Solid Acid Catalysts for Acylation of Aromatics

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1.0 Commercial significance of aromatics acylation reactions

Acylation of aromatic compounds to prepare aromatic ketones is of commercial relevance and significance in varied areas of fine chemical and pharmaceutical industry. In Friedel-Crafts acylation, an aromatic ketone is formed by reaction of an aromatic compound with an acylating agent, such as acyl halide, an acid anhydride, or an ester, in the presence of an acidic catalyst

$$C_6H_6 + RCOX \xrightarrow{\text{catalyst}} C_6H_5COR + HX \quad R= \text{alkyl or aryl}$$

Aromatic acylation reaction, an electrophilic introduction of an acyl (RCO) group to an aromatic ring, is normally carried out using over-stochiometric amounts of metal halides as catalysts. Acylation is extremely versatile, leading to a variety of products that include aromatic aldehydes, alkyl aryl ketones, symmetric and unsymmetric diaryl ketones and cyclization products (1-15). A variety of acylation reactions using aromatic substrates are carried out on a industrial scale largely as a batch reaction. The synthesis of substituted acetophenones employing acylation is an important step for the production of a variety of precursors which find application during the production of pharmaceuticals[1], paint additives[2], photoinitiators[3], fragrances[4], plastisizers [5], dyes[5], and other commercial products as listed below:

- Acetophenone is synthesized by acylation of benzene using acetic anhydride and finds usage as perfume, pharmaceutical, solvent and plasticizer [5].
- 4-Methylacetophenone prepared by acylation of toluene using acetic anhydride finds applications as a perfume[5].
- 4-Isobutylacetophenone prepared by acylation of isobutylbenzene is an intermediate for the production of ibuprofen, an over the counter pain killer[6].
- 2-Acyl-6-methoxynaphthalene prepared by acylation of 2-methoxynaphthalene is a precursors for synthesis of naproxen, a non steroidal anti inflammatory drug[7].
- Para acylated anisole synthesized by acylation of anisole and is a useful intermediate for the production of 2-(4-methoxy benzoyl) benzoic acid sodium salt of which is a sweetening agent[8].
- Para acylated veratrole synthesized by acylation of veratrole is useful intermediate for the production of vesnarinone, which is a cardiotonic[9].
- Benzophenone from acylation of benzene with benzoyl chloride is used in perfumery, pharmaceutical and insecticide industry[5].
- Chloropropyl-4-fluorophenylketone synthesized by acylation of fluorobenzene with chlorobutyroyl chloride is used in pharmaceutical industry[5].

- α,α, 2,4-tetrachloroacetophenone synthesized by acylation of 1,2-dichlorobenzene with dichloroacetylchloride is useful insecticide[5].

- Perfluoroacylbenzene sulfonates prepared by Friedel-Crafts acylation of perfluoroacylhalide and benzene followed by sulfonation are used as additives in fire extinguisher compounds and galvanizing baths.
- 1-(5-chloro-6-methoxy-2-naphthyl)-1-propanone prepared by acylation of 1-chloro-2-methoxy naphthalene with propanoyl chloride is used as an intermediate for the anti-inflammatory and anlgesic[10] .
- 4,4'-bis-dimethylaminobenzophenone by acylation of N,N-dimethylaniline with phosgene is useful in dyes industry[5].
- 2-benzoylbenzoic acid prepared by acylation of benzne with phthalic anhydride is used for the synthesis of anthraquinone[5].
- Trihaloacyl aromatics prepared by acylation of aromatics with CX_3COX (X=Cl, Br) are used as monomer in the preparation of polycarbonates, polyesters, polyamides, polyketones and polyurathene[11].
- 4-acylated thioether produced by Friedel-Crafts acylation of phenyl methyl thioethers with 3-methylbutanoyl chloride is used as an intermediate for antihypertensive drugs[12].
- 3,3-dimethyl-5-(3-carboxypropionyl)-2-indoline synthesized by Friedel-Crafts acylation of 3,3-dimethyl-2-indolinone by succinic anhydride is used as an intermediate in the preparation of inotropic agents for heart failure[13].
- 1-Naphthylacetic acid derivatives showing anti-inflammatory, analgesic and antipyretic activities are prepared by Friedel-Crafts acylation of methyl-1-naphthylacetate at the 4 position with $(CH_3)_2CHCOCl$ followed by Clemenson reduction[14].
- 4-cyclohexylacetophenone prepared by Friedel-Crafts acylation of cyclohexylbenzene is used as an intermediate for the preparation of 2,4-dioxo-4-substituted-1-butanoic acid derivatives, which useful in treating urinary tract calcium oxalate lithiasis.[15]

2.0 Conventional catalysts used and their drawbacks

Various type of acidic catalysts reported to be used for acylation reactions include:

- **Acidic Halides**

Friedel-Crafts acylation reactions are reported[16] to be catalyzed by a variety of Lewis acids such as $AlCl_3$, $FeCl_3$, BF_3, BCl_3, BBr_3, $BeCl_2$, $CdCl_2$, $ZnCl_2$, $GaCl_3$, $GaBr_3$, $SbCl_3$, $BiCl_3$, $TiCl_4$, $ZrCl_4$, $SnCl_4$, UCl_4, and $SbCl_5$.

- **Metal Alkyls and Alkoxides**

Metal alkyls and alkoxides are active catalysts in Friedel-Crafts reactions because of their Lewis acidity. However, the Lewis acidity in these systems, particularly for metal alkoxides, is weakened by hyperconjugation effects. Nevertheless, an important industrial application is the acylation of phenols, in which aluminum phenoxide is used as the catalyst.

- **Protonic Acids**

A variety of proton acids can be used in Friedel-Crafts reactions, the most important examples being sulfuric acid, anhydrous hydrogen fluoride, trifluoroacetic acid, hydrogen chloride, and phosphoric acids.[17] Combinations of Lewis acids and proton acids, such as $HCl\text{-}AlCl_3$, $HCl\text{-}GaCl_3$, $HF\text{-}BF_3$, $H_2SO_4\text{-}BF_3$, and $HF\text{-}SbF_5$, also can be applied and these act as conjugate proton superacids. [18,19]

- **Liquid super acid**

A acid stronger than 100% sulfuric acid (Ho values < –11.9) are called super acid[20] Fluorosulfonic acid is one of the strongest Bronsted acid known with Ho = -15.1. This acidity is some what lower than that of H_2SO_4-SO_3, i.e., $H_2S_2O_7$. Acid system stronger than anhydrous aluminium chloride are classified as super Lewis acid[20]. By this definition, Lewis acid such as SbF_5, NbF_5, AsF_5 and TaF_5 are categorized as Lewis super acid.

In industrial applications, Lewis acid metal halides such as $AlCl_3$, $FeCl_3$, $ZnCl_2$ in more than stoichiometric amounts are most widely used for acylation reactions because of the low cost and availability. However, these acids have following drawbacks which necessitates to look for alternative catalyst systems.

- Metal halides form stable 1:1 molar adduct with aryl ketone product which is more stable than the adduct formed between metal halide and acylating agent. Thus, the metal halides is often applied in stochiometric or higher amounts and not in catalytic amounts.At least a two fold amount of catalyst is necessary if carboxylic acids or esters are the acylating agent, and in case of anydrides, a threefold amount (but 1.5 mole per mole of product) is needed.
- Post synthesis work up to cleave the metal halide-product adduct by hydrolysis and neutralization generates a high amount of aqueous effluents, treatment of which adds to the overall process cost.
- Inability to recover and re-use the catalyst from the effluent.
- Corrosive reaction system that requires expensive reactors and equipment for the purification of the waste gas, which consist not only HCl, but also chlorinated hydrocarbons, which are hazardous to health as well as to environment.

Industrially, anhydrous hydrogen fluoride is used for the acylation of isobutylbenzene, which does avoid above mentioned waste formation, however, HF has associated problems due to its toxic, and corrosive nature and this requires special material of construction for the reactors. To overcome the above drawbacks, there have been concerted attempts to replace the conventional homogeneous catalysts by heterogeneous catalysts, which have to be used in stoichiometric amounts and are not corrosive;can be easily separated and re-used several times or used in a continuous fixed-bed process. Since the work of Chiche et al. (21-22) on the acylation of toluene by C_2-C_{22} alkanoic acids using transition metal or rare earth cation exchanged zeolite Y, it is well recognized that solid acids such as zeolites can advantageously replace conventional acylation catalysts, variety of zeolites have been studied[23] for acylation of aromatics. Besides, a large number of other solids namely modified clays, sulfated zirconia, ion exchange resins[24] heteropoly acid[25] supported ionic liquids[26], proton or Lewis acids on a support and Nafion or Nafion like composites have appeared in the literature for acylation of following aromatic substrates.

