoit, U. Göbel, M. Schneider and A. Baiker, *J. Catal.* **1996**, *164*, 433.

[37] R. Hutter, T. Mallat and A. Baiker, *J. Catal.* **1995**, *153*, 177.

[38] M. Dussi, C. A. Müller, T. Mallat and A. Baiker, *Chem. Commun.* **1999**, 197.

[39] R. Hutter, T. Mallat, A. Peterhans and A. Baiker, *J. Mol. Catal. A: Chemical* **1999**, *138*, 241; M. Dusi, T. Mallat and A. Baiker, *J. Catal.* **1999**, *187*, 191.

[40] C. A. Müller, M. Maciejewski, T. Mallat and A. Baiker, *J. Catal.* **1999**, *184*, 280.

[41] J. S. Reddy, R. Kumar and P. Ratnasamy, *Appl. Catal.* **1990**, *58*, L1.

[42] M. A. Camblor, A. Corma, A. Martinez and J. Perez-Pariente, *J. Chem. Soc. Chem. Commun.* **1992**, 589.

[43] M. van Klaveren and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1997**, *110*, 567.

[44] A. Corma, M. Iglesias and F. Sanchez, *J. Chem. Soc. Chem. Commun.* **1995**, 1635.

[45] T. Sato, J. Dakka and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1994**, *84*, 1853.

[46] ARCO (R. J. Saxton, G. L. Crocco, J. G. Zajacek and K. S. Wijesekea), Eur. Pat. 659 685 (1994).

[47] J. C. van der Waal, M. S. Rigutto and H. van Bekkum, *Appl. Catal. A: General* **1998**, *167*, 331.

[48] T. Blasco, M. A. Camblor, A. Corma, P. Esteve, A. Martinez, C. Prieto and S. Valencia, *Chem. Commun.* **1996**, 2367.

[49] T. Sato, J. Dakka and R. A. Sheldon, *J. Chem. Soc., Chem. Commun.* **1994**, 1887; A. Corma, P. Esteve, A. Martinez and S. Valencia, *J. Catal.* **1995**, *152*, 18.

[50] P. T. Tanev, M. Chibwe and T. J. Pinnavaia, *Nature* **1994**, *386*, 239; A. Corma, M. T. Navarro and J. Perez-Pariente, *J. Chem. Soc., Chem. Commun.* **1994**, 147; M. E. Raimondi, L. Marchese, E. Gianotti, T. Maschmeyer, J. M. Seddon and S. Coluccia, *Chem. Commun.* **1999**, 87.

[51] K. A. Koyano and T. Tatsumi, *Chem. Commun.* **1996**, 145.

[52] C. H. Rhee and J. S. Lee, *Catal. Lett.* **1996**, *40*, 261; L. Y. Chen, G. R. Chuah and S. Jaenicke, *Catal. Lett.* **1998**, *50*, 107.

[53] M. A. Camblor, A. Corma, P. Esteve, A. Martinez and S. Valencia, *Chem. Commun.* **1997**, 795; A. Corma, M. Domine, J. A. Gaona, J. L. Jorda, M. T. Navarro, F. Rey, J. Perez-Pariente, J. Tsuji, B. McCulloch and L. T. Nemeth, *Chem. Commun.* **1998**, 2211; A. Corma, J. L. Jorda, M. T. Navarro and F. Rey, *Chem. Commun.* **1998**, 1899.

[54] S. Krijnen, H. Abbenhuis, R. Hanssen, J. van Hooff and R. A. van Santen, *Angew. Chem.* **1998**, *110*, 374.

[55] M. J. Haanepen, A. M. Elemans-Mehring and J. H. C. van Hooff, *Appl. Catal. A* **1997**, *152*, 203.

[56] K. A. Vercruysse, D. M. Klingeleers, T. Colling and P. A. Jacobs, *Stud. Surf. Sci. Catal.* **1998**, *117*, 469.

[57] K. Chaudhari, T. K. Das, P. R. Rajmohanan, K. Lazar, S. Sivasankar and A. J. Chandwadkar, *J. Catal.* **1999**, *183*, 281.

[58] A. Vaccari, *Appl. Clay Sci.* **1999**, *14*, 161; F. Cavani, F. Trifiro and A. Vaccari, *Catal. Today* **1991**, *11*, 173.

[59] C. Cativiela, F. Figueras, J. M. Fraile, J. I. Garcia and J. A. Mayoral, *Tetrahedron Lett.* **1995**, *36*, 4125; see also B. M. Choudary, M. L. Kantam, B. Bharathi and C. V. Reddy, *Syn. Lett.* **1998**, 1023.

[60] S. Ueno, K. Yamaguchi, K. Yoshida, K. Ebitani and K. Kaneda, *Chem. Commun.* **1998**, 295.

[61] G. B. Payne, P. H. Deming and P. H. Williams, *J. Org. Chem.* **1961**, *26*, 659.

[62] K. Yamaguchi, K. Ebitani and K. Kaneda, *J. Org. Chem.* **1999**, *64*, 2966.

[63] G. Langhendries, D. E. De Vos, B. F. Sels, I. Vankelecom, P. A. Jacobs and G. V. Baron, *Chem. Prod. Proc.* **1998**, *1*, 21.

[64] B. F. Sels, D. E. De Vos and P. A. Jacobs, *Tetrahedron Lett.* **1996**, *37*, 8557; see also Y. Watanabe, K. Yamamoto and T. Tatsumi, *J. Mol. Catal. A: Chemical* **1999**, *145*, 281.

[65] R. A. Sheldon, I. W. C. E. Arends and H. E. B. Lempers, *Catal. Today* **1998**, *41*, 387.

[66] R. Neumann and M. Cohen, *Angew. Chem.* **1997**, *109*, 1810.

[67] Degussa (P. Goetz, S. Wieland, P. Panster, G. Goor and R. Siegmeier), US Pat. 5 286 885 (1994).

[68] A. L. Villa de P., B. F. Sels, D. E. De Vos and P. A. Jacobs, *J. Org. Chem.* **1999**, *64*, 7267.

[69] R. Neumann and T.-J. Wang, *Chem. Commun.* **1997**, 1915.

[70] D. E. De Vos, J. L. Meinershagen and T. Bein, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2211.

[71] Y. V. S. Rao, D. E. De Vos, T. Bein and P. A. Jacobs, *Chem. Commun.* **1997**, 355.

[72] M. M. Miller and D. C. Sherrington, *J. Catal.* **1995**, *152*, 377; J. H. Ahn, K. C. Kim, S. K. Ihm and D. C. Sherrington, *Stud. Surf. Sci. Catal.* **1997**, *110*, 957.

[73] T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.

[74] L. Canali, J. K. Karjaleinen, D. C. Sherrington and O. Hormi, *Chem. Commun.* **1997**, 123; J. K. Karjalainen, O. E. O. Homi and D. C. Sherrington, *Tetrahedron: Asymm.* **1998**, *9*, 1563.

[75] G. J. Hutchings, D. F. Lee and A. R. Minihan, *Catal. Lett.* **1995**, *33*, 369; C. Cativiela, J. M. Fraile, J. I. Garcia and J. A. Mayoral, *J. Mol. Catal.* **1996**, *112*, 259; W. Adam, A. Corma, A. Martinez, C. M. Mitchell, T. I. Reddy, M. Renz and A. K. Smertz, *J. Mol. Catal.* **1997**, *117*, 357; B. M. Choudary, V. L. K. Vialli and A. D. Prasad, *J. Chem. Soc., Chem. Commun.* **1990**, 1186.

[76] D. Meunier, A. Pieckaczyk, A. de Mallmann and J. M. Basset, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3540.

[77] S. Julia, J. Masana and J. C. Vega, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929; S. Julia, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziate and H. Molinari, *J. Chem. Soc., Perkin Trans.* **1982**, 1317.

[78] S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana and A. Alvarez, *Tetrahedron* **1983**, *39*, 1635; S. Banfi, S. Colonna, H. Molinari, S. Julia and J. Guizer, *Tetrahedron* **1984**, *40*, 5207.

[79] M. E. Lasterra-Sandez and S. M. Roberts, *Curr. Org. Chem.* **1997**, *1*, 187; M. J. Porter, S. M. Roberts and J. Skidmore, *Bioorg. Med. Chem.* **1999**, *7*, 2145; W. Kroutil, P. Mayon, M. E. Lasterra-Sanchez, S. J. Madrell, S. M. Roberts, S. R. Thornton, C. J. Todd and M. Tüter, *Chem. Commun.* **1996**, 845; M. E. Lasterra-Sanchez and S. M. Roberts, *J. Chem. Soc., Perkin Trans.* **1995**, *1*, 1467.

[80] S. Itsuno, M. Sakakura and K. Ito, *J. Org. Chem.* **1990**, *55*, 6047; P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts and L. E. Wu, *Chem. Commun.* **1997**, 739.

9.2 Oxidation of Alcohols and Aldehydes on Metal Catalysts

Michèle Besson, Pierre Gallezot

9.2.1 Introduction

Liquid-phase oxidations of alcohols in the presence of supported metal catalysts are potentially very attractive reactions for the preparation of intermediates and fine chemicals because high selectivities can be obtained with environmentally clean processes. Indeed, they proceed under mild conditions, with molecular oxygen as oxidizing agent and water as solvent. Supported catalysts, based mainly on platinum-group metals, are resistant to leaching, are recyclable, and are readily available from catalyst manufacturers in various compositions and forms.

It was found as early as the middle of the 19th century that oxidation of alcohols to aldehydes and acids with molecular oxygen is catalyzed by platinum metals, but these reactions have been comparatively little studied. After the pioneering work of Heyns et al. [1,2], most of the reports in the open literature were published by a small number of research groups at Eindhoven [3–24], Delft [25–39], Zürich [40–56], and Villeurbanne [57–68], and the oxidation of glycerol and derivatives was studied by Kimura [69–74]. A few review papers were devoted to the liquid-phase oxidation of alcohols and carbohydrates on metal catalysts [31,48, 75–77].

In Section 9.2.2 the physicochemical aspects of metal-catalyzed oxidation reactions of alcohols and aldehydes, including carbohydrates, will be analyzed. Selected examples of oxidation reactions will be considered in section 9.2.3 excluding those of carbohydrates, which are treated separately in Section 9.3.

9.2.2 Physicochemical and Engineering Aspects

9.2.2.1 Reaction Mechanism

It was suggested at a very early stage [1,2] that liquid-phase oxidation reactions of alcohols on metal surfaces proceed via a dehydrogenation mechanism followed by oxidation of the adsorbed hydrogen atom with dissociatively adsorbed oxygen. This was supported by kinetic modeling of oxidation experiments [3], and by direct observation of hydrogen evolving from aqueous solutions of aldose at basic pH (> 11) in the presence of metal catalysts [25]. The dehydrogenation mechanism was also supported by physical and chemical measurements. Thus, oxidation experiments of ethanol or 2-propanol conducted with ^{18}O-labeled oxygen showed that this isotope was not incorporated into the reaction products [78]. Measurement of electrode potential showed that the potential of the platinum catalysts in alcohol solutions was almost the same as that of the hydrogen electrode, i. e., Pt surface covered by adsorbed hydrogen [79]. Similar measurements during oxidation of 2-propanol demonstrated that the platinum surface was predominantly covered with hydrogen even though the oxidation reaction was run in an oxygen atmosphere [80].

Different formalisms were proposed for the oxidative dehydrogenation mechanism. For reducing sugars in basic solutions it was suggested [25] that aldose anions are adsorbed by the surface and then transfer a hydride (Section 9.3). Because oxidation reactions can also be conducted in neutral or acidic media, a dehydrogenation pathway occurring entirely on the metal surface was proposed [26,28,31]:

$$RCH_2OH_{sol} \rightleftharpoons RCH_2OH_{ads} \rightarrow RCHO_{ads} + 2H_{ads} \tag{1}$$

The surface reaction involves an initial dehydrogenation giving the alkoxide RCH_2O_{ads} , which is subsequently dehydrogenated into the corresponding aldehyde. The second step is more demanding, as demonstrated by experiments showing a strong isotope effect in the rate of oxidation of α-deuterated and non-deuterated 2-propanol [80]. Adsorbed hydrogen atoms are removed from the surface by reaction with oxygen dissociatively adsorbed on the metal.

If water is present in the reaction medium, aldehydes may hydrate to form geminal diols, which dehydrogenate to form the corresponding acids:

$$(RCHO)_{sol} + (H_2O)_{sol} \rightleftharpoons (RCH(OH)_2)_{sol} \rightleftharpoons (RCH(OH)_2)_{ads} \rightarrow$$
$$(RCOOH)_{ads} + 2H_{ads} \tag{2}$$

The aldehyde formed transiently was usually not detected in the reaction medium. In the oxidation of 5-hydroxymethylfurfural, however [28], the aldehyde intermediate was formed with high selectivity because the geminal-diol did not form readily, because of conjugation of the carbonyl group with the aromatic furan nucleus. Good selectivity was also obtained in the oxidation of cinnamyl alcohol to cinnamyl aldehyde, because the C=O group of the aldehyde conjugated with the C=C bond and the aromatic nucleus underwent negligible hydration [45,50]. In the presence of organic solvents, alcohol oxidation stops at the aldehyde stage because the geminal-diol could not form; this is, however, of limited practical importance because for safety reason most organic solvents should not be used in the presence of oxygen and metal catalysts.

From kinetic modeling of ethanol oxidation on platinum, Van den Tillaart et al. [19] proposed that the ethoxide species $CH_3CH_2O_{ads}$ formed after the first dehydrogenation step did not dehydrogenate further, but reacted with dissociatively adsorbed oxygen:

$$CH_3CH_2OH \rightarrow CH_3CH_2O_{ads} + H_{ads} \tag{3}$$
$$CH_3CH_2O_{ads} + O_{ads} \rightarrow CH_3CHO + OH_{ads} \tag{4}$$
$$H_{ads} + OH_{ads} \rightarrow H_2O \tag{5}$$

In conclusion, the oxidative dehydrogenation mechanism is widely accepted, but the reaction pathway will be under debate for some time because the nature and concentration of adsorbed species are not known.

9.2.2.2 Catalyst Deactivation

The conversion of alcohols in liquid-phase oxidation on metals does not go to completion, or proceeds at a very slow rate, because catalysts deactivate in the course of reaction. Deactivation could be irreversible when the catalyst structure is modified , e. g. by metal-particle growth or metal leaching, or partially reversible when the metal surface is partially blocked by oxygen or reaction products.

Irreversible Deactivation

Loss of metal surface area during reaction is usually a minor cause of catalyst deactivation. Thus, platinum dispersion during glyoxal oxidation [57,58], and palladium dispersion during D-glucose oxidation [60,61] were stable. A moderate increase of platinum particle size from 2.2 nm to 3.2 nm was observed in a Pt/C catalyst after methyl-α-D-glucoside oxidation [17]. In a recent reinvestigation of this reaction [23], it was concluded there was almost no growth of platinum particles on a Pt/graphite prepared by ion exchange, but treatment with hydrogen at high pH enhanced particle growth. Corrosion and restructuring of large platinum particles during L-sorbose oxidation was detected by STM [55].

Leaching of metals, particularly of metal promoters, is a more serious cause of deactivation. Palladium is leached away during oxidation of 2-methylphenoxyethanol on Pd/$CaCO_3$ [81]. The presence of dissolved platinum in 2–4 ppm concentration during oxidation of methyl-α-D-glucoside has been proved [17]. It was reported [32] that both platinum and aluminum of Pt/Al_2O_3 catalysts leached in aldopentose solutions (D-xylose, D-ribose, D-lyxose, and D-ribose); platinum leaching was much larger in the last two, because the configuration of these carbohydrates was favorable for metal complexation. Palladium, platinum, and bismuth did not leach from Pd–Bi/C catalysts during glucose oxidation carried out at basic pH [61], or during oxidation of glycerol to dihydroxyacetone over Pt–Bi/C even at slightly acidic pH [62]. Bismuth was leached in solutions during oxidation of tartronic to mesoxalic acid on Pt–Bi/C catalysts in a strongly acidic medium [67]. Loss of platinum and bismuth after oxidation of L-sorbose on Pt–Bi/Al_2O_3 was detected by XPS and ICP–AES measurement [46,53,55]. In conclusion, leaching of platinum metals in solution occurred mainly for catalysts supported on Al_2O_3 and $CaCO_3$, because these supports are unstable at acidic pH. Bismuth and lead promoters are liable to leach, particularly in the presence of chelating polyhydroxycarboxylic acids and at acidic pH.

Deactivation by Adsorbed Species

Metal catalysts could be deactivated by blocking the surface by adsorbed reaction products ('self-poisoning' or 'chemical deactivation'), or by adsorbed oxygen ('over-oxidation' or 'oxygen poisoning').

Chemical deactivation by adsorbed impurities or reaction products was identified as a primary cause of catalyst deactivation [42,43,45–48,50]. Deactivation of platinum catalysts in 1-methoxy-2-propanol oxidation was attributed to polymeric species formed by aldol-dimerization and detected by chromatographic and spectroscopic methods [42]. Poisoning by irreversibly adsorbed side-products was also invoked in cinnamyl alcohol oxidation [45] and in 1-phenylethanol oxidation [44]. Deactivation by D-gluconic acid during oxidation of D-glucose was observed in acidic media [35].

The deactivation of catalysts by so-called 'over-oxidation' is caused by strong chemisorption of oxygen on the metal surface and slow transformation into subsurface species. It depends primarily on the composition, structure, and texture of catalysts: (i) metals with high reduction potentials such as platinum and palladium [57,29], and particularly gold [82] are less prone to oxidation; (ii) small metal particles deactivate more readily than larger particles, as shown in the oxidation of 2-propanol [81] on Pt catalysts and D-glucose oxidation on Pd/C catalysts, the deactivation of which was attributed to the stronger affinity of oxygen for particles smaller than 2 nm [60]; (iii) metal particles uniformly distributed in extruded supports are more resistant to over-oxidation than egg-shell catalysts because oxygen access to metal particles can be limited by mass transfer in pores [27].

Deactivation by over-oxidation also depends on the reducing potential of the substrate. Thus, platinum catalysts were not deactivated by over-oxidation in the oxidation of glyoxal to glyoxylic acid because the dialdehyde is a strong reductant [57,58]; more generally, deactivation by over-oxidation is much lower for an aldehyde than for a primary alcohol. The absence of poisoning of platinum metals in the oxidation of 5-hydroxymethylfurfural was attributed to the strong π-bonding of the furan ring on the metal surface which hampers oxygen adsorption [28].

Finally, deactivation by over-oxidation depends on the oxygen pressure in the liquid phase. If the initial rate of oxidation is fast enough, oxygen dissolved in solutions will be totally consumed by reacting with the organic molecule on the metal surface; the reaction rate is then limited by gas–liquid oxygen mass transfer. For sluggish reactions, over-oxidation can be prevented by conducting the reaction at low concentration of oxygen, either by dilution with nitrogen, or by taking advantage of mass transfer limitation in the catalyst pores [27]. Measurement of the electrochemical potential of the catalyst was found to be a reliable means of monitoring the oxidation state of the surface and was used to regulate the rate of supply of oxygen to the reaction medium during oxidation of secondary alcohols to ketones or cinnamyl alcohol to cinnamaldehyde [43,51].

It can be concluded that 'chemical deactivation' and 'over-oxidation' have synergistic effects, because any blockage of surface sites by side products would reduce the rate of reaction and, therefore, the consumption of oxygen, thus favoring the over-oxidation of the surface.

9.2.2.3 Role of Metal Promoters

The discovery that *p*-electron metals such as lead and bismuth added to platinum or palladium catalysts improved the rate and selectivity of reactions was a great breakthrough [14,40,41,50,54,61,63,68,83]. For instance, the initial rate of oxidation of cinnamyl alcohol was 26 times higher on a Pt–Bi/Al_2O_3 catalyst ($Bi/Pt_s = 0.5$) than on unpromoted catalysts [50]. Similarly, the rate of oxidation of glucose to gluconate was 20 times higher on Pd–Bi/C catalysts ($Bi/Pd_s = 0.1$) than on Pd/C [61]. It was suggested that bismuth or lead reduced the size of surface active site ensembles, thus suppressing reactions leading to degradation products which poison the reaction [43,47], or that surface Pt–Bi–OH species acted as active sites [47]. In the oxidation of glucose, the promoting effect of bismuth was attributed to the mechanism described in Figure 3, Section 9.3, whereby bismuth acts as a co-catalyst protecting palladium from over-oxidation [61].

In addition to their beneficial effect on the rate of oxidation, bismuth or lead promoters can modify the selectivity of oxidation reactions. Thus, in the oxidation of D-gluconate on Pt/C catalysts, 2-keto-D-gluconate selectivity was greatly improved by the addition of lead [10,11] or bismuth [64]. In the same way, bismuth improved the selectivity of glyceric acid oxidation to *β*-hydroxypyruvic acid [36,63] and of glycerol oxidation to dihydroxy acetone [62,70,71]. In all these investigations the increase in selectivity to *α*-ketonic acids arising from the use of bismuth or lead was interpreted by the mechanism given in Figure 1, i. e. bidentate interaction of the promoter with the carboxylate and neighboring hydroxyl group favoring hydrogen abstraction.

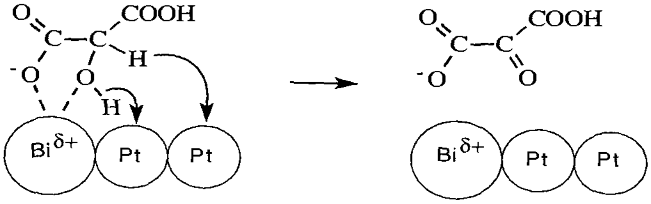


Figure 1. Proposed mechanism for the selective catalytic oxidation of secondary hydroxyl functions *α* to a carboxyl group.

9.2.2.4 Role of Organic Modifiers

Organic bases such as tetraalkylammonium hydroxides, tertiary amines, and phosphines [46,49,52–54] were employed as additives to improve the activity and selectivity of platinum catalysts in the oxidation of L-sorbose to 2-keto-L-gulonic acid (2-KLG). Rate acceleration was attributed to a beneficial effect of the amine on the hydration of the intermediate aldehyde. The selectivity enhancement obtained with hexamethylenetetramine (HMTA) was attributed to a steric effect involving a complex between HMTA and L-sorbose via hydrogen bonding [52] (see Section 9.3.3.2).

9.2.2.5 Reactors and Reaction Conditions

Oxidation reactions on metals were usually conducted in batch reactors containing a solution of the organic substrate to be oxidized and a well-stirred suspension of the catalyst in powder form. Typically, reactions were run at atmospheric pressure with air bubbling through the suspension maintained at constant temperature in the range 20 to 80 °C. Oxidation reactions were conducted at pH 2 to 13, often from 7 to 9. The pH was regulated by addition of dilute alkali under the control of a pH regulator. Oxygen electrodes were also used to monitor the oxygen pressure in the liquid phase. A platinum electrode associated with a reference electrode was used to measure the electrochemical potential of the catalyst, providing in situ information on the oxidation state of the active metal surface; these data can be used to optimize the oxygen supply to the metallic surface (see, e. g., Ref. [51]). The reaction kinetics were followed by monitoring the amount of alkali solution required to maintain constant pH or, more reliably, by chromatographic analysis of reaction mixture sampled periodically.

Reactions were also conducted in a stirred slurry reactor operating in continuous mode with the solution injected by means of a pump and the catalyst retained by a filter at the liquid outlet [19,21]. A fixed-bed reactor was used by Kimura [71,72,74] for the oxidation of glycerol and derivatives.

Most liquid-phase oxidation reactions were performed in water, sometimes on highly concentrated solutions, e. g. for glucose up to 1.7 mol L^{-1} [61]. For water-insoluble alcohols, organic solvent could, in principle, be used, but most should be strictly avoided for safety reasons. Acetic acid was, however, used as solvent for the oxidation of retinol (3,7 dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraen-1-ol) to retinal [84]. Oxidation of water-insoluble molecules can be performed in the presence of surfactants [50].

9.2.2.6 Preparation of Metal Catalysts

Most studies on liquid-phase oxidation reactions have been conducted on platinum or palladium catalysts supported on active carbon or on alumina. Carbon supports (activated carbon and graphite) have the advantage of high stability under all reaction conditions, particularly at low pH and in the presence of complexing molecules. Pt/C and Pd/C catalysts are available in different composition and in different forms from most catalysts manufacturers. For laboratory studies, metal precursors were loaded by impregnation (solvent evaporation or dry impregnation), by anionic adsorption ($PtCl_6^{2-}$ solution at acidic pH), and by cationic exchange ($Pt(NH_3)_4^{2+}$ solution at basic pH). Reduction of catalyst precursors was performed in the gas phase (H_2) or in the liquid phase (formaldehyde + KOH).

Bimetallic (Pt–Bi) or trimetallic (Pt–Pd–Bi) catalysts are available commercially from Degussa [85]. Metal promoters such as bismuth or lead, were added to platinum metals by co-impregnation, by impregnation of the supported noble metal catalyst with an aqueous promoter salt solution, or by redox surface reaction. A very simple and efficient way of loading Pt/C or Pd/C catalysts with bismuth is to add the required amount of aqueous $BiONO_3$ solution to a suspension of the catalyst in a solution of formaldehyde or reducing sugar such as glucose [14,61]. 5 % $[Pd_{88}Pt_{22}]$ –5 % Bi/C catalyst has been prepared by adsorption of colloidal metal particles stabilized by tetraoctylammonium chloride on active charcoal coated with 5 % *w/w* bismuth [86,87]. Wenkin et al. [88] prepared a variety of Pd–Bi alloys to investigate their role in the catalytic oxidation of glucose by thermal decomposition of carboxylates.

Gold catalysts supported on active carbon and alumina have been prepared by incipient wetness impregnation or by precipitation at basic pH using aqueous solutions of $HAuCl_4$ [82].

9.2.3 Selected Examples of Alcohol Oxidation Processes

According to Heinz et al. [1,2] the rate of oxidation with molecular oxygen on platinum catalysts follows the sequence CHO > CH_2OH > CHOH, although Bi or Pb promoters could favor the oxidation of secondary alcohol function in acidic media (see Section 9.2.2.3).

9.2.3.1 Oxidation of Aldehydes

Oxidation of Glyoxal to Glyoxylic Acid

Glyoxylic acid (CHOCOOH), used in the preparation of fine chemicals (e. g., vanillin and penicillin), is prepared industrially by oxidation of glyoxal with nitric acid. An attempt was made to replace this stoichiometric process by oxidation of glyoxal with air on platinum catalysts [57–59]. In a first series of experiments, catalysts containing different platinum metals (Pt, Ir, Pd, Rh, Ru) prepared on the same active carbon and with the same particle size (1–2 nm) were compared. The initial rate of reaction increased in the sequence $0 = \text{Ru} < \text{Rh} < \text{Pd} < \text{Ir} < \text{Pt}$, which is similar to that of the redox potentials of these elements.

The best yield of glyoxylic acid (70 % at 96 % conversion) was obtained by oxidizing 0.35 mol L^{-1} glyoxal solution over a 5 % Pt/C catalyst with an egg-shell distribution of particles. The maximum glyoxylic acid yield was only 47 % with a 1.8 % Pt/C catalyst containing metal particles uniformly distributed in the micropores of the support. The lower selectivity can be attributed to diffusional limitation in the micropores which increases the residence time of the reactants and products in the catalyst micropores so that glyoxylic acid molecules once formed have a higher probability of re-adsorption on metal particles, and further oxidation. The selectivity decreased when the glyoxal concentration was increased to 0.9 mol L^{-1}, the best results (54 % yield) were then obtained with Pt/graphite catalyst on which the Pt particles were located on graphite steps, and thus accessible from the liquid phase with less diffusional limitation. Platinum catalysts on TiO_2 and SiO_2 supports were almost inactive in the oxidation of glyoxal aqueous solutions, because glyoxal oligomeric species formed an immobile layer, hydrogen-bonded to the hydroxyl groups of the oxide surface. When Pt–Pb supported on silica at pH 7.5 was used, the selectivity to glyoxylic acid was 82 % at 97 % conversion [89].

Oxidation of Hydroxymethylfurfural to 2,5-Furan Dicarboxylic Acid

5-Hydroxymethylfurfural (HMF), derived from hexoses by dehydration, can be oxidized into 2,5-furan dicarboxylic acid (FDA), which is used in the preparation of polyesters and polyamides. Oxidation with air in a strongly alkaline medium on 5 % Pt–5 % Pb/C catalyst from Degussa resulted in 81 % selectivity for FDA at 100 % conversion [83]. Yields in excess of 95 % were claimed on Pt–Pb/C catalysts prepared by different methods [90]. On unpromoted catalysts at 25 °C, the aldehyde function was oxidized first giving 5-hydroxymethyl-2-furan carboxylic acid (HMFA) [84]. In contrast, it was reported that the main intermediate over Pt/Al_2O_3 at pH 8 and 65 °C was 5-formyl-2-furan carboxylic acid (FFCA), i. e. oxidation of the hydroxymethyl group [30]. This apparent discrepancy was explained in terms of the high dependency of selectivity on temperature and pH [83] (Figure 2).

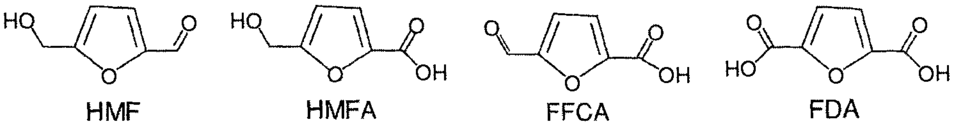


Figure 2. Oxidation of 5-hydroxymethylfurfural.

Oxidation of Hydroxypropionaldehyde

Oxidation of aqueous solutions (10 % *w/w*) of 3-hydroxypropionaldehyde (HPA) in the presence of 3 % Pd/C catalysts at pH 8 produces malonic acid. Complete conversion, with 96.7 % yield, was achieved with large amounts of catalyst (33 % *w/w* Pd relative to HPA) [91]. Starting from 3-hydroxypropionic acid the malonic acid selectivity was 95.4 % at 97 % conversion. In the presence of 5 % Pt/C catalysts (28 % *w/w* Pt with respect to HPA), aqueous solutions (10 % *w/w*) of 3-hydroxypropionaldehyde were oxidized into 3-hydroxypropionic acid, an intermediate used to prepare pharmaceutical and agricultural products. The best yield, obtained without pH regulation, was 92.9 % at 97.2 % conversion [92].

A solution of methacrolein in methanol and aqueous soda solutions were continuously oxidized by O_2 at 5 bar and 80 °C in a reactor packed with Pd–Bi/SiO_2–MgO–Al_2O_3 catalyst. Methyl methacrylate was obtained with 90.8 % selectivity at 63.4 % conversion [93].

9.2.3.2 Oxidation of Primary Alcohols

Oxidation of Glycerol and Derivatives

Glycerol can be oxidized to the high value-added products given in Figure 3. One of the two primary alcohol functions can be selectively oxidized in basic media to give sodium glycerate. This was best achieved with Pd/C catalyst at pH 11 [62]; glycerate selectivity was 70 % at 100 % conversion, tartronate and oxalate were the main by-products.

Although further oxidation of glycerate in the presence of palladium or platinum catalyst was slow, when oxidation was conducted with a 5 % Pt–1.9 % Bi/C catalyst under basic condition (pH 10–11), 83 % yield in tartronate was obtained at 85 % conversion [63].

Patents have been issued on the oxidation of glycerol and derivatives. A 54 % yield of sodium glycerate was claimed for oxidation of glycerol over Pd/C at pH 8–13 [94]. Amination of glyceric acid with NH_3 solution yielded 38 % serine [95]. This amino acid was also obtained by oxidation of serinol [96], prepared by reductive amination of dihydroxyacetone [97].

Oxidation of glycerol at a constant pH of 10 in the presence of 0.6 % Ce–1.2 % Bi–3 % Pd/C yielded 90.6 % sodium tartronate [98].

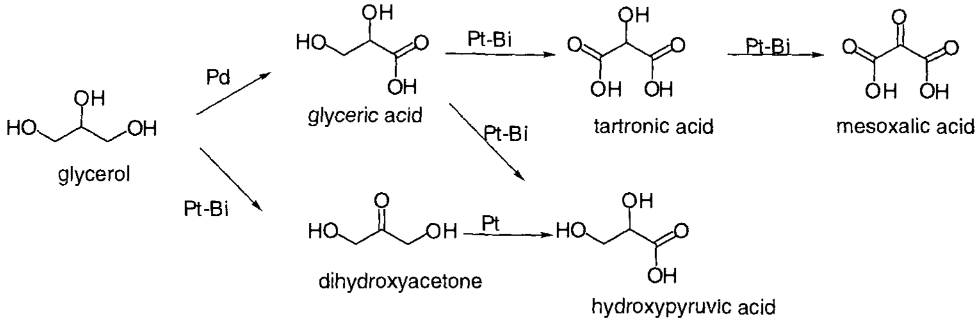


Figure 3. Reaction pathways to oxygenated derivatives of glycerol.

Oxidation of Cinnamyl Alcohol

The partial oxidation of cinnamyl alcohol (Ph–CH=CH–CH_2OH) to cinnamaldehyde was conducted in the presence of a surfactant (sodium dodecylbenzene sulfonate) because reactant and product were insoluble in water [45,50]. Oxidation on Bi-Pt/Al_2O_3 catalysts was performed at basic pH obtained by addition of Li_2CO_3, and by controlling the air supply to avoid over-oxidation of the metal. The maximum selectivity for cinnamaldehyde, 98.5 % at 95.5 % conversion, was obtained for a Bi/Pt_S ratio of 0.5. The high selectivity for cinnamyl aldehyde was attributed to the negligible hydration of the aldehyde because of the conjugation of C=O, C=C, and aromatic nucleus (see Section 9.2.2.1). Under similar conditions the selectivity for oxidation of 1-dodecanol [50] to dodecanal was poor, because the geminal diol was formed in water and was dehydrogenated to dodecanoic acid.

Oxidation of 9-Decen-1-ol in 9-Decenoic Acid

The oxidation of 9-decen-1-ol (rosalva) to 9-decenoic acid, a molecule of interest in the perfume industry, has been performed on palladium or platinum catalysts [68]. Because these molecules were insoluble in water the reaction was conducted in dioxane/water mixtures containing at least 50 % dioxane to dissolve 1.2 % *w/w* 9-decen-1-ol. Figure 4 indicates that at basic pH the oxidation of rosalva on PtBi/C resulted in almost quantitative yield of the desired product. It is remarkable that the C=C bond remained unchanged in the process. The initial rate (60 mol h^{-1} $(mol_{Pt})^{-1}$) was limited by gas-to-liquid mass transfer of oxygen. Attempts to conduct the reaction in the absence of dioxane, i. e. with the catalyst suspended in a well-stirred emulsion of the organic phase in water, resulted in a slower rate of reaction because of mass transfer effects between the four phases (water, rosalva, catalyst, air), but selectivity for the unsaturated acid was almost the same–83 % yield was obtained at total conversion.

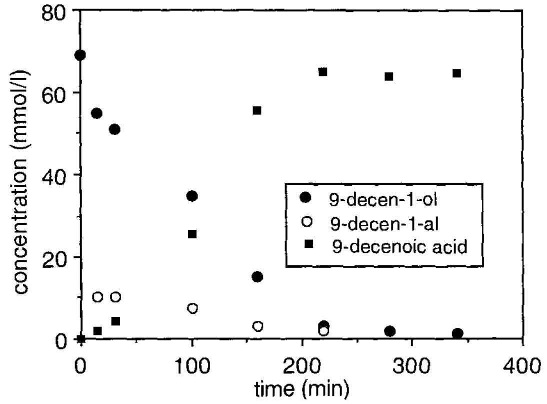


Figure 4. Oxidation of 9-decen-1-ol on 4.58 % Pt–2.95 % Bi/C (molar ratio Bi/Pt = 0.45) at pH 8. Temperature, 50 °C, 23 mmol 9-decen-1-ol, 1 g catalyst, 300 mL 50:50 dioxane–water [68].

Oxidation of Propanediols

Catalytic oxidation of vicinal diols to α-hydroxy carboxylates was performed by Prati and Rossi [82] in alkaline aqueous solution with gold-based catalysts prepared by deposition–precipitation with sodium carbonate from $HAuCl_4$ solutions on active carbon suspension. The 1 % Au/C catalysts had remarkable properties compared with conventional Pt/C and Pd/C catalysts in terms of selectivity and stability. Thus, Table 1 shows that at pH 8, 1,2-propanediol was very selectively oxidized to lactic acid, which indicates that gold was more selective than platinum and palladium in the oxidation of the primary alcohol function. The activity of gold catalysts was also very stable as a function of conversion or after several recycles, indicating that gold is less sensitive to over-oxidation and/or self-poisoning than platinum and palladium.

Table 1. Oxidation of 1,2-propanediol to lactic acid on gold catalyst [82].

Catalyst	t (h)	T (K)	LA (mol %)	HYDR (mol %)	PYR (mol %)	Conversion (%)	Selectivity (%)
1 % Au/C	10	363	30	–	–	30	100
5 % Pd/C	5	343	5	13	8	46	11
5 % Pt/C	5	343	18	24	4	56	32

Reaction conditions: diol/metal = 1000, $p(O_2)$ = 100 kPa, adjusted to pH 8 with 0.1 M NaOH. PYR = pyruvate; HYDR = hydroxyacetone; LA = lactate.

Aqueous solutions of 1,3 propanediol were oxidized at pH 11 in the presence of palladium catalysts (2.8 % Pd relative to 1,3-propanediol); the maximum yield of malonic acid was 86.1 % [99].

Miscellaneous Primary Alcohols

Several patents have been issued describing selective oxidation of alcohols to the corresponding aldehydes or acids.

A patent from Monsanto [100] disclosed the oxidation of alkaline solutions of amino alcohols and poly(ethylene glycol) in the presence of bimetallic catalysts prepared by deposition of copper on the surface of platinum. High yields to the corresponding carboxylates were reported.

Air Products and Chemicals have proposed a process for the synthesis of betaine from choline hydroxide $HOCH_2CH_2N(CH_3)_3OH$ without production of amine halocarboxylate contaminants [101]. An aqueous solution of choline hydroxide at 78 °C under atmospheric oxygen over a 5 % Pd/C catalyst yielded the acid with a selectivity of 87 % at 89 % conversion.

Oxidation of substituted benzyl alcohols to the corresponding aldehydes has been patented [102–107]. Oxidation of 3-hydroxybenzyl alcohol in alkaline solution over Pt- and/or Pd-type catalysts yielded 3-hydroxybenzaldehyde with high selectivity [103]. An alcohol and a tertiary ammonium salt were used to control formation of by-product 3-hydroxybenzoic acid. Oxidation of 2-hydroxybenzyl alcohol in aqueous basic medium in the presence of Pt and B and Bi derivatives (H_3BO_3 and Bi_2O_3) gave 97 % of the corresponding aldehyde (salicylaldehyde) [104]. A new route to vanillin has also been proposed; this involves condensation of guaiacol with formaldehyde, oxidation of the resulting 2,4-dihydroxymethyl-6-methoxyphenol to 2-carboxy-4-formyl-6-methoxyphenol in the presence of Pd or Pt/C catalysts promoted with bismuth, then decarboxylation [105–107].

9.2.3.3 Oxidation of Secondary Alcohols

Oxidation of Insoluble Secondary Alcohols

Good yields of ketones were obtained in the oxidation on Pt–Bi catalysts (Bi/Pt_S = 0.5) of secondary alcohols insoluble in water under the same conditions as for cinnamyl alcohol oxidation (see Section 9.2.3.2). Table 2 shows that selectivity in excess of 95 % was obtained at 97–99 % conversion [43].

Oxidation of Glycerol to Dihydroxyacetone

Dihydroxyacetone (DHA), the oxidation product of the secondary hydroxy group of glycerol, is an artificial tanning agent in cosmetics and a pharmaceutical intermediate. Glycerol oxidation in acidic medium on a platinum–bismuth catalyst (Bi/Pt atomic ratio = 3) prepared by coprecipitation of Pt^{VI} and Bi^{III} salts, yielded 20 % DHA at 30 % conversion [70]. The deposition of bismuth on platinum particles by oxido-reduction (Bi/Pt = 0.13) yielded 37 % DHA at 70 % conversion [62]. The use of a fixed-bed reactor improved both conversion and DHA yield (80 % selectivity at 80 % conversion) [71].

Oxidation of Glyceric Acid to β-Hydroxypyruvic Acid

β-Hydroxypyruvic acid, an intermediate in the preparation of L-serine, can be obtained by oxidation of glyceric acid or DHA. The oxidation of calcium glycerate on 5 % Pt–1.9 % Bi/C catalyst without pH regulation gave a maximum yield of 64 % at 80 % conversion at acidic pH (3–4) [62]. Better selectivity was obtained by conducting the oxidation of sodium glycerate on 5 % Bi–5 % Pt/C catalyst without pH regulation [36]. The pH decreased from 5.7 to 4.1 and β-hydroxypyruvic acid selectivity was 93 % at 95 % conversion.

Table 2. Oxidation of secondary alcohols to ketones [43].

Catalyst	α-Tetrol[a]		Diphenyl carbinol[b]		1-Phenylethanol[c]	
	Conv. (%)	Select. (%)	Conv. (%)	Select. (%)	Conv. (%)	Select. (%)
Bi–Pt/Al_2O_3	99	95	99	100	97	99.5
Pt/Al_2O_3	34	–	1.5	–	7.5	99

[a] Catalyst/ROH = 0.1; Li_2O_3/ROH = 0.01; surfactant/ROH = 0.05; T = 85 °C; reaction time = 5 h.
[b] Catalyst/ROH = 0.01; Li_2O_3/ROH = 0.01; surfactant/ROH = 0.003; T = 75 °C; reaction time = 3 h.
[c] Catalyst/ROH = 0.02; Li_2O_3/ROH = 0.01; surfactant/ROH = 0.01; T = 60 °C; reaction time = 4.5 h.

Oxidation of Tartronic Acid to Mesoxalic Acid

Mesoxalic acid (or ketomalonic acid) is a good chelating agent and potentially a valuable synthon for organic synthesis. It has been prepared by oxidation of sodium tartronate on PtBi/C catalyst at 60 °C without pH control; the maximum yield was 65 % at 80 % conversion [67]. Operating at 80 °C, 50 % mesoxalic acid was obtained at total conversion of tartronic acid. The solution was free from other oxidation products, which were totally oxidized to CO_2.

Mesoxalic acid selectivity of 95 % at complete conversion has been claimed in the oxidation of tartronic acid in the presence of Bi–Pt/C catalysts [108].

9.2.4 Concluding Remarks

The examples of metal-catalyzed oxidation of alcohols given in this review demonstrate that these reactions have great advantages compared to other oxidation processes, particularly with regard to green chemistry issues (air as oxidizing agent, water as solvent) and to process development (readily available, non-leaching catalysts, one-pot reactions). The selectivity for oxidation of hydroxyl groups is high because other functions such as C=C bonds are not oxidized. Primary alcohols are usually converted into the corresponding acids with high yields (90–95 %) at high conversion. High yields in ketones from secondary alcohols have also been reported. Catalyst deactivation by over-oxidation of the metal surface is not a major problem because it is reversible and can be avoided by using proper operating conditions. For all these reasons, and because metal-catalyzed oxidation processes can be applied with minor modification to almost all alcohols and aldehydes, this field deserves more attention in the future.

The main limitation of liquid phase oxidation with air on metals is that aldehydes cannot be obtained from primary alcohols because they are readily oxidized to the corresponding acids, except when the formation of the geminal diol of the aldehyde is not possible (absence of water or conjugation of the carbonyl group with a C=C bond or and aromatic ring). Aldehydes can, however, be obtained selectively from primary alcohols by vapor-phase oxidative dehydrogenation on metal catalysts at high temperatures but very short contact time. A recent example of this type of reaction applied to fine chemicals is the oxidation of rosalva to costenal on supported silver catalysts [109].

References

[1] K. Heyns, and H. Paulsen, *Angew. Chem.*, 69 (1957) 600; *Adv. Carbohydr. Chem.*, 17 (1962) 169–221.
[2] K. Heyns, H. Paulsen, G. Ruediger, and J. Weyer, *Fortschr. Chem. Forsch.*, 11 (1969) 285–374.
[3] H.G.J. de Wilt, and H.S. van der Baan, *Ind. Eng. Chem. Prod. Res. Develop.*, 11 (1972) 374–378.
[4] H.G.J. de Wilt, J. Lindhout, and B.F.M. Kuster, *Carbohydr. Res.*, 19 (1971) 5.
[5] H.G.J. de Wilt, J. Lindhout, and B.F.M. Kuster, *Carbohydr. Res.*, 23 (1972) 333–342.

[6] H. G. J. de Wilt, J. Lindhout, and B. F. M. Kuster, *Carbohydr. Res.*, 23 (1972) 343.
[7] J. M. H. Dirkx, H. S. van der Baan, and J. M. A. van den Broek, *Carbohydr. Res.*, 59 (1977) 6372.
[8] J. M. H. Dirkx, and H. S. van der Baan, *J. Catal.*, 67 (1981) 1–13.
[9] J. M. H. Dirkx, and H. S. van der Baan, *J. Catal.*, 67 (1981) 14–20.
[10] P. C. C. Smits, B. F. M. Kuster, K. van der Wiele, and H. S. van der Baan, *Carbohydr. Res.*, 153 (1986) 227–235.
[11] P. C. C. Smits, B. F. M. Kuster, K. van der Wiele, and H. S. van der Baan, *Appl. Catal.*, 33 (1987) 83–96.
[12] P. J. M. Dijkgraaf, M. J. M. Rijk, J. Meuldijk, and K. van der Wiele, *J. Catal.*, 112 (1988) 329–336.
[13] P. J. M. Dijkgraaf, H. A. M. Duisters, B. F. M. Kuster, and K. van der Wiele, *J. Catal.*, 112 (1988) 337–344.
[14] H. E. J. Hendriks, B. F. M. Kuster, and G. B. Marin, *Carbohydr. Res.*, 204 (1990) 121–129.
[15] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, in *New Developments in Selective Oxidation by Heterogeneous Catalysis, Studies in Surface Science and Catalysis* (P. Ruiz and B. Delmon, eds), 72 (1992) pp. 43–55, Elsevier, Amsterdam.
[16] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, *Appl. Catal. A*, 89 (1992) 31–46.
[17] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, *Appl. Catal. A*, 89 (1992) 47–68.
[18] J. H. Vleeming, F. A. de Bruijn, B. F. M. Kuster, and G. B. Marin, in *Catalyst Deactivation, Studies in Surface Science and Catalysis* (B. Delmon, and G. Froment, eds.), 88 (1994) p. 467, Elsevier, Amsterdam.
[19] J. A. A. van den Tillaart, B. F. M. Kuster, and G. B. Marin, *Appl. Catal. A: General*, 120 (1994) 127–145.
[20] H. E. J. Hendriks, B. F. M. Kuster, and G. M. Marin, *J. Mol. Cat.*, 93 (1994) 317–335.
[21] L. Jelemensky, B. F. M. Kuster, and G. B. Marin, *Catal. Lett.*, 30 (1995) 269–277.
[22] J. H. Vleeming, B. F. M. Kuster, and G. B. Marin, *Catal. Lett.*, 46 (1997) 187–194.
[23] J. H. Vleeming, B. F. M. Kuster, G. B. Marin, F. Oudet, and P. Courtine, *J. Catal.*, 166 (1997) 148–159.
[24] A. P. Markusse, B. F. M. Kuster, D. C. Koningsberger, and G. B. Marin, *Catal. Lett.*, 55 (1998) 141–145.
[25] G. de Wit, J. J. de Vlieger, A. C. Kock-van Dalen, R. Heus, R. Laroy, A. J. van Hengstum, A. P. G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 91 (1981) 125–138.
[26] H. E. van Dam, A. P. G. Kieboom, and H. van Bekkum, *Appl. Catal.*, 33 (1987) 361–372.
[27] H. E. van Dam, P. Duijverman, A. P. G. Kieboom, and H. van Bekkum, *Appl. Catal.*, 33 (1987) 373–382.
[28] P. Vinke, H. E. van Dam, and H. van Bekkum, in *New Developments in Selective Oxidation, Studies in Surface Science and Catalysis* (G. Centi, and F. Trifiro, eds.), 55 (1990) pp. 147–157, Elsevier, Amsterdam.
[29] H.E van Dam, L. J. Wisse, and H. van Bekkum, *Appl. Catal.*, 61 (1990) 187–197.
[30] P. Vinke, W. van der Poel, and H. van Bekkum, in *Heterogeneous Catalysis and Fine Chemicals II, Studies in Surface Science and Catalysis* (M. Guisnet et al. Eds.), 59 (1991) pp. 385–394, Elsevier Amsterdam.
[31] P. Vinke, D. de Wit, A. T. J. W. de Goede, and H. van Bekkum, in *New Developments in Selective Oxidation by Heterogeneous Catalysis, Studies in Surface Science and Catalysis* (P. Ruiz and B. Delmon, eds), 72 (1992) pp. 1–20, Elsevier, Amsterdam.
[32] F. R. Venema, J. A. Peters, and H. van Bekkum, *J. Mol. Cat.*, 77 (1992) 75–85.
[33] A. Abbadi, M. Makkee, W. Visscher, J. A. R. van Veen, and H. van Bekkum, *J. Carbohydr. Chem.*, 12 (1993) 573–587.
[34] A. Abbadi, and H. van Bekkum, *Appl. Catal. A*, 124 (1995) 409–417.
[35] A. Abbadi, and H. van Bekkum, *J. Mol. Cat. A*, 97 (1995) 111–118.
[36] A. Abbadi, and H. Van Bekkum, *Appl. Catal. A*, 148 (1996) 113–122.
[37] A. Abbadi, K. F. Gotlieb, J. B. M. Meiberg, and H. Van Bekkum, *Appl. Catal. A: General*, 156 (1997) 105–115.

[38] A. W. Heinen, J. A. Peters, and H. van Bekkum, *Carbohydr. Research,* 304 (1997) 155–164.

[39] D. L. Verraest, J. A. Peters, and H. van Bekkum, *Carbohydr. Research,* 306 (1998) 197.

[40] T. Mallat, and A. Baiker, *Appl. Catal., A,* 79 (1991) 41–58.

[41] T. Mallat, A. Baiker, and J. Patscheider, *Appl. Catal., A,* 79 (1991) 59–75.

[42] T. Mallat, A. Baiker, and L. Botz, *Appl. Catal. A,* 86 (1992) 147–163.

[43] T. Mallat, Z. Bodnar, and A. Baiker, in *Heterogeneous Catalysis and Fine Chemicals III, Studies in Surface Science and Catalysis,*(M. Guisnet et al. Eds.), 78 (1993) pp. 377–384 Elsevier, Amsterdam.

[44] T. Mallat, Z. Bodnar, and A. Baiker, in *Catalytic Selective Oxidations,* (S. T. Omaya, J. W. Hightower, eds.), ACS Symp. Series, Washington, 523 (1993) 308–317.

[45] T. Mallat, Z. Bodnar, M. Maciejewski, and A. Baiker, in *New Developments in Selective Oxidation II, Studies in Surface Science and Catalysis,* (V. Cortès Corberan and S. Vic Bellon, eds.), 82 (1994) pp. 561–570, Elsevier, Amsterdam.

[46] C. Brönnimann, Z. Bodnar, P. Hug, T. Mallat, and A. Baiker, *J. Catal.,* 150 (1994) 199–211.

[47] T. Mallat, Z. Bodnar, A. Baiker, O. Greis, H. Strübig, and A. Reller, *J. Catal.,* 142 (1993) 237–253.

[48] T. Mallat, and A. Baiker, *Catalysis Today,* 19 (1994) 247–284.

[49] C. Brönnimann, T. Mallat, and A. Baiker, *J. Chem. Soc., Chem. Commun.* (1995) 1377–1378.

[50] T. Mallat, Z. Bodnar, P. Hug, and A. Baiker, *J. Catal.,* 153 (1995) 131–143.

[51] T. Mallat, and A. Baiker, *Catalysis Today,* 24 (1995) 143–150.

[52] C. Brönnimann, Z. Bodnar, R. Aeschimann, T. Mallat, and A. Baiker, *J. Catal.,* 161 (1996) 720–729.

[53] T. Mallat, C. Brönnimann, and A. Baiker, *Appl. Catal. A,* 149 (1997) 103–112.

[54] T. Mallat, C. Brönnimann, and A. Baiker, *J. Mol. Cat A: Chemical,* 117(1997) 425–438.

[55] I. Bakos, T. Mallat, and A. Baiker, *Catal. Lett.* 43 (1997) 201–207.

[56] T. Mallat, L. Seyler, M. Mir Alai, and A. Baiker, *Spec. Publ.–R. Soc. Chem.,* 216 (1998) 66.

[57] P. Gallezot, R. de Mésanstourne, Y. Christidis, G. Mattioda, and A. Schouteeten, *J. Catal.,* 133 (1992) 479–485.

[58] P. Gallezot , F. Fache, R. de Mésanstourne, Y. Christidis, G. Mattioda, and A. Schouteeten, in *New Frontiers in Catalysis, Proceedings of the 10th International Congress on Catalysis,* (L. Guczi et al., eds.), (1993) pp. 195–204, Elsevier, Amsterdam.

[59] R. de Mesanstourne, and P. Gallezot (for Société France Hoechst), EP 0438 948 B1 (1993).

[60] M. Besson, P. Gallezot, F. Lahmer, G. Flèche, and P. Fuertes, in *Catalysis of Organic Reactions,* (J. R. Kosak, T. A. Johnson, eds), Marcel Dekker, New York, 53 (1993) pp. 169–180.

[61] M. Besson, P. Gallezot, F. Lahmer, G. Flèche, and P. Fuertes, *J. Catal.,* 152 (1995) 116–121.

[62] R. Garcia, M. Besson, and P. Gallezot, *Appl. Catal. A,* 127 (1995) 165–176.

[63] P. Fordham, M. Besson, and P. Gallezot, *Appl. Catal. A,* 133 (1995) L179–L184.

[64] M. Besson, G. Flèche, P. Fuertes, P. Gallezot, and F. Lahmer, *Recl. Trav. Chim. Pays-Bas,* 115 (1996) 217–221.

[65] P. Fordham, M. Besson, and P. Gallezot, in 11th *International Congress on Catalysis, Studies in Surface Science and Catalysis* (Eds. J. Hightower, W. N. Delgass, E. Iglesia, and A. T. Bell), 101A (1996) pp. 161–170, Elsevier, Amsterdam.

[66] P. Fordham, M. Besson, and P. Gallezot, in *Heterogeneous Catalysis and Fine Chemicals IV, Studies in Surface Science and Catalysis* (Eds H. U. Blaser, A. Baiker, R. Prins), 108 (1997) pp. 429–436, Elsevier, Amsterdam.

[67] P. Fordham, M. Besson, and P. Gallezot, *Catal. Lett., 46* (1997) 195–199.

[68] A. B. Crozon, M. Besson, and P. Gallezot, *New J. Chem.,* (1998) 269–273.

[69] H. Kimura, A. Kimura, I. Kokubo, T. Wakisaka, and Y. Mitsuda, *Appl. Catal. A,* 95 (1993) 143–169.

[70] H. Kimura, K. Tsuto, T. Wakisaka, Y. Kasumi, and Y. Inaya, *Appl. Catal. A,* 96 (1993) 217–228.

[71] H. Kimura, *Appl. Catal. A,* 105 (1993) 147–158.

[72] H. Kimura, and K. Tsuto, *J. Am. Oil Chem. Soc.*, 70 (1993) 1027–1030.

[73] H. Kimura, *J. Polym. Sc.*, 36 (1998) 189–193.

[74] H. Kimura, *J. Polym. Sc.*, 36 (1998) 195–205.

[75] H. van Bekkum, in *Carbohydrates as raw materials* (F. W. Lichtenthaler ed.), *Darmstadt, 1990,* VCH Weinheim (1991) pp. 289–310.

[76] P. Gallezot, and M. Besson, *Carbohydr. Eur.*, *13* (1995) 5–10.

[77] M. Besson, and P. Gallezot, *Catal. Today,* 57 (2000) 127–141.

[78] M. Rottenberg,' and P. Baertschi, *Helv. Chim. Acta,* 39 (1956) 1973–1975.

[79] V. E. Müller, and K. Schwabe, *Z. Electrochim. Acta,* 33 (1928) 170.

[80] R. Di Cosimo, and G. M. Whitesides, *J. Phys. Chem.*, 93 (1989) 768–775.

[81] M. Hronec, Z. Cvengrosova, J. Tuleja, and J. Ilavsky, in *Developments in Selective Oxidation, Studies in Surface Science and Catalysis.* (G. Centi and F. Trifiro, eds) 55 (1990) 169, Elsevier, Amsterdam.

[82] L. Prati, and M. Rossi, *J. Catal.*, 176 (1998) 552–560.

[83] P. Verdeguer, N. Merat, and A. Gaset, *J. Mol. Cat.*, 85 (1993) 327–344.

[84] P. Karrer, and W. Hess, *Helv. Chim. Acta,* 11 (1957) 265.

[85] B.M. Despeyroux, K. Deller, and E. Peldszus, in *New Developments in Selective Oxidation, Studies in Surface Science and Catalysis* (G. Centi and F. Trifiro, eds.), 55 (1990) 159, Elsevier, Amsterdam.

[86] H. Bönnemann, W. Brijoux, A. Schulze Tilling, and K. Siepen, *Topics in Catalysis*, 4 (1997) 217–227.

[87] H. Bönnemann, W. Brijoux, R. Brinkmann, A. Schulze Tilling, T. Schilling, B. Tesche, K. Seevogel, R. Franke, J. Hormes, G. Köhl, J. Pollmann, J. Rothe, and W. Vogel, *Inorg. Chimica Acta* 270 (1998) 95–110.

[88] M. Wenkin, C. Renard, P. Ruiz, B. Delmon, and M. Devillers, in *Heterogeneous Catalysis and Fine Chemicals IV, Studies in Surface Science and Catalysis* (H. U. Blaser, A. Baiker and R. Prins, eds) 108 (1997) 391, Elsevier, Amsterdam.

[89] K. Sudo, K. Wakimura, M. Tanaka, H. Inoe, and N. Iwane (for Mitsui Toatsu Chemicals) JP 07 173 099 (1995).

[90] N. Merat, P. Verdeguer, L. Rigal, A. Gaset, and M. Delmas (for Furchim) French Patent 90 14834 (1990).

[91] T. Haas, M. Meier, C. Broßmer, D. Arntz, and A. Freund (for Degussa AG) DE 196 29 372 (1996).

[92] T. Haas, C. Broßmer, M. Meier, D. Arntz, and A. Freund (for Degussa AG) DE 196 29 371 (1996).

[93] T. Matushita, T. Yamaguchi, S. Yamamatsu, and H. Okamoto (for Asahi Chem. Indus.) JP 98 263 399 (1997).

[94] T. Imanaka, H. Terasaki, A. Fujio, and Y. Yokota (for Kao Corp) JP 93 331 100 (1992).

[95] H. Kimura, and K. Yamada (for Kao Corp) JP 93 201 940 (1991).

[96] H. Kimura (for Kao Corp) JP 93 140 056 (1991).

[97] H. Kimura (for Kao Corp) JP 94 09 512 (1992).

[98] H. Kimura, T. Imanaka, and Y. Yokota (for Kao Corp) JP 94 279 352 (1993).

[99] A. Behr, A. Botulinski, F. J. Carduck, and M. Schneider (for Henkel KGaA) DE 4 107 986 (1991).

[100] J. R. Ebner, and T. S. Franczyk (for Monsanto Co.) US 5 689 000 (1995).

[101] D. Ramprasad, W. E. Carroll and J. F. Waller (for Air Products and Chemicals, Inc.) US 5 895 823 (1998).

[102] J. Le Ludec (for Rhône–Poulenc) French Patent FR A 2 305 420 (1975).

[103] Mitsui Toatsu Chem., Inc., JP 03 20238 (1992).

[104] H. Lefranc (for Rhône–Poulenc Chimie) EP 667 331 (1995).

[105] C. Maliverney, I. Jouve, and P. Métivier (for Rhône–Poulenc) WO 96 26 175 (1995).

[106] P. Métivier (for Rhône–Poulenc) WO 96 32 454 (1995).

[107] P. Denis, C. Malivernay, and P. Métivier (for Rhône–Poulenc) WO 98 16 493 (1996).

[108] H. Kimura (for Kao Corp) JP 96 151 346 (1996).

[109] P. Gallezot, L. Ceroni, and A. Perrard, *J. Mol. Cat. A*, 129 (1998) L127–L130.

9.3 Oxidation of Carbohydrates on Metal Catalysts

Michèle Besson, Pierre Gallezot

9.3.1 Introduction

The metal-catalyzed oxidation of carbohydrates with molecular oxygen is a remarkable example of green chemistry because reactants are obtained from renewable resources, processes are conducted under mild conditions with air as oxidizing agent and water as solvent, and reaction products are environmentally benign because of their biodegradability. In addition oxidized carbohydrate derivatives can often be obtained with high selectivity, and the catalysts are recyclable. These catalytic processes are, therefore, potentially very attractive for the preparation of specialties or intermediates employed in the food, cosmetic, pharmaceutical, and chemical industries.

The mechanism of carbohydrate oxidation with oxygen on metal catalysts, and the factors affecting the activity of the catalysts, are similar to those discussed for alcohol oxidation (Section 9.2), therefore, only mechanistic aspects specific to carbohydrate oxidation will be discussed. Because of the multi-functionality of carbohydrates molecules, emphasis will be placed on regio- and chemo-selectivity. Taking D-glucose as the model molecule (Figure 1), different functions can be oxidized–the anomeric position at C_1, the primary alcohol at C_6, and the secondary alcohols at C_2–C_4. Vicinal diol cleavage and over-oxidation reactions leading to a variety of degradation products can also occur.

The first example of carbohydrate oxidation on platinum catalysts was reported by von Gorup–Besanz in 1861 [1], but the field received little attention until the work of Heyns and coworkers [2–4]. These authors found the following reactivity scale for the different functional groups:

$$\text{Anomeric center at } C_1 > CH_2OH > CHOH_{\text{axial}} > CHOH_{\text{equat.}}$$

During the last twenty years, studies conducted by academic groups at Eindhoven [5–24], Delft [25–36], Zürich [37–42], Lyon [43–45], and in industrial research and development laboratories [46–49] have resulted in a better knowledge of these reactions and in industrial developments on the pilot or industrial stage.

Carbohydrate oxidation on metal catalysts has been reviewed [29,50–53]. In the first part of this section, the general features of carbohydrate oxidation on metal catalysts will be described. Illustrative examples of carbohydrate oxidation with high selectivity or of process innovation will then be examined in more detail.

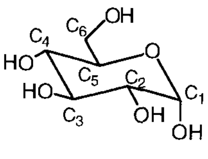


Figure 1. The D-glucose molecule.

9.3.2 Mechanistic and Engineering Aspects

Liquid-phase oxidation reactions of carbohydrates with oxygen on metal catalysts usually occur via an oxidative dehydrogenation mechanism similar to that described for alcohols (Section 9.2). Reactions are usually performed at basic pH so that carboxylate anions are desorbed from the metal surface into solution. In contrast, at acidic pH, undissociated carboxylic acids tend to remain adsorbed and undergo further oxidation reactions leading to degradation products. In strongly basic solutions (pH 11–13), reducing sugars can undergo Cannizzaro reactions in the presence of metal catalysts under ambient conditions, and spontaneous dehydrogenation in the absence of oxygen can also occur leading to the corresponding aldonic acid and formation of hydrogen gas [25,26,54]. The dehydrogenation of unprotected aldoses in alkaline media was thoroughly studied by De Wit et al. [26]. The mechanism proposed involves, as a first step, the adsorption of the aldose anion on the metal surface; this is followed by hydride transfer from the aldose to the metal and subsequent rapid hydrolysis of the resulting lactone to the aldonate (Figure 2). The hydrido-platinum species react with water to give hydrogen gas and the hydroxide. Different aldoses did not have the same reactivity because of their different configuration; thus, the highest reactivity of D-galactose (epimerization of glucose at C_4) was attributed [26] to favorable adsorption of the molecule because of the axial position of the C_4 hydroxyl group.

Carbohydrate oxidation reactions with air on metal catalysts are usually conducted in a batch reactor under conditions similar to those described for alcohol oxidation (Section 9.2). An innovative continuous process of carbohydrate oxidation by air on metal catalysts has been designed by Südzucker [48,49,52]. Oxygen-saturated carbohydrate solutions at controlled pH are passed continuously through a reactor packed with platinum or palladium catalysts. The partially oxidized solutions are passed through an electrodialysis unit to remove the ionic oxidation products. The solution containing non-oxidized products is then treated in a stirred vessel where the sugar concentration, oxygen saturation, and pH are regulated; the solution is then returned to the reactor. Selectivity is increased because the separation process avoids further oxidation of the primary oxidation products, and catalyst deactivation decreases because reaction products do not hinder the adsorption of carbohydrate reactants. The process, originally developed for the oxidation of isomaltulose to palatinose®, has been applied to the oxidation of sucrose, maltose, glucose, and methyl α-D-glucopyranoside. Continuous oxidation experiments in packed-bed reactors [55,56] and in a stirred airlift reactor [57] have also been reported.

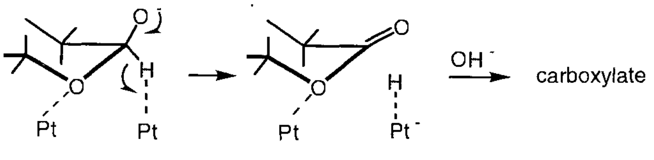


Figure 2. Mechanism of aldose oxidation in basic media in the absence of oxygen [26].

9.3.3 Selected Examples of Carbohydrate Oxidation Processes

9.3.3.1 Oxidation of Aldoses to Aldonic Acids

According to the reactivity scale proposed by Heyns et al. [2–4], oxidation at the anomeric position at C_1 is easier than for primary or secondary alcohol functions. Selectivity higher than 95 % for aldonic acids were indeed observed in the catalytic oxidation of D-glucose, and of reducing disaccharides such as lactose and maltose. Palladium catalysts or palladium–bismuth catalysts are more selective than platinum because they are less active in the oxidation of primary or secondary alcohol functions.

Oxidation of Glucose to Gluconate

D-Gluconic acid, used as a biodegradable chelating agent and as an intermediate in the food and pharmaceutical industries, is produced by enzymatic oxidation of D-glucose [58]. An alternative route employing bismuth-promoted palladium catalysts has been patented [46,47]. Unpromoted palladium catalysts are active in D-glucose oxidation but the rate of reaction decreases with conversion, and side oxidation reactions reduce selectivity. Besson et al. [43] have studied the oxidation of concentrated D-glucose solution (1.7 mol L^{-1}) at pH 9, on carbon-supported palladium catalysts of different particle size. The catalyst with particles larger than 3 nm resulted in a complete conversion within 6 h, whereas conversion almost reached a plateau at two-thirds conversion on the catalyst with particles smaller than 2 nm. This was attributed to a particle size-dependent oxygen poisoning of the surface, the smaller particles being the most prone to over-oxidation because of their greater affinity for oxygen.

The beneficial effect of bismuth on activity and selectivity was clearly demonstrated with Pd–Bi/C catalysts of homogeneous size and composition (5 % *w/w* Pd, Bi/Pd = 0.1) prepared by deposition of bismuth on the surface of 1–2 nm palladium particles via a redox surface reaction [44]. The rate of oxidation of glucose to gluconate was 20 times higher on Pd–Bi/C catalysts (Bi/Pd = 0.1) than on Pd/C. Table 1 gives the product distribution in four successive catalyst recycles. The selectivity was very high on the fresh and recycled catalysts and there was no bismuth leaching. These results were interpreted in terms of bismuth protecting palladium from over-oxidation because of its stronger affinity for oxygen, evidenced by calorimetric measurements. It was proposed that bismuth acted as a co-catalyst according to the oxidative dehydrogenation mechanism given in Figure 3. The use of commercial trimetallic catalysts (Pd–Pt–Bi/C) resulted in good selectivity for gluconate, but not better than that obtained with Pd–Bi/C catalysts [59]. Catalysts of the type 5 % [$Pd_{88}Pt_{22}$] –5 % Bi/C, containing a homogeneous distribution of 3.6-nm particles, prepared from colloids, were found to be more active than the commercial trimetallic catalysts [60]. Attempts to perform glucose oxidation at acidic pH on Pd or Pt catalysts resulted in a loss of selectivity and much lower reaction rates, because of surface poisoning by adsorbed reaction products, presumably gluconic acid in its free form [31,33].

Table 1. Product distribution in D-glucose oxidation.

Catalyst[a](run)	Conversion[b] (%)	Yield (mol %) 1	2	3	4	Selectivity (%)
PdBi/C (1st)	99.6	99.4	< 0.4	< 0.4	0.2	99.8
PdBi/C (2nd)	99.7	98.9	< 0.4	0.6	0.2	99.1
PdBi/C (3rd)	99.8	98.5	0.4	0.8	0.2	98.7
PdBi/C (4th)	99.9	98.5	0.4	0.7	0.2	98.6
PdBi/C (5th)	99.9	99.1	< 0.4	0.6	0.2	99.2
Pd/C	82.6	78.1	1.4	2.3	0.7	94.6

[a] 4.7 % *w/w* Pd; Bi/Pd = 0.1.
[b] After 155 min on PdBi/C and 24 h for Pd/C.
1, D-gluconate; *2*, 2-keto-D-gluconate; *3*, 5-keto-D-gluconate + D-glucarate; *4*, D-fructose.
Reaction conditions: 1.7 mol L^{-1}, $T = 313$ K, pH 9; [glucose]/[Pd] = 787; air at atmospheric pressure.

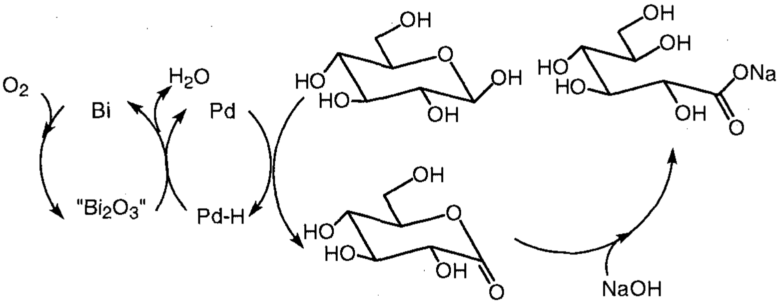


Figure 3. Proposed mechanism of oxidation of D-glucose on Pd–Bi catalysts [44].

Oxidation of Lactose to Lactobionate

Lactose, a cheap and abundant carbohydrate by-product of cheese and casein production, can be oxidized to lactobionate and 2-ketolactobionate (1-carboxylactulose) (Figure 4) which are intermediates in the preparation of biodegradable surfactants.

The selective oxidation of lactose to lactobionate with air on palladium–bismuth catalysts was first reported in patents [47]. Hendriks et al. [16] studied the oxidation of a 0.5 mol L^{-1} solution of lactose as a function of pH, temperature and Pd/Bi ratios of promoted Pd/C catalysts. Sodium lactobionate was obtained with 100 % selectivity up to 95 % conversion on Pd–Bi/C catalysts (Bi/Pd = 0.5) at 333 K and pH 9. Oxygen mass-transfer limited the maximum initial reaction rate (0.47 mol kg^{-1} s^{-1}). The catalyst was recycled 15 times without any significant loss of activity and selectivity.

Abbadi et al. [34] studied the oxidation of lactose and sodium lactobionate to 2-keto-Na lactobionate. The oxidation of lactose on Pt–Bi/C catalysts at pH 7 yielded lactobionate transiently (oxidation of the anomeric center at C_1); this

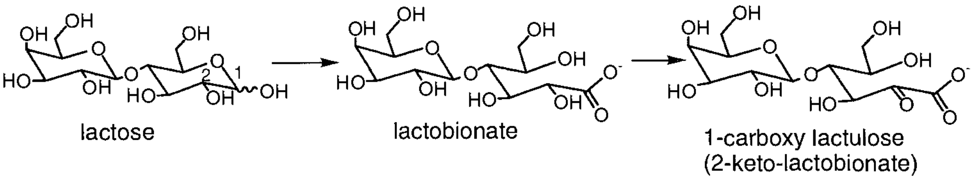
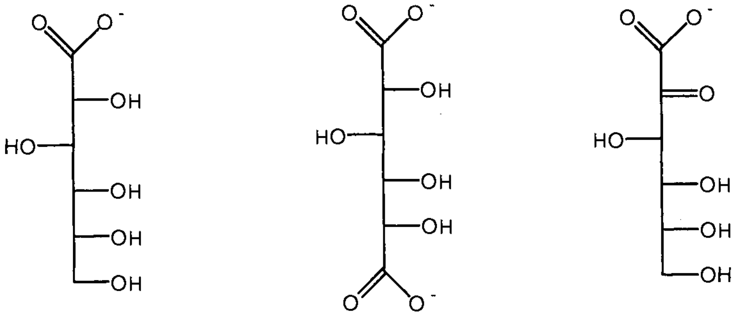


Figure 4. Lactose oxidation to lactobionate and 2-ketolactobionate.

was subsequently converted to 2-ketolactobionate (oxidation of alcohol at C_2) with a final yield of ca 80 %, because conversion of lactobionate was incomplete. Starting from lactobionate without pH control, 2-ketolactobionate was obtained with 95 % selectivity, but the oxidation reaction stopped at 50 % conversion because of poisoning of the Pt–Bi/C catalysts. Operation at pH 8 or replacement of the catalyst temporarily improved the conversion, but inhibition of the catalyst persisted. The maximum yield of 2-ketolactobionate was ca 80 %.

9.3.3.2 Oxidation of Primary Alcohol Functions

The introduction of carboxylate groups by selective oxidation of primary groups is also an important route to valuable products. Although platinum catalysts, which are more active than palladium in the oxidation of primary OH groups, are preferred, the rates of oxidation of primary OH groups in carbohydrates on platinum are usually low because metal surfaces are poisoned by over-oxidation or inhibition by strongly adsorbed products or by-products (see Section 9.2.2.2). Because of this low activity, the oxidation of primary OH is often accompanied by the parallel oxidation of secondary alcohol functions, so comparatively poor selectivity is obtained. Thus, the oxidation of D-gluconic acid **1** on Pt/C catalysts yielded only 55 % of D-glucaric acid **2** (Figure 5) [9,45].



1 **2** **3**

Figure 5. **1**, D-gluconic acid; **2**, D-glucaric acid; **3**, 2-keto-D-gluconic acid.

The oxidation of the primary OH groups in methyl α-D-glucopyranoside or α-D-glucopyranose 1-phosphate, in which the more reactive anomeric center is protected, on Pt/C catalysts gave a maximum yield of ca 70 % of the corresponding protected glucuronates [61,62]. Attempts to oxidize the three primary OH groups of sucrose on Pt/C catalysts [63–66] resulted in a mixture of degradation products, and of the mono-, bi-, and tricarboxysaccharose, which were obtained with 1.5, 30 and 35 % selectivity, respectively [65,66], (Figure 6). These unselective oxidations were performed in a batch reactor. In contrast, selective oxidation of the primary alcohol functions of carbohydrates was achieved in a flow reactor with a continuous separation of the oxidized products by electrodialysis (see Section 9.3.2 and Ref. [52]). Thus 99 % selectivity to methyl α-D-glucuronate was obtained in the oxidation of methyl α-D-glucopyranoside. Oxidation of sucrose led to 95 % selectivity for monocarboxysaccharoses with 47:44:5 distribution of the products of oxidation at $C_{6'}$, C_6 and C_1, respectively.

An extensive investigation of the oxidation of aldopentoses to the corresponding aldonic and aldaric acids has been reported [30]. Aldaric acid selectivity did not exceed 50–60 % because of the formation of degradation products; interpretation of the different reactivities of the molecules was impaired by significant leaching of the Pt/Al_2O_3 catalyst, particularly during D-ribose oxidation.

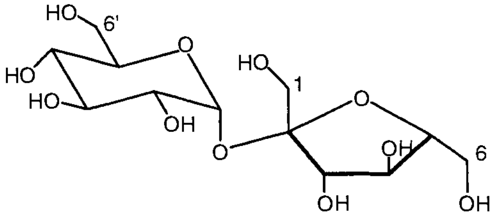


Figure 6. The sucrose molecule.

Oxidation of L-Sorbose to 2-Keto-L-gulonic Acid

The oxidation of L-sorbose to 2-keto-L-gulonic acid (2-KLG; Figure 7), an intermediate in the synthesis of vitamin C, has been studied extensively [37–42]. With unpromoted 5 % Pt/Al_2O_3 catalyst in a reactor working in a transport-limited regime, 67 % selectivity at 58 % conversion was obtained at neutral pH. On promotion with bismuth or lead the initial reaction rate improved, but the yield of 2-KLG was even lower [37]. Attempts to perform the reaction at higher pH resulted in a further drop of selectivity because of the instability of 2-KLG at high pH. Modification of the surface of metal catalysts with adsorbed nitrogen bases, without influencing significantly the pH of the solution, resulted in rate and selectivity enhancement [38,39]. Thus, addition of hexamethylenetetramine (HMTA) to Pt/C catalyst ($HMTA/Pt_s$ mol/mol = 0.1), improved selectivity from 51 to 95 % at 30 % conversion [39]. Rate acceleration was attributed to amine-catalyzed hydration of the intermediate aldehyde to a geminal diol; selectivity enhancement was attributed to the formation of a complex between one of the hydro-

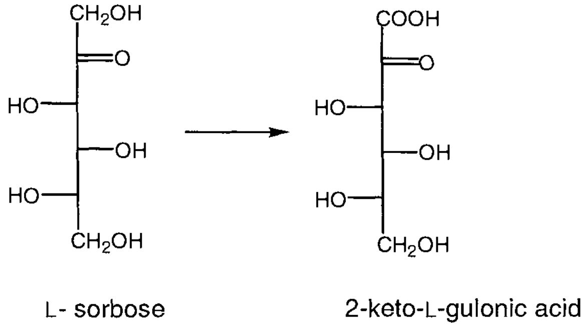


Figure 7. Oxidation of L-sorbose to 2-keto-L-gulonic acid.

xyl groups of the carbohydrate and a nitrogen atom in HMTA. Adsorption of this complex on the platinum surface results in a tilted position whereby only C-1 is exposed to oxidative dehydrogenation. 2-KLG selectivity was also improved (66 % at 50 % conversion) by addition of trace amounts of phosphines, particularly tributylphosphine, to the reaction medium, but the improvement was lower than with amines [40,41].

Oxidation of Inulin to Polycarboxylates

Verraest et al. [36] investigated the catalytic oxidation of methyl α-D-fructofuranoside and of inulin, a mixture of oligosaccharides based on (2→1)β-D-fructofuranoside chains attached to a glucose end-group (Figure 8). The aim was to prepare polycarboxylates that could be used in detergents because of their sequestering properties for calcium. Methyl α-D-fructofuranoside was oxidized at the C-6 position with 83 % selectivity at 100 % conversion by conducting the reaction at 60 °C on a 5 % Pt/C catalyst at pH 9 [65]. The oxidation of inulin derived from chicory, conducted under the same conditions, resulted in oxidation of only a fraction of the primary alcohol functions at C-6 and lower selectivity (typically 65 % selectivity at 25 % conversion of the fructose units). The longer the chain length, the lower the fraction of oxidized functionality. This was attributed to steric hindrance of the catalyst surface by the bulky reactant intermediate, and/or to the low affinity of the polycarboxylates already formed for the platinum surface.

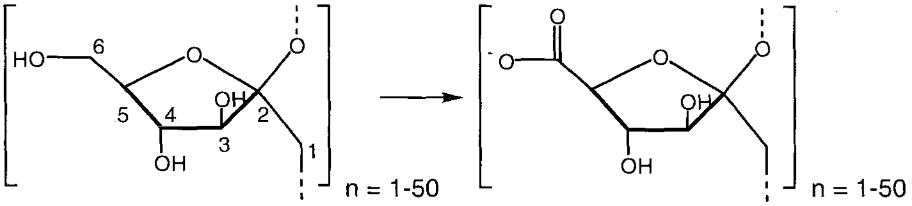


Figure 8. Oxidation of inulin (α-D-fructofuranoside chain).

9.3.3.3 Oxidation of Secondary Alcohol Functions

Although oxidation of secondary alcohol functions is usually an unwanted side-reaction occurring during the oxidation of primary alcohols, some occur with high selectivity and lead to valuable products.