- Benzene, Toluene, Xylene, Isobutylbenzene (21, 27-34)

- Ethers like anisole, veratrole (35-66), 2-methoxynaphthalene (67-78)
- Phenols (79-81)
- Alkenes (82-83)
- Naphthalene (84-85), biphenyls (86) and tetralin (87)
- Aromatic heterocyclic compounds like furan (88), thiophene (89,90), benzofurans (91-97)

However, among the above mentioned solid acids, only HY and Hβ have been commercially used for the acylation of anisole and veratrol. Rhodia introduced[44-45] first industrial application of solid acid liquid phase acylation of anisole and veratrole with acetic anhydride over HY and Hβ in a recyclic fixed bed reactor. Though. there are large variety of aromatic substrates studied for acylation reactions using solid acids, discussion is focused on the recent developments on the acylation of anisole, veratrole, 2-methoxy naphthalene toluene and isobutylbenene with emphasis on our recent work in the present paper.

3.0 Acylations of aromatic ethers

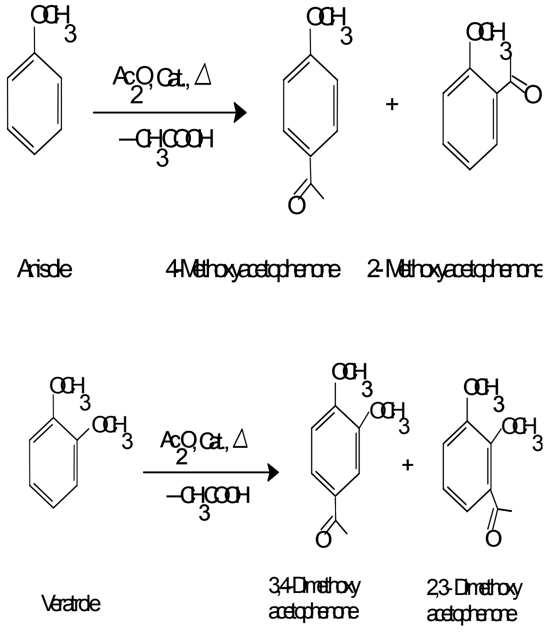
Studies on the acylation of anisole, veratrole and 2-methoxynaphthalene has drawn the attention of researchers due to commercial importance of their acylated ketones. The various solid acid studied for these ethers are briefly reviewed in the following sections.

3.1 Acylation of anisole and veratrole

Anisole (Methoxybenzene) and veratrole (1,2-Dimethoxybenzene) are aromatic ethers having one and two $-OCH_3$ groups respectively. As stated earlier, para acylated product of these aromatic ethers, 4-methoxyacetophenone (4-MAP) and 3,4-dimethoxy acetophenone (3,4-DMAP), as shown in Scheme-1, are of commercial importance in the fine chemicals industries, especially as intermediates for the synthesis of fragrances and pharmaceuticals. For example, acetoveratrone is an intermediate for the synthesis of papaverine (1-(3,4-dimethoxybenzyl)-6,7-dimethoxy isoquinoline) an opium-alkaloids antispasmodic.

The application of the zeolites namely H-Beta, H-Y, H-ZSM-5 and H-Mordenite in the acylation of anisole and veratrole has been reported using phenylacetyl and phenyl propionyl chloride by Corma et al.[41] and by acetic anhydride and phenyl acetyl chloride as acylating agent by Harvey et al.[42] H-Beta was observed to be the most active catalysts for the acylation of aromatic compounds. Akira et al.[55] have studied the reaction of veratrole and propionyl chloride, in the presence of zeolite-Beta. The reaction mixture was refluxed for three hours to give 70% of 3,4-dimethoxypropiophenone. Jaimol et al.[56] have been reported selective propionylation of veratrole to 3,4-dimethoxypropiophenone using zeolites as catalysts. They have studied the catalytic liquid phase propionylation of veratrole over a series of zeolite catalysts. Zeolite H-beta is found to be an effective catalyst for the selective conversion of veratrole to 3,4-dimethoxypropiophenone (3,4-DMPP). The SiO_2/Al_2O_3 ratio of zeolite H-Beta is higher (SiO_2/Al_2O_3)=26 than the H-Y and RE-Y (SiO_2/Al_2O_3=4.1). The performance of zeolite H-Beta is compared with that of conventional catalyst, $AlCl_3$. The conversion of veratrole increases with the increase in reaction time, catalyst concentration and reaction temperature., whereas it decreases with the increase in veratrole/propionic anhydride molar ratio. Propionlyation of 1,3-dimethoxybenzene (1,3-DMB) and 1,4-dimethoxybenzene (1,4-DMB) is also investigated over zeolite H-Beta catalyst. The zeolite H-Beta was recycled two times with a marginal decrease in catalytic activity.

Gunnewegh et al.[40] have studied the potential of zeolites to catalyze aromatic acylation with carboxylic acids**.** The intramolecular acylation of 4-phenylbutyric acid as a model reaction for Friedel-Crafts acylation catalyzed by zeolites in the liquid phase.



Scheme-1: Acylation of anisole and Veratrole.

Gunnewegh et al.[40] have studied the potential of zeolites to catalyze aromatic acylation with carboxylic acids**.** The intramolecular acylation of 4-phenylbutyric acid as a model reaction for Friedel-Crafts acylation catalyzed by zeolites in the liquid phase. This reaction is catalyzed by zeolite H-Beta in 4-chlorotoluene as a solvent. The catalytic ability of H-Beta was demonstrated by the fact that at reflux temperature the total turnover number (TON) was found to be 35. However, the acylation of toluene or butylbenzene with carboxylic acids was slow; the unbalanced adsorption equilibrium between the two reactants on the H-Beta (Si/Al=12) may be a contributing factor in this case. The acylation of anisole by carboxylic acids or acid anhydrides however, was readily catalyzed by zeolite H-Beta.

Raja et al.[57] have also reported the benzoylation of 1,2-dimethoxybenzene with benzoic anhydride and substituted benzoyl chlorides over large pore zeolites**.** The benzoylation of 1,2-

dimethoxybenzene with benzoic anhydride and substituted benzoylchlorides has been investigated in the liquid phase with chlorobenzene as a solvent over the H-forms of various zeolites. H-Y and H-Beta have been shown to be efficient catalysts in this reaction, and selective formation of the corresponding dimethoxybenzophenones was observed. The effect of various experimental parameters on the initial rate of the reaction of veratrole with benzoic anhydride over H-Y zeolite has been studied. A suitable mechanism based on the difference of adsorptions of the aromatic substrate and the acylating agent was proposed. Moreover, the study of the reaction of veratrole with a series of substituted benzoylchlorides (4-CH3, 4-OCH3, 4-tert-Bu, 4-Cl, 2-Cl and 2-Br-benzoyl chlorides, respectively) over the same H-Y zeolite led to conclusion that, due to the high reactivity of the aromatic substrate, the electrophilicity of the acylating agent does not play a relevant role under the given heterogeneous conditions.

Aromatic ketones, i.e., 4-acylanisoles, were prepared with high yield by using carboxylic acids as acylating agents and a HY zeolite as catalyst was reported[47] by Wang et al. The acylation of anisole with butanoic acid gave 4-butanoylanisole with 58% yield.

A series of aromatic ketones, 4-acyl anisoles, were synthesized[58] with high yield through Friedel-Crafts acylation of anisole with carboxylic acids over catalytic amounts of hydrothermally treated HY zeolites. The nature of the active sites of zeolites for the Friedel-Crafts acylation reaction was ascertained after a study of the reaction over HZSM-5 and H-Y at different temperatures. Both Lewis and Bronsted acid sites of the zeolites were active, but Lewis acid sites were more effective and selective for the acylation of the aromatics ring.
The reaction of anisole and acetic anhydride with mordenite as a catalyst at 160^{o}C under 20 bar of N_2 pressure to give 75% conversion with 98% selectivity for *p*-methoxyacetophenone is reported[54]. This process operates at high temperature and very high pressure and also needs a solvent for uniform mixing.

Modified zeolites were found [59] to be active catalysts in the Friedel-Crafts acylation of anisole by acetyl chloride and acetic anhydride. The effect of two different modifications of the zeolites namely rare earth exchange and varying the Si/Al ratio was studied. For the rare-earth modified zeolites, the activity was found to be dependent on the rare earth content, and the yield increased with the level of lanthanide even up to 93% exchange. Dealuminated Y-zeolites were also found to be very active, and an almost linear increase in the yield with decreasing aluminum fraction was found. This has been attributed to the increased hydrophobicity of dealuminated zeolites. Zeolite Beta was also found to be very active in the reaction.