Oxidation of Gluconic Acid to 2-Ketogluconic Acid

Unpromoted platinum catalysts selectively oxidize the primary alcohol function of D-gluconate **1** to yield D-glucarate **2** (see Section 9.3.3.2, Figure 5). Smits et al. [12,13] discovered that platinum catalysts modified by lead preferentially oxidize the secondary alcohol function adjacent to the carboxylic group to give 2-keto-D-gluconate **3** with a maximum yield of ca 60 %. The change in selectivity was attributed to complexation of carboxyl group and α-OH group by surface lead atoms.

In a similar investigation, Besson et al. [45] found that addition of bismuth to platinum had a similar effect. As in the previous investigation, however, the reaction was conducted at basic pH, and the yield of 2-keto-D-gluconate was limited by the formation of degradation products.

Abbadi and van Bekkum [32] reinvestigated this reaction on 5 % Bi/5 % Pt/C catalyst, starting from sodium D-gluconate, but without regulating the pH. Oxidation proceeded almost to completion giving the desired product with 98 % selectivity. The better selectivity at $\text{pH} < 6$ was attributed to selective complexation of the promoter with the carboxyl and α-hydroxyl group of the D-gluconic acid as shown in Figure 1 of Section 9.2.2.3, whereas in alkaline media the promoter can probably coordinate bidentatively with other hydroxyl groups. The resulting products are not stable and are oxidatively degraded. In the same way, other C5 aldonates, such as D-arabinonate and D-ribonate, were converted almost quantitatively to the corresponding 2-ketoaldonates [32].

Patents on oxidation of gluconic acid to 2-keto-D-gluconic acid on PtBi catalysts and on PtPb catalysts have been issued to Abbadi et al. [67] and Cerestar [68], respectively; they use essentially the same reaction conditions as those described elsewhere [32].

Oxidation of Fructose

Heinen et al. [35] investigated the oxidation of D-fructose on Pt/C catalyst at 30 °C and pH 7.3. Oxidation of both the C_1 primary alcohol and the C_5 secondary alcohol occurred. The reaction stopped at ca 80 % conversion giving mainly 2-keto-D-gluconic acid (45 % selectivity) and D-*threo*-hexo-2,5-diulose or '5-ketofructose' (27 % selectivity). In the presence of bismuth-promoted catalysts selectivity to the former was slightly increased. This was attributed to the complexation by bismuth of the β-D-fructofuranose structure via the *cis*-diol functions.

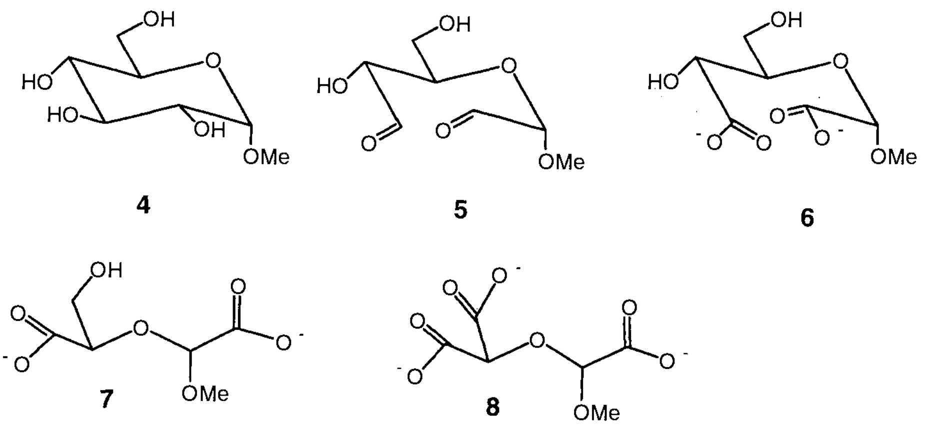


Figure 9. Oxidative cleavage of methyl α-D-glucopyranoside [69].

9.3.3.4 Oxidative Cleavage of Vicinal Diols

The oxidative cleavage of vicinal diols in polysaccharides could lead to biodegradable sequestrants employed as co-builders for detergents. Methyl α-D-glucopyranoside **4** (Figure 9), taken as model substrate, was oxidized with molecular oxygen (15–20 bar) at 50–75 °C in KOH solution on ruthenium–bismuth pyrochlore oxide catalysts prepared by co-precipitation of ruthenium and bismuth salts [70]. The oxidative cleavage of the C2–C3 bond of **4** resulted in the transient formation of the dialdehyde **5**, which was oxidized to the dicarboxylate **6**. The dialdehyde, however, underwent primarily oxidative decarboxylation leading to **7**, the primary alcohol function of which was subsequently partially oxidized to give the tricarboxylate **8**. At 85 % conversion of **4**, the product distribution was 3 % **6**, 45 % **7**, and 20 % **8**. This catalytic system was employed to oxidize β-cyclodextrin and maltodextrins, but hydrolysis was the main reaction. It was concluded that large substrate molecules could not be oxidized on heterogeneous catalysts.

9.3.4 Concluding Remarks

Liquid-phase oxidation of carbohydrates on supported metal catalysts results in high selectivity which occasionally, e. g. in glucose oxidation, can match or surpass that of enzymatic processes. Metal-catalyzed oxidation also affords high productivity, e. g. up to 8 mol h^{-1} $(g_{Pd})^{-1}$ for oxidation of glucose on Pd–Bi catalysts [39]. These processes have the important advantages of high simplicity of operation ('one-pot' reaction) and environmental acceptability, because almost no harmful effluents are generated.

For industrial applications, the metal catalyst should be repeatedly recycled or used in continuous mode for a long time. This implies the absence of irreversible deactivation as a result of significant leaching of the metal, promoters, and the supporting material. Carbon supports are particularly recommended because of their stability in acidic and chelating media. Platinum and palladium metals are resistant to leaching and to deactivation by over-oxidation. *p*-Electron promoters such as bismuth are readily leached in acidic and oxidizing conditions and should ideally be used in reactions conducted at controlled pH.

Continuous oxidation in flow reactors with the separation of oxidized products from unreacted substrates and recycling of solutions with controlled amounts of dissolved oxygen is a great improvement in activity and selectivity of catalysts compared with batch processes. This is because they reduce the probability of catalyst deactivation as a result of blockage of the metal surface by adsorbed oxygen and/or oxidized reaction products.

References

[1] E. von Gorup-Besanz, *Ann.*, 118 (1861) 257.
[2] K. Heyns, and H. Paulsen, *Angew. Chem.*, 69 (1957) 600; *Adv. Carbohydr. Chem.*, 17 (1962) 169–221.
[3] K. Heyns, H. Paulsen, G. Ruediger, and J. Weyer, *Fortschr. Chem. Forsch.*, 11 (1969) 285–374.
[4] K. Heyns, W. D. Soldat, and P. Köll, *Chem. Ber.* 108 (1975) 3619.
[5] H. G. J. de Wilt, and H. S. van der Baan, *Ind. Eng. Chem. Prod. Res. Develop.*, 11 (1972) 374–378.
[6] H. G. J. de Wilt, J. Lindhout, and B. F. M. Kuster, *Carbohydr. Res.*, 19 (1971) 5.
[7] H. G. J. de Wilt, J. Lindhout, and B. F. M. Kuster, *Carbohydr. Res.*, 23 (1972) 333–342.
[8] H. G. J. de Wilt, J. Lindhout, and B. F. M. Kuster, *Carbohydr. Res.*, 23 (1972) 343.
[9] J. M. H. Dirkx, H. S. van der Baan, and J. M. A. van den Broek, *Carbohydr. Res.*, 59 (1977) 63–72.
[10] J. M. H. Dirkx, and H. S. van der Baan, *J. Catal.*, 67 (1981) 1–13.
[11] J. M. H. Dirkx, and H. S. van der Baan, *J. Catal.*, 67 (1981) 14–20.
[12] P. C. C. Smits, B. F. M. Kuster, K. van der Wiele, and H. S. van der Baan, *Carbohydr. Res.*, 153 (1986) 227–235.
[13] P. C. C. Smits, B. F. M. Kuster, K. van der Wiele, and H. S. van der Baan, *Appl. Catal.*, 33 (1987) 83–96.
[14] P. J. M. Dijkgraaf, M. J. M. Rijk, J. Meuldijk, and K. van der Wiele, *J. Catal.*, 112 (1988) 329–336.
[15] P. J. M. Dijkgraaf, H. A. M. Duisters, B. F. M. Kuster, and K. van der Wiele, *J. Catal.*, 112 (1988) 337–344.
[16] H. E. J. Hendriks, B. F. M. Kuster, and G. B. Marin, *Carbohydr. Res.*, 204 (1990) 121–129.
[17] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, in *New Developments in Selective Oxidation by Heterogeneous Catalysis, Studies in Surface Science and Catalysis* (P. Ruiz and B. Delmon, eds), 72 (1992) pp. 43–55, Elsevier, Amsterdam.
[18] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, *Appl. Catal. A*, 89 (1992) 31–46.
[19] Y. Schuurman, B. F. M. Kuster, K. van der Wiele, and G. B. Marin, *Appl. Catal. A*, 89 (1992) 47–68.
[20] J. H. Vleeming, F. A. de Bruijn, B. F. M. Kuster, and G. B. Marin, in *Catalyst Deactivation, Studies in Surface Science and Catalysis* (B. Delmon, and G. Froment, eds.), 88 (1994) pp. 467, Elsevier, Amsterdam.
[21] H. E. J. Hendriks, B. F. M. Kuster, and G. M. Marin, *J. Mol. Cat.*, 93 (1994) 317–335.
[22] L. Jelemensky, B. F. M. Kuster, and G. B. Marin, *Catal. Lett.*, 30 (1995) 269–277.
[23] J. H. Vleeming, B. F. M. Kuster, and G. B. Marin, *Catal. Lett.*, 46 (1997) 187–194.

[24] J.H. Vleeming, B.F.M. Kuster, G.B. Marin, F. Oudet, and P. Courtine, *J. Catal.,* 166 (1997) 148–159.

[25] G. de Wit, J.J. de Vlieger, A.C. Kock-van Dalen, A.P.G. Kieboom, and H. van Bekkum, *Tetrahedron Letters*, 15 (1978) 1327–1330.

[26] G. de Wit, J.J. de Vlieger, A.C. Kock-van Dalen, R. Heus, R. Laroy, A.J. van Hengstum, A.P.G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 91 (1981) 125–138.

[27] H.E. van Dam, A.P.G. Kieboom, and H. van Bekkum, *Appl. Catal.*, 33 (1987) 361–372.

[28] H.E. van Dam, P. Duijverman, A.P.G. Kieboom, and H. van Bekkum, *Appl. Catal.*, 33 (1987) 373–382.

[29] P. Vinke, D. de Wit, A.T.J.W. de Goede, and H. van Bekkum, in *New Developments in Selective Oxidation by Heterogeneous Catalysis, Studies in Surface Science and Catalysis* (P. Ruiz and B. Delmon, eds), 72 (1992) pp. 1–20, Elsevier, Amsterdam.

[30] F.R. Venema, J.A. Peters, and H. van Bekkum, *J. Mol. Cat.*, 77 (1992) 75–85.

[31] A. Abbadi, M. Makkee, W. Visscher, J.A.R. van Veen, and H. van Bekkum, *J. Carbohydr. Chem.*, 12 (1993) 573–587.

[32] A. Abbadi, and H. van Bekkum, *Appl. Catal. A*, 124 (1995) 409–417.

[33] A. Abbadi, and H. van Bekkum, *J. Mol. Cat. A,* 97 (1995) 111–118.

[34] A. Abbadi, K.F. Gotlieb, J.B.M. Meiberg, and H. Van Bekkum, *Appl. Catal. A,* 156 (1997) 105–115.

[35] A.W. Heinen, J.A. Peters, and H. van Bekkum, *Carbohydr. Research,* 304 (1997) 155–164.

[36] D.L. Verraest, J.A. Peters, and H. van Bekkum, *Carbohydr. Research*, 306 (1998) 197.

[37] C. Brönnimann, Z. Bodnar, P. Hug, T. Mallat, and A. Baiker, *J. Catal.*, 150 (1994) 199–211.

[38] C. Brönnimann, T. Mallat, and A. Baiker, *J. Chem. Soc., Chem. Commun.* (1995) 1377–1378.

[39] C. Brönnimann, Z. Bodnar, R. Aeschimann, T. Mallat, and A. Baiker, *J. Catal.*, 161 (1996) 720–729.

[40] T. Mallat, C. Brönnimann, and A. Baiker, *Appl. Catal. A,* 149 (1997) 103–112.

[41] T. Mallat, C. Brönnimann, and A. Baiker, *J. Mol. Cat A: Chemical*, 117(1997) 425–438.

[42] I. Bakos, T. Mallat, and A. Baiker, Catal. Lett. 43 (1997) 201–207.

[43] M. Besson, P. Gallezot, F. Lahmer, G. Flèche, and P. Fuertes, in *Catalysis of Organic Reactions*, (J.R. Kosak, T.A. Johnson, eds), 53 (1993) pp. 169–180, Marcel Dekker, New York.

[44] M. Besson, P. Gallezot, F. Lahmer, G. Flèche, and P. Fuertes, *J. Catal.*, 152 (1995) 116–121.

[45] M. Besson, G. Flèche, P. Fuertes, P. Gallezot, and F. Lahmer, *Recl. Trav. Chim. Pays-Bas*, 115 (1996) 217–221.

[46] P. Fuertes, G. Flèche, (for Roquette Frères) Eur. Pat. 232 202 (1986).

[47] P. Fuertes, G. Flèche, (for Roquette Frères) Eur Pat. 233 816 (1987).

[48] M. Kunz, H. Puke, C. Recker, L. Scheiwe, and J. Kowalczyk, (for Südzucker), DE OS Pat. 43 07 388 A1 (1993).

[49] M. Kunz, H. Puke, and C. Recker. *Chem. Ing. Tech.* 67 (1995) 836.

[50] H. van Bekkum, in *Proc. Workshop Carbohydrates as Raw Materials* (F.W. Lichtenthaler ed.), *Darmstadt 1990,* (1991) pp. 289–310, VCH Weinheim.

[51] P. Gallezot, and M. Besson, *Carbohydr. in Europe,* 13 (1995) 5–10.

[52] M. Kunz, and C. Recker, *Carbohydr. in Europe,* 13 (1995) 11–15.

[53] M. Besson, and P. Gallezot, *Catal. Today,* 57 (2000) 127–141.

[54] M. Delépine, and A. Horeau. *Bull. Soc. Chim. Fr.* (1937) 1524.

[55] T. Matushita, T. Yamaguchi, S. Yamamatsu, and H. Okamoto (for Asahi Chem. Indus.) JP 98 263 399 (1997).

[56] H.O.J. Lemmens, S.M.J. Coomans, and H.W.W. Röper (for Cerestar Holding B.V.) EP 0 867 446 (1997).

[57] W. Bang, X. Lu, A.M. Duquenne, I. Nikov, and A. Bascoul, *Catal. Today,* 48 (1999) 125–130.

[58] H. Hustede, H. J. Haberstroh, and E. Schinzing, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A12,* (B. Elvers, S. Hawkins, M. Ravenseroft, J. F. Rounsaville, and G. Schulz, eds.), (1989) 449, VCH Verlag, Weinheim.
[59] M. Despeyroux, K. Deller, and E. Peldszus, in *New Developments in Selective Oxidation, Studies in Surface Science and Catalysis* (G. Centi and F. Trifiro, eds.), 55 (1990) pp. 159–168, Elsevier, Amsterdam.
[60] H. Bönnemann, W. Brijoux, A. Schulze Tilling, and K. Siepen, *Topics in Catalysis*, 4 (1997) 217-227.
[61] E. van Dam, PhD Thesis(1989), Delft University of Technology.
[62] P. Vinke, PhD Thesis (1991), Delft University of Technology.
[63] W. Fritsche-Lang, E. I. Leupold, and M. Schlingmann, DE 3 535 720.
[64] E. I. Leupold, K. H. Shoenwaelder, W. Fritsche-Lang, M. Schlingmann, A. H. Linkies, W. Gohla, and F. J. Dany, DE 3 900 677.
[65] L. A. Edye, G. V. Meehan, and G. N. Richards, *J. Carbohydr. Chem*, 10 (1991) 11–23.
[66] L. A. Edye, G. V. Meehan, and G. N. Richards, *J. Carbohydr. Chem*, 13 (1994) 273–283.
[67] A. Abbadi, K. F. Gotlieb, and H. van Bekkum, NL patent 9 302 127 (1993).
[68] M. Elseviers, H. O. J. Lenmmens, S. M. J. Coomans, and H. W. W. Röper, EP 0 867 446 (1998).
[69] L. Johnson, D. L. Verraest, J. van Haveren, K. Hakala, J. A. Peters, and H. van Bekkum, *Tetrahedron Asym.*, 5 (1994) 2475.
[70] S. J. H. F. Arts, F. van Rantwijk, and R. Sheldon, *J. Carbohydr. Chem.* 15 (1996) 317–329.

9.4 Allylic and Benzylic Oxidation

R. A. Sheldon

9.4.1 Introduction

Vapor-phase aerobic oxidations of lower olefins, e. g. propylene to acrolein or acrylic acid and isobutene to methacrolein or methacrylic acid, are well-established bulk chemical processes [1,2]. They are usually performed over oxidic catalysts, such as bismuth molybdate or heteropoly compounds, although the scope of these allylic oxidations is limited to olefins that cannot form 1,3-dienes via oxidative dehydrogenation. Thus 1- and 2-butene are converted to butadiene, and methylbutenes to isoprene, and with higher olefins complex mixtures result from further oxidation. Hence, such methodologies are not relevant in the context of fine chemicals.

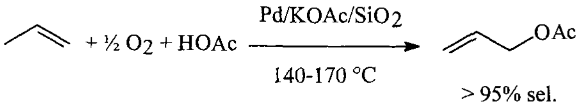
Indeed, one can easily conclude that selective allylic oxidation of olefins, in the context of fine chemicals, is a largely underdeveloped area of catalysis. Selenium dioxide catalyzes the allylic oxidation of a variety of olefins with TBHP, affording the corresponding allylic alcohols, but the system is homogeneous [3] and, hence, falls outside the scope of this book. The only heterogeneous catalysts for allylic oxidation which seem to have synthetic utility are palladium-based [4].

Benzylic oxidation of aromatic side-chains is also a well established technology in the bulk chemicals arena, e. g. toluene to benzoic acid and *p*-xylene to terephthalic acid [1,2]. These processes involve homogeneous catalysis by, e. g., cobalt compounds, however, and also fall outside the scope of this book. Ammoxidation of methyl-substituted aromatic and heteroaromatic compounds is performed over heterogeneous catalysts in the gas phase but this reaction is treated elsewhere (Section 9.5). Transition metal-substituted molecular sieves have been widely studied as heterogeneous catalysts for oxidation of aromatic side-chains in the liquid phase, but there are serious doubts about their heterogeneity [5,6]. Here again, a cursory examination of the literature reveals that supported palladium seems to be the only heterogeneous catalyst with synthetic utility [4].

9.4.2 Palladium-catalyzed Allylic Oxidations

In the well-known Wacker process ethylene is converted to acetaldehyde by aerobic oxidation in an aqueous medium in the presence of $PdCl_2$ as catalyst and $CuCl_2$ as cocatalyst [7]. Terminal olefins afford the corresponding methyl ketones. Oxidative acetoxylation of olefins with Pd(II) salts as catalysts in acetic acid was first reported by Moiseev and coworkers [8]. The addition of an alkali metal acetate, e. g. NaOAc, was necessary for the reaction to proceed. Palladium black was also found to be an active catalyst under mild conditions (40–70 °C, 1 bar) in the liquid phase, if NaOAc was added to the solution before reducing Pd(II) to Pd black, but not afterwards [9,10]. These results suggested that catalytic activity could be attributed to palladium atoms in a low oxidation state, rather than palladium metal or Pd(II) [10].

These pioneering studies formed the basis for the development of commercial processes for the production of allyl acetate by oxidative acetoxylation of propylene (Eq. 1). Processes are operated by Showa Denko and Daicel in Japan and Hoechst and Bayer in Europe [2,11]. The reaction is usually performed in the gas phase, e. g. at 140–170 °C over $Pd(OAc)_2/Cu(OAc)_2/KOAc/SiO_2$ or $Pd/KOAc/SiO_2$ catalysts and allyl acetate is formed with > 95 % selectivity. Allyl acetate is the raw material for the production of epichlorohydrin and glycerol.



(1)

The key catalytic intermediate in these processes is a palladium(II)–π-allyl complex. There are, in principle, two possible pathways for the formation of this intermediate–removal of a proton from a palladium(II)–olefin complex by a base (acetate ion) or oxidative addition of an olefin to a coordinatively unsaturated palladium(0) center (Figure 1).

The nature of the anion can also influence whether vinylic or allylic oxidation predominates. For example, with palladium trifluoroacetate allylic oxidation occurs even in the absence of a base [12]. The two different pathways–allylic and vinylic substitution–are illustrated in Figure 2.

Lyons [4] showed that aerobic oxidation of propylene in acetic acid containing NaOAc, over a Pd/C catalyst at 65 °C, afforded allyl acetate with > 99 % selectivity. To obtain high reaction rates it was necessary to pretreat the palladium cat-

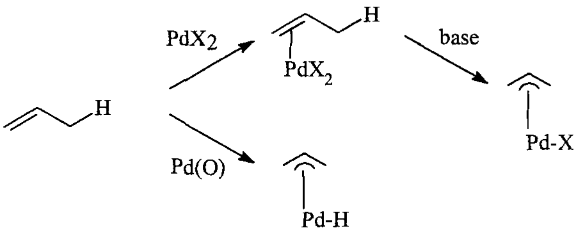


Figure 1. Two pathways for formation of a palladium–π-allyl intermediate.

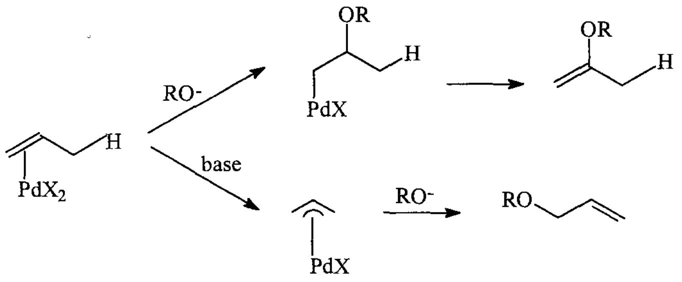


Figure 2. Comparison of allylic and vinylic acetoxylation.

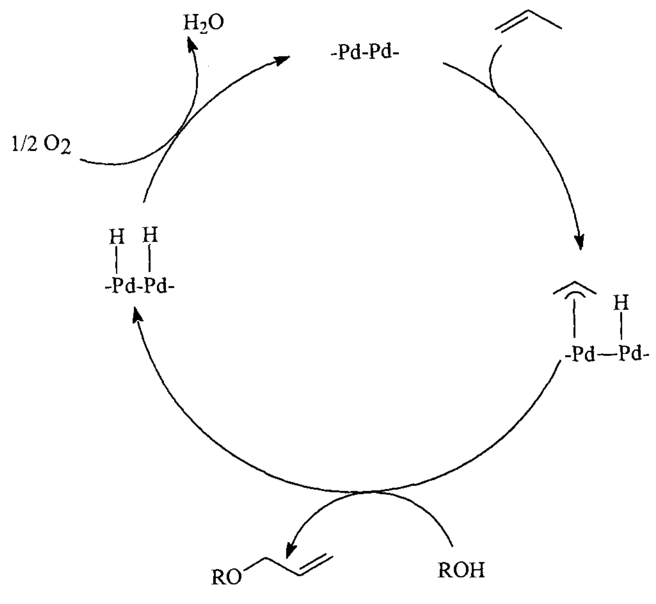


Figure 3. Catalytic cycle for allylic acetoxylation over palladium metal.

alyst with propylene in the absence of oxygen, presumably to ensure the formation of active Pd(0) centers on the surface. In contrast, if the palladium surface was oxidized by pretreatment with a strong oxidant, such as $S_2O_8^{2-}$, vinylic oxidation competed or even became predominant. Similarly, the presence of halide ion also promoted Wacker chemistry to the virtual exclusion of allylic oxidation. These observations suggest that the active catalyst for allylic oxidation is Pd(0) and under conditions where Pd(II) is formed vinylic oxidation predominates. Palladium(0) is known to activate the allylic C–H bonds of olefins and a catalytic cycle can be envisaged as shown in Figure 3.

When the reaction was conducted in water acrylic acid was obtained (Figure 4) with 88 % selectivity [4]. No leaching of the palladium into the aqueous phase was detected, and the clear water-white solution obtained on filtration had no activity.

Moiseev and coworkers showed [10,13] that giant palladium clusters with an idealized formula $Pd_{561}L_{60}(OAc)_{180}$ (L = phenanthroline or bipyridine) are highly active catalysts for allylic oxidation of olefins. The catalytically active solution was prepared by reduction of $Pd(OAc)_2$, e. g. with H_2, in the presence of the ligand, L, followed by oxidation with O_2. The giant palladium cluster catalyzed the oxidation of propylene to allyl acetate under mild conditions. Even in 10 % aqueous acetic acid, allyl acetate selectivity was 95–98 % [10]. Oxidation catalyzed by Pd-561 in water afforded a mixture of allylic alcohol (14 %), acrolein (2 %), and acrylic acid (60 %), and only 5 % acetone [10].

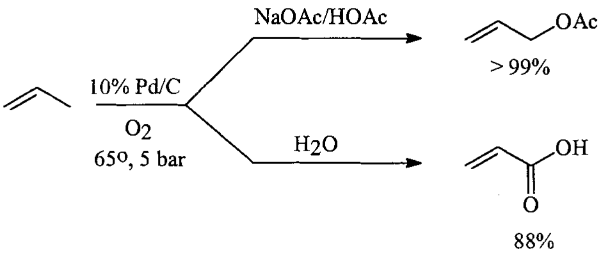
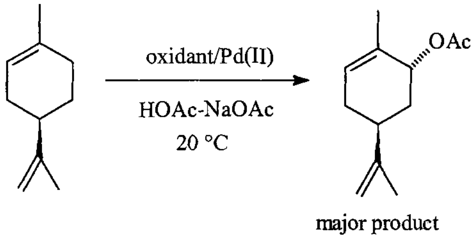


Figure 4. Oxidation of propylene over 10 % Pd/C.

Analogous allylic oxidations of higher olefins over heterogeneous palladium catalysts afford mixtures of products owing to the unsymmetrical nature of the π-allyl intermediate. For example, *cis*- or *trans*-2-butene gives a mixture of branched and linear allylic acetates. With olefins containing more than four carbon atoms palladium-catalyzed isomerization can lead to complex mixtures of products, which severely restricts the synthetic scope of these reactions.

Most studies of the scope of palladium-catalyzed allylic acetoxylation have involved homogeneous systems, usually comprising $Pd(OAc)_2$ in combination with a base (acetate) and benzoquinone and/or a heteropoly acid as an electron mediator [14,15]. The $Pd(OAc)_2$-benzoquinone system also catalyzes allylic acetoxylation with H_2O_2 as the primary oxidant [16]. Investigations of scope generally focused on cyclic olefins, e. g. cyclopentene and cyclohexene gave the corresponding allylic acetates with high selectivity [14–16].

Palladium-catalyzed allylic acetoxylation has also been applied to terpene substrates [17], e.g. (*R*)-limonene (Eq. 2), albeit using stoichiometric amounts of Cu(II) or benzoquinone as the oxidant.

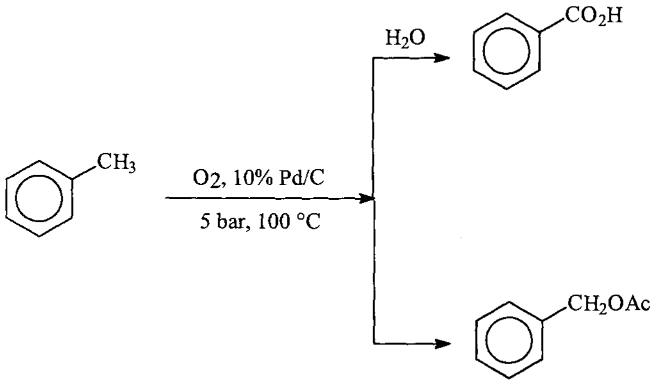


(2)

None of these reactions seem to have been investigated with heterogeneous palladium catalysts, e. g. Pd/C, by analogy with the work of Lyons (see above).

9.4.3 Palladium-catalyzed Benzylic Oxidations

It has long been known that $Pd(OAc)_2$ catalyzes the benzylic oxidation of toluene in acetic acid [18,19]. The catalyst was more active when reactions were performed in the presence of active charcoal [19] and low oxidation-state palladium was implicated in benzylic oxidations [20]. Optimum results were obtained in the presence of active charcoal and $Sn(OAc)_2$ as cocatalyst [19]. Similarly, Lyons [4] reported that Pd/C is an effective catalyst for benzylic oxidations under mild conditions, with little or no competing ring oxidation (Eqs. 3 and 4).

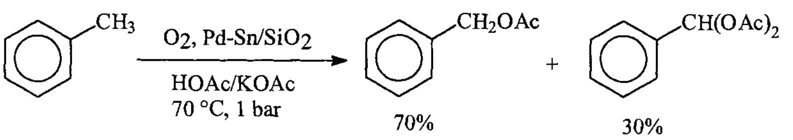


(3)

(4)

Tanielyan and Augustine [21] showed that a silica-supported Pd–Sn catalyst was effective in the aerobic oxidation of toluene in acetic acid, affording a mixture of benzyl acetate and benzylidene acetate (Eq. 5) at 98 % conversion.

Interestingly, the authors reported that benzyl acetate was not further oxidized under the reaction conditions, suggesting that benzylidene diacetate is formed in a parallel rather than consecutive reaction.



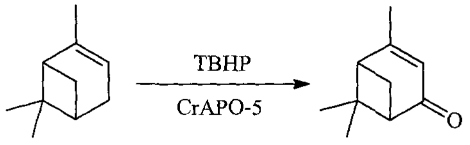
(5)

As with the allylic oxidation of olefins (see above) the giant Pd-561 cluster was also found to catalyze benzylic acetoxylation under mild conditions in acetic acid [10].

Few investigations have been devoted to the scope of palladium-catalyzed benzylic oxidation. Electron-donating substituents, e. g. MeO, in the aromatic ring have a promoting effect; no reaction was observed with *p*-nitrotoluene [18]. Other authors noted [19] that competing nuclear acetoxylation is observed when a methoxy group is present in the ring.

9.4.4 Metal-substituted Molecular Sieves as Catalysts for Allylic and Benzylic Oxidations

Soluble chromium compounds are known to catalyze the allylic oxidation of olefins [22,23] and benzylic oxidations of alkyl aromatics [22,24] using *tert*-butylhydroperoxide as the primary oxidant. Chromium-substituted aluminophosphates, e. g. CrAPO-5, were shown to catalyze the allylic oxidation of a variety of terpene substrates with TBHP to give the corresponding enones [25,26]. For example, α-pinene afforded verbenone with 77 % selectivity (Eq. 6) and 13 % of the corresponding alcohol.



(6)

Careful investigation [25,26] in which the catalyst was removed by filtration at the reaction temperature and the filtrate was left to react further revealed, however, that the observed catalysis was by soluble chromium(VI) leached from the framework. In separate experiments it was shown that a few ppm of soluble chromium(VI) could account for the observed catalysis. It was further shown that leaching was a result of reaction of framework chromium atoms with the alkyl hydroperoxide.

Similarly, the CrAPO-5- and chromium silicalite-1 (CrS-1)-catalyzed oxidation of aromatic side-chains with TBHP or O_2 as the primary oxidant [27–31] almost certainly arises as a result of soluble chromium(VI) leached from the catalyst. The same probably applies to benzylic oxidations with TBHP catalyzed by chromium-pillared montmorillonite [32]. More recently, a chromium Schiff's base complex tethered to the mesoporous silica, MCM-41, was claimed [33] to be an active and stable catalyst for the autoxidation of alkylaromatic side-chains. It would seem unlikely, however, that Schiff's base ligands can survive autoxidation conditions. Indeed, on the basis of our experience with chromium-substituted molecular sieves we consider it unlikely that a heterogeneous chromium catalyst can be developed that is both active and stable to leaching under normal oxidizing conditions with O_2 or RO_2H in the liquid phase. Similarly, vanadium-substituted molecular sieves are also unstable towards leaching under oxidizing conditions in the liquid phase [6,34].

Jacobs and coworkers [35] described the use of CoAPO-5 and CoAPO-11 as heterogeneous catalysts for the autoxidation of cyclohexane. The cobalt did not seem to be leached at low conversions. At higher conversions secondary products, such as adipic acid, leach the cobalt by forming chelate complexes. It would be interesting to investigate the activity and stability towards leaching of these and other cobalt-substituted molecular sieves [36,37] in benzylic oxidations with O_2.

9.4.5 Concluding Remarks

As noted in the introduction there is a paucity of effective and widely applicable methods for benzylic and allylic oxidation with heterogeneous catalysts. Palladium catalysts have been investigated the most extensively but studies of scope in organic synthesis have generally focused on homogeneous palladium catalysts. In short, the development of active and selective heterogeneous catalysts for allylic and benzylic oxidations in the liquid phase remains an important challenge in fine chemicals synthesis.

References

[1] R. A. Sheldon and J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981.

[2] G. Franz and R. A. Sheldon, *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A18, VCH, Weinheim, 1992, p. 299.

[3] M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 5526.

[4] J. E. Lyons, *Catal. Today* **1988**, *3*, 245.

[5] I. W. C. E. Arends, R. A. Sheldon, M. Wallau and U. Schuchardt, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1144.

[6] R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.

[7] R. Jira, in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils and W. A. Herrmann). VCH, Weinheim, **1996**, p. 374.

[8] I. I. Moiseev, M. N. Vargaftik and Ya. K. Syrkin, *Doklady Akad. Nauk. SSSR* **1960**, *133*, 377.

[9] M. N. Vargaftik, V. P. Zagorodnikov and I. I. Moiseev, *Kinet. Katal.* **1981**, *22*, 951.

[10] I. I. Moiseev, in *Catalytic Oxidation: Principles and Applications* (Eds. R. A. Sheldon and R. A. van Santen), World Scientific, Singapore, **1995**, pp. 203–238.

[11] A. Mitsutani, *Catal. Surveys Japan* **1997**, *1*, 121.

[12] B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.* **1980**, *102*, 3572; Institut Francais du Petrol (L. Saussine, J. P. Laloz and H. Mimoun), French Patent 2.450.802 (1980).

[13] N.Yu. Kozitsyna, M. N. Vargaftik and I. I. Moiseev, *J. Organomet. Chem.*, 2000, 593–594, 274.

[14] H. Grennberg, K. Bergstad and J. E. Bäckvall, *J. Mol. Catal. A: Chemical* **1996**, *113*, 355.

[15] T. Yokota, S. Fujibayashi, Y. Nishiyama, S. Sakaguchi and Y. Ishii, *J. Mol. Catal. A: Chemical* **1996**, *114*, 113.

[16] C. Jia, P. Müller and H. Mimoun, *J. Mol. Catal. A: Chemical* **1995**, *101*, 127.

[17] L. El Firdoussi, A. Baqqa, S. Allaoud, B. Ait Allal, A. Karim, Y. Castanet and A. Mortreux, *J. Mol. Catal. A: Chemical* **1998**, *135*, 11.

[18] C. H. Bushweller, *Tetrahedron Lett.* **1968**, 6123; see also J. M. Davidson and C. Triggs, *Chem. Ind. (London)* **1966**, 457.

[19] D. R. Bryant, J. E. McKeon and B. C. Ream, *J. Org. Chem.* **1968**, 33; D. R. Bryant, J. E. MeKeon and B. C. Ream, *Tetrahedron Lett.* **1968**, 3371.

[20] M. K. Starchevskii, M. N. Vargaftik and I. I. Moiseev, *Kinet. Katal.* **1979**, *20*, 1163; **1981**, *28*, 622.

[21] S. K. Tanielyan and R. L. Augustine, *J. Mol. Catal.* **1994**, *87*, 311; **1994**, *90*, 267.

[22] J. Muzart, *Chem. Rev.* **1992**, *92*, 113.

[23] J. Muzart, *Tetrahedron Lett.* **1987**, *28*, 4665.

[24] J. Muzart, *Tetrahedron Lett.* **1987**, *28*, 2131.

[25] H. E. B. Lempers and R. A. Sheldon, *J. Catal.* **1998**, *175*, 62; H. E. B. Lempers and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1997**, *105*, 1061.

[26] R. A. Sheldon, I. W. C. E. Arends and H. E. B. Lempers, *Coll. Czech. Chem. Commun.* **1998**, *63*, 1724.

[27] J. D. Chen and R. A. Sheldon, *J. Catal.* **1995**, *153*, 1.

[28] J. D. Chen, H. E. B. Lempers and R. A. Sheldon, *Colloids and Surfaces A: Physicochem. Eng. Aspects* **1995**, *101*, 137.

[29] J. D. Chen, M. J. Haanepen, J. H. C. van Hooff and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1994**, *84*, 973.

[30] R. A. Sheldon, J. D. Chen, J. Dakka and E. Neeleman, *Stud. Surf. Sci. Catal.* **1994**, *82*, 515; **1994**, *83*, 407.

[31] J. D. Chen, H. E. B. Lempers and R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1995**, *92*, 75.

[32] B. M. Chaudary, A. Durga Prasad, V. Bhuma and V. Swapna, *J. Org. Chem.* **1992**, *57*, 5841.

[33] I. C. Chisem, J. Chisem, J. S. Rafelt, D. J. Macquarrie, J. H. Clark and K. A. Utting, *J. Chem. Technol. Biotechnol.* **1999**, *74*, 923; I. C. Chisem, J. Rafelt, M. Tantoh Shieh,

J. Chisem, J. H. Clark, R. Jahuck, D. Macquarrie, C. Ramshaw and K. Scott, *Chem. Commun.* **1998**, 1949.

[34] M. S. Rigutto and H. van Bekkum, *J. Mol. Catal.* **1993**, *81*, 77; C. Marchal, A. Tuel and Y. Ben Taarit, *Stud. Surf. Sci. Catal.* **1993** H. E. B. Lempers and R. A. Sheldon, **1993**, *78*, 447.

[35] D. L. Vanoppen, D. E. De Vos, P. G. Rouxhet, M. J. Genet and P. A. Jacobs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 560.

[36] J. M. Thomas, R. Raja, G. Sankar and R. G. Bell, *Nature* **1999**, *398*, 227.

[37] T. Maschmeyer, R. D. Oldroyd, G. Sankar, J. M. Thomas, I. J. Shannon, J. A. Klepetko, A. F. Masters, J. K. Beattie and C. R. A. Catlow, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1639.

9.5 Ammoxidation of Aromatic Side-chains

B. Lücke, A. Martin

9.5.1 Introduction

Ammoxidation refers to the formation of nitriles by oxidation of hydrocarbons with oxygen in the presence of ammonia (Figure 1) [1]. Ammoxidation is best conducted with olefins, or with aromatic or heteroaromatic compounds, containing a readily abstractable H atom (allylic or benzylic intermediates are formed), although the ammoxidation of alkanes (e.g. propane to acrylonitrile [e.g. 2–4] or ethane to acetonitrile [e.g. 5]) is also possible. An exceptional example is the ammoxidation of methane to hydrogen cyanide by the Andrussov reaction [6].

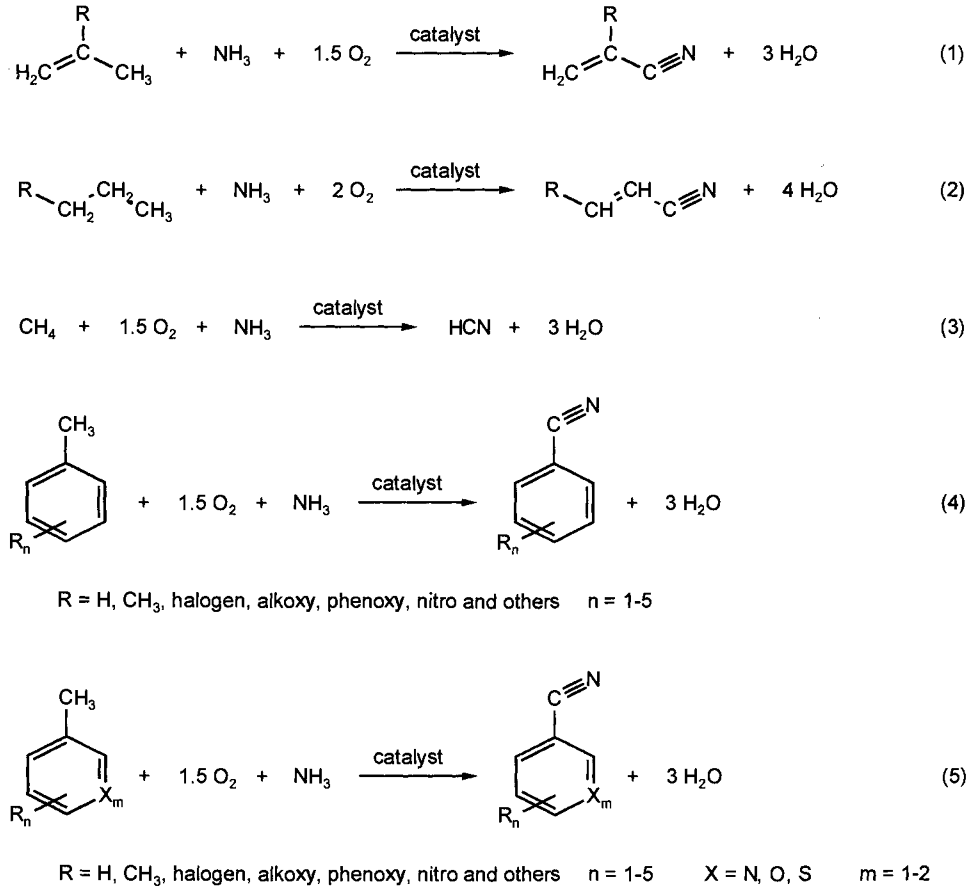


Figure 1. Formation of nitriles by ammoxidation of alkanes, alkenes, methyl aromatic and heteroaromatic compounds.

Whereas the ammoxidation of lower hydrocarbons leads to more large-scale products such as acrylonitrile [7] or methacrylonitrile [8], the ammoxidation of substituted aromatics or heteroaromatics opens the way for the synthesis of fine chemicals or intermediates for fine-chemical syntheses. A variety of pharmaceuticals, pesticides, dyestuffs, and other speciality products are produced from substituted aromatic or heteroaromatic nitriles [e. g. 9,10].

Conventional organic synthesis for aromatic nitriles [e. g. 10], for example the Rosenmund–von Braun reaction, the Sandmeyer reaction, or the oximation of aldehydes in the presence of dehydrating agents, performed in batch processes, are cumbersome and result in different amounts of by- and waste products. The ineffectiveness of such processes with regard to the amount of feedstock necessary per formed nitrile and the waste produced is rather high (in terms of the effectiveness factor defined by Sheldon [11]).

The ammoxidation reaction can, on the other hand, be performed continuously in fixed-bed and fluid-bed reactors, and by-products (particularly CO_2) can be easily removed. The fluidized bed has some advantages in terms of heat transfer but demands are made on the mechanical durability of the catalyst and so catalyst choice is limited. The long-term stability of the catalysts is also important and so multicomponent systems are recommended [e. g. 1,12]. The separation of the nitrile formed can be achieved by condensation, centrifugation, filtration, or rectification. Sometimes the formation of hazardous by-products (HCN, CO) must be considered.

9.5.2 Catalysts, General Reaction Conditions, Reaction Mechanism

In 1922 Wohl [13] published his observation that the oxidation of naphthalene in the presence of ammonia over vanadia gives phthalimide but this result went unnoticed both by the scientific community and by industry. Andrussov [6] found, in 1935, a route to produce hydrogen cyanide effectively by conversion of methane in the presence of air and ammonia over platinum catalysts at ca 1273 K. Thus, the first steps towards the development of ammoxidation had been taken. The conversion of aliphatic olefins was first claimed by Cosby in the late forties [e. g. 14] and the conversion of toluene to benzonitrile was first performed by Cosby and Erchak in 1950 [15]. The term 'ammoxidation' was introduced by Hadley in 1961 [16]. Since the fifties the fundamentals of the reaction and the reaction technique, for different aromatic compounds, have been reviewed [e. g. 9,16,17].

Many heterogeneous catalytic systems have been developed and applied to ammoxidation reactions. Vanadium-containing oxides are preferred as supported, bulk, or multicomponent catalysts for the ammoxidation of aromatic or heteroaromatic compounds. Favored supports are titanium oxide (anatase) [18,19], zirconium oxide [20,21], tin oxide [22], or mixed supports such as titanium–tin oxide [23]. Catalytic systems used as bulk materials include vanadium–phosphorus oxides [24], crystalline vanadium phosphates [25], and vanadium oxide combined with antimony oxide [26] or molybdenum oxide [27]. Other important catalysts include multicomponent systems such as $KNiCoFeBiPMoO_X$ on silica

[12], $AgAlBO_x$ [28], $VMoCrPdO_x$ [29], SbVTi with additives [30], and perovskite systems such as $YBaCu_3O_6$ [31]. Cerium oxide (on titania) [32] or nickel oxide (on alumina) have also been used as catalysts in special circumstances. Nowadays, zeolite-supported catalysts, e. g. Cu-exchanged materials such as Cu-H-ZSM-5 [33,34], Cu-Na-ZSM-5 [35], and Cu–Na-mordenite [36], are used for the shape-selective ammoxidation of isomeric xylenes. Molecular sieves of the VAPO and VSAPO family [37] are also used as catalysts.

The selectivity of a partial-oxidation catalyst can change with slight variations in its composition but is also dependent on the substrate and the reaction conditions. The design of catalysts optimized for a specific reaction should be based on a detailed knowledge and understanding of the reaction mechanism. The 'state of the art' of catalyst development, mechanistic features, kinetics, and reaction technology in the ammoxidation of methyl aromatic compounds was summarized in 1992 by Rizayev et al. [38].

A redox mechanism (Mars–van Krevelen) is generally accepted for the ammoxidation reaction of methyl aromatic compounds, thus most catalysts applied contain transition metal oxides (e. g. vanadium, molybdenum) readily enabling changes in valence states.

Essential steps of the catalytic reaction are: (i) chemisorption of the aromatic reactant on the catalyst surface and H abstraction to form a benzylic intermediate, (ii) insertion of ammonia into a surface bonded partial oxidized intermediate and (iii) desorption of the nitrile formed and reoxidation of the catalyst by gas-phase oxygen. The position, size, and electronic effects of substituents significantly influence all these steps [e. g. 39]. Over vanadium–tin oxide [40] and vanadium phosphate [41] catalysts the reactivity of substituted toluenes with electron-withdrawing substituents is enhanced compared with unsubstituted toluene, as shown for the ammoxidation of halogen-substituted toluenes. In contrast with this activity-enhancing effect, electron-donating substituents lead to decreasing activity and selectivity [41], because of stronger chemisorption of substrates, intermediates, and products on the electrophilic catalyst surface, resulting in a delayed desorption of desired products that readily become subject to consecutive oxidation. The electronic interaction of substituted toluenes with structurally well-defined vanadium phosphates can be directly observed by in situ ESR spectroscopy. The interaction of the substrates with the catalytic system is stronger for toluenes with electron-donating substituents, whereas with electron-withdrawing substituents interaction is distinctly less [42].

Two closely adjacent VO groups are necessary for the chemisorption step and the subsequent catalytic reaction over vanadyl-containing catalysts. One VO site of edge-shared VO_6 octahedra, present for example in vanadium phosphate catalysts, acts in the chemisorption of a toluene reactant as a coordinatively unsaturated (Lewis) site via π-interaction, the other as an oxidation site via the V=O group [43] (Figure 2). High catalytic activity also requires effective exchange pathways for electron transport. In active vanadium phosphate catalysts changes in electron density, because of effective spin–spin exchange (detected by in situ ESR) at a discrete surface vanadyl ion, can be easily delocalized via the overlapping d-orbitals of the exchange-coupled centers [44].

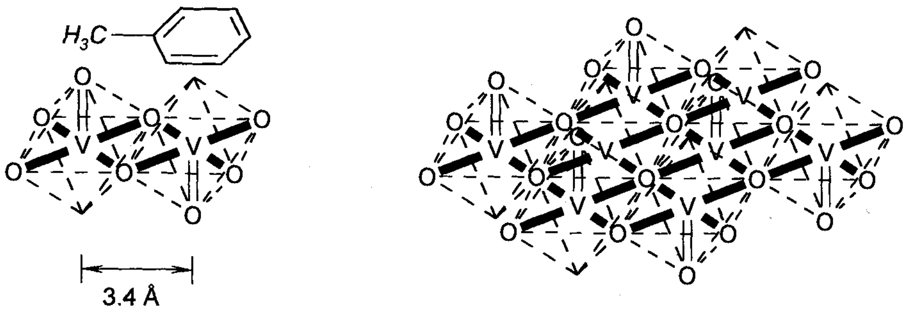


Figure 2. Schematic view of the surface VO_6 octahedra (100) of $(VO)_2P_2O_7$ (in relation to chemisorption of toluene) and VO_x domains or clusters on vanadium oxide catalysts [43].

Benzylamine- [e. g. 45] or benzaldehyde-like [e. g. 46] species have been proposed as reaction intermediates. Ammonia, which must be inserted, is chemisorbed and activated by the catalyst [47–49] and does not act directly from the gas-phase. Recent investigations using transient experiments with ^{15}N support this idea [50]. As indicated for vanadium phosphate catalysts, NH_4^+ ions can act as potential insertion species in the ammoxidation cycle, suitable chemisorption sites (OH groups) will be formed during the catalytic reaction [51]. Otherwise, the formation of imido species (=NH) is often discussed as active site for the N-insertion of catalysts, containing, e. g., molybdenum instead of vanadium [1,52–54].

Ammonia not only plays the role of reactant, it is also important in the formation of the catalytically effective surface necessary for selective reaction. Thus, ammonia partly reduces the surface, enhancing the selectivity [43,51], or can block sites for weakly bound oxygen, increasing the selectivity for partial oxidation compared with that for total oxidation [38,55].

Reaction steps of the ammoxidation of toluene over a vanadium phosphate catalyst in combination with structural changes of the catalyst surface during the reaction have been intensively studied by XRD, TPR, TPSR, transient experiments, and FTIR, Raman, and ESR spectroscopy, resulting in the comprehensive mechanistic scheme shown in Figure 3 [42–44,50,56].

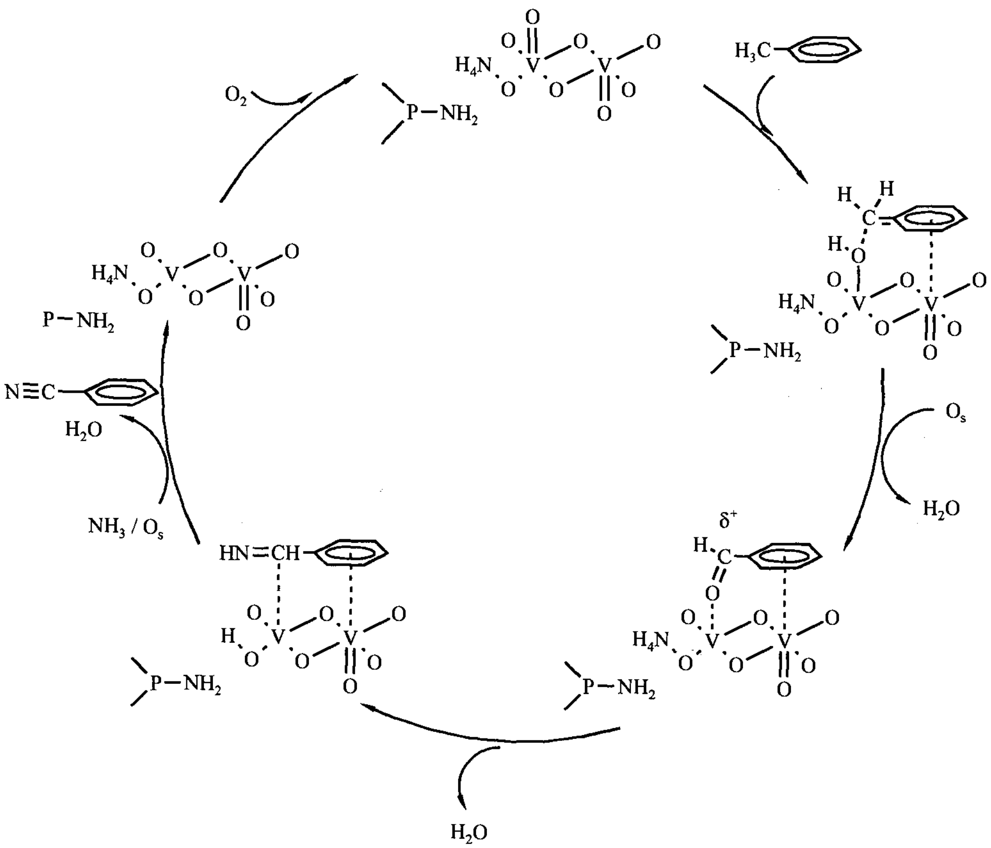


Figure 3. Reaction pathway for formation of benzonitrile over a $(VO)_2P_2O_7$ catalyst, including toluene chemisorption, partial oxidation, N-insertion, nitrile desorption and catalyst reoxidation steps [46].

9.5.3 Ammoxidation of Toluene and Alkylbenzenes

Toluene can be readily ammoxidized to benzonitrile, usually over supported vanadium oxide and vanadium phosphate catalysts [e. g. 9,57]. Besides catalyst choice, catalytic performance mainly depends on the reaction conditions. Excess ammonia, as mentioned above, significantly increases nitrile selectivity by blocking sites responsible for consecutive oxidation; ammonia also frequently reduces catalyst activity [1]. Water vapor in the reactant stream can also improve selectivity by blocking sites for total oxidation [38] or providing Brønsted sites for the activation of ammonia [51].

The temperature range for the catalytic reaction may reach from 600 K to about 700 K. Increasing temperature normally results in increasing conversion and reduced selectivity and, hence, for every catalyst used the optimum conditions must be carefully determined. Toluene conversion ranges from 50 to 100 % and benzonitrile selectivity between 70 and 95 % have been reported. Normally, the ammoxidation of toluene (and the ammoxidation of substituted toluenes and heteroaromatic compounds, see below) needs relatively simple technology.

Ammoxidation of alkylbenzenes with side-chains of different length leads to reaction at the position α to the benzene ring [38]. Reactivity increases with increasing length of the alkyl group (toluene < ethyl benzene < isopropyl benzene [58,59]), but in all cases only benzonitrile is formed.

In addition to toluene higher condensed methyl aromatic compounds and biphenyl derivatives, e. g. 1-methylnaphthalene (on Cu–Na-mordenite [36]) or *p*-methylbiphenyl (to *p*-cyanobiphenyl and terephthalodinitrile [60]) can also be ammoxidized. The ammoxidation route can also be used to insert nitrogen into very highly condensed products, e. g. lignins [61,62], or active carbon [63].

9.5.4 Ammoxidation of Substituted Toluenes

9.5.4.1 Methyl-substituted Toluenes

1,2-, 1,3- or 1,4-Methyl-substituted toluenes can be ammoxidized to mono- or dinitriles [e. g. 9,38]. The ammoxidation of *o*-xylene gives either phthalimide (e. g. over vanadium oxide on alumina [64] or vanadium oxide on zirconia [65]) or, under different reaction conditions, *o*-phthalodinitrile (e. g. over vanadium oxide on alumina [66]). *m*-Xylene is converted to isophthalodinitrile over multicomponent catalysts [67], and tellurium- [68] and niobium- [69] exchanged zeolite catalysts. *p*-Xylene is ammoxidized to either *p*-tolunitrile or terephthalonitrile, e. g. over multicomponent catalysts [12]. *p*-Tolunitrile and terephthalodinitrile are also formed with good selectivity from a mixture of *m*- and *p*-xylenes by shape-selective ammoxidation with copper-containing ZSM-5 zeolites [33,34].

Toluenes with more than one additional methyl group are also converted to nitriles [70,71], although with higher substitution the number of products resulting from partial ammoxidation increases, e. g. the ammoxidation of mesitylene results in a mixture of 1-cyano-3,5-dimethylbenzene, 1,3-dicyano-5-methylbenzene and 1,3,5-tricyanobenzene. Over vanadium–tin oxide [72] or over a VBPNa oxide catalyst (with addition of halocarbons to the feed) the yield of tricyanobenzene is markedly enhanced [73].

9.5.4.2 Halogen-substituted Toluenes

Halogen substituted toluenes are readily converted into nitriles because electron-withdrawing substituents enhance the reactivity of such compounds in the ammoxidation reaction. The fluoro-, chloro-, bromo-, and iodo-substituted toluenes [e. g. 41,74–76] can, therefore, be converted to the corresponding nitriles. Whereas the conversion rate of *p*-halotoluenes (over vanadium phosphate catalysts [41,75]) is nearly independent of the nature of the halogen substituent, the selectivity decreases in the sequence *p*-Cl > *p*-Br >> *p*-I. Ammoxidation of isomeric chlorotoluenes results in different conversion (*p* >> *o* > *m*) and selectivity (*p* > *o* > *m*) sequences [41,75,76].

The reaction of dichloro-substituted toluenes is much more influenced by the position of the substituents–closer proximity of the substituents to the methyl group results in lower conversion and nitrile selectivity (2,6-di-Cl < 2,5-di-Cl < 2,3-di-Cl < 2,4-di-Cl ~ 3,4-di-Cl) [39,77]. Because, however, 2,6-dichlorobenzonitrile has special importance as an intermediate for pesticides, catalysts and conditions have been described which afford acceptable yields [29,78]. Thus 2,6-dichlorobenzonitrile is formed in 85 % yield by use of a fluid-bed reactor with separate introduction of the educt gases over a vanadium–molybdenum-containing multicomponent catalyst [79].

Halogen-substituted xylenes can also be ammoxidized; 3,4,5,6,-tetrachlorophthalodinitrile is formed from the corresponding *o*-xylene derivative (45 % yield) [80].

9.5.4.3 Hydroxy- and Alkoxy-substituted Toluenes

As mentioned above, the ammoxidation of toluenes substituted with electron-donating groups is rather less selective. The reaction can, nevertheless, be performed if optimum conditions (catalyst, feed composition, temperature) are carefully chosen.

p-Hydroxybenzonitrile can be synthesized directly from *p*-cresol over the bismuth–molybdenum oxide, iron–antimony oxide or uranium–antimony oxide catalysts [81] normally used for the ammoxidation of propylene, although the catalysts are rapidly deactivated by coke-like deposits [81].

Ammoxidation of *p*-methoxytoluene (protection of the OH group in the *p*-cresol feed by methylation) over vanadium–titanium oxide catalysts gives *p*-methoxybenzonitrile in 65 % yield [81,82]. Because of the greater reactivity of *p*-methoxytoluene compared with the *m* isomer the ammoxidation of *m*,*p*-methoxytoluene mixtures results in the formation of only *p*-methoxybenzonitrile and the *m* isomer remains mainly unreacted. This presents the possibility of reactive separation of differently substituted toluenes [82].

p-Phenoxytoluene is converted to the corresponding nitrile over a multicomponent catalyst at 690 K with 58 % selectivity (85 % conversion [83]).

Acylation as protection for the OH group seems not to be preferred because the acyl group is readily removed during reaction, resulting in a loss in selectivity. Thus, acetoxy-*o*-xylene can not be ammoxidized to acetoxyphthalic acid derivatives [84]. On the other hand, 9,10-bis(acetoxymethyl)anthracene has been converted to 10-(acetoxymethyl)-9-anthracenecarbonitrile in 64 % yield [85].

The joint influence of the electron-donating effect, and the position, in polysubstituted toluenes significantly hampers conversion and selectivity. This results in rather poor yields and selectivity, particularly for 2,6-disubstituted toluenes [e.g. 41,75].

9.5.5 Ammoxidation of Heterocyclic Compounds

Methylpyridines are easily converted into the corresponding nitriles. The ammoxidation of 3-methylpyridine to nicotinonitrile has been particularly extensively investigated, mainly because of the importance of the nitrile as precursor of vitamins. The catalysts used are mostly vanadium-containing oxides, e. g. vanadium–titanium oxide [86], vanadium–zirconium oxide [87], or multicomponent systems [30,88]. Yields of more than 90% at nearly complete conversion were recently reported (e.g. 100% selectivity for vanadium oxide on titania (anatase) catalysts with V_2O_5 loading $\leq$ 3.4 mol% [89].

High selectivity was also reported for the ammoxidation of 4-methylpyridine, e.g. over vanadium–molybdenum oxides [90] highly dispersed vanadia on silicated alumina [91] or on vanadium-containing molecular sieves (VSAPO, VAPO [92], also used for the ammoxidation of 3-methylpyridine [93,94]). The ammoxidation of 2-methylpyridine leads to the formation of large amounts of pyridine, by total oxidation of the methyl group and subsequent decarboxylation, in addition to the desired nitrile [95]. Yields in excess of 90% can, nevertheless, be achieved, e. g. over vanadium–tin oxide at ca 670 K [23] or over molybdenum phosphates [96]. When the ammoxidation of 2-, 3- and 4-methylpyridine over vanadium phosphates was compared catalyst activity and the nitrile selectivity reflected the reactivity order 4- > 3- > 2-methylpyridine, probably as a result of different steric hindrance [41].

Pyridines containing more than one methyl group are also ammoxidized, as mentioned for xylenes. The methyl groups are successively converted, e. g. reaction of 3,5-dimethylpyridine over vanadium–titanium–tin oxide gives a mixture of 3-cyano-5-methylpyridine and 3,5-dicyanopyridine (75–85% yield [97]). The ammoxidation of 2-methyl-5-vinylpyridine results in two products: 2-cyano-5-vinylpyridine and 2,5-dicyanopyridine [98].

The ammoxidation of heterocyclic compounds is not limited to methylpyridines. Other examples include the ammoxidation of 2,5-dimethylpyrazine, over molybdenum–cerium–titanium oxide [99], giving the corresponding mono- and dinitriles, and the ammoxidation of 4-methylthiazole to 4-cyanothiazole [100].

9.5.6 Future Developments

The ammoxidation of methyl aromatic and heteroaromatic compounds is a convenient route to many nitriles required for further synthesis of fine chemicals. For example, for the production of amines by hydrogenation or of carboxylic acids and amides by hydrolysis.

For further extension of the scope of the ammoxidation reaction new catalytic systems (based on detailed mechanistic knowledge) must be developed to establish more selective reactions, e. g. at lower temperature or under shape-selective conditions. For extension of application, effective protection of side-chains in the educts are also necessary. Finally, the search for more selective catalysts should include the development of biomimetic catalytic systems for application under moderate reaction conditions, and the introduction of new host/guest materials.

References

[1] R. K. Grasselli in *Handbook of Heterogeneous Catalysis, Vol. 5* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), VCH, Weinheim, **1997**, p. 2302.

[2] V. D. Sokolovskii, A. A. Davydov, O.Yu. Ovsitser, *Catal. Rev.-Sci. Eng.* **1995**, *37*, 425.

[3] H.-W. Zanthoff, S. Buchholz, *Catal. Lett.* **1997**, *49*, 213.

[4] G. Centi, F. Marchi, S. Perathoner, *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 5141.

[5] Y. Li, J. N. Armor, *Chem. Commun.* **1997**, 2013.

[6] L. Andrussov, *Angew. Chem.* **1935**, *48*, 593.

[7] R. K. Grasselli, *J. Chem. Ed.* **1986**, *63*, 216.

[8] D. D. Suresh, M. S. Friedrich, M. J. Seely (Stand. Oil Co.), U. S. Patent 5,212,137, 1993 [*Chem. Abstr.* **1994**, *120*, 55269w].

[9] M. C. Sze, A. P. Gelbein, *Hydrocarbon Processing* **1976**, 103.

[10] P. Pollak, G. Romeder, F. Hagedorn, H.-P. Gelbke, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 17A* (Eds.: B. Elvers, S. Hawkins, G. Schulz), VCH, Weinheim, 1991, p. 371.

[11] R. A. Sheldon, *ChemTech* **1994**, 38.

[12] R. K. Grasselli, J. C. Callahan (Standard Oil Co. (Ohio)), Ger. Offen. DE 2 314 151, 1973 [*Chem. Abstr.* **1974**, *80*, 3281e].

[13] A. Wohl, *Angew. Chem.* **1922**, *35*, 593.

[14] J. N. Cosby (Allied Chemical & Dye Corp.), U. S. Patent 2 481 826, 1949 [*Chem. Abstr.* **1950**, *44*, 653g].

[15] J. N. Cosby, M. Erchak (Allied Chemical & Dye Corp.), U. S. Patent 2 499 055, 1950 [*Chem. Abstr.* **1950**, *44*, 6885d].

[16] D. J. Hadley, *Chem. Ind.* **1961**, 238.

[17] B. V. Suvorov, *Okislitelnij ammonolis organiceskich soedinenii*, Nauka, Alma Ata, **1971**.

[18] P. Cavalli, F. Cavani, I. Manenti, F. Trifirò, *Catal. Today* **1987**, *1*, 245.

[19] M. Sanati, A. Andersson, *J. Mol. Catal.* **1990**, *59*, 233.

[20] M. Sanati, A. Andersson, L. R. Wallenberg, B. Rebenstorf, *Appl. Catal. A* **1993**, *106*, 51.

[21] L. Makedonski, V. Nikolov, N. Nikolov, V. Blaskov, *React. Kinet. Catal. Lett.* **1999**, *66*, 237.

[22] M. Shanshal, H. Al-Ghatta, S. F. Tahir, *React. Kinet. Catal. Lett.* **1991**, *43*, 335.

[23] B. V. Suvorov, L. K. Glubokovskikh, I. I. Kan, S. V. Berstenev, *Zh. Prikl. Khim. (S.-Petersburg)* **1991**, *64*, 2451.

[24] M. B. Reddy, M. V. Kumar, B. Manohar, *Chem. Ind. Series, Vol. 62* (Eds.: M. G. Scaros, M. L. Prunier) Marcel Dekker, New York, **1995**, 487.

[25] A. Martin, G.-U. Wolf, U. Steinike, B. Lücke, *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 2227.

[26] A. Andersson, S. L. T. Andersson, G. Centi, R. K. Grasselli, M. Sanati, F. Trifirò, *Appl. Catal. A* **1994**, *113*, 43.

[27] W. S. Chen, H. B. Chiang, M. D. Lee, *J. Chin. Inst. Chem. Eng.* **1994**, *25*, 45.

[28] L. Satek, L. Wilwerding, J. L. Melquist, M. L. Luetkens (Amoco Corp.), U. S. Patent 4 766 102, 1988 [*Chem. Abstr.* **1990**, *112*, 12538a].

[29] K. Otomo, A. Imai, T. Hanada, H. Mito (Hodogaya Chemical Co.), Japan Patent 03 44 362, 1991 [*Chem. Abstr.* **1991**, *114*, 246976k].

[30] L. v. Hippel, A. Neher, D. Arntz (Degussa AG), European Patent 726 092, 1996 [*Chem. Abstr.* **1996**, *125*, 225060u].

[31] J. C. Otamiri, S. L. T. Andersson, A. Andersson, *Appl. Catal.* **1990**, *65*, 159.

[32] P. K. Rao, K. S. R. Rao, S. K. Masthan, K. V. Narayana, T. Rajiah, V. V. Rao, *Appl. Catal. A* **1997**, *163*, 123.

[33] K. Beschmann, L. Riekert, *Chem.-Ing.-Tech.* **1993**, *65*, 1251.

[34] K. Beschmann, S. Fuchs, T. Hahn, *Chem.-Ing.-Tech.* **1998**, *70*, 1436.
[35] S.H. Kim, H. Chon, *Appl. Catal. A* **1992**, *85*, 47.
[36] J. Fu, I. Ferino, R. Monaci, E. Rombi, V. Solinas, L. Fornib, *Appl. Catal. A* **1997**, *154*, 241.
[37] S.J. Kulkarni, R.R. Rao, M. Subrahmanyam, A.V.R. Rao, A. Sarkany, L. Guczi, *Appl. Catal. A* **1996**, *139*, 59.
[38] R.G. Rizayev, E.A. Mamedov, V.P. Vislovskii, V.E. Sheinin, *Appl. Catal. A* **1992**, *83*, 103.
[39] A. Martin, B. Lücke, G.-U. Wolf, M. Meisel, *Catal. Lett.* **1995**, *33*, 349.
[40] I.M. Chmyr, N.R. Bukeikhanov, B.V. Suvorov, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **1983**, *36*, 43.
[41] A. Martin, B. Lücke, *Catal. Today* **1996**, *32*, 279.
[42] A. Brückner, A. Martin, B. Lücke, F.K. Hannour, *Stud. Surf. Sci. Catal.* **1997**, *110*, 919.
[43] A. Martin, A. Brückner, Y. Zhang, B. Lücke, *Stud. Surf. Sci. Catal.* **1997**, *108*, 377.
[44] A. Brückner, A. Martin, N. Steinfeldt, G.-U. Wolf, B. Lücke, *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 425.
[45] G. Busca, *ACS Symp. Series* **1993**, *523*, 168.
[46] Y. Zhang, A. Martin, H. Berndt, B. Lücke, M. Meisel, *J. Mol. Catal. A* **1997**, *118*, 205.
[47] G. Busca, F. Cavani, F. Trifirò, *J. Catal.* **1987**, *106*, 471.
[48] Yu.V. Belokopytov, K.M. Kholyavenko, S.V. Gerei, *J. Catal.* **1979**, *60*, 1.
[49] M. Takagi-Kawai, M. Soma, T. Onishi, K. Tamaru, *Can. J. Chem.* **1980**, *58*, 2132.
[50] A. Martin, Y. Zhang, H.-W. Zanthoff, M. Meisel, M. Baerns, *Appl. Catal. A* **1996**, *139*, L11.
[51] H. Berndt, K. Büker, A. Martin, A. Brückner, B. Lücke, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 725.
[52] R.K. Grasselli, J.D. Burrington in *Advances in Catalysis, Vol. 30* (Eds.: D.D. Eley, H. Pincs, P.B. Weisz) Academic Press, New York, **1981**, p.133.
[53] J.C. Otamiri, A. Andersson, *Catal. Today* **1988**, *3*, 211.
[54] J.D. Burrington, C.T. Kartisek, R.K. Grasselli, *J. Catal.* **1984**, *87*, 363.
[55] P. Cavalli, F. Cavani, I. Manenti, F. Trifirò, M. El-Sawi, *Ind. Eng. Chem. Res.* **1987**, *26*, 804.
[56] Y. Zhang, M. Meisel, A. Martin, B. Lücke, K. Witke, K.-W. Brzezinka, *Chem. Mater.* **1997**, *9*, 1086.
[57] A. Martin, G.-U. Wolf, U. Steinike, B. Lücke, *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 2227.
[58] Kh.I. Areshidze, G.O. Chivadze, C.I. Naskidashwili, *Izv. Akad. Nauk Gruz. SSR* **1974**, *76*, 89.
[59] A.D. Kagarlitskii, B.V. Suvorov, S.R. Rafikov, A.S. Kostromin, *Zh. Prikl. Khim.* **1963**, *36*, 1848.
[60] A.A. Shapovalov, D.Kh. Sembaev, S.G. Koshel, *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim* **1990**, *4*, 71.
[61] D. Meier, V. Zuniga-Partida, F. Ramirez-Cano, N.-C. Hahn, O. Faix, *Bioresour. Technol.* **1994**, *49*, 121.
[62] E.A. Nascimento, S.A.L. Morais, D.P. Veloso, S.M.C. Menezes, *J. Braz. Chem. Soc.* **1994**, *5*, 5.
[63] R.J.J. Jansen, H. van Bekkum, *Carbon* **1994**, *32*, 1507.
[64] L.I. Saurambaeva, I.S. Kolodina, D.Kh. Sembaev, *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1991**, *4*, 80.
[65] D.Kh. Sembaev, F.A. Ivanovskaya, B.V. Suvorov, N.I. Chukhno (Inst. of Chemistry, Acad. of Sciences, Kazakh. S.S.R.), SU Patent 1 699 998 1991, [*Chem. Abstr.* **1992**, *116*, 235437a].
[66] L. Karrer, F.-F. Pape, H.-J. Kneuper, M. Huellmann (BASF A.-G.), European Patent 767,165, 1997 [*Chem. Abstr.* **1997**, *126*, 293193k].
[67] C. Paparizos, W.G. Shaw (Standard Oil of Ohio Co.), U.S. Patent 5 183 793, 1993, [*Chem. Abstr.* **1993**, *118*, 194026m].
[68] T. Romotowski, J. Komorek, J. Stock, *Pol. J. Chem.* **1998**, *72*, 2450.
[69] T. Romotowski, J. Komorek, V. Tershikh, *Pol. J. Chem.* **1998**, *72*, 2564.
[70] A.S. Zulkasheva, N.R. Bukeikhanov, B.V. Suvorov, *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1986**, *1*, 56.
[71] T. Ono, Y. Nakagawa, Y. Kubokawa, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 343.

[72] P.S.S. Prasad, N. Lingaiak, S.K. Masthan, K.S.R. Rao, P.K. Rao, *Catal. Lett.* **1996**, *36*, 195.

[73] B.V. Suvorov, N.R. Bukejkhanov, A.S. Zulkasheva (Institut Khimicheskikh Nauk An Kazssr, USSR), SU Patent 801494, 1995 [*Chem. Abstr.* **1996**, *125*, 142299c].

[74] B. Lücke, A. Martin, *Chem. Ind. Series, Vol. 62* (Eds.: M.G. Scaros, M.L. Prunier) Marcel Dekker, New York, **1995**, 479.

[75] A. Martin, B. Lücke, *Chem. Ind. Series, Vol. 68* (Ed.: R.E. Malz, Jr.) Marcel Dekker, New York, **1996**, 451.

[76] A. Martin, B. Lücke, H. Seeboth, G. Ladwig, E. Fischer, *React. Kinet. Catal. Lett.* **1989**, *38*, 33.

[77] A. Martin, B. Lücke, G.-U. Wolf, M. Meisel, *Chem.-Ing.-Tech.* **1994**, *66*, 948.

[78] Q. Zheng, C. Huang, Q. Han, C. Xu, G. Chen, Y. Chen, Wuhan Daxue Xuebao, Ziran Kexueban **1998**, *44(2)*, 167 [*Chem. Abstr.* **1998**, *129*, 291385u].

[79] Y. Sasaki, H. Utsumi, A. Morii, K. Morishita (Nitto Kagaku Kogyo K.K.), Ger. Offen. DE 19746883, 1998 [*Chem. Abstr.* **1998**, *128*, 323131z].

[80] A.A. Shapovalov, D.Kh. Sembaev, Izv. Minist. Nauki-Akad. Nauk Resp. Kaz., Ser. Khim., **1996**, *2*, 89.

[81] A. Martin, PhD thesis, Berlin, **1986**.

[82] A. Martin, J. French, H. Seeboth, B. Lücke, E. Fischer, *J. Prakt. Chem.* **1990**, *332*, 551.

[83] H. Yamachika, H. Nakanishi, T. Nakaishi (Sumitomo Chemical Co., Koei Chemical Co.), Japanese Patent 07145521, 1993 [*Chem. Abstr.* **1995**, *123*, 339406a].

[84] A.A. Shapovalov, D.Kh. Sembaev, *Izv. Akad. Nauk, Resp. Kaz., Ser. Khim.* **1992**, *3*, 80.

[85] D.V. Suvorov, L.A. Krichevskii, A.K. Amirkhanova, *Izv. Akad. Nauk Kaz. SSR. Ser. Khim.* **1991**, *1*, 74.

[86] K.V. Narayana, A. Venugopal, K.S.R. Rao, V.V. Rao, S.K. Masthan, P.K. Rao, *Appl. Catal. A* **1997**, *150*, 269.

[87] K.V.R. Chary, G. Kishan, K.V. Narayana, T. Bhaskar, *J. Chem. Res., Synop.* **1998**, *6*, 314.

[88] R. DiCosimo, J.D. Burrington, D.D. Suresh (Stand. Oil Co. (Ohio)), U.S. Patent. 4603207, 1986 [*Chem. Abstr.* **1987**, *106*, 86669s].

[89] K.V. Narayana, S.K. Masthan, A. Venugopal, V.V. Rao, K.S.R. Rao, P.K. Rao, *Stud. Surf. Sci. Catal.* **1998**, *113*, 947.

[90] A.R. Prasad, M. Subrahmanyam, *React. Kinet. Catal. Lett.* **1992**, *47*, 143.

[91] S.K. Masthan, K.V. Narayana, V.V. Rao, P.K. Rao, *Indian J. Chem. Technol.* **1996**, *3*, 313.

[92] R.R. Rao, S.J. Kulkarni, M. Subrahmanyam, A.V.R. Rao, *Zeolites* **1996**, *16*, 254.

[93] S.J. Kulkarni, R.R. Rao, M. Subrahmanyam, S. Farsinavis, P.K. Rao, A.V.R. Rao, *Indian J. Chem.* **1996**, *35A*, 740.

[94] S.J. Kulkarni, R.R. Rao, M. Subrahmanyam, S. Farsinavis, P.K. Rao, A.V.R. Rao, *Stud. Surf. Sci. Catal.* **1995**, *98*, 161.

[95] A. Martin, B. Lücke, H. Seeboth, G. Ladwig, *Appl. Catal.* **1989**, *49*, 205.

[96] Y.K. Lee, Ch.-H. Shin, T.-S. Chang, D.-H. Cho, D.-K. Lee (Korea Research Inst. Of Chemical Technology), European Patent 684074, 1995 [*Chem. Abstr.* **1996**, *124*, 120769h].

[97] N.A. Belova, B.V. Suvorov, *Izv. Akad. Nauk Resp. Kaz., Ser. Khim.* **1992**, *1*, 70.

[98] B.V. Suvorov, L.B. Stambekova (Inst. Khimicheskikh Nauk An Kazssr, USSR), SU Patent 571065, 1995 [*Chem. Abstr.* **1996**, *124*, 343132w].

[99] A.K. Amirkhanova, L.A. Krichevskii, A.D. Kagarlitskii, *Kinet. Katal.* **1994**, *35*, 907.

[100] R.K. Grasselli, J.D. Burrington, R. DiCosimo, M.S. Friedrich, D.D. Suresh, *Stud. Surf. Sci. Catal.* **1988**, *41*, 317.

9.6 Aromatic Ring Hydroxylation

Mario G. Clerici

Most routes to phenolic compounds involve the transformation of a pre-existing functional group, via a sequence of steps, eventually producing the hydroxyl group in the aromatic ring. Few methods have been devised for the direct hydroxylation of aromatic C–H bonds. Even fewer, and generally of recent discovery, are catalytic methods based on clean oxidants, namely, molecular oxygen, hydrogen peroxide, and nitrous oxide. Industrial production, in this regard, is no exception. The use of stoichiometric reagents is still a key step in the production of chemicals such as resorcinol (from *m*-benzenedisulfonic acid), hydroquinone (from *p*-diisopropylbenzene) and even phenol (cumene process). Inherent to this method is the co-production of other chemicals (acetone in the cumene process) and of wastes, often in larger amounts than the phenolic compound itself.

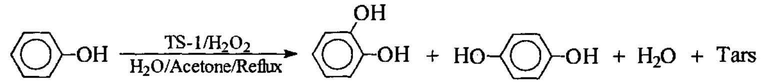
A promising and cleaner route was opened by the discovery of titanium silicalite-1 (TS-1) [1,2]. Its successful application in the hydroxylation of phenol started a surge of studies on related catalysts. Since then, and mostly in recent years, the preparation of several other zeolites, with different transition metals in their lattice and of different structure, has been claimed [3]. Few of them have been tested for the hydroxylation of benzene and substituted benzenes with hydrogen peroxide. Ongoing research on supported metals and metal oxides has continued simultaneously. As a result, knowledge in the field of aromatic hydroxylation has experienced major advances in recent years. For the sake of simplicity, the subject matter will be ordered according to four classes of catalyst: medium-pore titanium zeolites, large-pore titanium zeolites, other transition metal-substituted molecular sieves, and supported metals and mixed oxides.