The synthesis in high yield of a series of 4-acylanisoles was performed through the Friedel-Crafts reaction of anisole with alkanoic or substituted benzoic acids in the presence of an ultra stable Y zeolite (USY) catalyst by M. Y. Dao et al.[47]

Regio-selective acylation of anisole with carboxylic acids over H-ZSM-5 gave [58] the phenyl carboxylic ester at <130^{o}C while at >150°C temperature, 4-acyl anisole was the predominant product. Acylation of anisole with AcOH at 120°C gave a 1.1:98.9 mixture of 4-acyl veratrole and PhOAc with 29.2 mol% conversion whereas; at 150°C a 63.3:36.7 mixture of the same products was obtained with 90.4 mol% conversion

Recently, Hölderich et al.[60] has been reported the acylation of aromatics using supported ionic liquids as catalyst. They used chloroferrate ionic liquid and charcoal as a carrier. Acylation of benzene, anisole and toluene were performed on various type of ionic liquid. Besides zeolites, acylation of anisole was also investigated[61] in the presence of silica supported HPA using acetic anhydride, as an acylating agent. They exhibit very high activity, yielding 98 % para product at 90-110° C.

Choudary et al.[62] studied the acylation of aromatic ethers with acid anhydrides in the presence of cation exchanged clays viz., $Fe^{+3}$and Zn^{+2} exchanged montmorillonite clays. The reaction mixture of 46 millimoles of anisole and 10 millimoles of acetic anhydride and 250mg of catalysts was stirred under nitrogen atmosphere. Conversion in the range of 25 to 70 percent with 100% selectivity towards the para position after 10 hours is reported.

Yadav et al.[63] has reported acylation of veratrole (70% within 2 hours) by acetic anhydride using 20% dodeca tungstophosphoric acid supported on HMS mesoporous silica as a catalyst. This catalyst unlike zeolite based catalyst was reported to be stable without any deactivation.

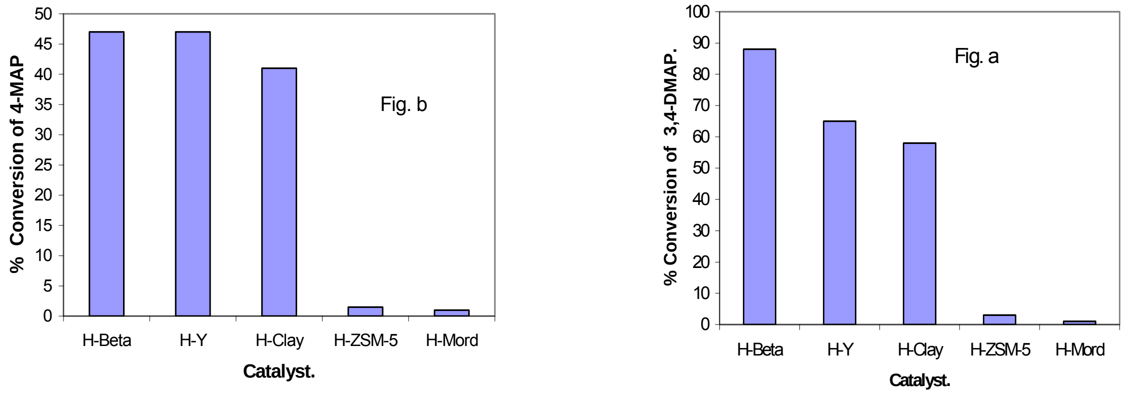


Figure-1: Percent conversion of 4-MAP a) 3,4-DMAP (b) obtained on acylation of veratrole

We have studied the acylation of anisole and veratrole with rare earth exchanged zeolites and clays without using any solvent. Acylation of anisole and veratrole was studied using zeolites BEA, Y, ZSM-5, Mordenite and clay Montmorrilonite both in their H and rare earth cation exchanged forms. Reaction conditions used were as : 40 mmol. of anisole/veratrole and 40 mmol. of acetic anhydride; Cat. weight 2g; Activation of zeolite based catalyst was done at 400 °C for 4 hrs. in muffle furnace while clay was activated at 120 °C for 12 h. Reaction temperature-100° C; Pressure=1 Atm.

Percentage conversion for 4-methoxy acetophenone (4-MAP) and 3,4-dimethoxy acetophenone (3,4-DMAP) is given in Figure 1 for different H-zeolites and proton exchanged clay. From the data, it is observed that among all the catalysts, zeolite- Beta, zeolite -Y and H-Montmorillonite show high activity towards both the reactions, but Mordenite and H-ZSM-5 do not catalyze these reactions under the reaction conditions studied. Lower conversion for mordenite and ZSM-5 is attributed to their smaller pore dimensions compared to Y and Beta which might be causing lower diffusion of reactants / products in the pores. Molecular diameters of anisole, veratrole, 4-acylanisole and 4-acylveratrole from molecular volumes calculated using software Desktop Molecular Modeler are 6.3, 7.0, 7.0 and 7.4A^o respectively. Pore aperture dimensions of ZSM-5 and mordenite are 5.1 x 5.5 and 6.5 x 7.0A^o. Low activity observed for ZSM-5 and mordenite is due to inability of reactant/products molecules to diffuse in or out of the zeolite pores. These zeolites possess channel type pore structure with uniform size throughout the structure except at channel intersections, diffusion of molecules having molecular dimensions similar to channel diameters will be restricted. On the other hand, zeolite Y and BEA possess pore aperture diameters of 7.4 and 7.6 x 6.4A^o respectively opening into large diameter (11-13A^o) cavities, diffusion of molecules of anisole, veratrole or their acylated products will be facile resulting into catalytic activity. As zeolite-BEA, zeolite-Y and H-montmorillonite have shown results for the acylation of anisole and veratrole, further study was carried out to modify these catalysts and to obtain higher activity. Figs 2 and 3 show the catalytic activity of the lanthanide cation exchanged zeolite Y, BEA and montmorrilonite clay for anisole and veratrole. The data in Figures 2-3 show that the catalytic activity significantly vary with the nature of rare earth cations exchanged in to the zeolites / clays. The order of activity observed for acylation was as under.Ce-β > La-β = H-β > Nd-β > Pr-β > Sm-β; Ce-Y > La -Y = Sm-Y > H-Y > Pr-Y > Nd-Y; Ce-Clay > La - Clay = Sm- Clay > H- Clay > Pr- Clay > Nd-Clay.To determine the acidity of modified zeolites and clay samples, we have carried out the dehydration of cyclohexanol as a model reaction, generally done to characterize Bronstead acidity of solid acid catalyst[28]. Comparative acidity determined for zeolites Y, BEA and clay having different rare earth exchanged cations using dehydration of cyclohexanol is plotted in Fig. 4 along with the catalytic activities trend for acylation of anisole and veratrole. As observed from these Figures, the trend in acylation catalytic activity of the rare exchanged zeolite Beta, Y and clay follow the same trend as observed for dehydration of cyclohexanol showing the correlation between catalytic activity and acidity of these catalysts and its lanthanide cation exchanged forms. These data show that once the diffusion of reactant / products in the pore of zeolites is not hindered, the catalytic activity of the catalysts depends on the acidity of the catalysts. Cerium exchanged Y, Beta and Clay shows the highest conversion among other rare earth cations. The rare earth cation exchange for lanthanum has been correlated with the formation of Bronsted acid sites with enhanced acid strength, being linked to the presence of La(OH)$^{2+}$, which may be formed by the mechanism as shown[21] below.