9.6.1 Medium-pore Titanium Zeolites

Titanium silicalite (TS-1) is a porous crystalline titanium silicalite with the MFI structure, analogous to ZSM-5 [1]. Catalytic centers are isolated Ti sites in a silica framework [4]. Unlike TiO_2/SiO_2 with a similar elemental composition but an amorphous structure, TS-1 is an effective catalyst for the selective oxidation of different functional groups with dilute aqueous hydrogen peroxide [2]. The structural properties of lattice Ti sites, the hydrophobicity, and the size of the tridimensional channel system (ca 0.55 nm) are thought to be critical factors in determining the unusual catalytic properties of TS-1.

9.6.1.1 Hydroxylation of Phenol

The hydroxylation of phenol, developed by Enichem up to the industrial scale, was the event that initially attracted most interest in TS-1 (Eq. 1) [2].



(1)

The yields, relative to both hydrogen peroxide and phenol, were superior to those of the homolytic and acidic catalysts already used in commercial processes (Table 1) [5,6]. TS-1 enabled the more efficient use of a relatively expensive oxidant and minimized the need for phenol separation/recycle steps. The reaction conditions and the results of a number of studies are given below (Table 2) [2,7–10].

Yields and kinetics depend on the type and number of Ti species and the crystal size of the catalyst used. Ti distribution between lattice (selective) and extra-lattice (unselective) sites is, in turn, closely linked to synthesis and characterization procedures, both of which require special thoroughness [4]. Inadequate characterization and, therefore, the impossibility of clear assessment of siting of Ti in the catalyst, is a frequent obstacle to a correct evaluation of the literature, especially early publications. These considerations are of general value, but are central to the hydroxylation of phenol where extra-framework species are a major source of hydrogen peroxide decomposition and radical chain oxidations. The hydroxylation of phenol was indeed proposed by three different groups as an additional test to assess the purity of TS-1 [2, 9, 11]. Van der Pool et al. estimated from Weisz

Table 1. Hydroxylation of phenol with hydrogen peroxide on different catalysts.

Catalyst	*ortho/para*	Phenol conv. (%)	Yields (%, relative to H_2O_2)	Yields (%, relative to phenol)
TS-1	0.5–1.3	30	82	92
Radical (Co^{2+}, Fe^{2+})	2–2.3	9	66	79
Acid (H^+)	1.2–1.5	5	85–90	90

Reprinted from Ref. 2 (Copyright 1990), with kind permission of La Chimica e l'Industria.

Table 2. Hydroxylation of phenolon TS-1. Summary of reaction conditions and results.

Solvent	Water, acetone, methanol
Temperature	80–100 °C
TS-1 crystal size	0.1–0.5 μm
H_2O_2/Phenol molar ratio	0.20–0.30
Phenol conversion	20–30 %
H_2O_2 conversion	100 %
Selectivity on phenol	90–95 %
Selectivity on H_2O_2	80–90 %
Catechol/hydroquinone molar ratio	0.5–1.3

Table 3. Effects of crystal size on the hydroxylation of phenol.

Sample	Average size (µm)	v_0 (mol m^{-3} s^{-1})	Yield (%)
1	0.2	10.2	93
2	0.3	9.00	92
3	5.0	1.07	40
4	10.0	0.46	18

Adapted from Ref. [10] (Copyright 1992), with kind permission from Elsevier Science.

theory, and confirmed experimentally, the reduction of rate and selectivity as a function of crystal dimensions (Table 3) [10]. Declining catalyst efficiency became increasingly evident for sizes larger than 0.3 µm. Further corroboration came from the work of Tuel and Ben Taarit with TS-1 samples with crystal sizes of 0.2–0.4 and 0.5–0.8 µm, respectively. The rate on the former was approximately twice as that on the latter [8].

Yields and product distribution are closely related to the composition of the reaction medium. High selectivity, relative to both phenol and hydrogen peroxide, designates acetone and methanol as the solvents of choice. Catechol/hydroquinone ratio varies in the range 0.5–1.3, well removed from the statistical distribution, owing to the shape selectivity of TS-1. Hydroquinone formation predominates in methanol, whereas the reverse occurs in acetone or acetone–water mixtures. At elevated phenol concentrations, however, even in the presence of methanol the catechol/hydroquinone ratio can approach unity [9]. In acetonitrile and 2-butanone, kinetics and selectivity were both significantly reduced [12]. However the nature of the TS-1 used in this study has been the subject of some disputes [8,13].

The effect of the solvent on product distribution is not well understood, even though some light has been shed on it [8]. Tuel et al. showed that the formation of catechol at the very beginning, even in methanol as solvent, was significantly faster than that of hydroquinone (cat./hydr. = 4). It then decreased rapidly as the reaction proceeded, with inversion in the product selectivity. At the end, hydroquinone was the main product in the reaction mixture (cat./hydr. = 0.5). In acetone, in contrast, catechol was always the main component throughout the course of the reaction. These results, coupled with the observation that acetone dissolved the tarry deposits on the catalysts whereas methanol did not, led to the proposal of preferential formation of catechol at the outer crystal surface, and hydroquinone production mainly inside the micropores. It was suggested that the rapid variation of product selectivity with t.o.s in methanol was the result of the fouling of external sites by insoluble organic deposits.

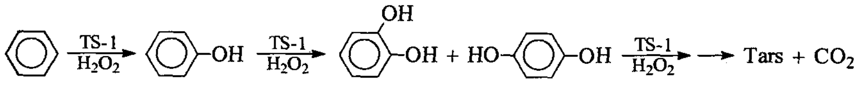
Catalyst concentration and reaction temperature have a major effect on yield [2,8]. In aqueous acetone, tar production was almost halved by increasing the amount of catalyst from 1 to 4 % *w/w*. An analogous effect was achieved by increasing the temperature to ca 100 °C. At higher temperatures, tar production rapidly grew to unacceptable levels [2]. Similar temperature effects were observed in the only study on a fixed-bed reactor [14]. No information is available on deactivation rate and regeneration procedures. High thermal stability makes the regeneration of TS-1 under oxidizing conditions a viable process.

The catalysts used in the aforementioned studies were always titanium silicates of MFI structure prepared by hydrothermal synthesis. Ti can, however, be inserted in the silica lattice by post-synthesis treatment of a dealuminated H-ZSM-5 with $TiCl_4$ vapor [11]. Titanium silicalite-2 (TS-2), with the MEL structure of ZSM-11, was prepared shortly after the first synthesis of TS-1 [15]. Both catalysts have been used for the hydroxylation of phenol. Kraushaar-Czarnetzki and van Hooff showed that no major catalytic differences resulted from the method of synthesis of TS-1 [11]. The slow rate of reaction they observed was probably the result of large crystal size and low titanium content [7]. Tuel and Ben Taarit demonstrated there was no perceptible difference between the catalytic activity of TS-2 and TS-1 [8]. This was predictable, because of the close similarity of the Ti-site structure, chemical composition, and pore dimensions of the two titanium silicates.

9.6.1.2 Hydroxylation of Benzene and Substituted Benzenes

Compared with phenol, benzene and substituted benzenes have received less attention. Their oxidation was occasionally mentioned, with few details, in studies mostly focusing on other aspects of TS-1 chemistry. Only recently have benzene and alkylbenzenes provoked sufficient interest to become the main subject of a few papers.

The hydroxylation of benzene on TS-1 produces phenol as the primary product. Conversion is generally kept low, because introduction of a hydroxyl group activates the aromatic nucleus to further oxidation to hydroquinone, catechol, and eventually to tarry products (Eq. 2). Acetone, methanol, 2-butanone or just water are suitable reaction media [2,16,17]. In aqueous solution, benzoquinone was also found, in appreciable amounts, among the products. Hydroxylation of benzene with a mixture of hydrogen and oxygen, an in situ source of hydrogen peroxide, can be achieved on Pd-containing TS-1 [18]. This is, in principle, an easier route to phenol than that based on the preformed oxidant [19]. In practice, it proved less effective, because of faster catalyst decay (maximum TON 13.5 mol $(mol_{Ti})^{-1}$).



(2)

The oxidation of hydrocarbon compounds in aqueous hydrogen peroxide, without added organic solvent (triphase catalysis: solid TS-1 + two immiscible liquids) has been found to be faster than in organic solution (biphase catalysis: solid TS-1 + one liquid). Similarly, the initial rate of epoxidation of propylene was also the highest when conducted in totally aqueous hydrogen peroxide (M. G. Clerici, unpublished results).

This specific aspect, i. e. the omission of organic solvent from the reaction mixture, has been the subject of recent detailed investigations on the hydroxylation of aromatic compounds [20–23]. According to Kumar et al., the hydroxylation of benzene under triphase conditions was up to 20 times faster than in acetonitrile or acetone (biphase methodology); this resulted in higher benzene conversion and shorter reaction time [21,22]. A probable explanation of the reported superiority of triphase catalysis lies in the organophilic properties of TS-1 and in selective adsorption phenomena.

The hydrophobicity index (*HI*), introduced by Weitkamp and coworkers, is most useful in this context [24]. According to the *HI*, benzene is expected to compete more favorably with water than with acetonitrile, acetone, or methanol for adsorption in TS-1 micropores, thus maximizing under triphase catalysis the probability of interaction with active sites. This interpretation is supported by competitive adsorption experiments which revealed that the amount of adsorbed benzene in the system TS-1–benzene–H_2O was almost ten times greater than for TS-1–benzene–CH_3CN [22].

The selectivities under triphase catalysis were also reported to be very high. For benzene–H_2O_2 molar ratios in the range 1–3, benzene conversion and hydrogen peroxide selectivity varying between 74 and 29 % and between 85 and 90 %, respectively, were reported [22]. The products were phenol (86–95 %), and catechol, hydroquinone, and benzoquinone (14–5 % overall). In acetonitrile solutions, the best selectivity relative to hydrogen peroxide was ca 20 %. An analogous effect of triphase catalysis on kinetics was recently reported for TS-2 also, albeit conversion and TON were markedly lower [25]. No details about the purity and crystal size of catalyst were given.

Electron-withdrawing groups strongly reduce the rate of hydroxylation of the aromatic nuclei, indicating the electrophilic nature of the oxidant species. Accordingly, nil or negligible yields were reported for chlorobenzene, nitrobenzene, benzonitrile, benzaldehyde, and benzoic acid [2]. In a recent patent the hydroxylation of 1,4-dichlorobenzene, based on unusually large amounts of catalyst, was claimed. Yields of 2,5-dichlorophenol were not indicated [26].

Electron-donating groups have a dual effect: rate enhancement owing to electronic factors, as expected for electrophilic aromatic substitution, and a rate decrease as a result of steric and transport restrictions. Even the size of the methyl group in toluene is sufficient to compensate for the increased electron density on the aromatic nucleus, as shown by competition kinetics (benzene/toluene 1:1.3 for TS-1/H_2O_2, 1:10 for trifluoroperacetic acid) [2,27]. The nuclear reactivity trend of alkylbenzenes was in the sequence toluene $>$ *p*-xylene $\geq$ ethylbenzene $>$ *p*-methylethylbenzene, in accordance with increasing molecular size [2,16,28,29]. Ring hydroxylation was suppressed by bulkier substituents, e. g. in 2-propylbenzene [30].

Three kinds of product, phenols, *sec* alcohols and ketones, were formed in different ratios by the attack at aromatic and side-chain C–H bonds (Table 4). No oxidation occurred at tertiary and primary carbons, not even at benzylic positions [2,16,30]. Benzyl chloride was significantly *p*-hydroxylated under triphase conditions, and underwent only side-chain attack in acetonitrile solution (Table 4) [21]. Little or no propensity for ring hydroxylation was shown by acetophenone and benzyl alcohol, respectively. In agreement with the empirical rule that the double bond is the preferred site of attack by TS-1/H_2O_2, epoxidation was the only reac-

Table 4. Oxidation of substituted benzenes.

Compound	Ring hydroxylation		Side-chain oxidation		Ref.
	(Sel. %)	Product	(Sel. %)	Product	
Toluene	100	*o*- (50), *m*- (10), *p*-cresol (40)	0	–	2,16,21,31
Ethylbenzene	30–40	Ethylphenols	60–70	1-Phenylethanol, acetophenone	2,16,30,31
1-Propylbenzene	53	1-Propylphenols	47	1-Phenyl-1-propanol, 1-phenyl-1-propanone	31
2-Propylbenzene	0	–	0	–	2[a]
1-Butylbenzene	n. a.	1-Butylphenols	n. a.	1-Phenyl-1-butanol, 1-phenyl-3-butanol, 1-phenyl-1-butanone, 1-phenyl-3-butanone	30
p-Xylene	100	2,5-Dimethylphenol	0	–	16
p-Methylethylbenzene	31	2-Methyl-5-ethylphenol	69	1-(*p*-Methylphenyl)ethanol, *p*-methylacetophenone	16
Benzyl alcohol	0	–	100	Benzaldehyde, benzoic acid	2,20,21
Benzyl chloride	81	*o*- (13), *p*-Hydroxybenzyl chloride (87)	19	Benzaldehyde, benzoic acid	21[b]
Acetophenone	12	*o*- (33), *p*-Hydroxyacetophenone (67)	88	Phenyl acetate, phenol	21
Styrene	0	–	100	Styrene oxide, β-phenylacetaldeyde	19
α-Methylstyrene	56	Phenols	44	Epoxide	25
1-Phenyl-2-butene	14	Phenols	86	Epoxide	25
4-Phenyl-1-butene	12	Phenols	88	Epoxide	25

[a] 2-Propylbenzene is *o*-hydroxylated at a rate comparable with that for the 1-propyl isomer in Ref. [31].

[b] Triphase catalysis. Benzyl chloride/H_2O_2 molar ratio 3.

tion to occur on styrene and β-methylstyrene. However shape selectivity can alter chemoselectivity in sterically hindered alkenylbenzenes. For example, in *α*-methylstyrene, aromatic hydroxylation was competitive with side-chain epoxidation (Table 4) [25]. Less tendency to phenolic derivatives was shown by 1-phenyl-2-butene and 4-phenyl-1-butene. Anisole was readily hydroxylated to *o*- (30 %) and *p*-methoxyphenol (70 %) [2,23]. *m*-Cresol produced 3,4- (36 %), 2,3- (20 %), and 2,5-dihydroxytoluene (40 %) [20].

9.6.2 Large-pore Titanium Zeolites

It is apparent from the first part of this section that TS-1 and TS-2, owing to pore size restrictions, are compatible with a limited number of molecules. The need to overcome the limits imposed by steric hindrance, an element shared by most fine chemicals, created a strong stimulus for the synthesis of large-pore redox zeolites. Initial studies, aimed at the preparation of [Ti,Al]-Y and [Ti,Al]-β by secondary synthesis, were not particularly rewarding, owing to the lack of conclusive evidence about Ti siting and poor catalytic activity [32]. More promising was the preparation of [Ti,Al]-β and Ti-β by the hydrothermal method, which led to well-defined materials. In sharp contrast with the number of studies dedicated to their use in the oxidation of olefins, however, a short report with few details is all that is available on aromatic compounds, i. e., the hydroxylation of phenol. Catechol and hydroquinone were produced in nearly equimolar amounts on [Ti,Al]-β at 100 °C [33]. The overall yield, 65 % relative to hydrogen peroxide, is typical of a rather modest catalyst. Surprisingly, nothing has been published on the oxidation of bulkier aromatic compounds, for which the pore dimensions make β zeolites potentially better catalysts than TS-1.

More interest was apparently attracted by [Ti,Al]-MOR, which was studied by three different groups [28,29,34,35]. In an early report, Kim et al. employed [Ti,Al]-MOR samples, prepared by both hydrothermal and secondary synthesis, for the hydroxylation of benzene in aqueous/organic and wholly aqueous hydrogen peroxide [34]. Quantitative comparison of the two types of catalyst and with catalysts used in other studies is made arduous by their different purity and unspecified crystal dimensions. On a qualitative basis, the yields were probably low, because reported benzene conversions were at the best 30 % of the maximum attainable value. Worthy of note are the effects of solvent and Al content on catalytic activity. At variance with previous reports about TS-1, the rate of reaction and the conversion were favored in organic solvents, decreasing in the sequence methanol > acetonitrile > water. Increasing the Al content also reduced conversion. Yields were not significantly better in a subsequent study by Belheker et al. on the hydroxylation of benzene and phenol, possibly because of the large crystal size of [Ti,Al]-MOR (10–15 μm) [35].

More informative studies were published by Wu et al. [28,29]. They compared, operating under triphase conditions, the catalytic and transport properties of [Ti,Al]-MOR and TS-1 of similar Ti content and crystal dimensions (1 and 0.2 μm, respectively). The oxidations were performed employing unusually low

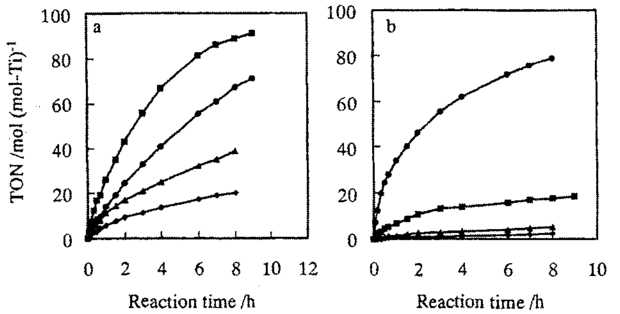


Figure 1. Hydroxylation of benzene and alkylbenzenes on Ti-MOR (a) and TS-1 (b). Benzene (●), toluene (■), ethylbenzene (▲) and cumene (◆). Reprinted with permission from Ref. [29]. Copyright (1998) American Chemical Society.

catalyst concentrations. Absolute yields were consequently low, but TON for TS-1 were comparable with those previously reported, under analogous condition [22]. Phenol was produced from benzene and the corresponding phenolic derivatives from toluene, ethylbenzene, and xylene isomers. Side-chain oxidation was negligible on both catalysts, in partial contrast with previous studies on the oxidation of ethylbenzene on TS-1 (Table 4). Cumene yielded predominantly phenol, acetone and 2-propanol, presumably as a result of decomposition of intermediate cumyl hydroperoxide. The oxidation of *t*-butylbenzene, an excessively bulky molecule even for large-pore mordenite, was negligibly low. The reactivity sequence toluene > benzene > ethylbenzene > cumene was different in part from that on TS-1, benzene > toluene >> ethylbenzene (Figure 1). This reflects the reduced influence of steric factors in the large-pore mordenite. Accordingly, electron donation by the relatively small methyl group prevails over steric hindrance, making the hydroxylation of toluene faster than that of benzene. Similarly, the rate of hydroxylation of xylene isomers increased in the order *para* < *ortho* < *meta*, in contrast with the sterically controlled order, *ortho* < *meta* << *para*, on TS-1 [28]. It is worth mentioning that the least hindered *p*-xylene had the same reactivity on either catalyst. With bulkier substituents than methyl, e. g. ethyl, *i*-propyl, and *t*-butyl, steric effects prevail also on [Ti,Al]-MOR, although to a lesser extent than on TS-1.

The specific activity of Ti sites was confirmed to be highly dependent on aluminum content. It increased ca 40 times as the Si/Al atomic ratio increased from 11 to 200, then leveled off [28]. Similar behavior had previously been reported for [Ti,Al]-β in the epoxidation of olefins [36]. Two possible explanations have been suggested [28,36]. One suggests that increased micropore hydrophobicity, caused by the decrease in the number of aluminum sites, promotes the adsorption of organophilic reagents. The other raises the question of possible modification of the redox properties of Ti sites, induced by the changes in the electronegativity of the zeolite lattice. Titanium content also had an effect on the activity of both [Ti,Al]-MOR and TS-1. The specific activity of Ti sites apparently decreased as their number rose. In reality, the reduced activity was shown to be the result of the formation of bulky Ti-peroxo species, which hindered the diffusion of reagents in the micropores. It was consistent with this interpretation that the effect was more evident on the medium pore TS-1 than on the large pore [Ti,Al]-MOR.

9.6.3 Other Transition Metal-substituted Molecular Sieves

Apart from the few already mentioned, the synthesis of several other transition metal-substituted zeolites has been claimed [42]. The isomorphous substitution of Ti has been reported for zeolitic structures ZSM-48 (Ti-ZSM-48), MTW (TS-12), CIT-1 (Ti-SSZ33), FER (TS-FER), NU-1 (TS-NU-1), UTD-1 (Ti-UTD-1). V-substituted S-1, S-2 have been the subject of several studies, including the oxidation of aromatic compounds [37–39]. Sn, Zr, Fe, Co, Mn, and other metals have been reported in the composition of siliceous and aluminophosphate molecular sieves [39–42]. If little is known about the catalytic properties of the newly discovered Ti-zeolites, a different problem is often faced with other metal containing zeolites, i. e. uncertainty about the heterogeneous nature of the catalysis [43]. These materials in liquid phase oxidations can function as a reservoir of homogeneous catalytic species, by releasing metal ions into solution. The solvent, the products, and the oxidant have an influence on metal leaching, the extent of which is, therefore, variable for a given material, depending on the type of reaction [44]. Apart from instances when the stability of the catalyst was assessed, the participation of homogeneous catalytic pathways cannot be excluded with metals other than Ti. The latter is an exception because, irrespective of whether lattice Ti releases soluble Ti ions or aggregates to form TiO_2 phases, these are poor catalysts with aqueous hydrogen peroxide. In terms of catalytic performance, redox zeolites have a common property: their activity, whatever metal they contain, is generally inferior to that of the Ti related material.

Vanadium silicalite-1 and silicalite-2, and their Ti analogs, were studied by Ramaswamy et al. in the oxidation of different aromatic compounds [37–39]. The vanadium catalysts generally had lower selectivity relative to hydrogen peroxide (more decomposition) and preference for side-chain attack. The products in the oxidation of toluene were benzaldehyde (52 %) and minor amounts of *o*- (20 %) and *p*-cresols (17 %). Ethylbenzene produced *o*- (4 %) and *p*-hydroxyethylbenzene (5 %), 1-phenylethanol (21 %) and acetophenone (62 %). Solvent effects also, as shown by the hydroxylation of phenol, were very different. Yields of catechol and hydroquinone were maximum and minimum in water and acetone, respectively, and there was no reaction in methanol [37]. [V,Al]-β catalyzed the hydroxylation of phenol with hydrogen peroxide efficiency (65–74 %) comparable with that of [Ti,Al]-β [45]. Large-pore V-NCL-1 was suitable for the oxidation of bulky molecules [46]. *m*-Xylene and 1,3,5-trimethylbenzene were mainly oxidized at one methyl group to the corresponding alcohols and aldehydes (selectivity to ring hydroxylation $<$ 13 %). On *p*- and *o*-xylene and on 1,2,4-trimethylbenzene only benzylic oxidation was observed (alcohol/aldehyde ca 1). Naphthalene afforded a mixture of several products, among which 1- and 2-naphthol (6 %), 1,4-naphthoquinone (16 %), and phthalic anhydride (50 %) were identified. Sn-silicalite-1 was tested in the hydroxylation of ethylbenzene and phenol. The products of the former were 1-phenylethanol and acetophenone (78 %), with minor amounts (22 %) of *o*- and *p*-hydroxyethylbenzene [39]. The rate of hydroxylation of phenol was low, but with hydrogen peroxide efficiency up to 80 % (*ortho*/*para* ratio 1.6). In common with V-silicalites, yields were the highest in water and the lowest in acetone and methanol [40]. Sn-S-1 probably acted as a heterogeneous catalyst, because only trace amounts (10 ppm) of dissolved tin were found in solution. Iron-, cobalt- and manganese-substituted aluminophosphates with different structures were studied in the hydroxylation of phenol [41]. The yields of catechol and hydroquinone (1:1 ratio) were typically low, as inferred from reported conversions (< 1/3 of maximum attainable).

The limited accessibility of active sites in micropores was a compelling incentive for the synthesis of redox catalysts in the mesoporous range of porosity. Several materials containing different transition metals and with pore size up to 40 Å were prepared, but only occasionally tested for the oxidation of aromatic compounds. 2,6-di-*tert*-Butylphenol (2,6-DTBP) was usually selected to test their capacity to catalyze the oxidation of sterically hindered molecules. Catalytic tests were far from systematic, functioning largely as additional characterization tools. Possibly partly for this reason, metal leaching was an issue generally ignored, although previous remarks apply in particular to this class of catalyst [43,44]. Framework stability also can be an issue, as shown by the irreversible degradation of Ti-MCM-41 upon exposure to water vapor for 1–3 days at room temperature [47]. Despite their limitations, however, the few studies available provide some useful information on the catalytic potential of mesoporous materials.

Ti-substituted MCM-41 and HMS silicas have been used to catalyze the oxidation of benzene and 2,6-DTBP with hydrogen peroxide [48,49]. Phenol selectivity was reported to approach 100 % at conversions below 10 %. Better conversion (55 %) and selectivity (ca 90 %) was obtained in the oxidation of 2,6-DTBP to the corresponding *p*-quinone. It is worth mentioning that, in a subsequent study on the epoxidation of cyclohexene, Ti-MCM-41 proved unstable toward leaching by H_2O_2 [50]. Similarly high was the selectivity on Zr-HMS (86 %) [51]. Incidentally, no leaching of zirconium into the liquid phase could be detected. Sn-MCM-41 catalyzed the hydroxylation of 1-naphthol to give 1,4-naphthoquinone (83 %), 1,4- (12 %) and 1,2-dihydroxynaphthalene (5 %), with 85 % selectivity relative to hydrogen peroxide [52]. Lower selectivity (<65 %) was obtained in the hydroxylation of phenol (*ortho*/*para* 3.3).

The catalytic properties of V-HMS were investigated in detail by Reddy et al. [44]. Naphthalene and 2-methylnaphthalene were oxidized at the 1,4-positions to afford the related 1,4-naphthoquinones. Under analogous conditions, 2,6-DTBP (83 % conv.) led to the corresponding *p*-quinone (87 %) and *p*-diphenoquinone (4 %). The relative role of homogeneous and heterogeneous pathways in catalysis remained uncertain, because different amounts of V^{5+} ions were released into the liquid phase under different conditions.

It is quite evident that if there is no major restriction to the application of mesoporous catalysts as a result of pore accessibility, more serious limitations might arise as a result of their relatively low activity with aqueous hydrogen peroxide. It has been shown that the specific activity of Ti sites in the epoxidation of olefins decreased in the order TS-1 > [Ti,Al]-β > Ti-MCM-41 [53]. An analogous, qualitative, trend seems to exist for the hydroxylation of benzene and phenol: TS-1 > [Ti,Al]-β, [Ti,Al]-MOR > Ti-MCM-41, Ti-HMS. Among several reasons, two can be suggested. The first is the reduction in the specific activity of Ti sites in parallel with progressively different structural features. The second is the gradual change of adsorption properties, up to their reversal in the hydrophilic mesoporous silicas. It has been remarked that on a hydrophilic surface, a layer of adsorbed water molecules would screen Ti sites from approaching organophilic reagents, unless anhydrous conditions were observed [16]. This drawback can, in principle, be avoided by using *t*-butyl hydroperoxide in aprotic solvents or by grafting organophilic groups on to surface silanols [54]. Both solutions, shown to be viable routes in the epoxidation of olefins, have not yet been applied to the hydroxylation of aromatics.

A special case is the hydroxylation of benzene with nitrous oxide as oxidant, for which commercialization has been announced [55]. The reaction occurs on Fe-silicalite-1, in the gas phase, at temperatures close to 400 °C, producing molecular nitrogen as by-product. Other zeolites and supported metals and metal oxides are less satisfactory catalysts. Toluene, chlorobenzene, and fluorobenzene are similarly hydroxylated, yielding all three possible isomers. Phenol produces catechol and hydroquinone.

9.6.4 Supported Metals and Mixed Oxides

It has been pointed out that metal substituted MCM-41 and HMS silicas should be regarded as mesoporous organized mixed oxides, with physical and chemical properties comparable with those of amorphous mixed oxides [51]. Few mixed oxides have been prepared by sol–gel routes or grafting techniques; their activity is quite similar to that of the MCM-41 and HMS catalysts. Micro-mesoporous titanosilicates obtained by the sol–gel route have been reported to catalyze the hydroxylation of benzene and phenol and the oxidation of toluene, mostly on the methyl group, by aqueous hydrogen peroxide [56]. Ti and Zr grafted on to silica by reaction of surface silanols with TiF_3 and $Zr(C_5H_9)_4$, respectively, were active in the hydroxylation of phenol with hydrogen peroxide [57,58]. The high yields reported for Ti/SiO_2 were attributed to extreme metal dispersion and modification of the silica surface by the fluoride ions.

Supported noble metals catalyze the hydroxylation of benzene to phenol, under mild conditions, with H_2/O_2 and CO/O_2 mixtures as oxidants [59,60]. Yields of practical value were obtained on noble metals supported on silica modified by various metal oxides. The highest productivity was shown by $Pt/V_2O_5/SiO_2$, at 45 °C [60]. Under analogous conditions, cresols with minor amounts of benzaldehyde and benzyl alcohol were produced by toluene, α- and β-naphthols by naphthalene, hydroxybiphenyls by biphenyl.

9.6.5 Conclusions

High activity and selectivity, mildness, and cleanliness are typical aspects of catalysis by redox molecular sieves. Their potential, however, in the hydroxylation of large aromatic molecules is still undefined. The latest studies still concentrate on simple aromatic compounds, chiefly phenol, benzene, and their alkylated derivatives, with limited relevance to fine chemicals, and largely involve the use of microporous zeolites. Few studies relate to large-pore and mesoporous catalysts, potentially valuable in the oxidation of complex molecules. Reasons might possibly be the relative youth of redox molecular sieves, mostly at the stage of material optimization, and the lower activity of mesoporous catalysts. The latter is a major problem, as already shown for Ti-molecular sieves, for which only partial solutions have been proposed.

The catalytic activity of Ti-MCM-41 was increased by use of grafting techniques for introducing metal sites to preformed MCM-41, in a second stage of the preparation [61]. The catalysts' hydrophilic and hydrophobic properties can be modulated by silylating surface silanols with organosilanes, to favor the adsorption of organophilic reagents [54]. A third solution, practical for relatively small productions, consists in the use of large amounts of catalyst relative to the substrate [26].

A final comment is necessary on the stability of redox molecular sieves, because in this chapter emphasis was placed on studies in which the heterogeneity of catalysis was most plausible (but in many cases not rigorously proven). Yet, catalysts for which metal leaching was once detected should be not automatically excluded from further consideration, because the extent of metal solubilization depends, inter alia, on the kind of reaction performed [44].

References

[1] M. Taramasso, G. Perego and B. Notari, *U.S. Patent* 4410501 (1983).
[2] U. Romano, A. Esposito, F. Maspero, C. Neri and M.G. Clerici, *Chim. Ind. (Milan)*, **72**, 610 (1990).
[3] G. Bellussi and M.S. Rigutto, in *Advanced Zeolite Science and Applications* (J.C. Jansen, M. Stöcker and H.G. Karge, Eds.), Studies in Surface Science and Catalysis, Vol. 85, p. 177. Elsevier, Amsterdam, 1994.
[4] R. Millini, G. Perego and G. Bellussi, in *Molecular Sieves – Science and Technology* (H.G. Karge and J. Weitkamp, Eds.), Vol. 1, p. 187. Springer Verlag, Heidelberg, 1998.
[5] J. Varagnat, *Ind. Eng. Chem., Prod. Res. Dev.*, **15**, 212 (1976).
[6] P. Maggioni and F. Minisci, *Chim. Ind. (Milan)*, **59**, 239 (1977).
[7] A. Tuel, S. Moussa-Khouzami, Y. Ben Taarit and C. Naccache, *J. Mol. Catal.*, **68**, 45 (1991).
[8] A. Tuel and Y. Ben Taarit, *Appl. Catal. A*, **102**, 69 (1993).
[9] J.A. Martens, Ph. Buskens, P.A. Jacobs, A. van der Pol, J.H.C. van Hooff, C. Ferrini, H.W. Kouwenhoven, P.J. Kooyman and H. van Bekkum, *Appl. Catal. A*, **99**, 71 (1993).
[10] A.J.H.P. van der Pol, A.J. Verduyn and J.H.C. van Hooff, *Appl. Catal. A*, **92**, 113 (1992).
[11] B. Kraushaar-Czarnetzki and J.H.C. van Hooff, *Catal. Lett.*, **2**, 43 (1989).
[12] A. Thangaraj, R. Kumar, P. Ratnasamy, *J. Catal.*, **131**, 294 (1991).
[13] R. Millini, E. Previde Massara, G. Perego and G. Bellussi, *J. Catal.*, **137**, 497 (1992).
[14] B. Tendulkar, S.S. Tambe, I. Chandra, P.V. Rao, R.V. Naik and B.D. Kulkarni, *Ind. Eng. Chem. Res.*, **37**, 2091 (1998).

[15] G. Bellussi, A. Carati, M.G. Clerici, A. Esposito, R. Millini and F. Buonomo, *Be. Pat. 1001038* (1989).

[16] C.B. Khouw, C.B. Dartt, J.A. Labinger and M.E. Davis, *J. Catal.*, **149**, 195 (1994).

[17] A. Thangaray, R. Kumar and P Ratnasamy, *Appl. Catal.*, **57**, L1 (1990).

[18] T. Tatsumi, K. Yuasa and H. Tominaga, *J. Chem. Soc., Chem. Commun.*, 1446 (1992).

[19] M.G. Clerici and P. Ingallina, *Catal. Today*, **41**, 351 (1998).

[20] A. Bhaumik and R. Kumar, *J. Chem. Soc., Chem. Commun.*, 349 (1995).

[21] R. Kumar and A. Bhaumik, *Microporous Mesoporous Mater.*, **21**, 497 (1998).

[22] A. Bhaumik, P. Mukherjiee and R. Kumar, *J. Catal.*, **178**, 101 (1998).

[23] A. Bhaumik, P. Mukherjiee and R. Kumar, *Catal. Today*, **49**, 185 (1999).

[24] J. Weitkamp, S. Ernst, E. Roland, G.F. Thiele, in *Progress in Zeolites and Microporous Materials* (H. Chon, S.-Ihm, Y.S. Uh, Eds.), Studies in Surface Science and Catalysis, Vol. 105, p. 763. Elsevier, Amsterdam, 1997.

[25] T. Tatsumi, M. Yako, K. Yanagisawa and K. Asano, *Chem. Ind. (Dekker)*, **62**, 341 (1998).

[26] C.A. Henrick, *U.S. Pat. 5648562* (1997).

[27] R.O.C. Norman and R. Taylor, in *Electrophilic Substitution in Benzenoid Compounds* (C.E. Eaborn, Ed.). Elsevier, Amsterdam, 1965.

[28] P. Wu, T. Komatsu and T. Yashima, in *Progress in Zeolites and Microporous Materials* (H. Chon, S.-Ihm, Y.S. Uh, Eds.), Studies in Surface Science and Catalysis, Vol. 105, p. 663. Elsevier, Amsterdam, 1997.

[29] P. Wu, T. Komatsu and T. Yashima, *J. Phys. Chem. B*, **102**, 9297 (1998).

[30] M.G. Clerici, *Appl. Catal.*, **68**, 249 (1991).

[31] G.N. Vayssilov, Z. Popova, S. Bratinova and A. Tuel, in *3rd World Congress on Oxidation Catalysis* (R.K. Grasselli, S.T. Oyama, A.M. Gaffney and J.E. Lyons, Eds), Studies in Surface Science and Catalysis, Vol. 110, p. 909. Elsevier, Amsterdam, 1997.

[32] C. Ferrini and H.W. Kouwenhoven, in *New Developments in Selective Oxidations* (G. Centi and F. Trifirò, Eds.), Studies in Surface Science and Catalysis, Vol. 55, p. 53. Elsevier, Amsterdam, 1990.

[33] M.A. Camblor, M. Constantini, A. Corma, P. Esteve, L. Gilbert, A. Martinez and S. Valencia, *Appl. Catal. A*, **133**, L185 (1995).

[34] G.J. Kim, B.R. Cho and J.H. Kim, *Catal. Lett.*, **22**, 259 (1993).

[35] A.A. Bhelhekar, T.K. Das, K. Chaudhari, S.G. Hegde and A.J. Chandwadkar, in *Recent Advances in Basic and Applied Catalysis* (T.S.R. Prasada Rao and G. Murali Dhar, Eds.), Studies in Surface Science and Catalysis, Vol. 113, p. 195. Elsevier, Amsterdam, 1998.

[36] A. Corma, M.A. Camblor, P. Esteve, A. Martinez and J. Perez-Pariente, *J. Catal.*, **145**, 151 (1994).

[37] P.R. Hari Prasad Rao and A.V. Ramaswamy, *Appl. Catal. A*, **93**, 123 (1993).

[38] A.V. Ramaswamy, S. Sivasanker and P. Ratnasamy, *Microporous Mesoporous Mater.*, **2**, 451 (1994).

[39] N.K. Mal and A.V. Ramaswamy, *Appl. Catal. A*, **143**, 75 (1996).

[40] N.K. Mal and A.V. Ramaswamy, *J. Mol. Catal. A*, **105**, 149 (1996).

[41] P.-S.E. Dai, R.H. Petty, C.W. Ingram, R. Szostak, *Appl. Catal. A*, **143**, 101 (1996).

[42] R. Szostak, *Molecular Sieves, 2nd Ed.*, Black Academic & Professional, London, 1998.

[43] R.A. Sheldon, M. Wallau, I.W.C.E. Arends and U. Schuchardt, *Acc. Chem. Res.*, **31**, 485 (1998).

[44] J.S. Reddy, P. Liu and A. Sayari, *Appl. Catal. A*, **148**, 7 (1996).

[45] H. Du, M. Fang, Y. Liu, S. Qiu and W. Pang, *Zeolites*, **18**, 334 (1997).

[46] K.R. Reddy, A.V. Ramaswamy and P. Ratnasamy, *J. Catal.*, **143**, 275 (1993).

[47] K.A. Koyano and T. Tatsumi, *Microporous Mater.*, **10**, 259 (1997).

[48] W. Zhang, J. Wang, P.T. Tanev and T.J. Pinnavaia, *Chem. Commun.*, 979 (1996).

[49] W. Zhang, M. Froeba, J. Wang, P.T. Tanev, J. Wong and T.J. Pinnavaia, *J. Am. Chem. Soc.*, **118**, 9164 (1996).

[50] L.Y. Chen, G.K. Chuah and S. Jaenicke, *Catal. Lett.*, **50**, 107 (1998).

[51] A. Tuel, *Microporous Mesoporous Mater.*, **27**, 151 (1999).

[52] T. K. Das, K. Chaudhari, A. J. Chandwadkar and S. Sivasanker, *J. Chem. Soc., Chem. Commun.*, 2495 (1995).
[53] J. C. van der Waal, P. Lin, M. S. Rigutto, H. van Bekkum, in *Progress in Zeolite and Microporous Materials* (H. Chon, S.-Ihm, Y. S. Uh, Eds.), Studies in Surface Science and Catalysis, Vol. 105, p. 763. Elsevier, Amsterdam, 1997.
[54] A. Corma, M. Domine, J. A. Gaona, J. L. Jorda, M. T. Navarro, F. Rey, J. Perez-Pariente, J. Tsuji, B. McCulloch and L. Nemeth, *Chem. Commun.*, 2211 (1998).
[55] G. I. Panov, A. S. Kharitonov and V. I. Sobolev, *Appl. Catal. A*, **98**, 1 (1993).
[56] A. Keshavaraja, A. Ramaswamy, H. S. Soni, A. V. Ramaswamy, and P. Ratnasamy, *J. Catal.*, **157**, 501 (1995).
[57] P. J. Kooyman, K. C. Jansen, and H. van Bekkum., in *Proceedings from the 9th International Zeolite Conference* (R. von Ballmoos, J. B. Higgins, M. M. J. Treacy, Eds.), p. 505. Butterworth-Heinemann, Boston, 1993.
[58] F. Quignard, A. Choplin and R. Teissier, *J. Mol. Catal. A*, **120**, L27 (1997).
[59] T. Jintoku, H. Taniguchi and Y. Fujiwara, *Chem. Lett.* 1865 (1987).
[60] T. Miyake, M. Hamada, Y. Sasaki, M. Oguri, *Appl. Catal. A*, **131**, 33 (1995).
[61] T. Maschmeyer, F. Rey, G. Sankar and J. M. Thomas, *Nature*, **378**, 159 (1995).

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

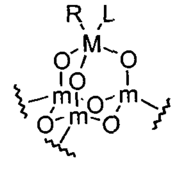
10 Carbon–Carbon Bond Formation

10.1 Carbon–Carbon Bond Formation via Surface Organometallic Chemistry (SOMC)

C. Copéret, J. Thivolle-Cazat, J.-M. Basset

10.1.1 Introduction

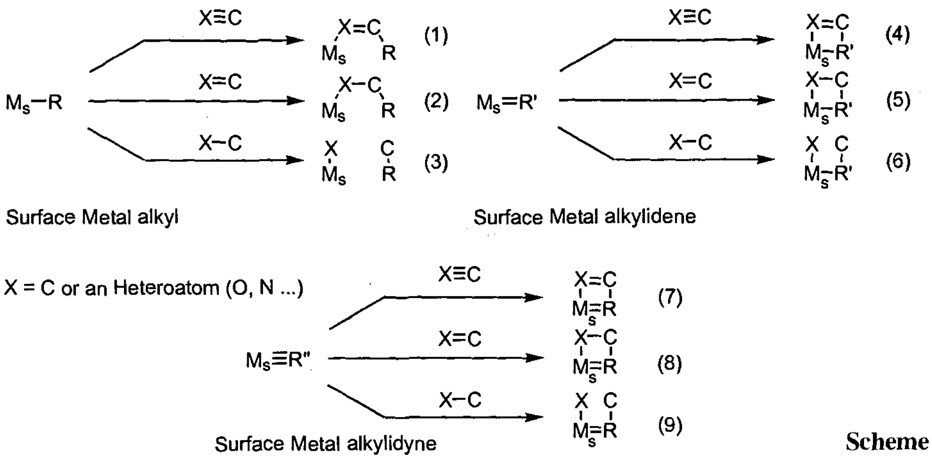
Heterogeneous catalysts are widely used in industrial applications; they are often easily prepared at low cost and can be conveniently separated from the reaction medium. It is, however, difficult to define and control the active site and then to determine the elementary steps of a catalytic reaction. In contrast, homogeneous catalysis has been based on the rules of molecular organometallic chemistry, which affords better understanding of the active species and elementary steps of a process. Thus there is a need to create a new type of heterogeneous catalyst to which the concepts and the rules of molecular organometallic chemistry are applicable. This has been achieved in surface organometallic chemistry (SOMC) just by considering the support as a solid ligand; it has led to the preparation of well-defined coordination spheres around a metal anchored to a surface, but requires throughout a rigorous control of the grafting of the molecular complexes and of their subsequent treatments. By this approach it has been possible to build coordination spheres that are similar to, but not necessarily identical with those of the homogenous complexes. The strategy is radically different from other approaches where the metal is bound to a ligand previously grafted on to the surface (supported homogenous catalysis), which has an inherent problem: the loss of the metal center by leaching (loss of activity). By surface organometallic chemistry it is also possible to realize unprecedented coordination spheres associated with unusual catalytic activity (compared with both homogenous and heterogeneous systems). For instance, $(\equiv Si{-}O)_3Zr{-}H$, formally an eight-electron complex, readily catalyzes the hydrogenolysis of hydrocarbons and polyolefins [1], and $(\equiv Si{-}O)_2Ta{-}H$ catalyzes alkane metathesis (vide infra) [2]. This approach also provides single-site catalysts that are readily characterized by IR spectroscopy, CP MAS NMR, EXAFS and their chemical reactivity [3].



M = grafted metal
(transition metals, lanthanides, actinides)
R = organic ligand
L = other ligands
m = main group element or M type

Scheme 1.

The potential of this concept has recently emerged, and the formation of carbon–carbon bonds via surface organometallic complexes has been investigated. This can be achieved by addition of a carbon–metal bond to carbon–carbon or a carbon–heteroatom bond systems (or insertion of the C–X bond systems into the carbon–metal bond) and can be referred to as a carbometallation (Scheme 2). If metallacycles are excluded, three different types of organometallic complexes contain carbon–metal bonds: metalalkyls, -alkylidenes, and -alkylidynes. For example, all three types can in principle interact with carbon–carbon bonds (X = C) to generate new structures; most of these patterns are readily encountered in organometallic reactions and correspond to important elementary steps of catalytic cycles. Although reactions of alkynes with organometallic compounds have not been reported in SOMC, there are numerous reports on reactions involving alkenes; more recently the first example of a carbon–carbon bond-forming reaction using alkanes has been disclosed. The insertion of alkenes into a metal–alkyl bond (Scheme 2, Eq. 2) is the key step of the Ziegler–Natta polymerization, and the reaction of an alkene with a metalalkylidene (Scheme 2, Eq. 5) is that of alkene metathesis. A closely related mechanism has been proposed for alkane metathesis in which an alkane interacts directly with a metal–alkyl bond (Scheme 2, Eq. 3). This review will mainly focus on alkene and alkane metathesis [4].

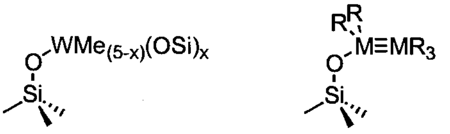


Scheme 2.

10.1.2 Alkene Metathesis and Related Reactions

Alkene metathesis is one of the most important reactions for carbon–carbon bond formation in organic synthesis. The key step of the mechanism of this reaction involves the reversible addition of an alkene to an alkylidene to form a metallacyclobutane (the Chauvin mechanism) [5]. This was a matter of debate for more than 10 years since the first catalytic transformation of olefins into their metathesis products was discovered using metal oxides supported on oxides as catalysts (MoO_3/Al_2O_3 or Re_2O_7/Al_2O_3), which did not contain an alkylidene moiety in their original coordination sphere. Organometallic chemistry was the key to understanding this mechanism, but also brought to homogeneous catalysis new complexes with very high activity and tolerance of functional groups [6]. Some key features of the catalyst have emerged in these studies: (i) the electrophilicity of the metal center (d^0 12–16 electron complexes in combination with electron-withdrawing ligands such as aryloxys, fluorinated alkoxys, and imidos), (ii) the stereoselectivity and the stability of the reaction, plus the functional group compatibility of the catalyst (group VII–VIII better than group IV–VI metal complexes). This has enabled SOMC to emerge as a potential route to the design and synthesis of a new generation of heterogeneous catalysts for olefin metathesis.

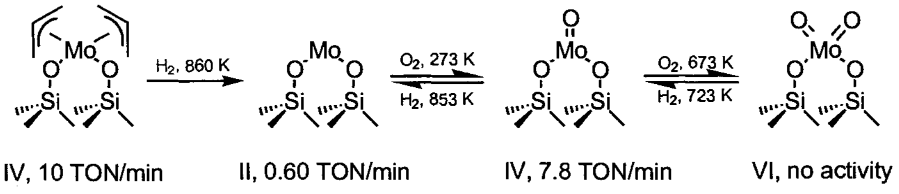
The first reports of surface organometallic compounds that catalyze alkene metathesis appeared in the early 70's [7]. Alkyl complexes of Mo and W had high activity (0.1–5 ton. min^{-1} at room temperature), but little was known about their structure because the starting complexes were either highly unstable (WMe_6) or dimeric (M_2R_6, M = Mo and W; for a proposed pictorial representation see Scheme 3).



OSi = Surface Siloxy

Scheme 3.

The grafting of $Mo(allyl)_4$ or other allyl compounds (Nb, W) on silica and other oxides has also been investigated, but the mechanism of grafting remains unclear [8]. These catalysts had some activity in olefin metathesis, but several activation steps under H_2 and O_2 at high temperature were usually needed to obtain the best activity. Iwasawa et al. [8] were able to establish a structure–activity relationship showing that Mo(IV) was the most active (Scheme 4; activity for propene metathesis at 90 °C in ton. min^{-1}). These steps, however, dramatically modified the coordination sphere of the metal, depending on the thermal treatment applied.



Scheme 4.

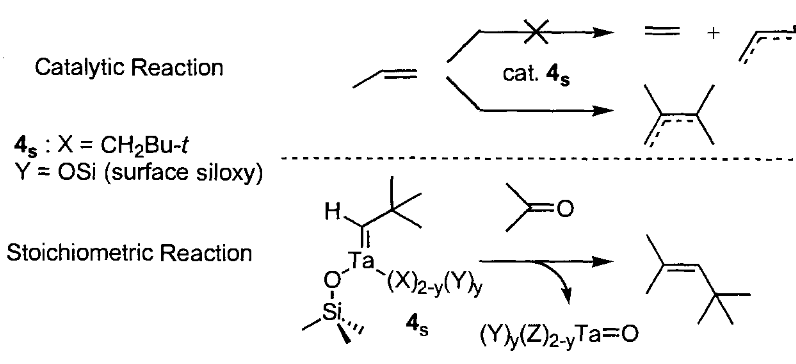
In 1989 Weiss et al. prepared the first well-defined surface organometallic compounds for alkene metathesis by grafting several tungsten(VI) alkylidyne complexes on to silica [9]. The reaction of **1**, **2**, and **3** with surface silanols gave the corresponding surface alkylidenes $\mathbf{1}_s$, $\mathbf{2}_s$, and $\mathbf{3}_s$ (Scheme 5). The activity of these surface organometallic complexes in the metathesis of 1-octene at 69 °C was 260, 60, and 30 ton. min^{-1}, respectively, activity which decreased with increasing electron-donating capacity of the surrounding ligands (Np $<$ *t*-BuO $<$ Cl), in accord with a decrease in the electrophilicity of the metal center. Another aspect of SOMC is the tuning of the catalyst by changing the support, which might, after all, be regarded as a ligand. For example, the activity of grafted **1** for the metathesis of *cis* 2-pentene at room temperature on SiO_2 ($\mathbf{1}_s$) and Nb_2O_5 was 60 and 370 ton. min^{-1} respectively; an increase which can be correlated with increasing acidity of the support [10]. This investigation stemmed from previous reports, which showed that supported $MeReO_3$ on Nb_2O_5 had an optimum activity in olefin metathesis corresponding to the maximum number of Lewis acidic sites [11,12]. Interestingly, if ^{13}C-labeled $MeReO_3$ was used, no ^{13}C-label was incorporated into the metathesis products, showing that the methyl does not seem to generate a carbene for alkene metathesis. Although the structure of $MeReO_3/SiO_2–Al_2O_3$ surface complex remains unknown, it has high activity and functional group compatibility compared with supported group VI metals or more classical heterogeneous catalysts [12]. For instance, metathesis of ethyl 1-undecanoate, allyltrimethylsilane, allyl bromide, and methyl oleate occur readily whereas a sluggish reaction was obtained with the corresponding heterogeneous catalysts prepared via NH_4ReO_4 and $NH_4ReO_4/SnMe_4$ [11].

Organometallic Precursors
1 (X = CH_2Bu-*t*), **2** (X = OBu-*t*), **3** (X = Cl)

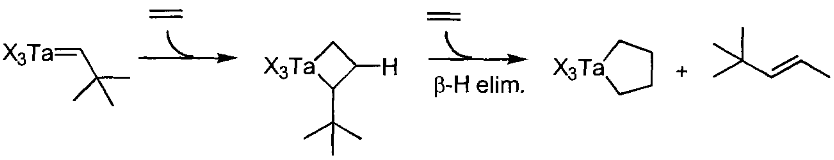
The Corresponding Organometallic
Surface Complexes : $\mathbf{1}_s$, $\mathbf{2}_s$, $\mathbf{3}_s$

Scheme 5.

A new Ta surface carbene, $\mathbf{4}_s$, which has been fully characterized [13], is not active in olefin metathesis but catalyzed olefin dimerization [14]. This is not totally surprising, since the molecular complex Ta(=CHBu-*t*)(CH_2Bu-*t*)$_3$ **4** behaved similarly, probably because of the intrinsic tendency of Ta to favor *β*-H elimination and elimination of the ligand, thus enabling the formation of a metallacyclopentane by oxidative coupling of two olefins (Scheme 6, Eq. 10) [15]. A key step in the characterization of $\mathbf{4}_s$ was, moreover, the pseudo-Wittig reaction, which also involves the formation of a carbon–carbon bond, and confirmed the presence of a surface alkylidene complex (Scheme 6). This further shows that concepts of organometallic chemistry apply to SOMC and once again enables better understanding of these types of heterogeneous catalysts.

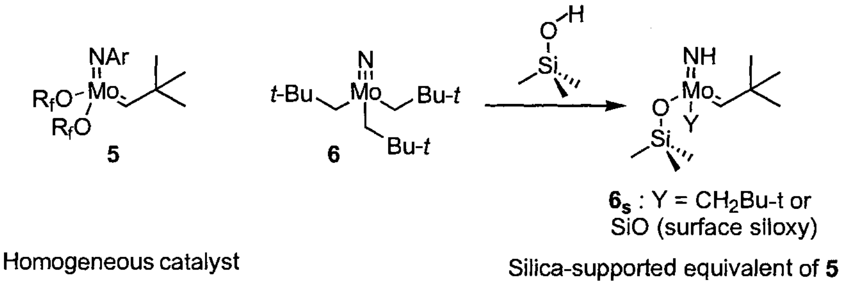


Scheme 6.



(10)

Schrock et al. have also developed a highly active catalyst based on Mo, **5** [15]. Heterogenizing this catalyst was of prime interest, and a SOMC approach was investigated which led to the synthesis of its surface analog $\mathbf{6}_s$. This was achieved by grafting the nitrido complex **6** on to silica, by addition of ≡SiO–H on to the nitrido moiety, giving the imidoalkylidene surface complex $\mathbf{6}_s$ (Scheme 7) [16]. Despite structural features similar to those of **5**, the complex $\mathbf{6}_s$ (R = H) was not very active (< 0.1 ton. min^{-1} for *trans* 2-pentene at room temperature). This was probably because of the electron-rich nature of this imido ligand, which reduced the electrophilicity of the metal center. This subject is still at an early stage of development and new ways of generating highly active well-defined surface organometallic compounds for olefin metathesis are currently investigated by us and others [17].



Scheme 7.

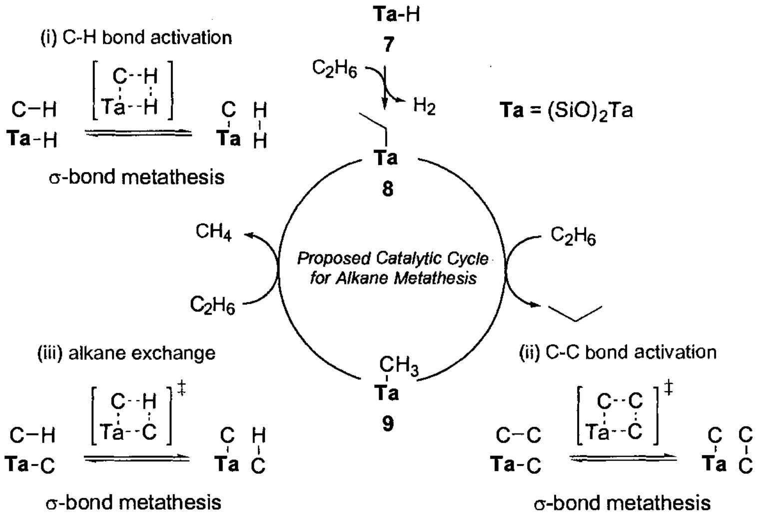
10.1.3 Alkane Metathesis

SOMC has also enabled the development of new kinds of catalyst–hydrides such as $(\equiv SiO)_2Ta–H$, **7**, which led to the discovery of a new reaction: the catalytic transformation of an alkane into its lower and higher homologs (Eq. 11) [2].

$$2C_nH_{2n+2} \xrightarrow{\text{Ta-H (7)}} \sum C_{n-i}H_{2(n-i)+2} + \sum C_{n+i}H_{2(n+i)+2} \qquad (11)$$

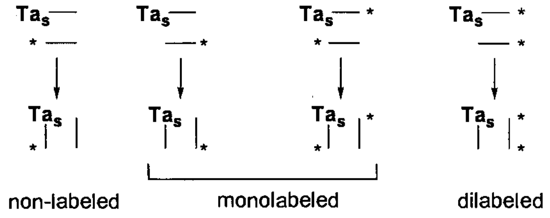
in which i=1, 2, ... n-1, but with i=1 generally favoured.

This discovery arose from a long investigation on early transition metal hydrides and their potential in alkane activation. [18] During attempts to find better systems for alkane activation the chemistry of group V metals, and more specifically tantalum, was investigated; this led to the synthesis of $(\equiv SiO)_xTa(=CHBu\text{-}t)(Np)_{3-x}$ and **7** [13,19]. These surface complexes were fully characterized by their chemical reactivity, IR spectroscopy, and EXAFS. This hydride readily activates cycloalkanes at room temperature into a surface cycloalkyl complexes $(\equiv SiO)_2Ta–C_nH_{2n-1}$. When ethane was brought into contact with **7** at 150 °C, however, methane and propane were produced catalytically as a roughly one-to-one mixture. This reaction must involve cleavage and formation of carbon–carbon bonds; the mechanism proposed explained the distribution of the products (Scheme 8). After activation of the alkane, for example ethane, and formation of a surface ethyl species, the latter reacts with another molecule of ethane via a four-centered transition state, which leads to the formation of propane and a Ta–Me species, **9**. This surface species can then give $(\equiv SiO)_2Ta–Et$, **8**, via an exchange reaction, which involves a related σ-bond metathesis mechanism.



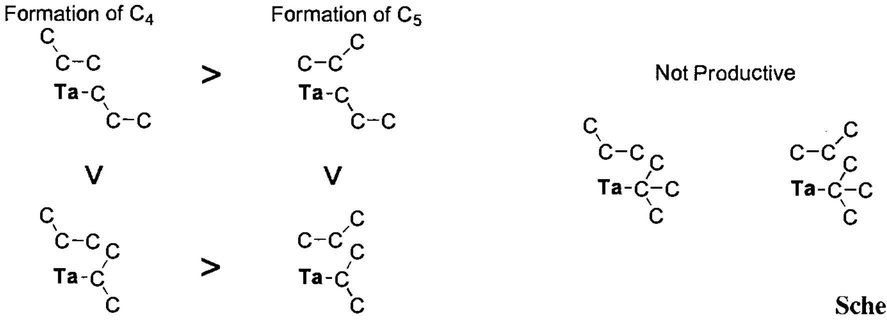
Scheme 8.

On the basis of knowledge accumulated in olefin metathesis, a degenerate process was expected in which the Ta–Me surface species could also interact with ethane to form another molecule of ethane. This reaction was deconvoluted by the use of ^{13}C-monolabeled ethane. Upon contact of this reagent with **7** rapid evolution of non-labeled and ^{13}C-dilabeled ethane was detected by GC–MS until a statistical distribution was reached (1:2:1 distribution of non-, mono- and dilabeled ^{13}C-ethane, Scheme 9). This reaction occurs ca five time faster than the productive metathesis.



Scheme 9.

Noteworthy also is the selectivity for higher alkanes. For example the metathesis of propane gives mainly butanes rather than pentanes, and butane rather than isobutane. This is in agreement with stereoelectronic factors that favor the transfer of one carbon on to, preferentially, primary alkyl surface species, leaving tertiary alkyl species unreactive (Scheme 10). The alkane selectivity also depends on the structure of the starting alkane (Figure 1). Overall, this reaction shows the potential of surface organometallic chemistry, and new, unprecedented reactions will be probably discovered in the near future.



Scheme 10.

10.1.4 Conclusion

In the two last decades, surface organometallic chemistry has emerged as a powerful tool for the generation of highly active heterogeneous catalysts that can be readily tuned by ligand effects (surface + conventional ligands). This opens the field to a better understanding of surface chemistry and to a new generation of heterogeneous catalysts.

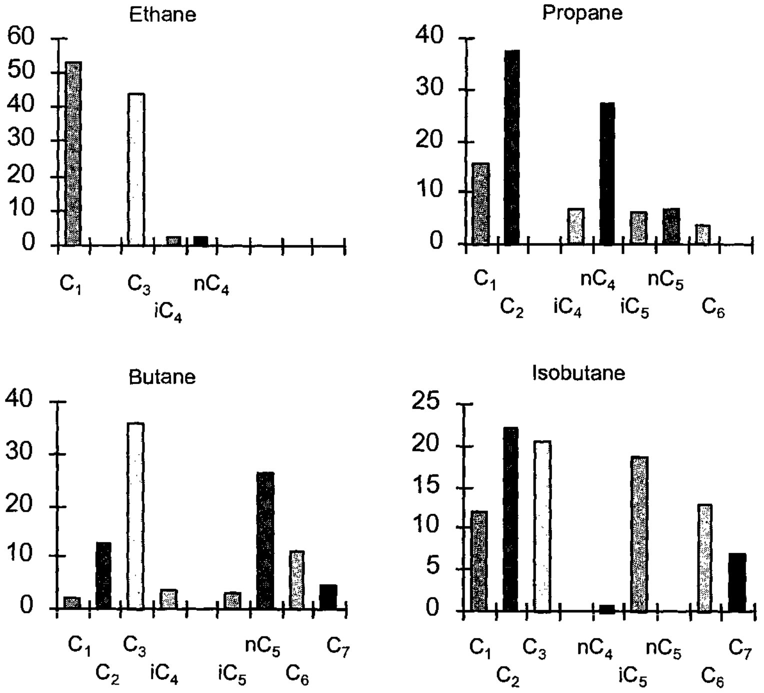


Figure 1. Product selectivity (methane, ethane, propane, isobutane, butane, isopentane, pentane, hexanes, heptanes) in metatheses of ethane, propane, butane, and isobutane.

References

[1] C. Lecuyer, F. Quignard, A. Choplin, D. Olivier, J.-M. Basset, *Angew. Chem. Int. Ed.* **1991**, *30*, 1660, J. Corker, F. Lefebvre, C. Lécuyer, V. Dufaud, F. Quignard, A. Choplin, J. Evans, J.-M. Basset, *Science* **1996**, *271*, 966; V. Dufaud, J.-M. Basset, *Angew. Chem. Int. Ed.* **1998**, *37*, 806.

[2] V. Vidal, A. Théolier, J. Thivolle-Cazat, J.-M. Basset, *Science.* **1997**, *276*, 99, O. Maury, L. Lefort, V. Vidal, J. Thivolle-Cazat, J.-M. Basset, *Angew. Chem. Int. Ed.* **1999**, *38*, 1952; M. Chabanas, L. Lefort, O. Maury, G. Saggio, C. Copéret, J. Thivolle-Cazat, J.-M. Basset, manuscript in preparation.

[3] S. L. Scott, J.-M. Basset, G. P. Niccolai, C. C. Santini, J.-P. Candy, C. Lécuyer, F. Quignard and A. Choplin, *New. J. Chem.*, **1994**, *18*, 115; F. Lefèbvre, J. Thivolle-Cazat, V. Dufaud, G. P. Niccolai and J.-M. Basset, *Applied Catalysis A*, **1999**, *182*, 1; F. Lefebvre, J. P. Candy, C. Santini and J.-M. Basset, *Topics in Catalysis*, 1997, 211; F. Lefebvre, C. Santini and J.-M. Basset, *Coord. Chem. Rev.*, **1998**, *178–180*, 1703, C. Copéret, F. Lefebvre, J.-M. Basset, *in ABC of Catalysis*, W. A. Herrmann, Ed., VCH, in press.

[4] For some examples of Polymerization Catalysts Prepared via SOMC: M. Jezequel, PhD Thesis, Université Claude Bernard Lyon I, **1999**; J. Amor Nait Ajjou, S. L Scott, *J. Am. Chem. Soc.* **1998**, *120*, 415; J. Amor Nait Ajjou, G. L. Rice, S. L. Scott, *J. Am. Chem. Soc.* **1998**, *120*, 13436. For a review on Polymerization, see: T. J. Marks, *Acc. Chem. Res.* **1992**, *25*, 57.

[5] K. J. Ivin, J. C. Mol, *In Olefin Metathesis and Metathesis Polymerization*, Academic Press, 1997.

[6] J.-L. Couturier, C. Paillet, M. Leconte, J.-M. Basset, K. Weiss, *Angew. Chem. Int. Ed.* **1992**, *31*, 628; R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875; S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974.

[7] J. Smith, W. Mowat, D. A. Whan, *J. Chem. Soc., Chem. Comm.*, **1974**, 34; J. Smith, W. Mowat, D. A. Whan, E. A. V. Ebsworth, *J. Chem. Soc., Dalton Trans.*, **1974**, 1742.

[8] I. A. Oreshkin, L. I. Red'kina, K. L. Makovetskii, E. I. Tinyakova, B. A. Dolgoplosk, *Isvest Akad. Nauk S. S. S. R., Ser. Khim.*, **1971**, *5*, 1123; Yu. I. Yermakov, B. N. Kuznetsov, Yu. A. Ryndin, *J. Catalysis*, **1976**, *42*, 73; Y. Iwasawa, Y. Nakano, S. Ogasawara, *J. Chem. Soc., Faraday I*, **1978**, 74, 2968; for a complete report on earlier works involving allyl complexes of Mo and W, see: Yu. I. Yermakov, B. N. Kuznetsov, V. A. Zakharov, *In Studies in Surface Science and Catalysis*, Elsevier, **1981**, Vol. 8, p 251.

[9] K. Weiss, G. Loessel, *Angew. Chem. Int. Ed.* **1989**, *28*, 62.

[10] R. Buffon, M. Leconte, A. Choplin, J.-M. Basset, *J. Chem. Soc., Chem. Commun.*, **1993**, 361; R. Buffon, M. Leconte, A. Choplin, J.-M. Basset, *J. Chem. Soc., Dalton Trans.*, **1994**, 1723.

[11] W. A. Herrmann, W. Wagner, U. N. Flessner, U. Volkhardt, H. Komber, *Angew. Chem. Int. Ed.* **1991**, *30*, 1636.

[12] R. Buffon, A. Auroux, F. Lefebvre, M. Leconte, A. Choplin, J.-M. Basset, W. A. Herrmann, *J. Mol. Cat.* **1992**, *76*, 287–95; R. Buffon, A. Choplin, M. Leconte, J.-M. Basset, R. Touroude, W. A. Herrmann, *J. Mol. Cat.* **1992**, *72*, L7-10.

[13] V. Dufaud, G. P. Niccolai, J. Thivolle-Cazat, J.-M. Basset, *J. Am. Chem. Soc.* **1995**, *117*, 4288–4294; L. Lefort, M. Chabanas, O. Maury, D. Meunier, C. Copéret, J. Thivolle-Cazat, J.-M. Basset, *J. Organomet. Chem.* **2000**, *593–594*, 96.

[14] C. Copéret, J. Thivolle-Cazat, J.-M. Basset, unpublished results.

[15] S. J. McLain, J. Sancho, R. R. Schrock, *J. Am. Chem. Soc.* **1980**, *102*, 5610.

[16] W. A. Herrmann, A. W. Stumpf, T. Priermeier, S. Bogdanovic, V. Dufaud, J.-M. Basset, *Angew. Chem. Int. Ed.* **1996**, *35*, 2803.

[17] R. Petroff Saint-Arromans, Master Thesis, Université Claude Bernard Lyon I; M. Chabanas, R. Petroff Saint-Arromans, C. Copéret, J.-M Basset, unpublished results; R. Buffon, private communications.

[18] G. P. Niccolai and J.-M. Basset, in Catalytic Activation and Functionalisation of Light Alkanes: Advances and Challenges, (Eds.: E. G. Derouane, J. Haber, F. Lemos, F. Ramoa Ribeiro, M. Guisnet), NATO ASI Series 3/44, Kluwer Academic Publishers, Dordrecht/Boston/London, 1998.

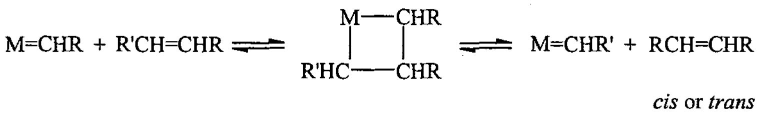
[19] V. Vidal, A. Théolier, J. Thivolle-Cazat, J.-M. Basset, J. Corker, *J. Am. Chem. Soc.* **1996**, *118*, 4595.

10.2 Olefin Metathesis

J. C. Mol

10.2.1 Introduction

Olefin metathesis is a catalytic process in which alkenes are converted into new products via the rupture and reformation of carbon–carbon double bonds. The key step in this process is the 2 + 2 reaction between an olefin and a transition metal alkylidene (carbene) complex, generating an unstable metallacyclobutane intermediate. This intermediate can either revert to the starting material, or open productively to regenerate a metal carbene and produce a new olefin (Eq. 1).



$$\mathrm{M{=}CHR} + \mathrm{R'CH{=}CHR} \rightleftharpoons \begin{array}{c}\mathrm{M{-}CHR}\\ |\qquad|\\ \mathrm{R'HC{-}CHR}\end{array} \rightleftharpoons \mathrm{M{=}CHR'} + \underset{cis\ \text{or}\ trans}{\mathrm{RCH{=}CHR}} \qquad (1)$$

Different types of monoolefin and diolefin undergo metathesis via contact with a suitable catalyst, resulting in a wide variety of possible products (Eqs 2–5) [1].

Acyclic Olefins

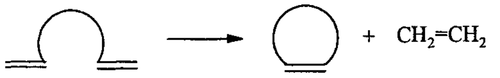
$$2\ \mathrm{RCH{=}CHR'} \rightleftharpoons \mathrm{RCH{=}CHR} + \mathrm{R'CH{=}CHR'} \qquad (\mathrm{R\ and\ R'} = \text{alkyl or H}) \qquad (2)$$

Diolefins

Intermolecular Reaction

$$n\ \mathrm{CH_2{=}CH(CH_2)_xCH{=}CH_2} \longrightarrow \left[\mathrm{CH(CH_2)_xCH}\right]_n + n\ \mathrm{CH_2{=}CH_2} \qquad (3)$$

Intramolecular Reaction



(4)

Cyclic Olefins

(5)

(where  represents a hydrocarbon chain with or without a heteroatom)

All the reactions are reversible, and when volatile or insoluble products are formed displacement of the equilibrium occurs. Thus when R = H, removal of ethene from the system of Eq. (2) can drive the reaction to completion. The reverse reaction is called ‘cross-metathesis’ and cross-metathesis with ethene is called ‘ethenolysis’. Both linear and branched olefins can undergo metathesis.

Diolefins, such as α,ω-dienes, can undergo intermolecular and intramolecular metathesis. Intermolecular reactions, as shown in Eq. (3), eventually lead to the production of high polymers, known as acyclic diene metathesis (ADMET) polymers. If the diolefin couples intramolecularly to produce a cyclic alkene, as shown in Eq. (4), the process is called ring-closing metathesis (RCM). The reverse reaction is called ring opening cross-metathesis. RCM has become an important tool in the hands of synthetic organic chemists and has been widely applied to the preparation of useful carbo- and heterocyclic intermediates [1–3]. In general, ADMET is favored in highly concentrated solutions or when the substrate is neat, whereas RCM is favored at low concentrations. The relative occurrence of ADMET and RCM also depends on the size of the ring formed.

Equation (5) is an example of ring-opening metathesis polymerization (ROMP). This reaction is driven by the release of ring strain in the starting cycloalkene. Living polymerization can occur when the metal carbene catalyst reacts more rapidly with the cyclic olefin than with a C=C bond in the growing polymer chain. All the double bonds from the monomer molecules are preserved in ROMP, resulting in the formation of polymers with highly unsaturated backbones.

Metathesis is a versatile reaction that forms the basis for several important industrial processes, such as the Phillips triolefin process, which produces propene by cross-metathesis of 2-butene with ethene, and the Shell higher olefins process (SHOP), which involves a combination process that converts ethene to detergent-range olefins. Several interesting polymeric materials are commercially produced via the ROMP of different types of unsaturated cyclic monomers, including norbornene, cyclooctene, and dicyclopentadiene [1].

Olefin metathesis is being used increasingly in the specialty chemicals market. Olefin interconversion can be used to produce isomerically pure symmetrical internal olefins from α-olefins (Eq. 2; $R' = H$), and α-olefins can be produced from internal olefins via ethenolysis. Metathesis of olefins bearing heteroatom functional groups is also a very promising application of the metathesis reaction, which enables the synthesis, in only a few reaction steps, of many products that would otherwise be difficult to obtain.

Considering the many possibilities of the metathesis of unsaturated hydrocarbons in chemical synthesis, it is not surprising that a significant amount of research has been (and still is) directed towards the development of active and selective catalysts for this reaction. The metathesis reaction can be catalyzed by both heterogeneous and homogeneous catalysts. These catalysts include a wide range of transition metal compounds, the most important being based on molybdenum, tungsten, ruthenium and rhenium.

In general, homogeneous catalysts consist of either a well-characterized carbene complex of a transition metal (e. g. Ru, Mo or W), or of a combination of a transition metal compound (usually an (oxo)chloride) and an organometallic compound as co-catalyst [1]. In the latter case (i. e. the classical catalysts) the active carbene species is generated from the alkyl groups on the co-catalyst. Since the recent discovery of new, well-defined transition metal carbene catalysts with a high tolerance of functional groups, tremendous progress has been achieved in fine chemical, natural product, and polymer synthesis by use of homogeneously catalyzed metathesis [1–7].

Because this book is devoted to fine chemical synthesis by heterogeneous catalysis, homogeneously catalyzed metathesis reactions will not be discussed. After a short overview of heterogeneous metathesis catalysts, the synthesis of fine chemicals from normal (unfunctionalized) olefins in the presence of these heterogeneous catalysts will be discussed. This is followed by a discussion of fine chemicals synthesized from functionalized olefins.

10.2.2 Heterogeneous Metathesis Catalysts

The heterogeneous metathesis catalysts generally consist of a transition metal oxide (e. g. rhenium, molybdenum, or tungsten oxide) supported on a high-surface-area inorganic oxide such as alumina or silica [1]. The catalysts are usually prepared by impregnation of the support with an aqueous solution of the ammonium salt of the transition metal, then drying in air at 110 °C and calcination at temperatures between 500 and 550 °C. Re_2O_7/Al_2O_3 is a particularly attractive heterogeneous catalyst because it is highly active and highly selective under mild reaction conditions (20–100 °C). Its surface structure has been extensively characterized [8]. The activity of this catalyst can be further increased by addition of a tetraalkyltin compound as promoter (co-catalyst). When this promoter is present the Re_2O_7/Al_2O_3 catalyst is also active in the metathesis of functionalized olefins. Several factors can affect the performance of this catalytic system, e. g. the transition metal loading, the kind of support used, the calcination procedure, the transition metal/promoter ratio, etc.

The $Re_2O_7/Al_2O_3/Me_4Sn$ catalyst system was the first heterogeneous catalyst system found to be effective for the metathesis of functionalized olefins such as olefinic esters [9,10], ethers [11], bromides [11], and nitriles [12,13], etc. The catalytic performance of this system has since been improved by (i) incorporating a third metal oxide (e. g. V_2O_5, MoO_3, or WO_3), (ii) the use of modified supports (e. g. SiO_2–Al_2O_3, Al_2O_3–B_2O_3, phosphated alumina or borated silica–alumina), and (iii) the use of other promoters, e. g. Bu_4Sn, Et_4Sn, or R_4Pb [1,8]. Low rhenium loadings are useful for the modified supports (e. g. 3 % *w/w* Re_2O_7 for a modified support compared with 18 % *w/w* Re_2O_7 for an alumina support).

Other heterogeneous catalyst systems have also been developed for the metathesis of unsaturated esters and other functionalized olefins. They include $MoCl_5/SiO_2/R_4Sn$, where R is alkyl (e. g. Me or Et) [14], and CH_3ReO_3/SiO_2–Al_2O_3 [15]. Photoreduction of MoO_3/SiO_2 in a CO atmosphere with either a Hg lamp [16] or with a laser beam of 308 nm [17] in a CO atmosphere, then treatment with cyclopropane also results in an active catalyst for olefinic esters.

Many heterogeneous metathesis catalysts cannot catalyze the metathesis of functionalized olefins because of their intolerance to functional groups. Interference of the functional groups also reduces the activity of the catalysts that are active in this case. This increases the costs of the catalyst because much higher catalyst/substrate ratios must be used than are required for normal olefins.

Table 1. Examples of heterogeneous catalyst systems for the metathesis of unsaturated esters.

Catalyst	Substrate[a]	[Ester]/ [Metal atom]	T (°C)	t^b (h)	TON	Ref.
$Re_2O_7/Al_2O_3/Et_4Sn$	MeOl	60	20	2	3	18
$Re_2O_7/MoO_3/Al_2O_3/Et_4Sn$	MeOl	60	20	2	30	18
Re_2O_7/SiO_2–Al_2O_3/Bu_4Sn	MeOl	240	40–45	3	120	19
$Re_2O_7/B_2O_3/SiO_2$–Al_2O_3/Bu_4Sn	MeUn	350	50	13	348	43
CH_3ReO_3/SiO_2–Al_2O_3	MeOl[c]	100	25	2	27	15
$MoCl_5/SiO_2/R_4Sn$	EtOl[d]	110	90	4	99	14
MoO_3/SiO_2/(CO, $h\nu$)/ cyclopropane	EtOl	250	50	0.17	125	16
MoO_3/SiO_2/(CO, laser)/ cyclopropane	MeOl	1250	40	3	500	19

[a] MeOl = methyl oleate; MeUn = methyl undecenoate; EtOl = ethyl oleate.
[b] Time to reach the highest conversion.
[c] Ethenolysis (7 bar).
[d] Cross-metathesis with 5-decene.

Table 1 shows some of the heterogeneous catalysts used for the metathesis of unsaturated carboxylic esters. These esters can be used as test substrates for functionalized olefin metathesis.

10.2.3 Metathesis in Fine Chemistry

10.2.3.1 Fine Chemicals Produced from Normal Olefins

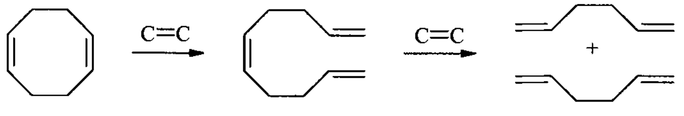
Commercial Processes

In the field of fine chemistry, the Phillips neohexene process was an early commercial application of olefin metathesis [20]. Neohexene (3,3-dimethyl-1-butene) is an important intermediate in the synthesis of musk perfume. The Phillips neohexene process is based on ethenolysis of an isobutene dimer consisting of a mixture of 2,4,4-trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene. Ethenolysis of the former yields the desired product (Eq. 6).

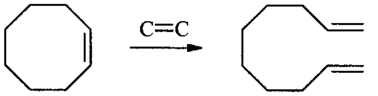
$$(Me)_3CCH{=}C(Me)_2 + CH_2{=}CH_2 \rightleftharpoons (Me)_3CCH{=}CH_2 + CH_2{=}C(Me)_2 \qquad (6)$$

The 2,4,4-trimethyl-1-pentene is not wasted because a dual catalyst can be used to ensure that it is converted into 2,4,4-trimethyl-2-pentene as this gets used up by ethenolysis. With a 1:3 catalyst mixture of a WO_3/SiO_2 metathesis catalyst and a MgO isomerization catalyst (at 370 °C and 30 bar ethene pressure), an average of 65–70 % conversion of the diisobutene can be achieved with approximately 85 % selectivity for neohexene. The coproduct isobutene can be recycled to an isobutene dimerization reactor. Neohexene is used to make the class of synthetic musks known as bicyclic musks. These musks simulate macrocyclic musks and have excellent odor and fixative properties [1].

Ethenolysis of cycloalkenes is a convenient route for production of certain polyunsaturated compounds. Shell have developed a process for the manufacture of α,ω-diolefins via ethenolysis of cyclic olefins (the reverse of Eq. 4) [21,22]. Thus, 1,5-hexadiene and 1,9-decadiene were produced via ethenolysis of cyclooctadiene and cyclooctene, respectively (Eqs. 7a,b).



(7a)



(7b)

There are many potential outlets for these unconjugated dienes, including their use as cross-linking agents, as specialty (co)monomers, or as starting intermediates for specialty chemicals. For example, 1,9-decadiene can be hydroformylated to produce aldehydes such as 10-undecenal, which can be used to modify the fragrance of perfumes. A commercial plant with a capacity of 3000 tons year^{-1} was opened in Berre l'Etang (France) in 1987. The plant used a Bu_4Sn-promoted Re_2O_7/Al_2O_3 catalyst for an ethenolysis reaction in the liquid phase under mild conditions (0–20 °C, 1–2 bar). These conditions suppress side reactions such as double bond shift. Because of limited product sales, however, the plant was closed after only a few years of operation.