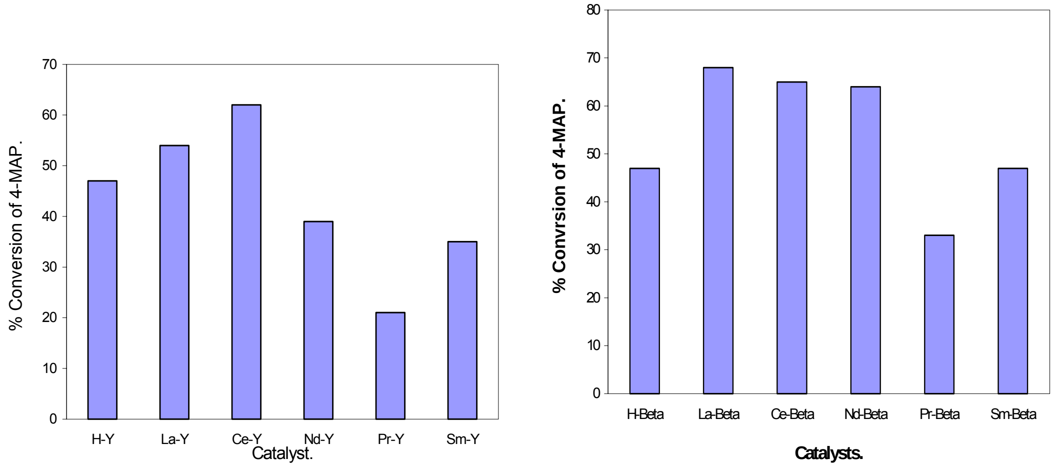


Figure-2a: Acylation of anisole with rare earth exchanged zeolites Y and BEA

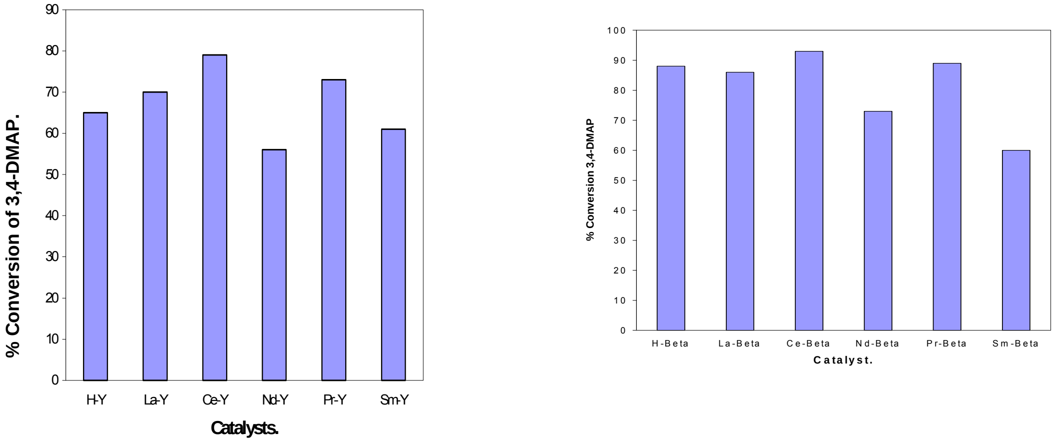


Figure-2b: Acylation of veratrole with rare earth exchanged zeolites Y and BEA

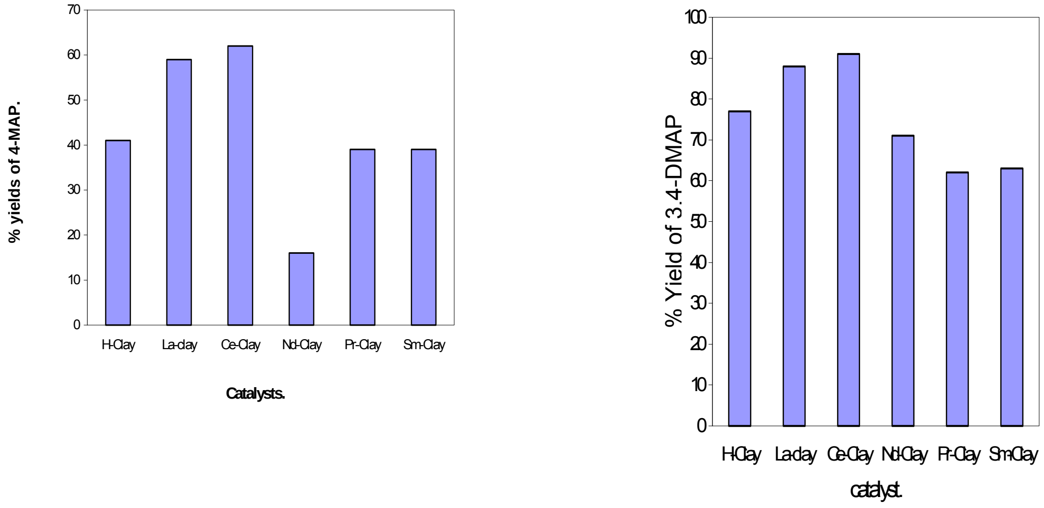


Figure 3: Acylation of anisole and veratrole with rare earth exchanged H-montmorillonite

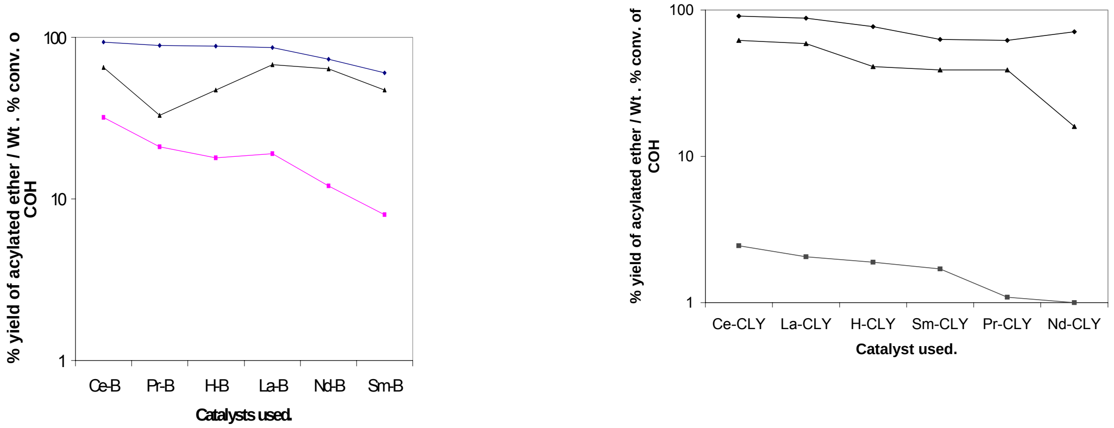


Figure:4: Comparison of acylation of anisole(▲), veratrole(◆) and dehydration (■)reactions over zeolite β and clay catalysts.

$$La^{3+}(H2O)_x(O^{-}Zeol)_3 \xrightarrow{\text{Calcination}} La^{2+}(H2O)_{x-1}\,(OH)\,(O^{-}Zeol)_2 + H^{+}\,O\text{-}Zeol$$

Rare earth cations possessing high charge density interacts with water molecules inside the zeolite cavities and results into formation of acidic protons which are responsible for the enhanced acidity. Cerium ions due to their two valence states +3 and +4 might have higher charge density when in +4 state and higher ability to form acidic protons. Acidity observed will also depend on the locations these cations will occupy inside zeolite cavities.

Some relevant and interesting studies on deactivation of zeolites during acylation reactions and the use of structured zeolites have appeared in the literature recently and are briefly discussed below.

Deactivation of zeolite catalysts

Recently, Guignard et al.[64] have reported very interesting study that throws light on the reasons for the rapid deactivation of zeolites HY and HBA during acylation reactions. The reaction under mild conditions of 90°C, 1 atm pressure was very selective and gave acetoveratrole with good yield (63% for HY and 40% for Hβ after 6h). However, they have reported the rapid deactivation of the two catalysts within two hours. Analysis of the compounds remaining on the used catalyst were categorized of two types:

(a)Veratrole and acetoveratrole products were easily removed from the catalyst by simple soxhlet extraction with methylene dichloride

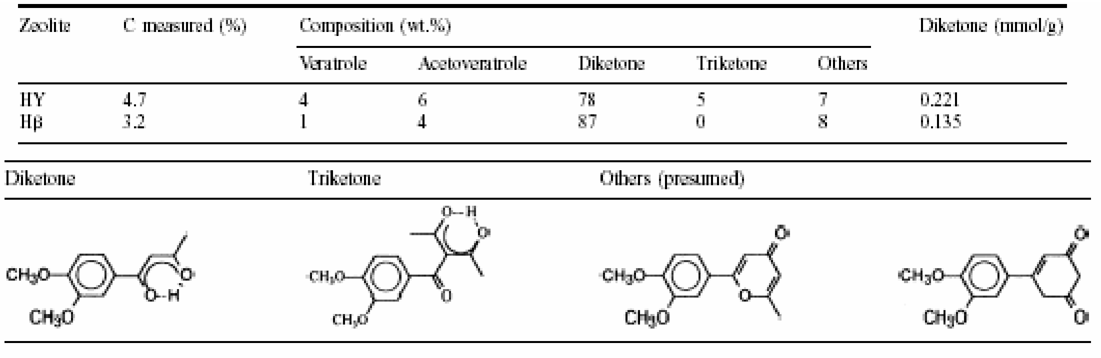
(b)Other types of compounds remained on the catalyst even after soxhlet extraction. These were identified after destruction of the catalyst with HF as diketone as well as cyclization products as shown in Table 1. In case of HBEA, triketone was also formed due to C-acylation of the diketone.

Deactivation of the catalyst, therefore, is resulting from

-a significant adsorption of the reaction products, which limits the acess of the reactants to the acid sites. This, however, is reversible deactivation as these adsorbed products can be solvent extracted from the catalyst.

-The formation of di- and tri-acylated products which are entrapped in the zeolites and cause irreversible deactivation. Part of the zeolite activity can be recovered by treating the catalyst at above 500°C in air atmosphere

Table 1. Structures and Distribution of the compounds obtained after dissolution of the zeolites with HF after Soxhlet extraction[64]

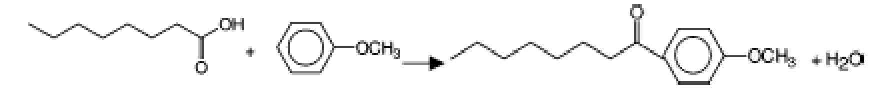


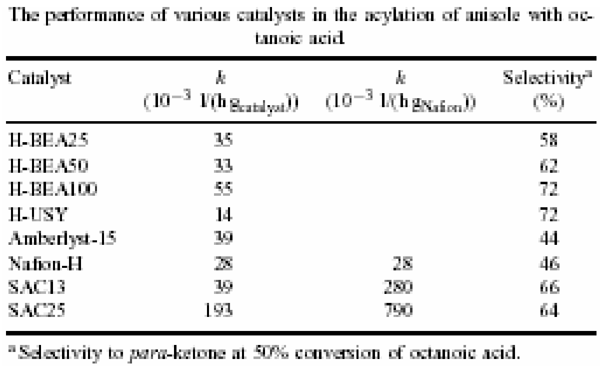
Zeolite	C measured (%)	Composition (wt.%)					Diketone (mmol/g)
		Veratrole	Acetoveratrole	Diketone	Triketone	Others	
HY	4.7	4	6	78	5	7	0.221
Hβ	3.2	1	4	87	0	8	0.135

Diketone	Triketone	Others (presumed)	

Structured zeolite catalysts

The potential of nafion/silica composites has been demonstrated[65] for acylation of aromatic ethers. However, Beers et al.[66] has reported a structured catalyst (Figure 5) made from nafion (25%) /silica composite which has shown higher performance compared to zeolites BEA and USY for acylation of anisole with octanoic acid.





The performance of various catalysts in the acylation of anisole with octanoic acid

Catalyst	k (10^{-3} l/(h $g_{catalyst}$))	k (10^{-3} l/(h g_{Nafion}))	Selectivity[a] (%)
H-BEA25	35		58
H-BEA50	33		62
H-BEA100	55		72
H-USY	14		72
Amberlyst-15	39		44
Nafion-H	28	28	46
SAC13	39	280	66
SAC25	193	790	64

[a] Selectivity to *para*-ketone at 50% conversion of octanoic acid.

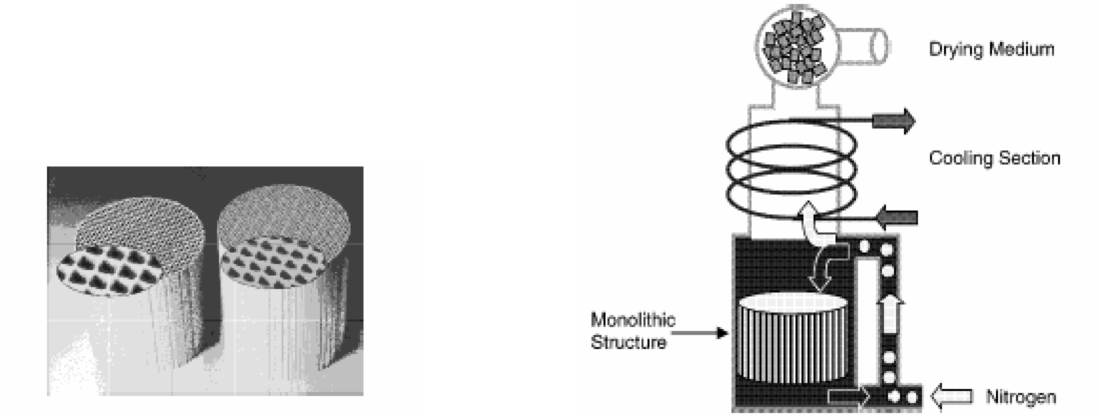


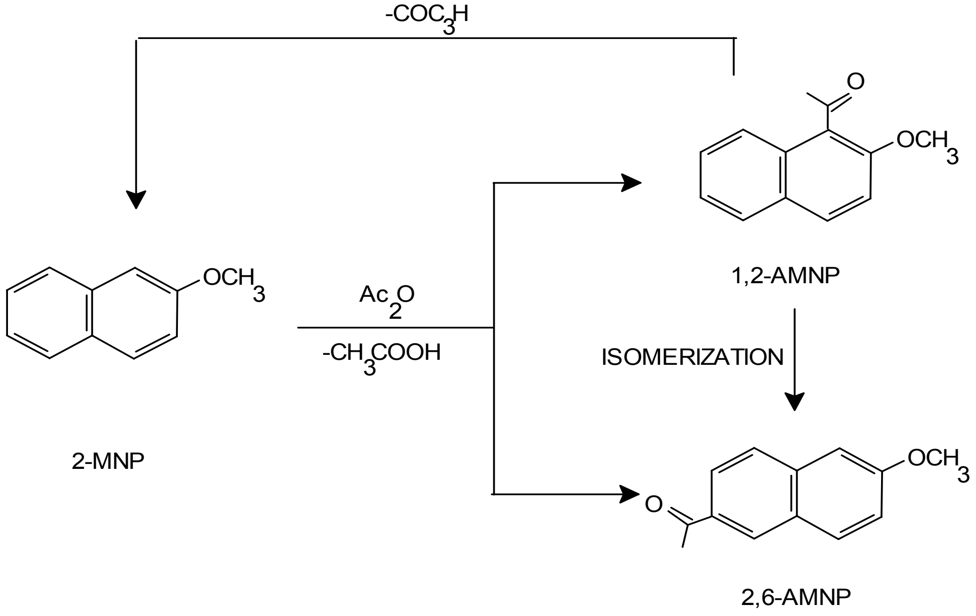
Figure 5. The structure of the monolith and a schematic of the set-up for measuring the catalyst activity of the monlith

The monolith (400 & 600 cells per square per inch) was coated with Nafion using a dip coating technique and coated monolith were converted to H-form. This study was under taken with an objective to develop a structured catalyst for the solid acid catalyzed acylation of aromatic compounds using carboxylic acids as acylating agents. From Environment point of view, this is attractive as only water is formed as a by product. How-ever, it is observed that carboxylic acid when present in large amounts , adsorb strongly on the acidic catalyst surface. As a result, aromatic reactant is unable to approach the acid sites. In continuous process operation a CSTR (continuous stirred tank reactor) system is preferred since it operates at low acid concentration levels. The fresh reactant feed has to be mixed before it reaches the catalyst, otherwise the catalyst is deactivated. This is only achievable with a fixed catalyst with a re-circulation of the reaction mixture. A structured catalyst is therefore needed to allow for higher re-circulation rates and avoid pressure drop over the catalyst.

3.2 Acylation of 2-MethoxyNaphthalene

Acylation of substituted naphthalene leads to products, which are useful in pharmaceutical and polymer industries. The acylation of 2-methoxynaphthalene, (2-MNP) by aluminium chloride was a step in the first large-scale synthesis of naproxene.[1]

The acylation of 2-MNP has recently been investigated over MCM-41, H-Y, H-BEA, ZSM-5 and Mordenite with an objective to look for an eco-friendly replacement to $AlCl_3$. The acylation of 2-MNP leads to 1-acyl-2-methoxynaphthalene (1,2-AMNP) and 2-acyl-6-methoxynaphthalene (2,6-AMNP). 2-Acyl-6-methoxynaphthalene is the precursor for naproxen. However, during acylation reactions, 1,2-AMNP is a predominating product as the acylation of 2-MNP occurs at kinetically controlled 1- position, however, the deacylation of the acyl group has also been observed to give back 2-MNP, as shown in the following reaction Scheme-2.



Scheme-2. Possible secondary reaction over the acylation of 2-MNP.

In the following section, research efforts directed in this direction are briefly reviewed. Acylation of 2-MNP in the presence of modified zeolite H-BEA[67], have been reported. Modification of the parent zeolite was carried by acid treatment using hydrochloric acid. It was observed that the activity of the acid treated catalyst increases, with conversion going up from 32 to 49 %. However, the selectivity goes down from 26 to 14 % for 6-isomer. Acid treatment leads to the preferential formation of the bulky product, which be due to the extraction of catalytically active extra-framework alumina species. Similar observations were reported by Casagrande et al.[68]

G. D. Yadav et al.[69], have studied the role of intraparticle diffusional resistance on the kinetics of the Acykltionof 2-MNP using Al-PILC , S-ZrO_2, K-10 clay, Filtrol clay, Amberlyst and HPA loaded zeolite and have shown more activity toward 1-position only, and none of these catalysts is capable to activate 6 position of naphthalene ring in 2-MNP. Among all the catalyst studied, Amberlyst-15 showed maximum conversion, but ZSM-5 and Mordenite did not showed any conversion.

Acylation of 2-MNP in the presence of zeolite BEA reported by Andy et al.[70] showed that the formation of 1,2-AMNP occurs in the external surface of BEA , a significant increase in the selectivity of 2,6 –AMNP occurs when zeolite external surface was coated by silica.

Cation exchanged clays[62] have been shown to be only active towards 1-position of 2-MNP. MCM-41 type molecular sieve[71] as catalysts for the Friedel-Crafts acylation of 2-MNP was also found more active towards 1-position when modification was done by treating it with the solution of Zn-salts, It showed selectivity of 81% towards 6-posistion in nitrobenzene as solvent.