Pheromone Synthesis

Interesting results have been obtained in the synthesis of biologically active compounds such as insect pheromones. Conventional synthetic routes to these pheromones are often multistep sequences, which make many pheromones too expensive for widespread use [23]. Metathesis offers a shorter, alternative route to pheromone synthesis, generating these compounds in a few steps only. The use of insect sex pheromones is an environmentally friendly, effective, and selective method of pest control. Küpper and Streck [24] synthesized insect sex pheromones by cross-metathesis reactions between linear olefins. In the presence of the catalyst Re_2O_7/Al_2O_3, 9-tricosene was synthesized by cross-metathesis of the readily available alkenes 2-hexadecene and 9-octadecene (Eq. 8).

$$\begin{aligned}&\mathrm{MeCH{=}CH(CH_2)_{12}Me + Me(CH_2)_7CH{=}CH(CH_2)_7Me}\\ &\rightleftharpoons \mathrm{Me(CH_2)_7CH{=}CH(CH_2)_{12}Me + MeCH{=}CH(CH_2)_7Me}\end{aligned} \tag{8}$$

The *cis* isomer of 9-tricosene is the sex pheromone of *Musca domestica* (housefly). It should be noted that cross-metathesis reactions involving unsymmetrical internal alkenes can lead to a complex product mixture, as self-metathesis and other cross-metathesis reactions also occur. 13-Heptacosene, the *cis* form of which is the sex pheromone of *Musca autumnalis* (face fly), was synthesized by cross-metathesis of 1-tetradecene and 2-hexadecene, and 2-methyl-7-octadecene, the *cis* epoxide of which is the sex pheromone of *Lymantria dispar* (gypsy moth), was synthesized by cross-metathesis of 1-dodecene and 7-methyl-1-octene. By use of these cross-metathesis reactions, between 6.7 and 13.0 % yield of the target molecules was achieved. 9-Tricosene was synthesized by Bykov et al. [14] via cross-metathesis of 1-decene and 1-pentadecene at 50 °C in the presence of a $MoCl_5/SiO_2/Me_4Sn$ catalyst system, giving a 79 % yield of *cis* and *trans* isomers.

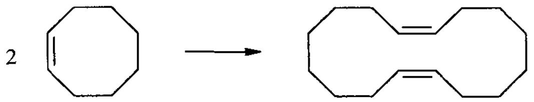
Product stereochemistry is a critical factor determining the applicability of metathesis pheromones to insect control [23]. The steric course of the metathesis reaction normally results in a (thermodynamic) *cis/trans* mixture, whereas the physiologically active pheromones are either isomerically pure compounds or specific *cis/trans* mixtures. When it is necessary to obtain a single stereoisomer, the separation step required is tedious and expensive. The synthesis of pure *cis* isomers via the metathesis reaction, therefore, forms a challenge for catalyst development.

Via stereoselective ethenolysis of 1,5-cyclooctadiene (COD), Bykov et al. [25] prepared 1,*cis*-5,9-decatriene, a precursor for the synthesis of many *cis*-isomeric insect sex pheromone compounds. In the presence of the $MoCl_5/SiO_2/Me_4Sn$ catalyst system, at 20 °C and an ethene pressure of 25 bar, a 80 % conversion of COD was obtained with a selectivity of 68.4 % for 1,*cis*-5,9-decatriene. From this triene, many long-chain (C_{10}–C_{18}) unsaturated acetates, alcohols and aldehydes can be obtained with the required biologically active *cis* conformation. Cross-metathesis of cyclooctene with α-olefins in the presence of the same catalyst gave 1-Δ-dienes. The 1-Δ-dienes were subsequently functionalized via selective hydroboration of the terminal bonds and then used for the synthesis of insect sex pheromone components [26].

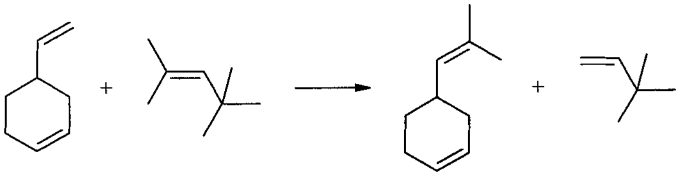
Synthesis of Perfume Components and Other Products

Warwel et al. [27] synthesized 1,8-nonadiene in 75 % yield via ethenolysis of cycloheptene over a Re_2O_7/Al_2O_3 catalyst (at 60 °C and an ethene pressure of 80 bar). The diene was subsequently subjected to intermolecular metathesis (release of ethene), again over a rhenium oxide catalyst (at 35 °C and 15 torr vacuum), giving 80 % yield of 1,8,15-hexadecatriene. The latter was converted, via oxidation, intramolecular aldol condensation, and hydrogenation, to muscone (3-methylcyclopentadecanone), an important perfume ingredient.

Cyclic alkenes can be dimerized to larger cyclic dienes that are used as intermediates in the synthesis of fine chemicals. For example, cyclooctene was converted to its cyclic dimer, 1,9-cyclohexadecadiene (Eq. 9), in the presence of a $Re_2O_7/Al_2O_3/Me_4Sn$ catalyst at 35–50 °C, in 30 % yield (in the equilibrium proportions of 16 % *trans/trans*, 58 % *trans/cis* and 26 % *cis/cis*) [28]. This dimer can be converted into the synthetic musk perfume 8-cyclohexadecanone. In such dimerization reactions it is important to work with low substrate concentrations and to remove the dimer rapidly from the reaction mixture, to avoid secondary reactions that generate higher oligomers and polymers.


(9)

In the presence of Re_2O_7/Al_2O_3 that has been pretreated with $Cu(NO_3)_2$ to suppress side reactions, the cross-metathesis of 2,4,4-trimethyl-2-pentene with 4-vinylcyclohexene (Eq. 10) proceeds with > 75 % selectivity [29]. The product isobutenyl cyclohexene can be converted to isobutylbenzene, which is the starting material for the synthesis of the over-the-counter analgesic, ibuprofen.


(10)

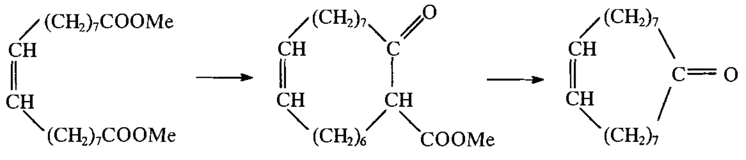
10.2.3.2 Fine Chemicals Produced from Functionalized Olefins

Unsaturated fatty acid esters are very promising and cheap feedstocks for metathesis. For this reason, the metathesis reaction is of interest in the field of oleochemistry (i. e. making products from natural fats and oils of vegetable and animal origin) [19,30]. In the presence of a suitable catalyst, the metathesis of unsaturated fatty acid esters provides a convenient and highly selective route to unsaturated diesters that can be used for the production of valuable chemical products, such as macrocyclic compounds. Many mono- (and also poly-) unsaturated esters undergo metathesis in the presence of a suitable catalyst, leading to a range of interesting products, while metathesis and cross-metathesis (especially ethenolysis) of fatty oils has also been studied [19,30,31].

Synthesis of Perfume Components

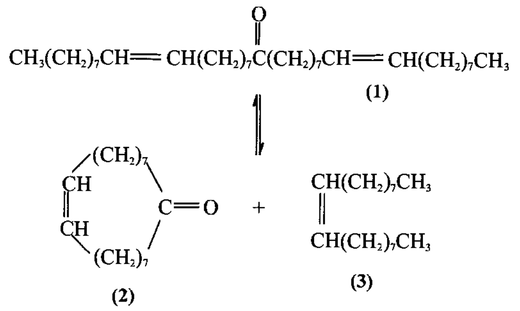
Methyl oleate (methyl *cis*-q-octadecenoate) is an attractive functionalized olefin for metathesis because of its ready availability and the utility of the metathesis products. An early example is the proposed route to civetone by metathesis of methyl oleate followed by cyclocondensation (Eqs. 11a,b). Civetone is a seventeen-membered unsaturated macrocyclic ketone (*cis*-9-cycloheptadecen-1-one) identical with the natural compound (civet cat). It has an intense musk odour, and is therefore an attractive perfume component.

$$2Me(CH_2)_7CH{=}CH(CH_2)_7COOMe \rightleftharpoons Me(CH_2)_7CH{=}CH(CH_2)_7Me + MeOOC(CH_2)_7CH{=}CH(CH_2)_7COOMe \qquad (11a)$$


(11b)

The metathesis of methyl oleate is readily achieved at room temperature with catalyst systems consisting of Re_2O_7 supported on alumina or silica–alumina promoted with a tetraalkyltin compound [32]. The result is an equilibrium mixture consisting of 50 mol % starting material and 25 mol % of each of the two products, in accordance with thermodynamics. Product selectivity is very high (> 97 %), possibly because ester group complexation with the Brønsted acid sites on the support prevents side reactions such as double bond shift. Transformation of the diester into civetone (Eq. 11b) has been performed by Tsuji and Hashiguchi [33] and gave 54 % of the desired product with a *cis:trans* ratio of 1.3:1. After dimerization and hydrogenation the co-product 9-octadecene gives 10,11-dioctyleicosane, a lube-oil range hydrocarbon intermediate [34].

Very pure substrate is required for the metathesis of methyl oleate. In an alternative process for the synthesis of civetone, methyl oleate was first converted to oleon (**1**), the doubly-unsaturated ketone 9,26-pentatriacontadien-18-one, which can be separated in pure form from the reaction mixture. Oleon was then converted into 9-cycloheptadecen-1-one (**2**) via a ring-closing metathesis reaction (see Scheme 1).



Scheme 1. Metathesis of oleon.

At room temperature in the presence of a $Re_2O_7/SiO_2–Al_2O_3$ catalyst promoted with Bu_4Sn, a mixture of isomers was obtained in 14 % yield. To reduce the possibility of *inter*molecular metathesis between two oleon molecules, it is necessary to perform the reaction at high dilution [35].

Synthesis of Pheromones and other Products via Cross-metathesis

Cross-metathesis reactions are useful for the production of fine chemicals such as synthetic perfumes, prostaglandin intermediates, and insect pheromones. An example of the last is the cross-metathesis of ethyl oleate with 5-decene in the presence of a $MoCl_5/SiO_2/Me_4Sn$ catalyst at 90 °C [14], or a MoO_3/SiO_2/cyclopropane catalyst at 50 °C [16], resulting in a *cis/trans* mixture of ethyl 9-tetradecenoate, an insect pheromone precursor (Eq. 12).

$$\begin{aligned}&Me(CH_2)_7CH{=}CH(CH_2)_7COOEt + BuCH{=}CHBu\\ &\rightleftharpoons Me(CH_2)_7CH{=}CHBu + BuCH{=}CH(CH_2)_7COOEt \qquad (12)\end{aligned}$$

Cross-metathesis of oleyl acetate and 3-hexene produces, with 3-dodecene and self-metathesis products of the acetate, 9-dodecenyl acetate, the pheromone of a leaf roller, *Eucosma sonomana*. Even the isomeric mixture obtained from this metathesis reaction was active in disrupting insect mating [23]. Although many other pheromones have been synthesized by use of homogeneous catalysts; these reactions might also be performed with suitable heterogeneous catalysts.

Cross-metathesis of unsaturated fatty acid esters with a normal alkene is an elegant way of synthesizing homologs of these esters, and greatly extends the versatility of the metathesis reaction in the field of oleochemistry. Long-chain fatty acid esters (C_{16}–C_{20}) can be shortened via cross-metathesis with a lower olefin in the presence of a supported Re_2O_7 catalyst to give unsaturated detergent-range C_{12}–C_{14} esters [10,36]. The alkene by-products, with the double bond near the end of the chain, can be transformed into useful linear C_{12}–C_{14} alcohols by hydroformylation, or transformed into linear alkyl benzene sulfonates via alkylation of benzene.

Medium-chain unsaturated fatty acid esters (C_{12}–C_{16}) are also starting materials for the synthesis of pheromones of the general formula $Me(CH_2)_nCH{=}CH(CH_2)_7X$, where X is CH_2OAc, CH_2OH or CHO, and $n = 1$–5.

Ethenolysis of unsaturated esters results in the synthesis of shorter-chain ω-unsaturated esters, compounds with a broad range of application. Excess ethene can easily be used (e. g. by use of ethene pressures of 30–50 bar) to suppress self-metathesis of the ester and to force the conversion to completion. Ethenolysis of methyl oleate produces methyl 9-decenoate and 1-decene (Eq. 13) [37,38]. High conversion of methyl oleate can be obtained at room temperature by use of a Re_2O_7 catalyst promoted with tetraalkyltin.

$$\begin{aligned}&Me(CH_2)_7CH{=}CH(CH_2)_7COOMe + CH_2{=}CH_2\\&\rightleftharpoons Me(CH_2)_7CH{=}CH_2 + CH_2{=}CH(CH_2)_7COOMe\end{aligned}\tag{13}$$

Methyl 9-decenoate is an intermediate in the synthesis of many chemical products. It is the hypothetical source of many polymers and copolymers and can, for example, be converted into the ω-amino acid and then used for the production of nylon-10. On hydrolysis and hydrogenation it yields decanoic acid or decanol, substances used in lubricants and plasticizers. It can also be used to produce fragrances (e. g. 9-decen-1-ol and civetone), pheromones, and prostaglandins etc., which are easily isolated in the pure form [31]. When civetone is the target molecule, methyl 9-decenoate can, after separation from the reaction mixture, undergo the same sequence as methyl oleate in Eq. (11). However, if the ethene formed in the metathesis step is continuously removed from the system, nearly quantitative conversion into the diester can be achieved. Furthermore, methyl 9-decenoate is the key intermediate in the synthesis of 9-oxo-*trans*-2-decenoic acid, a honey bee pheromone (the 'queen substance'), and 9-oxodecanoic acid, a prostaglandin intermediate. 1-Decene, like other 1-alkenes, is an important intermediate in organic syntheses, and has a variety of uses in polymers, surfactants, and lubricants. Ethenolysis of methyl erucate gives another ω-unsaturated ester, methyl

13-tetradecenoate, which could have applications analogous to those of methyl 9-decenoate.

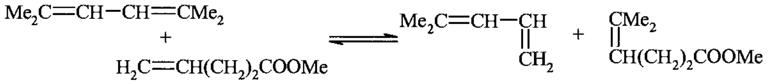
The selectivity of cross-metathesis reactions has been demonstrated by the reaction of *trans*-3-hexene with vinyl acetate or α,β-unsaturated esters (e. g. methyl *trans*-crotonate) in the presence of a supported rhenium oxide catalyst (Eq. 14).

$$\begin{aligned}&MeCH{=}CHCOOMe + EtCH{=}CHEt\\ &\rightleftharpoons EtCH{=}CHCOOMe + MeCH{=}CHEt\end{aligned} \tag{14}$$

This gives the desired cross-metathesis product without any self-metathesis of the crotonate [10], and creates the possibility of synthesizing distinct α-methyl, α,β-unsaturated esters via cross-metathesis reactions.

Conjugated dienoic esters are important aroma ingredients in food, drinks and tobacco, and several insect pheromones are conjugated dienoic esters or alcohols. Cross-metathesis between a conjugated alkadiene and an ester could be a synthetic route in the production of conjugated dienoic esters. Although the metathesis of conjugated alkadienes is difficult to perform, because they usually strongly deactivate metathesis catalysts, Woerlee et al. [39] have been able to perform the reaction between 2,5-dimethyl-2,4-hexadiene and methyl 4-pentenoate in the presence of the $Re_2O_7/Al_2O_3/Me_4Sn$ catalyst system. New unsaturated esters were formed according to Eqs. (15a,b).

$$\begin{array}{c}Me_2C{=}CH{-}CH{=}CMe_2\\ +\\ H_2C{=}CH(CH_2)_2COOMe\end{array} \rightleftharpoons \begin{array}{l}CMe_2\\ \|\\ CH_2\end{array} + \begin{array}{l}CH{-}CH{=}CMe_2\\ \|\\ CH(CH_2)_2COOMe\end{array} \tag{15a}$$

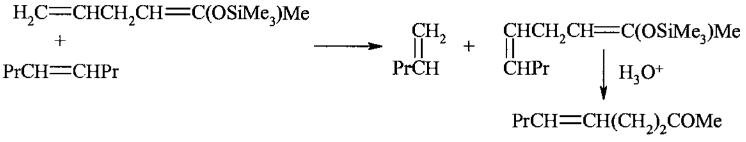


$$\begin{array}{c}Me_2C{=}CH{-}CH{=}CMe_2\\ +\\ H_2C{=}CH(CH_2)_2COOMe\end{array} \rightleftharpoons \begin{array}{r}Me_2C{=}CH{-}CH\\ \|\\ CH_2\end{array} + \begin{array}{l}CMe_2\\ \|\\ CH(CH_2)_2COOMe\end{array} \tag{15b}$$

(4)

All the expected products were found in the reaction mixture, and 15 % of the starting ester was converted into the most interesting product, methyl 7-methyl-4,6-octadienoate (**4**). Cross-metathesis of 2,4-hexadiene and 8-nonenyl acetate, then hydrolysis of the reaction product results in 8,10-dodecadien-1-ol, whose *trans–trans* component is a pheromone of the codling moth.

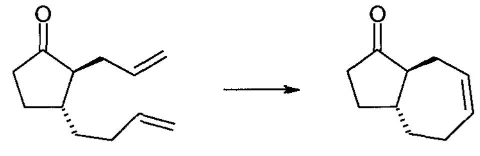
The perfume constituent 5-nonene-2-one (**5**) was obtained in 61 % yield via cross-metathesis of silylated allyl acetone with two equivalents of 4-octene (using $Re_2O_7/MoO_3/Al_2O_3/Me_4Sn$ as catalyst) and elimination of the protecting group (Eq. 16) [40].



$$\begin{array}{c}H_2C{=}CHCH_2CH{=}C(OSiMe_3)Me\\ +\\ PrCH{=}CHPr\end{array} \longrightarrow \begin{array}{l}CH_2\\ \|\\ PrCH\end{array} + \begin{array}{l}CHCH_2CH{=}C(OSiMe_3)Me\\ \|\\ CHPr \\ \quad\big\downarrow H_3O^+\\ PrCH{=}CH(CH_2)_2COMe\end{array} \tag{16}$$

(5)

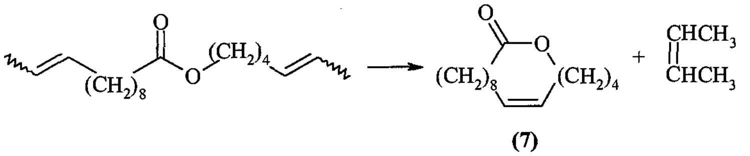
As previously described, RCM is a powerful tool for the preparation of useful carbo- and heterocyclic intermediates. Almost all of the recent RCM reactions have been performed homogeneously with well-defined metal carbene complexes as catalysts. An example of the use of a heterogeneous catalyst in RCM is the synthesis of hydroazulenes such as **6** via RCM of highly functionalized diolefins (Eq. 17) catalyzed by CH_3ReO_3/SiO_2–Al_2O_3 and with heating under reflux at 80 °C [41].



(6)

(17)

Such ring systems occur in many natural products of pharmacological interest. The same catalyst system was also successfully used for the RCM of an ester unsaturated in both the acid and alcohol fragment. Thus, the 5-heptenyl ester of 10-dodecenoic acid gave an unsaturated macrocyclic lactone (**7**) which, on hydrogenation afforded the natural product exaltolide (1,15-pentadecanolide), a perfume ingredient (Eq. 18).



(7)

(18)

Many other (cross-) metathesis reactions of functionalized olefins have been shown to be possible in the presence of rhenium-based catalysts, such as self-metathesis (or cross-metathesis with normal olefins) of allyl- and vinylsilanes, unsaturated nitriles, chlorides, bromides etc. The products of these reactions are not yet of use in fine chemistry, but this might be remedied by future developments in this area.

10.2.3.3 Catalyst Deactivation

One problem in catalysis is gradual loss of activity of the catalyst. There are many reasons underlying the deactivation of heterogeneous metathesis catalysts [42]. The most important causes of catalyst deactivation are: (i) intrinsic deactivation reactions, such as the reductive elimination of metallacyclobutane intermediates, (ii) impurities in the substrate (oxygen, water) poisoning the active site; and (iii) adsorption of product molecules or polymeric by-products onto the surface of the catalyst, blocking the active sites or even the catalyst pores. An alkyltin-promoted catalyst is deactivated more rapidly than an unpromoted one. After deactivation of the catalyst, the issue becomes not only whether, but also how many times the catalyst can be regenerated. For instance, unpromoted supported rhenium oxide catalysts can be regenerated many times without any loss of activity. Although the activity of a deactivated tetraalkyltin-promoted catalyst can be restored via calcination and further addition of the promoter, there is a limit to the number of times a catalyst can be regenerated in this way, because tin accumulation on the catalyst surface eventually prevents the formation of active sites [30]. After total deactivation, the rhenium can be recovered from these catalysts.

10.2.4 Conclusion

Olefin metathesis is a versatile reaction for the production of fine chemicals. Through metathesis, many different products, which are otherwise difficult to obtain, can be produced from readily available olefins in only a few reaction steps. With heterogeneous catalysts metathesis can be performed under mild reaction conditions and with high selectivity. Metathesis routes that use cheap raw material, such as esters from natural sources, and accessible heterogeneous catalysts are technologically viable.

References

[1] Ivin, K.J. and Mol, J.C. (1997) Olefin Metathesis and Metathesis Polymerization, Academic Press, San Diego, London, pp. 472.

[2] Fürstner, A. (1997) Recent advancements in ring-closing metathesis, *Topics in Catalysis* **4**, 285–299.

[3] Armstrong, S.K. (1998) Ring Closing Diene Metathesis in Organic Synthesis, *J. Chem. Soc., Perkin Trans 1.* p. 371–388.

[4] Schuster, M. and Blechert, S. (1997) Olefin Metathesis in Organic Chemistry, *Angew. Chem. Int. Ed. Engl.* **36**, 2036–2056.

[5] Grubbs, R.H. and Chang, S. (1998) Recent Advances in Olefin Metathesis and Its Application in Organic Synthesis, *Tetrahedron* **54**, 4413–4450.

[6] Fürstner, A. (Ed.) (1998) Alkene Metathesis in Organic Synthesis, *Top. in Organomet. Chem.* **1**, 1–231.

[7] Wrigh, D.L. (1999) Application of Olefin Metathesis to Organic Synthesis, *Current Organic Chemistry,* **3**, 211–240.

[8] Mol, J.C. (1999) Olefin Metathesis over Supported Rhenium Oxide Catalysts, *Catalysis Today* **51**, 289–299; **52**, 377.

[9] Verkuijlen, E., Kapteijn, F., Mol, J.C. and Boelhouwer, C. (1977) Heterogeneous Metathesis of Unsaturated Fatty Acid Esters, *J. Chem. Soc., Chem. Commun.*, 198–199.

[10] Bosma, R.H.A., Van den Aardweg, G.C.N. and Mol, J.C. (1983) Heterogeneous Metathesis of Unsaturated Esters using a Rhenium-Based Catalyst, *J. Organomet. Chem.*, **255**, 159–171.

[11] Mol, J.C. and Woerlee, E.F.G. (1979) Heterogeneous Metathesis of Alkenes having Functional Groups, *J. Chem. Soc., Chem. Commun.*, 330–331.

[12] Van den Aardweg, G.C.N., Bosma, R.H.A. and Mol, J.C. (1983). Heterogeneous Metathesis of Unsaturated Nitriles, *J. Chem. Soc., Chem. Commun.*, 262–263.

[13] Bosma, R.H.A., Van den Aardweg, G.C.N. and Mol, J.C. (1985) Metathesis of Unsaturated Nitriles, *J. Organomet. Chem.*, **280**, 115–122.

[14] Bykov, V.I., Butenko, T.A., Finkelshtein, E.S., Petrovskii, P.V., Vdovin, V.M., (1988). Preparation of Pheromone Components by Cometathesis Reactions in the Presence of a $MoCl_5/SiO_2/R_4Sn$ Catalyst, *Izv. Akad. Nauk SSSR, Ser. Khim.* **37**, 1580–1583.

[15] Hermann, W. A., Wagner, W., Flessner, U. N., Volkhardt, U. and Komber, H. (1991) Methyltrioxorhenium as Catalyst for Olefin Metathesis, *Angew. Chem. Int. Ed. Engl.* **30**, 1636–1638.

[16] Berezin, M. Y., Ignatov, V. M., Belov, P. S., Elev, I. V., Shelimov, B. N., Kazansky, V. B. (1991) Mechanism of Olefin Metathesis and Active Site Formation on Photoreduced Molybdenum Catalysts. 5. Metathesis of Unsaturated Fatty Acid Esters, *Kinet. Katal.* **32**, 379–389.

[17] Mol, J. C. (1994). Activity and stability of laser-photoreduced supported molybdenum oxide metathesis catalysts, *Catal. Lett.* **23** (1994) 113–118.

[18] Mol, J. C. (1991) Metathesis of functionalized acyclic olefins, *J. Mol. Catal.* **65**, 145–162.

[19] Mol, J. C. (1994). Metathesis of unsaturated fatty acid esters and fatty oils, *J. Mol. Catal.* **90**, 185–199.

[20] Banks, R. L., Banasiak, D. S., Hudson, P. S. and Norell, J. R. (1982). Specialty Chemicals via Olefin Metathesis, *J. Mol. Catal.*, **15**, 21–33.

[21] Chaumont, P. and John, C. S. (1988) Olefin Disproportionation Technology (Feast) – A Challenge For Process Development, *J. Mol. Catal.*, **46**, 317–328.

[22] Short, H. C. (1987), How to produce olefins via disproportionation, *Chem. Week*, 3 June, 30–31.

[23] Banasiak, D. S. (1985) Insect Pheromones from Olefin Metathesis, *J. Mol. Catal.* **28**, 107–115.

[24] Küpper, F-W., Streck, R. (1976). Synthese von Insektenlockstoffen an Metathesekatalysatoren, *Z. Naturforsh.* **31b**, 1256–1264.

[25] Bykov, V. I., Butenko, T. A., Petrova, E. B. and Finkelstein, E. Sh. (1999) Synthesis of Z-Isomeric Insect Sex Pheromone Components via Ethenolysis of 1,5-Cyclooctadiene, *Tetrahedron*, **55**, 8249–8252.

[26] Bykov, V. I. and Finkelshtein, E.Sh. (1998) Synthesis of natural compounds via the cycloolefin cometathesis with α-olefins. *J. Mol. Catal. A: Chemical.* **133**, 17–27.

[27] Warwel, S., Bachem, H., Deckers, A., Döring, N., Kätker, H., Rose, E. (1989) Synthesen von Moschus-Riechstoffen durch Olefin-Metathese, *Seifen-Öle-Fette-Wachse*, **115**, 538–545.

[28] Warwel, S., Kätker, H. and Rauenbusch, C. (1987). Macrocyclic Dienes by Metathetic Dimerization of Cycloheptene and Cyclooctene on Re_2O_7/Al_2O_3. *Angew. Chem., Int. Ed. Eng.* **26**, 702–703.

[29] Lyons, D., MacAlpine, D.K. (1988) Process for the production of an isobutenylcyclohexene, *Eur. Pat. Appl. 282,313.*

[30] Mol, J. C. and Buffon, R. (1998) Metathesis in Oleochemistry, *J. Braz. Chem. Soc.* **9**, 1–11.

[31] Boelhouwer, C. and Mol, J. C. (1985) Metathesis Reactions of Fatty Acid Esters, *Prog. Lipid Research* **24**, 243–267.

[32] Sibeijn, M. and Mol, J. C. (1991). Activity of supported Re_2O_7 catalysts for the metathesis of methyl oleate, *Applied Catalysis* **67**, 279–295.

[33] Tsuji, J. and Hashiguchi, S. (1980). Application of Olefin Metathesis to Organic Synthesis of Civetone and Macrolides, *Tetrahedron Lett.* **21**, 2955–2958.

[34] Choo, Y-M., Ooi, K-E., Ooi, I-H. and Tan, D. D. H. (1996) Synthesis of a Palm-Based Star-Shaped Hydrocarbon via Oleate Metathesis, *J. Am. Oil Chem. Soc.* **73**, 333–336.

[35] Plugge, M. F. C. and Mol, J. C. (1991) A New Synthesis of Civetone, *Synlett*, p. 507–509.

[36] Warwel, S and Deckers, A. (1989). Olefin-Metathese ungeättigter C_{18}-Fettstoffe, *Tenside Surf. Det.* **26**, 252–259.

[37] Bosma, R. H. A., Van den Aardweg, F. and Mol, J. C. (1981) Cometathesis of Methyl Oleate and Ethylene: A Direct Route to Methyl Dec-9-enoate. *J. Chem. Soc., Chem. Commun.* 132–133.

[38] Sibeijn, M. and Mol, J. C. (1992) Ethenolysis of Methyl Oleate over supported Re-based catalysts, *J. Mol. Catal.* **76** 345–358.

[39] Woerlee, E. F. G., Bosma. R. H. A., Van Eijl, J. M. M. and Mol, J. C. (1984) Metathesis of conjugated dienes: a possible way to synthesize insect pheromones and other specialty chemicals, *Applied Catalysis*, **10**, 219–229.

[40] Warwel, S. and Pütz, G. (1989). Olefin Metathese. XXII. Metathese von carbonylgeschütztem Allylaceton mit Monoolefinen an zinnalkylaktiviertem Re_2O_7/Al_2O_3. *J. Organomet. Chem.* **364**, 323–329.

[41] Junga, H. and Blechert, S. (1993) A new Approach to Hydroazulenes via Olefin Metathesis, *Tetrahedron Lett.* **34**, 3731–3732.

[42] Mol, J. C. (1997) Alkene Metathesis, *in* "Handbook of Heterogeneous Catalysis", (G. Ertl, H. Knözinger and J. Weitkamp, Eds), VCH, Weinheim, 2387–2400.

[43] Warwel, S., Jägers, H-G. and Thomas, S. (1992) Metathese ungesättigter Fettsäureester – ein einfacher Zugang zu langkettigen Dicarbonsäuren, *Fat. Sci. Technol.* **94**, 323–328.

10.3 Heck Coupling

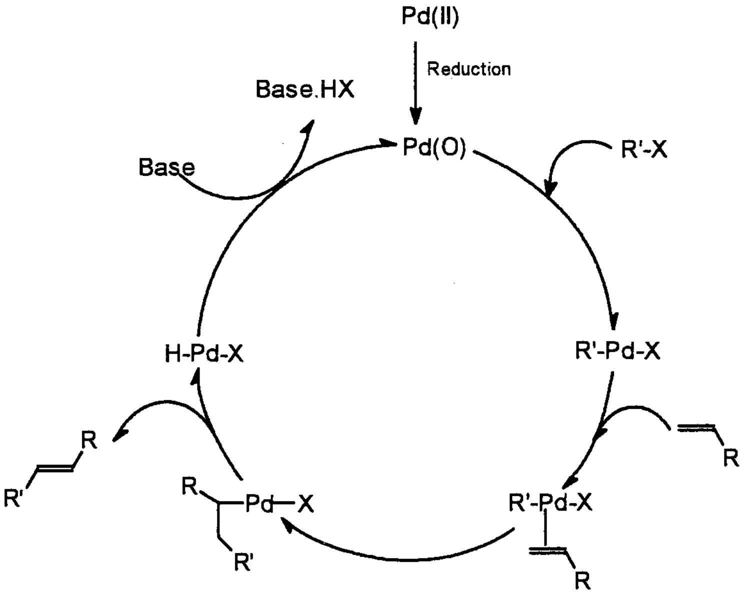
Amichai Eisenstadt, David J. Ager

10.3.1 Introduction

The Heck and Suzuki couplings are common carbon–carbon bond-forming reactions that exemplify the use of palladium catalysis in organic synthesis. The Heck reaction, which was discovered in 1971, is now considered to be a general method for the arylation of olefins by use of ArX (where X = Cl, Br, I, OSO_2Me, $OSO_2C_6H_4Me$, or OSO_2CF_3) in a single step. Much effort has been expended on the optimization of the reaction conditions, and most of this involves the use of homogeneously-catalyzed processes. The use of palladium on carbon, with solvent and high temperatures, has enabled the application of heterogeneous catalysis to this valuable vinylation methodology.

The generally accepted mechanism for the homogeneous Heck reaction can be used as a working model (Scheme 1), without specifying the exact nature of the Pd atoms in the Pd/C-catalyzed reaction.

In the reaction, an organic halide first forms an organopalladium halide complex with the catalyst, by oxidative addition. This complex then adds to an olefin and the adduct decomposes, by elimination of a hydrido-palladium halide, to form a new olefin in which a vinylic position is substituted by the organic moiety of the substrate halide.



Scheme 1. Proposed mechanism for the Heck reaction.

The use of the homogeneously catalyzed Heck arylations in the synthesis of a variety of compounds is well documented [1–6]. This includes, among many other possible examples, synthesis of lilial (fragrance), developed by Givaudan [7], metoprolol (β-blocker) [8] and nabumetone (a non-steroidal anti-inflammatory drug, or NSAID) [9].

Some of the problems associated with the implementation of Heck technology can be removed by the use of heterogeneous catalysts but, although there have been reports stating that Pd/C can promote the Heck arylation, data are limited [10]. A more complete investigation of the usefulness of supported metals as catalysts for this reaction might lead to a better appreciation of the use of heterogeneous catalysts by organic chemists.

10.3.2 Background of Heterogeneous Heck Coupling

A variety of heterogeneous palladium catalysts has been used to promote the Heck reaction. Some examples are given in this section. Pd–Cu-exchanged montmorillonite K10 clay is reported to be an efficient and reusable heterogeneous catalyst for the reaction between aryl halides and acrylates or styrenes, affording (*E*)-cinnamates or stilbenes, respectively, in high yields [11]. Multi-nuclear Pd(II) –Ni(II) (1:1) phthalocyanine has been found to catalyze the synthesis of a series of stilbenes and substituted cinnamic acids. Catalytic activity was comparable with that of the homogeneous Pd $(OAc)_2$ [12]. A copolymer of 4-vinylpyridine and styrene has been used as a support for a Pd(0) catalyst, which was then used to make the above target molecules. The catalyst was reported to be stable in air and moisture and could be recycled by use of NaOAc in aq. DMF [13].

The immobilized, colloidal palladium catalyst, SiO_2–$(C_3H_6SH)_nPd$ is reported to induce the Heck reaction [14a] between ethyl iodide and ethyl acrylate. XPS data showed the presence of Pd(II) on the surface of the colloidal Pd particles, owing to air oxidation; this explains the different behavior of this and the Pd/C catalyst. Addition of $Bu_3N.HI$ and iodine greatly reduced the induction period. The catalytic activity of propylene carbonate-stabilized palladium colloids in the Heck reaction has been investigated [14b].

Semmelhack demonstrated that the addition of alkali metal chloride salts can sometimes markedly increase the yields of coupling products in heterogeneous Pd-catalyzed reactions, especially when the olefin component contains an amide function [15]. It has been claimed that palladium-grafted mesoporous material (MCM-41), designated Pd-TMS11, is one of the most active heterogeneous catalysts for the Heck reaction and enables C–C formation with activated and non-activated aryl substrates [16a,b]. Nanoscale particles of palladium clusters prepared by the ultrasonic reduction of $Pd(OAc)_2$ and NR_4X in THF or methanol, were also active for C–C couplings [17].

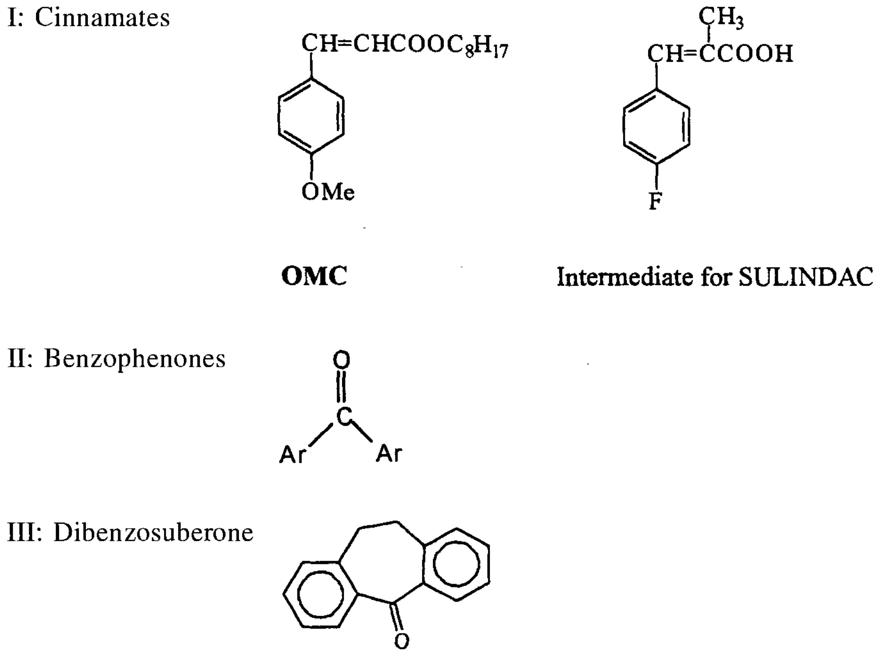
Pd metal on supports such as Al_2O_3, MgO, SiO_2, and $CaCO_3$, and Raney Pd, have been reported to be effective in the Heck arylation, including that promoted by use of microwaves [18a–c]. With MgO supports electron transfer from the surface of the support to that of the metal leads to “anchoring of the metal to the support" [18b] which leads to higher activity. Catalysts of the type SiO_2–X–$(NH)_2$–Pd–L_2 (where X = Sn, Al, or Ti, and L = PPh_3 or CH_3CN) can be used in the vinylation of methyl acrylate with iodobenzene without significant loss of activity after several catalytic cycles [18d]. Efficient Heck alkenylation with substituted arenediazonium salts in the presence of Pd and $CaCO_3$ has been reported [18e].

Polycinnamamide has been synthesized by use of the Heck reaction catalyzed by a recyclable Pd–graphite catalyst [19a]. Because the catalyst is easily separated from the reaction mixture, the Pd content of the polymer can be lower and the polymer is less colored; polymerization is more selective than when homogeneous catalysis is used [19b].

Phosphinated cellulose-bound Pd complexes (P–$OPPh_2PdCl_2$) [20a] and the polymer catalyst, P–Ph–Phen–Pd (reduced) have been used in Heck coupling reactions [20b].

10.3.2.1 IMI Contribution to Fine Chemical Manufacture via Heck Coupling

IMI has recently issued several reports describing industrial applications of heterogeneous Heck catalysis for the manufacture of chemical building blocks [21–23]. This contribution focused on two classes of organic compounds in industrial use–cinnamates (sunscreens and intermediates for pharmaceuticals) and benzophenones (Scheme 2).



Scheme 2. IMI applications of heterogeneous Heck catalysis.

Cinnamates

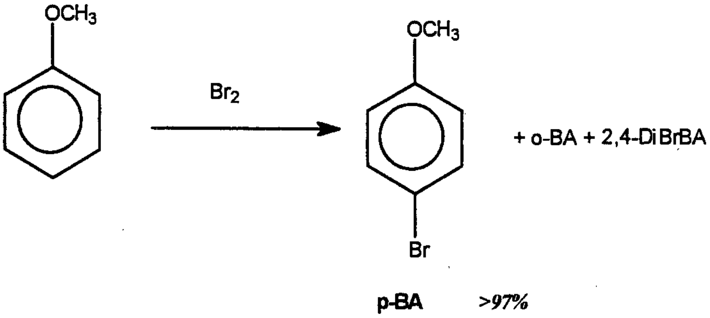
Sunscreen-active Material–OMC

OMC (Octyl *p*-methoxycinnamate) is the most common UV-B sunscreen on the market with an estimated world consumption of ca 5000 tons year^{-1}. The production of this compound is an example of the novel chemistry and economic attractiveness of the Heck reaction on an industrial scale.