D. Das et al.[72] have reported the acylation of 2-MNP using zeolite based catalysts, they have also observed that the all catalysts were giving the conversion in the range of 35 to 45 % weight conversion in the temperature range of 100 –150°C. They were also found 1,2-AMNP as a major product. They concluded that not only the catalyst but also other reaction conditions like temperature and solvent plays an important role in the selective formation of 2,6-AMNP.

Patil and Yadav[73] from molecular modeling studies have inferred that zeolites mordenite, BEA and ITQ-7 are potential catalyst for selective synthesis of 2,6-AMNP.

Acylation of 2-MNP was performed[74] on a tri-directional 12 membered ring pore zeolite named ITQ-7 which has a slightly smaller pore diameter than that of H-Beta. It is as active as Beta but give better selectivity for 6-position. This may due to the difference in the relatively higher diffusion co-efficient of 2,6-AMNP whose rates are 2.7 and 15.5 in BEA and ITQ-7 respectively. Beta zeolite seems to have good pore dimensions favoring the diffusion of the 2,6-AMNP molecule with respect to the 1,2-AMNP isomer.

Regioselective acylation of 2-MNP to 2,6-AMNP over zeolite Beta[9] shows that secondary structure of the zeolite was found to be an important factor for the selectivity, because of its effect on diffusion process of reactants into internal pores.

An important work on the acylation of 2,6-AMNP using zeolites as catalysts was carried out.[75] In this work the authors studied the acylation of 2-MNP by using anhydrides and acid chlorides on a series of zeolites such as HEU-1, Beta and ZSM-12 using a ration of 2-MNP to acetic anhydride of 1:3 at temperature up to 573K. They found that with acetyl chloride and acetic anhydride the ratio of 2,6-AMNP to 1,2-AMNP was always lower than 1.

We have studied the liquid phase acylation of 2-MNP by using acetic anhydride as an acylating agent and nitrobenzene as a solvent in the presence of zeolite BEA, Y and their lanthanum and cerium exchanged forms. Zeolite BEA and Y only, as 2-MNP and 2,6-AMNP having estimated molecular diameter as 7.1 and 7.8A° respectively will not be able to access zeolite channels of ZSM-5 and mordenite. The conversion and selectivity data for the acylation of 2-MNP with acetic anhydride as an acylating agent and nitrobenzene as solvent at 120°C over various zeolites catalysts are shown in Table-3.

All the catalysts yielded 1, 2-MNP as a major product. However, Zeolite Beta showed higher selectivity for 2, 6-AMNP than that of other catalysts. It was also observed that the Cerium and Lanthanum exchanged zeolites are more active than its H-form, but are less selective for 2,6-AMNP. In the case of zeolite-Y, conversion of 2-MNP remains almost same even by changing the Si/Al ratio from 10 (ZF-510) to 20(H-Y).

During the Friedel- Craft acylation of 2-MNP, the formation of 1,2-AMNP is a kinetic product whereas formation of 2,6-AMNP is a thermodynamically controlled. In homogeneous catalytic system, the acylation of 2-MNP gives a mixture of 1,2-AMNP and 2,6-AMNP followed by1,2-AMNP is converted into 2,6-AMNP after long reaction time, because the homogeneous catalysts provides free catalytic sites, substituted acyl group at the sterically hindered 1-position migrates to more stable 6-position. However, with the increase in the contact time, not only conversion but also selectivity for 2,6-MNP increases, which involves the deacylation of 1,2-AMNP as well as migration of acetyl group from 1 to 6-position as shown in Scheme-2.

Table-1: Acylation of 2-MNP using modified zeolite catalysts.

Catalyst used.	Time (h).	Wt % Conversion of 2MON	Selectivity to 1-acetyl- 2-methoxynaphthalene.	Selectivity to 2-acetyl 6-methoxynaphthalene.
H-Beta	5	22	45	46
	10	34	40	55
	15	36	39	52
	20	38	35	52
La-Beta	5	55	68	30
	10	58	58	38
	15	59	57	38
	20	62	57	39
Ce-Beta	5	70	70	29
	10	72	68	31
	15	70	68	31
	20	68	65	35
H-Y	5	54	97	2
	10	54	96	3
	15	57	96	3
	20	59	95	4
La-Y	5	62	97	2
	10	62	95	4
	15	64	94	5
	20	66	94	5
Ce-Y	5	60	91	8
	10	66	94	8
	15	66	89	10
	20	69	90	9

The reaction conditions employed were as : 10 milimoles of 2-MNP, 20 millimoles of Ac_2O; 10 ml of solvent nitrobenzene; Cat. Weight 0.5 g.; reaction temperature 120^{o}C.

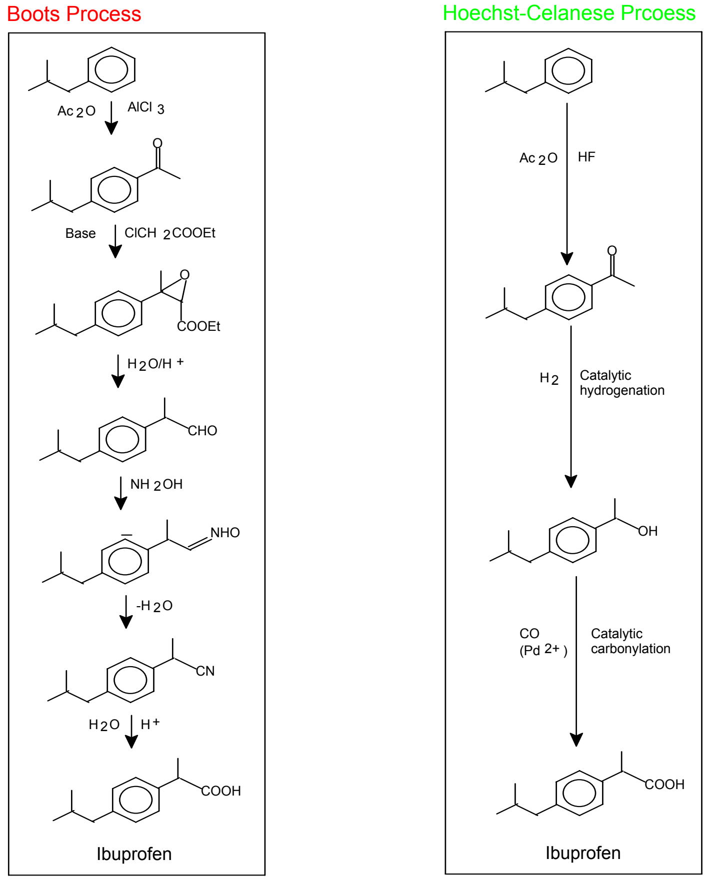
4.0 Acylation of isobutylbenzene

α-Arylpropionic acids (Profens) such as Ibuprofen has immerged as an important class of non-steroidal anti-inflammatory drugs (NSAIDs) having analgesic and anti-inflammatory properties.[2,3] Ibuprofen is a main component for pain killer drugs sold with trade name of Advil, Bayer, Midol 200, Motrin IB and Nuprin. It is used for the treatment of inflammation and pain caused by rheumatoid arthritis and osteoarrthritis, as well as soft tissue injuries, such as tendentious and bursitis. It is also used for the rapid relief of fever and in mild to moderate pain, such as menstrual cramps. The industrial process for the synthesis of ibuprofen is a multi-step process which involves acylation of isobutylbenzene using conventional Friedel-Crafts catalysts as a first step. Currently, two major commercial processes described below are used for the production of Ibuprofen.

Boots-Process

Boots company of England in 1976 developed a process[98] having six steps for the production of Ibuprofen as shown below in Sheme-3. In Boots process, acylation of isobutylbenzene carried out in the presence of $AlCl_3$ using acetic anhydride as an acylating agent. This is followed by reaction of p-isobutylacetophenone with mono-chloro-ethylacetate in the presence of sodium acetate. This results in the formation of a cyclic compound. Hydrolysis and subsequent reaction with hydroxylamine give an oxime, which on dehydration gives an intermediate, hydrolysis of it finally give Ibuprofen as shown below.

Production routes for ibuprofin



Scheme 3: Commercial processes used for ibuprofen

Hoescht-Process It is a three-step synthesis of Ibuprofen[99] as shown in Scheme-3. In this process, acylation of isobutylbenzene is done in the presence of HF by acetic anhydride as an acylation agent followed by hydrogenation in the presence of Raney-Nickel to produce hydroxyl derivative which on carbonylation in the presence of palladium, produce Ibuprofen as shown. Though, Hoescht process is a vast improvement over Boots process, there are still two points, which are of concern.

(a) Use of hazardous HF during acylation of Isobutylbenzene.
(b) Synthesis of racemic mixture of ibuprofen.

There are very few studies reported in the literature briefly discussed below wherein zeolites / clays have been studied as substituents to $AlCl_3$ and HF for acylation of IBB

Andy et al.[70] have reported the zeolite Beta catalyzed acylation of IBB using acetic anhydride as an acylating agent. The major product reported is 4-IBAP, a small amount of 2-IBAP was also observed. However, the activity of the catalyst is very low (16 Wt %). The following zeolite beta based catalysts were reported to be used.

Zeolite sample (Si/Al)	**Crystallite size, nm**	**Conversion after 11h, (%)**	**Selectivity for 4-IBAP (%)**
BEA1 (12)	<1	16.6	>99
BEA2 (40)	2.5	10	>99
BEA3 (40)	9	11	97

The reaction was carried out at 100°C under reaction conditions of : 0.25g of the catalyst, isobutylbenzene:acetic anhydride ratio = 1:1 and 1.1mmol, 0.860 ml of solvent. The zeolite with lower Si/Al ratio and the smallest crystal size is the more active for the transformation of IBB into 4-IBAP, probably due to exposure of high number of active sites available on the external surface of zeolites and a shorter intracrystalline diffusion path lengths.

Acylation of isobutylbenzene using acetic anhydride as an acylating agent in the presence of nano-crystalline zeolite was recently reported by Choudary et al.[100] They have studied the cation exchanged nano-crystalline zeolite Beta and have shown conversion up to (30 Wt %).

Acylation of anisole, veratrole, toluene and isobutylbenzene was carried out in the presence of zeolitic catalysts.[101] The catalysts comprising 40 % of binder (alumina) and 60 % of zeolite Beta, having Si /Al ratio of 12.5 and it was used in an amount of 60 % with respect to acetic anhydride. The reaction was carried out at 150°C and yielded 75 % of 4-IBAP based on acetic anhydride taken. We have studied liquid phase acylation of IBB using solid acids namely, Zeolite-Beta, Zeolite Y, H-ZSM-5, H-Mordenite and H-Montmorillonite.

Of various zeolites studied, only zeolite beta showed encouraging conversion (11 wt %) and selectivity (95%) which is quite similar to that reported by M Davis.[70] Other catalysts, i.e, .H-ZSM-5, H-Mordenite and clays showed no conversion. The factors which might be responsible for the catalytic activity of these zeolites towards acylation IBB are:

- Acid strength and number of acid sites of zeolites
- Availability of acid site on the zeolite surface

Diffusion of isobutyl benzene and isobutylacetophenone inside zeolite cavities

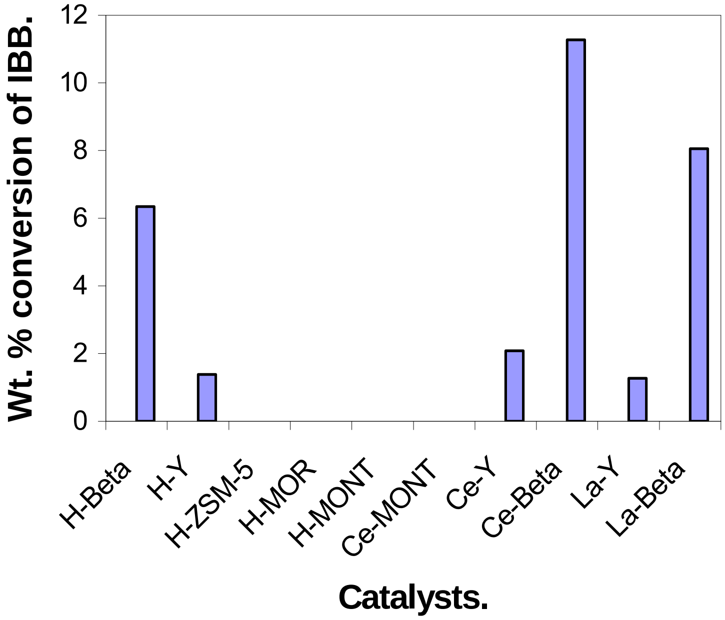


Figure-5: IBB conversion with various solid acid catalysts.

It is well know that zeolites HZSM-5 and H-mordenite possess sufficient acidity to catalyze alkylation and acylation reactions. Therefore, lack of catalytic activity of these zeolites for acylation of isobutylbenzene cannot be attributed to lack of acidity in these zeolites. The most probable reason for nil activity of these solids is due to inability of isobutylbenzene molecules to enter the channels of these zeolites. For example, the molecular diameter of isobutyl benzene and isobutylacetophenone estimated from its molecular volume is around 7A^o and 7.7A^o respectively. The size of pore apertures for ZSM-5 and mordenite are 5.1 X 5.5A^o and 6.5 X7.0A^o respectively. Therefore, accessibility of acid sites inside the channels of zeolites to isobutylbenzene molecules is not feasible due to steric reasons. Even if some molecules of IBB are able to enter the channels of zeolites like mordenite at higher temperatures, the diffusion of isobutylacetophenone molecules out of the channels will be highly restricted resulting to nil catalytic activity of the zeolites. The lack of catalytic activity of clays for IBB acylation is probably due to absence of acid sites of sufficient acid strength in the clay samples.

Zeolite Y samples show very low activity for as seen from Figure 5. The dehydration of cyclohexanol using H-Y and H-BEA gives 23 and 20% cyclohexene, showing similar surface acidities for these two zeolites, however conversion of IBB is higher in Zeolite

Beta. This may be due to small pore dimension of Zeolite Y (7.4A^o) compared to BEA (7.6 X6.4A^o) . This is also confirmed from cyclohexanol conversion data on Ce-Y and Ce-BEA where respective conversion values are 27 and 32%. However, IBB conversion is much lower for Ce-Y (2.1 wt %) compared to Ce-BEA (11 wt %). Similarly, for La-Y and La-BEA, cyclohexanol conversion values are 25 and 19% respectively. However, IBB conversion on these zeolites are 1.2 and 8.1% again confirming that in addition to zeolite acidity, pore dimensions also plays a role during the acylation of IBB molecules. It was reported by Andy et al. [70] that in the acylation of isobutylbenzene, external surface of zeolite contributes significantly to the formation of 4-IBAP, which was further confirmed by the measurement of surface acidity using cyclohexanol dehydration as model reaction. From our data on crystallite size, it is observed that zeolite BEA has crystallite size of about 2 micron whereas crystallite size of Zeolite Y was more than 10 microns. There might be some influence on the catalytic activity of the external surface area due to smaller crystallite size of zeolite BEA. Zeolite acidity and its pore dimension plays significant role in determining the activity of a catalyst for acylation of IBB as discussed above. Studies on the various solid acids discussed in earlier section has shown that amongst various zeolites, Ce-BEA displays higher conversion for IBB, and appears to be a potential catalyst for this transformation. Therefore to further explore its potential for acylation of IBB, detailed study to optimize the following reaction parameters for higher IBB conversion was carried out [8].

- Reaction temperature.
- Substrate / acetic anhydride ratio.
- Different amount of solvent.(Substrate / solvent ratio)
- Substrate / catalysts ratio.
- Different solvents.
- Reaction kinetics.

The comparison of cyclohexanol conversion and IBB conversion under optimized conditions is presented graphically in Figure-6. Reaction was carried out at following conditions: activation of the catalysts was done at 400^{o}C in air. Ratio of IBB/AC$_2$O=1:1, IBB taken 10 mmol, Solvent used : Nitrobenzene (10 ml). Cat used Ce-Beta, Cat. Weight=0.5g.; Reaction temperature=100, 120 and 140^{o}C, Pressure=1 atm.

A good correlation of conversion of cyclohexanol and activity for acylation of IBB was observed showing that Bronstead acid sites paly an important role in acylation of IBB. Furthermore, zeolite Ce-Beta has shown high degree of conversion for both the substrates.

Table-4: Effect of time on conversion and selectivity with zeolite Beta.

Time (h)	Conversion (wt %)	**Selectivity (%)**
5	10.07	97.21
8	27.16	87.05
10	34.29	89.21
15	37.21	92.46
20	36.55	60

Reaction conditions. Activation of the catalysts at 400 ^{o}C in air; IBB: Acylating agent =1:2; IBB taken 10 mmol, Cat used Ce-Beta;Cat. Weight=0.5 g. Temperature=120^{o}C; Pressure=1 atm; Solvent; Nitrobenzene (10 ml).

IBB is mainly transformed into 4-IBAP and small amounts of 2-IBAP as well as other by-products like di-acylated products are formed. It was observed (Table-4) that in the initial stage (after 5 hours reaction time) the weight percent conversion of IBB was about 10 % (with 97%. selectivity towards 4-IBAP) which increases with time and after 10 hours reaches up to the 34% with 89% selectivity for 4-IBAP. The conversion of IBB after 10 hours does not increase significantly. It is also observed that with time (> 15 hrs.), the selectivity for 4-IBAP decreases. This could be due to isomerization or simultaneously de-acylation of the 4-IBAP, which has also been reported in the case of acylation reaction of other organic substrates.