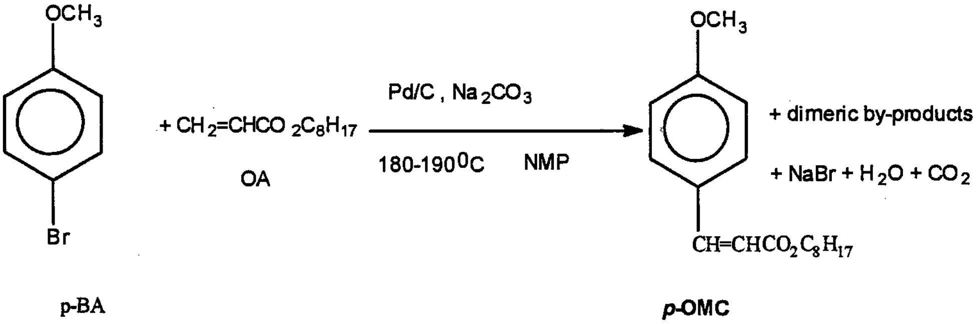
The IMI OMC production process involves two main chemical transformations (Scheme 3) [24]–bromination of commercial anisole produces *p*-bromoanisole (*p*-BA) with *para*-regioselectivity $> 97\,\%$. Heterogeneous Heck coupling between the *p*-BA and commercially available octyl acrylate (OA), in the presence of a Pd/C catalyst, with Na_2CO_3 as HBr sponge, and *N*-methylpyrrolidone (NMP) as the polar, non-protic solvent, furnishes OMC.

A major by-product, 3,3′-dianisyloctyl acrylate (DAOA), results from double Heck coupling between *p*-BA and OA. The dimeric 2,3-DAOA, present in

a. Bromination of anisole



b. Catalyzed Heck coupling between p-BA & OA



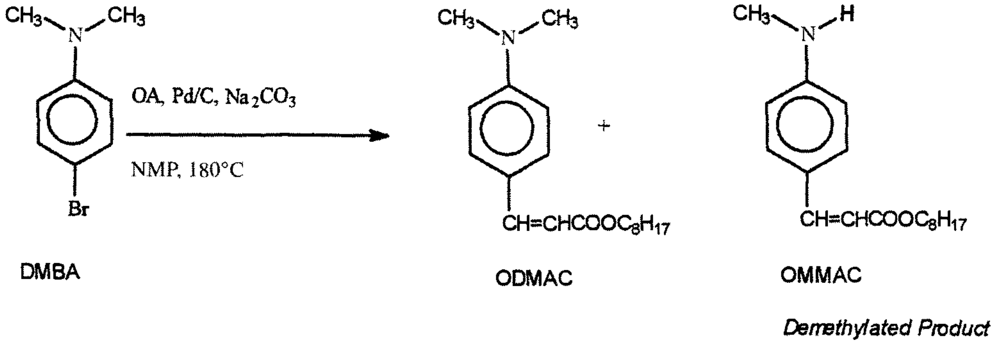
c. Separated by vacuum distillation *75-92%*

Scheme 3. IMI process for production of OMC.

small amounts in the final reaction mixture, undergoes thermal decomposition to give *trans*-dimethylstilbene. Because the IMI OMC process is different from that used by Givaudan [25], and because the FDA considers the active ingredients of sunscreens to be 'over the counter' (OTC) drugs, any new active ingredient must pass the new drug application (NDA). It was important, therefore, because of safety considerations, to prove that IMI OMC product was not mutagenic; this was achieved by separation and Ames testing of each of the four isomers and two by-products.

Mallinckrodt has reported a similar process for manufacture of OMC that involves the diazotization of *p*-anisidine in aqueous iodide to produce *p*-iodoanisole which is then reacted with OA in the presence of trialkylamine (as a base) and Pd/C, without solvent, to yield OMC; the process requires the recovery of iodide and the R_3N with alkali hydroxide [26].

IMI has used its Heck technology to make another sunscreen, ODMAC (octyl dimethylaminocinnamate) a potential UVA + B filter reagent (Scheme 4).



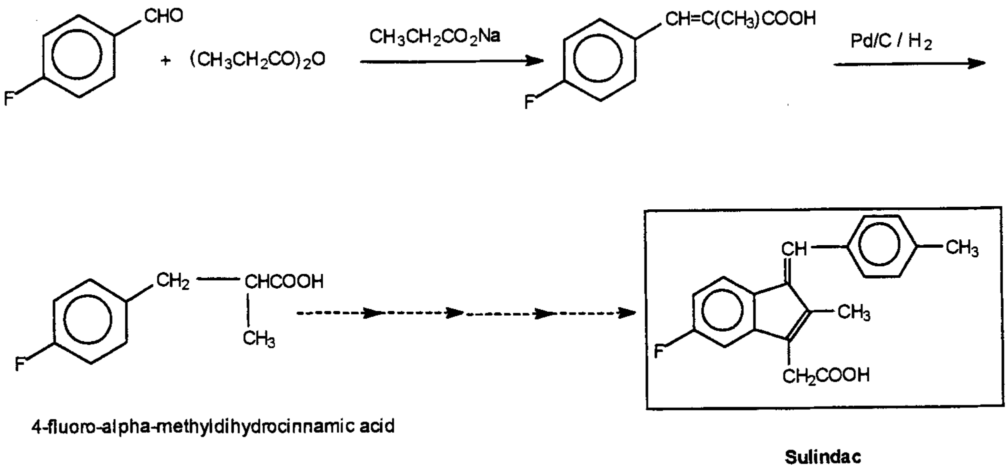
Scheme 4. Preparation of octyl dimethylaminocinnamate (ODMAC).

Intermediates for Sulindac

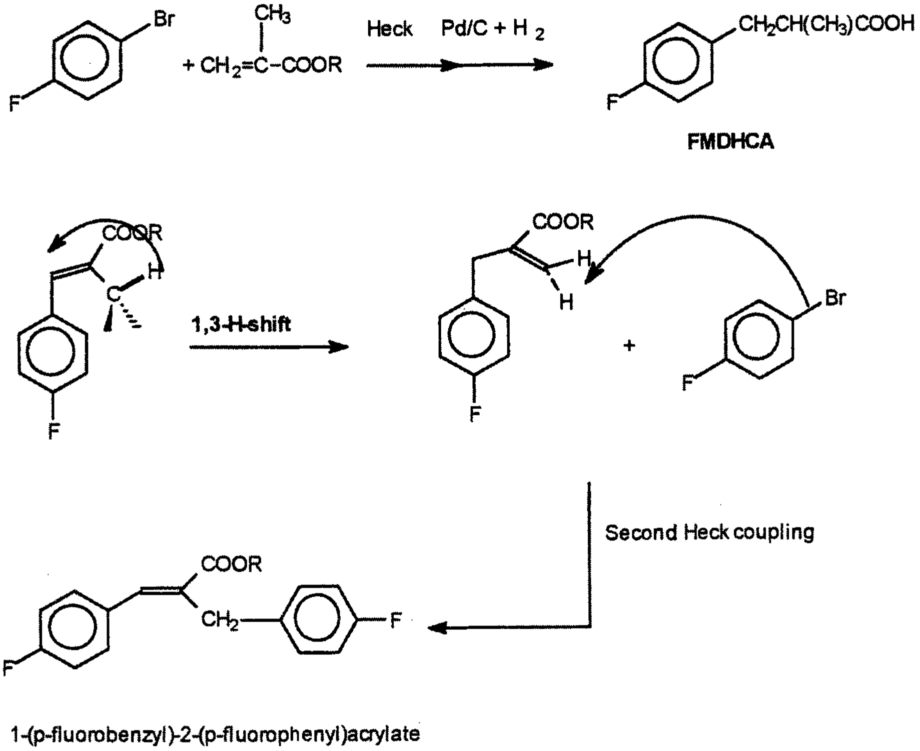
The Heck reaction can also be used to prepare pharmaceutical intermediates for NSAID, e. g. sulindac and dehydronabumetone, from bromoaromatic precursors and commercially available alkenes. The central intermediate in the synthesis of sulindac, as developed by Merck [27], is *p*-fluoro-*α*-methylcinnamic acid ester; condensation of *p*-fluorobenzaldehyde with propionic anhydride gives *p*-fluoro-*α*-methylcinnamic acid. The starting aldehyde is relatively expensive and unstable, and the yield of the Knoevenagel transformation is fairly low (Scheme 5).

The use of Heck technology at IMI has enabled the preparation of the same acid in either one step (in an aqueous medium) or two steps (in a polar non-protic solvent) (Scheme 6) [28]. The *p*-fluoroalkylmethacrylate conversion stage involves an unusual 1,3-hydrogen shift.

Substituted phenyldiazonium salts have been used by Hoechst as precursors for palladium-catalyzed coupling with acrylic acid derivatives. FMDHCA (*p*-fluoro-*α*-methyldihydrocinnamic acid) and its derivatives, for example, were also pre-

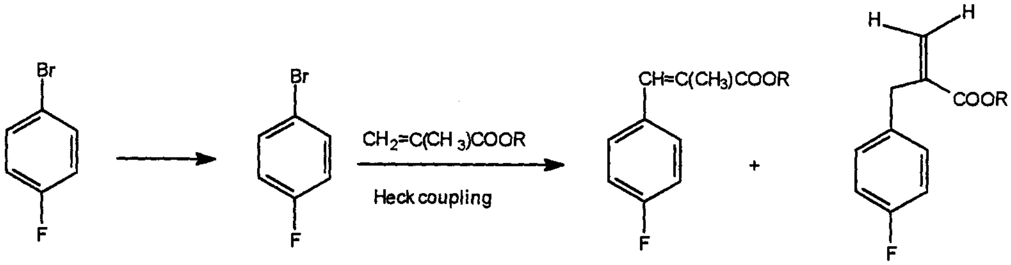


Scheme 5. The Merck route to sulindac.



Scheme 6. The IMI route to FMDHCA.

pared, starting from *p*-fluoroaniline, which is less expensive than *p*-fluorobenzaldehyde (Scheme 7) [29a–d]. A large solvent effect was observed for reaction in methanol or ethanol, which gave the highest yields, but the nature of the catalyst support (Pd/C, Pd/Al_2O_3, Pd/$BaSO_4$, Pd/SiO_2) had little influence [29d].



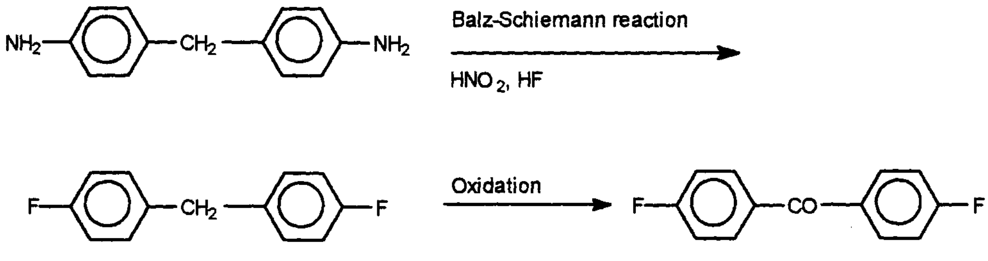
Scheme 7. Preparation of *p*-fluorophenyl-*α*-methylpropenic acid derivatives.

Substituted Benzophenones

IMI has also developed a general route for the synthesis of homo- and heterodisubstituted benzophenones such as 4,4′-difluorobenzophenone (DFBP), 4,3′-difluorobenzophenone, and 4,4′-diphenoxybenzophenone (DPOBP). These substituted benzophenones are important materials, with a variety of uses as specialty monomers (for polyether ketones and polyarylene ether ketones) and pharmaceutical intermediates. These benzophenones are prepared by utilizing Heck technology in conjunction with an oxidative cleavage reaction.

Synthesis of 4,4′-Difluorobenzophenone [30]

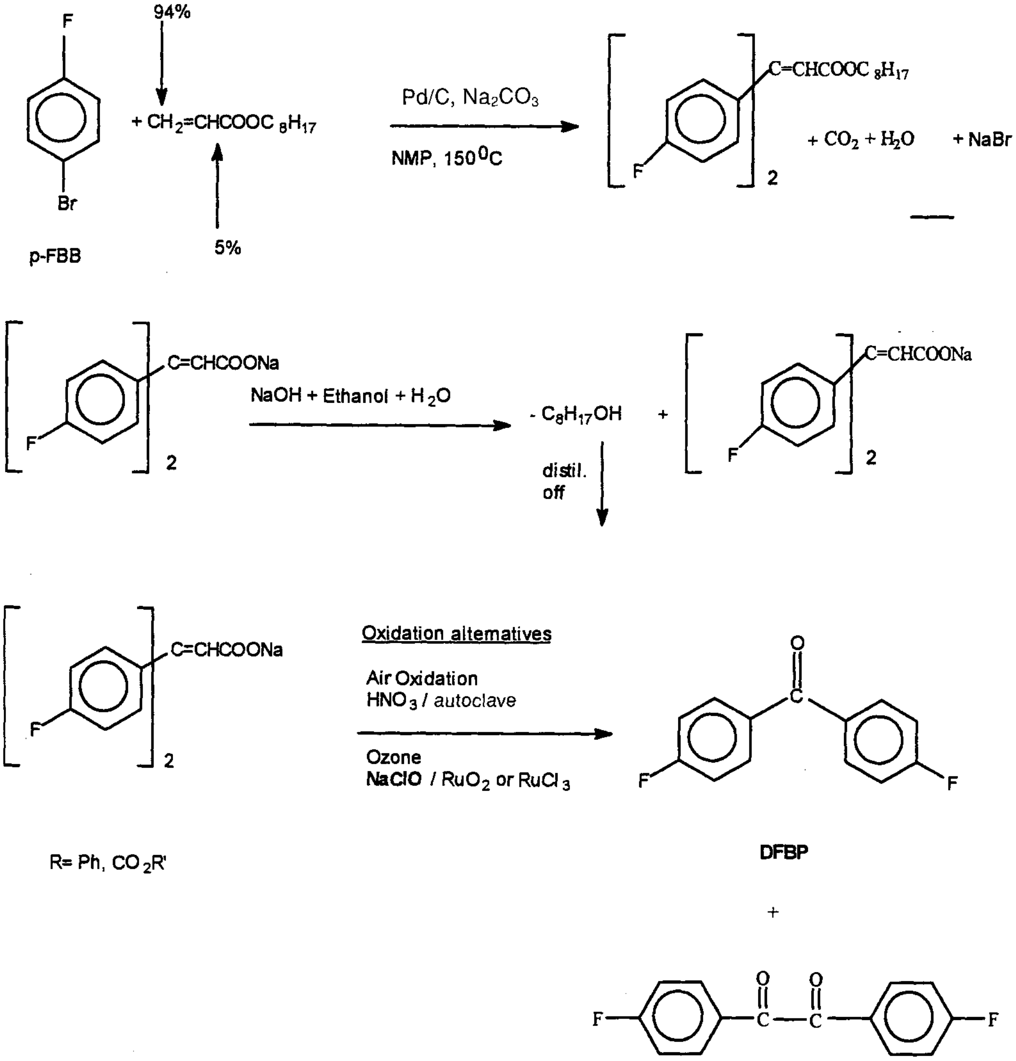
4,4′-Difluorobenzophenone (DFBP) is used by Victrex for the manufacture of the polymer PEEK (ICI), and in the synthesis of the drugs lidoflazine, flunarizine, mioflazine, fluspirilene, and flunarizine (Janssen). The PEEK market grew from 200–300 tons year^{-1} in 1988 to 1000 tons year^{-1} in 1998. Victrex's current production of PEEK consumes ~700 tons DFBP; this will increase to 1400 tons in 2–3 years. DFBF is manufactured by a single producer, Laporte. Their process (Scheme 8) suffers from the drawbacks that the basic raw material, methylenedianiline, is carcinogenic; that it is based on relatively expensive and hazardous technology (Balz–Schiemann), and that large volumes of wastes and effluents are produced.



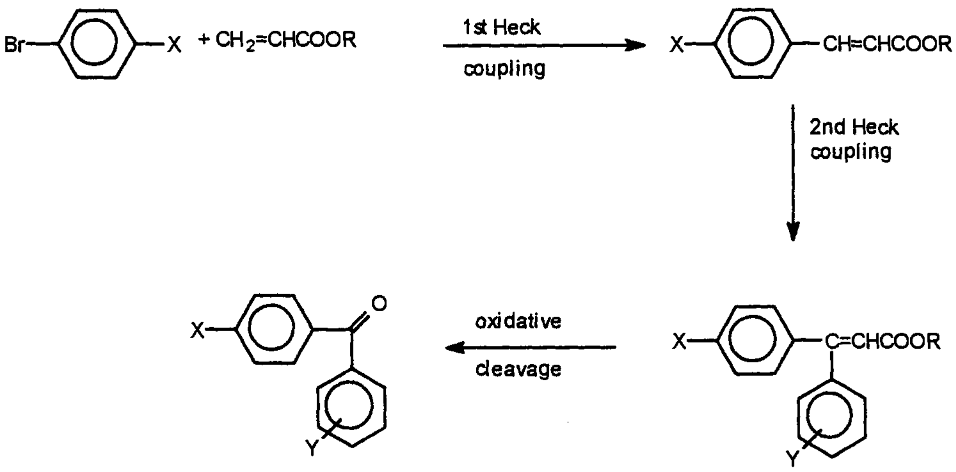
Scheme 8. Laporte manufacturing process for DFBP.

The IMI approach for the synthesis of DFBP starts from *p*-bromofluorobenzene (BFB) and substituted styrene or acrylate at a ratio of 2:1 [30]. The reaction involves the formation of a double-Heck adduct (yield > 90 % with a regioselectivity of 94 % at the C-2 of the acrylate) then catalyzed oxidative-cleavage (95 %) (Scheme 9).

The current method is to perform oxidative cleavage on the corresponding bis-arylacrylic acid sodium salt; this requires an additional step involving alkaline hydrolysis of the bis-aryl acrylate and isolation of the salt. Conducting the Heck reaction in an aqueous medium should shorten the route to the target mole-



Scheme 9. Synthesis of DFBP starting from *p*-bromofluorobenzene.



Scheme 10. Preparation of dihetero-substituted benzophenones.

cule (see, also, the section on the preparation of substituted acrylic acids in aqueous media, below).

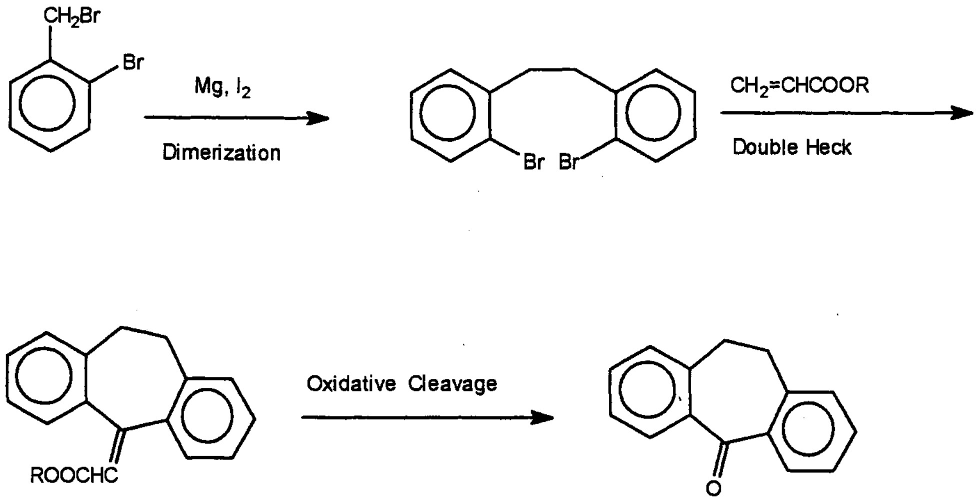
A similar general synthetic route has been used for the preparation of 4,4′- and 4,3′-dihetero-substituted benzophenones [31].

Dibenzosuberone

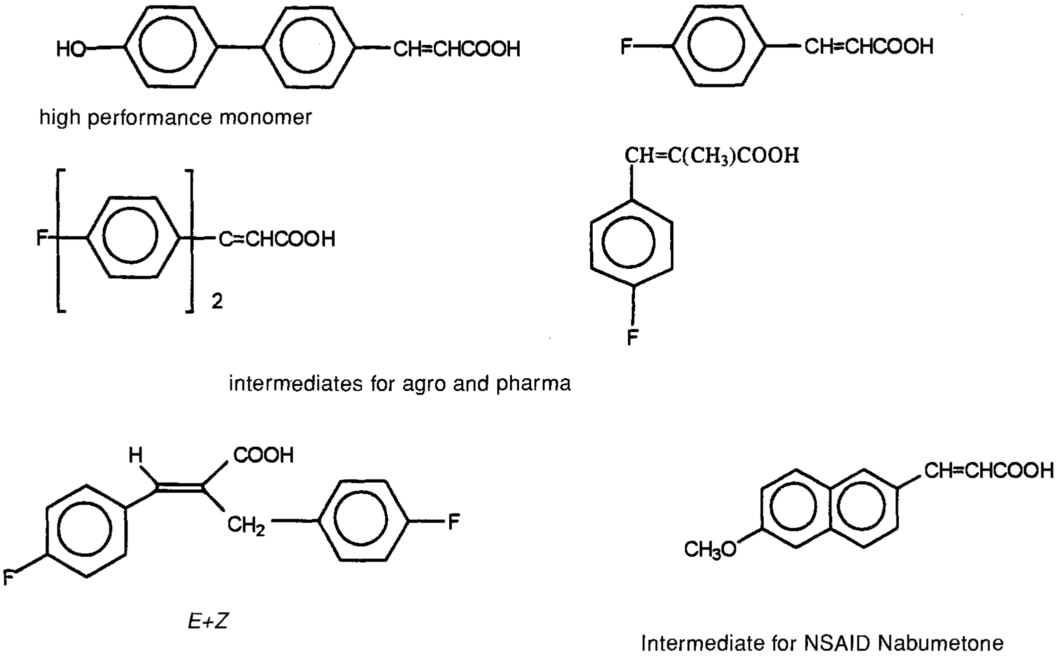
Dibenzosuberone, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one, is an important intermediate in the preparation of psychotropic agents, e. g. the antidepressants amitiptyline and nortiptyline, and other drugs, and was made by an *internal* double Heck coupling in which the dibenzodibromo derivative gave, in the presence of Pd/C, the corresponding dibenzocycloheptane-*exo*-acrylate derivative (Scheme 11) [31b].

Preparation of Substituted Aromatic Acrylic Acids in Aqueous Media

The use of palladium on a solid support in the Heck reaction has been implemented in the synthesis of substituted cinnamic and naphthylacrylic acids (Scheme 12) by reacting appropriate bromoaromatic compounds with the sodium salt of the olefinic acid. These reactions are conducted in a mixed aqueous polar-aprotic medium (2:1 water/NMP) at moderate temperatures (106–110 °C), low loading (ca 11 %), a substrate/Pd ratio of ca 3000, and in an open vessel. NMP was usually found to be the most efficient co-solvent, Na_2CO_3 was used as a base, and NaOH to convert the acrylic acid to the corresponding acrylate salt. A representative example is 4-hydroxyphenylcinnamic acid, a useful intermediate for liquid crystal polymers, prepared from 4-hydroxy-4′-bromobiphenyl. The corresponding esters were manufactured in an autoclave with homogeneous catalysis [32a,b]. This technology has also been implemented in a scale-up manufacture of OMC [33] and DFBP [30a].



Scheme 11. Preparation of dibenzosuberone.



Scheme 12. Intermediates prepared by the Heck reaction.

Aroylation of Alkyl Vinyl Ethers

Halberg [1c] and Augustine [10, 34a–c] studied the reaction of aroyl chlorides and aroyl triflates (as arylating reagents) with alkyl vinyl ethers, in the presence of heterogeneous Pd catalysts, and have analyzed their impact on the regioselectivity of this substitution.

2-Methoxyethenylnitrobenzenes, which are useful as pharmaceutical intermediates, were prepared by application of the Heck coupling reaction between *p*-bromonitrobenzene and methyl vinyl ether in the presence of Pd/C, to give 81 % of a mixture of *E* and *Z* isomers and 10% *p*-nitroacetophenone [35].

10.3.3 Conclusions

It has been demonstrated that the heterogeneously catalyzed Heck reaction affords many new synthetic routes for the preparation of commercial compounds. Numerous products cited in the literature, and the above mentioned cinnamates, ketones, aldehydes, and acids, demonstrate the potential of the technology.

This is a relatively new industrial area that demonstrates the potential growth and advantages of bromine chemistry over that of the other halides [36].

References

[1] (a). Heck, R. F., Accounts of Chemical Research, **1979**, 12, 146; Org. Rx., **1982**, 27, 345; Palladium Reagents in Organic Synthesis, Acad. Press, 1985; (b) Alper, H., Chem. Rev., **1994**, 94, 1047–1062; (c) Hallberg A., Chem. Rev. **1989**, 89, 1433–1445.
[2] Jeffery, T., Adv. Met. Org. Chem. **1996**, 5, 153.
[3] Crisp, G. T., Chem. Soc. Rev. **1998**, 27, 427.
[4] Tsuji, J., Expanding Industrial Application of Pd Catalysts, Synthesis, **1990**, 739
[5] A. de Meijere, Angew. Chem. Int. Ed., **1994**, 33, 2379.
[6] Cabri, W., Acc. of Chem. Res., **1995**, 28, 2.
[7] Chalk, A. J., J. Org. Chem. **1976**, 41, 1206; Givaudan US 1,548,595 (1976).
[8] Hallberg, A., et al, Synthetic Comm. **1985**, 15, 1131.
[9] Hoechst Celanese, EP 03765; Beecham PLC, 88 03,088; Nl 8900,721.
[10] Augustine, R. L., J. Mol. Catal. **1992**, 72, 229.
[11] Ramachandani, R.K et al, Chem. Commun. **1997**, 2071–2.
[12] S. Qiang et al., *Hecheng Huaxue* **1994**, 2, 282–5.
[13] Gou S, et al, CA 112:216310, *Fenzi Cuihua* **1989**, 3, 165–7.
[14] (a) Z. Gou, et al, CA 118:59089 *Fenzi Cuihua* **1992**, 6, 248–54 (b) Reetz, M. T., PCT Int. Appl WO 9804763 A1(1998); (c) M. T. Reetz, Chem. Commun. **1996**, 1921–2.
[15] Semmelhack, M. F. and C. A. Merlic, J. Organomet. Chem. **1990**, 391 C23–C27.
[16] (a) Menhert, C. P. et al., J. Am. Chem. Soc. **1998**, 120, 12289–96; (b) Chem. Commun. 1997, 22, 2215–16.
[17] Gedanken, A., et al, J. Mater. Chem. **1998**, 8, 445050.
[18] (a) Vali, A., et. al, React. Kinet. Catal. Lett. 1997, 60, 189 (b) Dossi, C., Chem. Commun. **1994**, 1245. (c) Shmidt, A. F., Kinetics and Catalysis **1996**, 37, 406 (d). Kiviaho, J., J. Mol. Catal. **1995**, 101, 25. (e) Genet, J. P., Tetrahedron Let. **1999**, 4440, 4815.
[19] (a) Kakimoto., Masa-aki et al, Reactive & Functional Polymers **1996**, 30, 117
(b) Kakimoto., Masa-aki et al., Macromol. **1995**, 28, 7924–28.
[20] (a) Kaneda, K., J. Mol. Catal. **1985**, 29, 99 (b) Reactive Polymers **1990**, 12, 229.

[21] The Industrial Potential of the Palladium Catalyzed Heck Reaction. Eisenstadt, A., 2nd International Conference: Organic Process Research and Development, New Orleans, USA, 21–23 April 1999.

[22] Eisenstadt, A. Utilization of the Heterogeneous Palladium-on-Carbon Catalyzed Heck reaction in Applied Synthesis. Chem. Ind. (Dekker), 75 (Catalysis of Organic Reactions), **1998**, 415–42 Marcel Dekker, Inc.

[23] Eisenstadt, A., Utilization of the Heterogeneous Palladium-on-Carbon Catalyzed Heck Reaction in Applied Synthesis. 17th ORCS, March 29–April 2, 1998, New Orleans.

[24] Eisenstadt, A., and Y. Keren, 'Process for the preparation of OMC', Israel Pat. 97850 (1991), EP 509426 (1992), USP 5 18730 (1993).

[25] GB patent 856411 (1960).

[26] Caskey, D.C., USP 4970332 (1990).

[27] USP 3654349 Merck & Co. (1975).

[28] Eisenstadt, A., 'Process for the preparation of *p*-fluoro-α-methylcinnamic acid derivatives', Israel. Application 108884 (1994).

[29] Beller, M. (a) EP 606058; (b) EP 606057; (c) DE 94116175 (1994); (d) Synlett. **1995**, 441; (e) Tetrahedron Let. **1994**, 35, 8773.

[30] (a) Eisenstadt, A. and Effenberger, R., 'A process for the preparation of DFBP', Israel Pat. Application 103506 (1992); (b) Eisenstadt, A. and Effenberger, R., A process for the preparation of DFBP in aq. medium (personal communication).

[31] Eisenstadt, A. and Effenberger, R., 'Process for the preparation of disubstituted benzophenones', Israel application 115855 (1995); b. Eisenstadt, A. and Maidan, R., personal communication (1993).

[32] a. Hanaoka, T., J. Mol. Catal. **1994**, 88, L113–L116; b. JP 94313956293.

[33] Evenson, A. BCL, 'A process for the preparation of OMC', Israel Application 115060 (1997).

[34] (a) Augustine, R.L. et al,. J. Mol. Catal., **1995**, 95, 277. (b) Chem. Ind., (catalysis of organic reactions) **1996**, 62, 585 (c) Chem. Ind., (catalysis of organic reactions) **1996**, 68, 465.

[35] Hallberg, A., Swedish Pat. SE 447,989.

[36] Bernhagen, *W.*, Specialty Chemicals, **1996**, *16*, 200–206 and references cited therein.

Fine Chemicals through Heterogeneous Catalysis
Roger Arthur Sheldon, Herman van Bekkum
copyright © WILEY-VCH Verlag GmbH,2001

11 Future Outlook

Roger Sheldon, Herman van Bekkum

In the past, catalysis (particularly heterogeneous catalysis) has played a central role in oil refining and commodity chemicals manufacture. Driven by increasingly stringent environmental legislation, there is currently a marked trend towards the application of clean, catalytic methodologies in the synthesis of fine chemicals. Although, hopefully, this book has shown that much progress has been made towards the goal of developing effective methods, based on the use of solid, heterogeneous catalysts, for a plethora of synthetically important organic reactions, the challenge remains formidable–catalysts must have broad scope, high chemo-, regio-, and stereoselectivity, and be sufficiently active and operationally stable. Although much progress has been achieved in the use of solid acids and, more recently, solid bases in organic synthesis, there is still much room for improvement, e. g. development of solid-acid catalysts with broader scope in Friedel–Crafts acylations. Often it is not clear whether the desired catalysis arises from Lewis acid or Brønsted acid sites and, by the same token, Lewis or Brønsted basicity. It was, for example, recently shown that aromatic hydroxyalkylation with epoxides, which was singularly unsuccessful with solid Brønsted-acid catalysts, is catalyzed by solids containing only Lewis acid sites [1].

Selectivity is the key to success and one way to influence the selectivity of heterogeneous catalysts is by addition of modifiers such as metal cations, strongly adsorbing anions, and heteroatom (O, N, S, P)-containing organic compounds. In a recent review of the subject Mallat and Baiker [2] distinguished two types–catalyst modifiers and reaction modifiers. In the former the modifier is added to the catalyst during synthesis whereas in the latter the catalyst is modified before or during the reaction by adding modifiers to the reaction mixture, i. e. modification is in situ.

The use of both types of modifier to influence the selectivity of heterogeneous catalysts is not new. It has long been known, for example, that modifiers can have a powerful selectivity-enhancing effect in catalytic hydrogenation; the Rosenmund reduction of acid chlorides to aldehydes is an early example of this. Another well-known modifier effect is rate and selectivity enhancement by bismuth in precious metal-catalyzed oxidations (Section 9.3). We feel, however, that the enormous potential of catalyst and reaction modifiers for influencing selectivity has yet to be exploited.

Progress is often hampered by a lack of understanding of the underlying mechanisms of the rate- and/or selectivity-enhancing effects of modifiers. The lack of mechanistic understanding is largely a result of the paucity of available techniques for in situ characterization. A prerequisite for a modifying effect is generally a sufficiently strong interaction with the active site. As was noted by Paracelsus a long time ago, in another context, it is the dosage that counts–substances that are catalyst poisons in high concentrations might often have a positive, selectivity-enhancing effect at low concentrations, typically 0.01–1 mol% relative to the substrate [2].

An important example, in the context of the synthesis of fine chemicals is the use of chiral modifiers to promote enantioselective catalysis, e. g. of hydrogenations as described in Section 8.11. The mechanism of enantioselection is often poorly understood. A better understanding of the underlying mechanisms of chiral modification could broaden the scope of enantioselective hydrogenation over solid catalysts, which is currently rather limited.

Alternatively, solid catalysts for a wide variety of processes involving organometallic intermediates, including enantioselective variants thereof, can be prepared by immobilization of metal complexes on solid supports [3]. Considerable progress is being made, for example, in the heterogenization of (chiral) metal complexes by grafting or tethering to the inner walls of the MCM-41 family of mesoporous silicas. Functionalization of pendant surface silanol groups, with amine, carboxylate, or phosphine moieties, provides the possibility of designing novel solid catalysts containing high concentrations of accessible and well-defined active sites [4]. Confinement of the active site and substrate within the mesoporous channels is expected to enhance the effect of (chiral) directing groups on regio- and enantioselectivity, compared to the situation in homogeneous solution. The feasibility of this approach was recently demonstrated in a palladium-catalyzed allylic amination where both regio- and enantioselectivity were enhanced by use of a mesopore-confined catalyst rather than homogeneous or silica-supported equivalents [5]. Another recent example involves enantioselective diethylzinc addition in a proline-derived ligand immobilized on mesoporous silicas [6]. This approach seems to hold considerable promise for meeting the future challenge of developing robust, recyclable catalysts for asymmetric syntheses.

Similarly, the fabrication of nanostructured noble metals in micro-/mesoporous cavities and channels affords improved catalysts for a variety of reactions [7,8]. According to a recent review [7] novel ship-in-a-bottle nanotechnology and related techniques could provide the possibility of designing tailor-made noble metal catalysts, including chirally modified variants, for use in the synthesis of fine chemicals.

Catalysis in water, or aqueous biphasic systems, continues to attract attention [9]. The pioneering studies of Kobayashi and coworkers [10] demonstrated that lanthanide triflates are, contra-intuitively, excellent Lewis acid catalysts in aqueous media. More recently this has been extended to their immobilization, by microencapsulation in polystyrene films [11] or attachment to organic polymers [12], affording catalysts which have high activity in water and can be recycled by filtration or centrifugation. Similarly, the use of palladium complexes of guanidinium-substituted phosphines as supported aqueous phase catalysts for Heck couplings and related reactions has recently been reported [13].

Although development times which do not coincide with the time constraints imposed by market demands remain a major obstacle to the widespread application of (heterogeneous) catalysis in fine-chemicals manufacture, this situation is rapidly changing with the advent of high-throughput screening techniques [14–17]. As noted in a recent review [14] the development of this powerful new technology will breathe new life into chemical catalysis. Libraries of (chiral) ligands and novel solid-state materials can be synthesized by combinatorial methodologies and subjected to automated high-throughput screening. The effects of catalyst and reaction modifiers (see earlier) can be similarly screened. The combination of high-throughput screening and process intensification via miniaturization [18] will lead to a substantial acceleration of both catalyst discovery and development.

The future development of catalytic processes for the fine chemicals industry will also be stimulated by the integration of catalysis with process technology and reactor engineering. For example, the classical concept of reaction and product separation steps as separate unit operations is becoming rather out-dated and there is a distinct trend towards integration of these operations. Thus reactive distillation, e. g. over sulfonic acid resins, is already industrial practice. Recent developments in zeolitic (catalytic) membranes [19,20] are certainly relevant in this context. Similarly, integration of different catalytic steps to give catalytic cascade reactions, e. g. by using bi- or multifunctional catalysts also has obvious benefits for the overall economics of processes. For example, epoxidation combined with regioselective ring closure has been executed over Ti-zeolites and Ti mesoporous materials [21,22]. Acid-catalyzed hydrolysis of polysaccharides has been combined with metal-catalyzed hydrogenation [23,24].

Nature offers a broad spectrum of interesting starting materials. An increasing number of short routes from natural compounds to useful chiral building blocks has been identified. A recent fine example is the synthesis of the two enantiomers of a chiral lactone starting from inexpensive carbohydrates [25]. Nature's catalysts are based on proteins and these can be used as scaffolds for the design of semisynthetic catalysts, e. g. the vanadate–phytase system as a novel enantioselective oxidation catalyst [26]. Indeed, a mechanistic understanding of enzyme catalysis can provide a basis for the design of new efficient biomimetic catalysts [27].

In conclusion, the time seems ripe for the widespread application of (heterogeneous) catalysis in fine-chemicals synthesis, and recent developments seem to suggest that this will happen in the near future. The result will be fine-chemicals manufacturing that is both cost-effective and environmentally benign. A worthy goal.

References

[1] A. Brait and M.E. Davis, in Abstracts California Catalysis Society Meeting, 14 October 1999, Los Angeles, p. 10.
[2] T. Mallat and A. Baiker, *Appl. Catal. A:* General 2000, 200, 3–22.
[3] K. Fodor, S.G.A. Kolmschot and R.A. Sheldon, *Enantiomer* **1999**, *4*, 489.
[4] J.M. Thomas, *Angew. Chem. Int. Ed.* **1999**, *38*, 3588; T. Maschmeyer, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 71.
[5] B.F.G. Johnson, S. Raynor, D.S. Shephard, T. Maschmeyer, J.M. Thomas, G. Sankar, S.Bromley, R. Oldroyd, L. Gladden and M.D. Mantle, *Chem. Commun.* **1999**, 1167.
[6] S.J. Bae, S-W. Kim, T. Hyeon and B.M. Kim, *Chem. Commun.* **2000**, 31.
[7] M. Ichikawa, *Plat. Met. Rev.* **2000**, *44*, 2.
[8] D.S. Shephard, T. Maschmeyer, G. Sankar, J.M. Thomas, D. Ozkaya, B.F.G. Johnson, R. Raja, R.D. Oldroyd and R.G. Bell, *Chem. Eur. J.* **1998**, *4*, 1214.
[9] G.A. Verspui, G.J. ten Brink and R.A. Sheldon, *Chemtracts–Org. Chem.* **1999**, *12*, 777.
[10] S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15.
[11] S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.* **1998**, *120*, 2985.
[12] S. Nagayama and S. Kobayashi, *Angew. Chem. Int. Ed.* **2000**, *39*, 567.
[13] J. Williams and M. Leese, *SynLett.* **1999**, 1645.
[14] B. Jandeleit and W.H. Weinberg, *Chem. Ind. (London)* **1998**, 795.
[15] B. Jandeleit, H.W. Turner, T. Uno, J.A.M. van Beek and W.H. Weinberg, *Cattech* **1998**, *2*, 101.
[16] M.T. Reetz, M.H. Becker, K.M. Kühling and A. Holzwarth, *Angew. Chem. Int. Ed.* **1998**, *37*, 2647.
[17] A. Holzwarth, H-W. Schmidt and W.F. Maier, *Angew. Chem. Int. Ed.* **1998**, *37*, 2644.
[18] C. Ramshaw, *Green Chemistry* **1999**, *1*, G15.
[19] M. Tsapatsis, G. Xomeritakis, H. Hillhouse, S. Nair, V. Niokakis, G. Bonilla and Z. Lai, *CATTECH* **1999**, *3*, 148.
[20] K. Jansen and T. Maschmeyer, *Top. Catal.* **1999**, *9*, 113.
[21] A. Corma, M. Iglesias and F. Sánchez, *Chem. Commun.* **1995**, 1635.
[22] A. Bhaumik and T. Tatsumi, *Chem. Commun.* **1998**, 463.
[23] Synfina-Olefina S.A. (P.A. Jacobs and H. Hinnekens), Eur. Pat. Appl. 329.923 (1989).
[24] A.W. Heinen, Thesis Delft University of Technology, 2000.
[25] See *Chem. Eng. News*, February 14, 2000, pp. 102–104.
[26] F. van de Velde, L. Könemann, F. van Rantwijk and R.A. Sheldon, *Chem. Commun.* **1998**, 1891.
[27] For a recent review see: A.E. Shilov, *Cattech* **1999**, *3*, 72.

Index