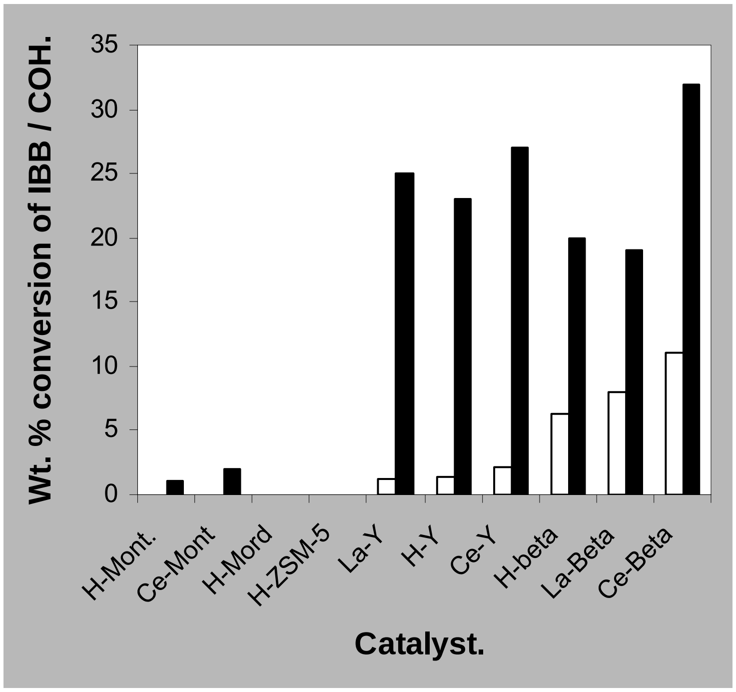


Figure: 6. Comparison of cyclohexanol dehydration and isobutylbenzene conversion.

■ Isobutylbenzene conversion

☐ Cyclohexanol conversion.

Table-4: Effect of time on conversion and selectivity with zeolite Beta.

Time (h)	Conversion (wt %)	**Selectivity (%)**
5	10.07	97.21
8	27.16	87.05
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Reaction conditions. Activation of the catalysts at 400 °C in air; IBB: Acylating agent =1:2; IBB taken 10 mmol, Cat used Ce-Beta;Cat. Weight=0.5 g. Temperature=120°C; Pressure=1 atm; Solvent; Nitrobenzene (10 ml).

5.0 Acylation of toluene

Methyl-p-tolylketone, para isomer of acylated toluene is a colorless liquid with a penetrating floral fruity odor and finds applications in perfumery, flavors and fragrance industry. There are some reports on the acylation of toluene with different acylating agents using solid acids. For example, Chiche et al.[21] has reported the acylation of toluene with C_2 to C_{22} alkanoic acids with CeNa-Y (70% cation exchange) and reported the maximum yield for C_{12} and C_{14} acids. Acetic acid was not observed to effective for acylation. Gauthier et al.[28] from their study of acylation of toluene with octanoic acid and cation exchanged zeolite-Y concluded that acylation can also be catalyzed by Bronsted acid sites. Phosphotungstic acid ($H_3PW_{12}O_{40}$) supported on silica was shown[102] to be more active than zeolite-Y and β for acylation of toluene with crotonic acid. The acylation of lower aromatics with ion exchanged montmorillonite clay has been discussed by Chiche et al.[22] and showed that Al^{+3} exchanged clay was most active for acylation. Acylation activity of La-exchanged zeolite-Y for toluene with acetyl chloride as an acylating agent was reported[31] to increase with an increase of La^{+3} content in the zeolite. It was observed from earlier studies on the acylation of aromatic compounds like anisole, veratrole and isobutylbenzene[42] that rare earth cations exchanged zeolites and acid activated clays display potential activity for acylation of aromatic compounds. We have studied toluene acylation with an objective to explore the potential of rare earth cations (La^{3+}, H^+, Ce^{3+}, Dy^{3+}, Eu^{3+}, Sm^{3+}, Gd^{3+}, Nd^{3+}, Pr^{3+}) exchanged zeolite-β for the acylation of toluene. Acetic anhydride was used as an acylating agent as acetyl chloride despite its higher activity leads to hazardous hydrogen chloride emission during the acylation reaction, which also decreases the catalytic activity [43].

Toluene conversion and selectivity data for H-BEA and various rare earth exchanged zeolite BEA under the optimized reaction conditions are given in Table 5. H-BEA and rare earth cation exchanged zeolite BEA show 12-66% toluene conversion with very high selectivity (86-100%) towards para isomer of the product. Among the catalyst systems studied, La-BEA, H-BEA, Ce-BEA, and Dy-BEA, showed toluene conversion in the range of 46-66% with almost 100% selectivity (except Ce-BEA). Nd-BEA, Sm-BEA, Eu-BEA, and Gd-BEA catalysts gave lower toluene conversion ranging from 27 to 35% with almost 100% selectivity. Pr-β has shown the least conversion (12%), even though the para isomer selectivity is 100%. It is observed from the EDTA volumetric analysis that the extent of cation exchange in zeolite beta for rare earth cations is of similar range (100%). Therefore, the observed difference in the catalytic activity for toluene acylation cannot be attributed to rare earth content of the zeolite.

It is known that zeolites possess both Lewis and Brönsted acid sites, which are catalytically active sites for acylation and alkylation reactions[102] In rare earth cations exchanged zeolites will display both the types of acidity due to high charge density rare cations which generates acidic hydroxyl groups inside the zeolite cavities. The electrostatic field of the cation ionizes the water molecules, which lead to the formation of acidic hydroxyl group[103]. The strength and the number of such acidic hydroxyl groups generated inside the cavities will depend upon the nature and number of rare earth cations [104]. The presence of acidic hydroxyl group has been ascertained using FTIR spectroscopy. DRIFT spectra of all the zeolite samples obtained at ambient temperature do not show the well-resolved peaks in hydroxyl region (3400-3600 cm^{-1}) due to the presence of physisorbed water. After heating at 473K, all the rare earth exchanged zeolite samples showed the bands at around 3734, 3662 and 3535 cm^{-1}. The band at 3734 cm^{-1} is attributed to terminal SiOH groups. The band at around 3662 cm^{-1} is attributed to accessible and acidic hydroxyl groups and 3535 cm^{-1} for inaccessible and non-acidic rare earth -OH present in the sodalite cages. The lower intensity of 3535 cm^{-1} band in all these samples show that the exchanged cations first replace H$^+$ ions in the super cages, i.e., accessible sites representing the band at 3662 cm^{-1}. All the zeolite samples showed a well resolved peak between 3660 cm^{-1}-3680 cm^{-1}, which is due to the

Table 5. Toluene conversion and para isomer selectivity for different cation exchanged zeolite-BEA

Catalyst	Conversion (%)	Para selectivity (%)
H-BEA	50	100
Ce-BEA	51	86
La-BEA	66	100
Dy-BEA	46	100
Eu-BEA	35	98
Sm-BEA	31	99
Gd-BEA	30	100
Nd-BEA	27	100
Pr-BEA	12	100

Toluene (0.01 mol);Acetic anhydride (0.02); Nitrobenzene solvent (10 ml); Catalyst (0.25 g); Reaction temperature 408K for 6 h

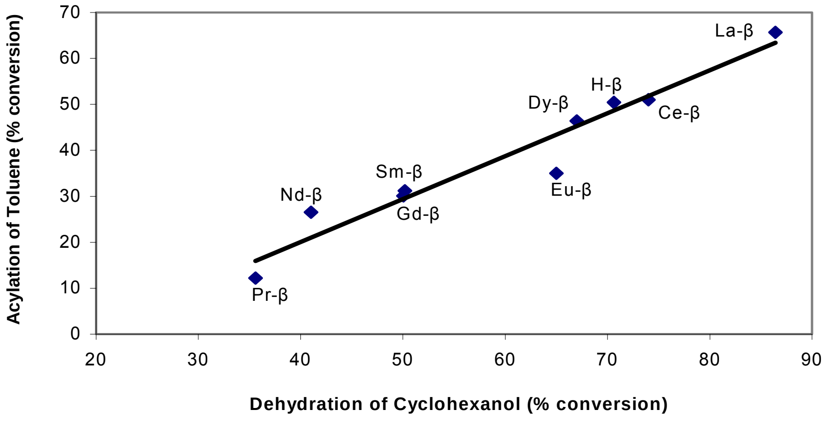

Figure 7. Correlation of catalytic activity with dehydration of cyclohexanol

presence of acidic hydroxyl groups in the supercage, thereby, showing the presence of Brönsted acidity. The dehydration of cyclohexanol conversion data of these samples was plotted against toluene conversion values for various zeolite catalysts. Linear correlation of toluene acylation with cyclohexanol dehydration, shown in Figure 7, strongly suggests that acylation of toluene over cation exchanged zeolite BEA is a Brönsted acid catalyzed reaction.

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