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Acetylation of dimethoxybenzenes with acetic anhydride in the presence of acidic zeolites

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Abstract

The acetylation of 1,2-, 1,3- and 1,4-dimethoxybenzenes with acetic anhydride has been investigated in the liquid phase (chlorobenzene as solvent) over the H-forms of various zeolites. H-Y and H-Beta have been shown to be efficient catalysts in such a reaction, and led to the selective formation of the corresponding dimethoxyacetophenones. 1,2-Dimethoxybenzene (veratrole) has been chosen as a model substrate for the kinetic study of the reaction over H-Y (Si/Al = 15) as catalyst. The reaction proceeds through a modified Eley–Rideal type mechanism, wherein the chemisorbed acetic anhydride generates the electrophilic acylium ion, which then reacts with veratrole in the liquid phase. The competitive adsorption of both reactants and products has been evidenced. It has been especially shown that the deactivation of the catalyst was due to a partial adsorption on the active sites of the catalyst of either the reaction product (3′,4′-dimethoxyacetophenone in the case of 1,2-dimethoxybenzene as the substrate) or/and of acetic acid formed in the reaction. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

It is now well-established that the application of catalysis by zeolites to the Friedel–Crafts acylation of aromatics can constitute a considerable improvement in the production of aromatic ketones as intermediates for fine chemicals, even so a possible extent to an industrial scale has just been reported so far [1–3]. During the past decade, zeolites have been adequate and efficient catalysts in acylation reactions of a variety of aromatic and heterocyclic-aromatic systems [4–39]. In most of the published works, it has been emphasized that the disadvantages of the traditional procedures, using acyl halides as acylating agents in the presence of Lewis acids such as aluminum chloride, could be overcome by the use of such zeolite catalysts in the acylation reaction with carboxylic aliphatic and benzoic acids. This is especially the case for the acylation of activated aromatic rings, such as

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anisole, for which the acidity of zeolites is sufficient enough to carry out the reactions under moderate conditions. For this reason, aryl ethers constitute an interesting class of aromatic derivatives as starting materials for acylation reactions. Attention has been especially paid, in the recent years, to the use of various solid catalysts containing Brönstëd acid sites, including clays and zeolites, in the acylation of anisole [7,19,20,26,32–35] with various acylating agents, aliphatic carboxylic acid, chlorides and anhydrides or substituted benzoic acids. Acylation of 2-methoxynaphthalene with acetic anhydride over zeolites and mesoporous molecular sieves has also been investigated by different groups [8,18,25,31,34,39], due to the particular interest of the selective acetylation at the 6-position of 2-methoxynaphthalene for the production of the anti-inflammatory drug Naproxen. More recently, Smith et al. [35] have achieved acylation of anisole and analog aryl ethers, such as ethoxybenzene and phenetole, with acetic anhydride, under moderate conditions, over H-Beta zeolites. Only very few papers deal with acetylation or acylation of activated disubstituted aromatics; among them the acetylation of veratrole (1,2-dimethoxybenzene) has been studied, either in the presence of zeolites [2] or cation-exchanged clays [34].

In the continuation of our studies on the catalytic activities of zeolites in acylation reactions [29], we became interested in the acetylation of aryl ethers, especially dimethoxybenzenes, due to the importance of the acetylated analogues as precursors of pharmaceuticals with anti-cough properties. The present work deals with the results obtained in the acetylation reaction, over various acidic zeolites and under liquid phase conditions, of the three dimethoxybenzene isomers with acetic anhydride, which has been shown to be the best acetylating agent over zeolites [1,40,41]. Attention has been especially focused to the acetylation of the 1,2-dimethoxybenzene isomer (veratrole), chosen as model substrate for the kinetic and deactivation studies.

2. Experimental

2.1. Catalysts and reactants

The H-Y (Si/Al = 15) and the beta sample, H-Beta (Si/Al = 12.5) were from PQ (CBV 720 and CP 810 B-25, respectively). The H-mordenite (H-Mor) (Si/Al = 11) was from Zeocat, Montoir de Bretagne (ZM510). The properties of the catalysts are listed in Table 1. The same programme was applied in the activation of the different samples. The calcination was performed at 500°C for 6 h, with a heating rate of 60°C h^{-1} from room temperature (RT) to 500°C. All the calcinations were performed in a flow of dry air.

1,2-Dimethoxybenzene (veratrole), 1,3-dimethoxybenzene (resorcinol dimethyl ether) and 1,4-dimethoxybenzene (hydroquinone dimethyl ether) were pure samples (99%) commercially available from Aldrich. Chlorobenzene was of pure analytical grade from Aldrich, and was used after drying over molecular sieves.

2.2. Catalytic experiments and analytical method

The reactions were carried out under atmospheric pressure in a 100-ml round bottom flask equipped with a condenser, a dropping funnel, a thermometer and a stirring mechanism. A typical reaction was carried out as follows: a solution of 1.38 g of dimethoxybenzene (10 mmol, 0.2 M) in 50 ml chlorobenzene was introduced in the flask and magnetically stirred (600 or 1000 rpm) under nitrogen atmosphere. The freshly activated catalyst (0.5 g) was added and

Table 1
Properties of zeolite catalysts

Catalyst	Si/Al (molar ratio)	Pore opening (nm)	BET surface area (m^2 g^{-1})
H-Y	15	0.74	762
H-Beta	12.5	0.55×0.55, 0.76×0.64	658
H-Mor	11	0.65×0.70, 0.26×0.57	494

the reaction mixture was allowed to heat to reflux of chlorobenzene (130°C); 0.95 ml (10 mmol) of acetic anhydride was then added through a syringe, and the mixture was stirred. Samples were periodically collected and analysed by gas chromatography (Hewlett Packard 5890 series II gas chromatograph equipped with a flame ionization detector, capillary column HP-1, 25 m × 0.2 mm, 0.33-μm film thickness, carrier gas hydrogen).

The structure of the products (3′,4′-dimethoxyacetophenone, 2′,4′-dimethoxyacetophenone and 2′,5′-dimethoxyacetophenone, respectively) was confirmed by comparison with authentic samples available from Aldrich, and by GC–MS analysis (Hewlett Packard 5890, with a 5970A series mass selective detector).

The initial rates were deduced from the experimental curves of concentration vs. time by determination of the slope at the origin.

3. Results and discussion

3.1. Acylation of 1,2-dimethoxybenzene with acetic anhydride: influence of the zeolite structure

The acetylation reaction of 1,2-dimethoxybenzene (veratrole), chosen as a model reaction for the determination of the best experimental conditions, has been carried out, under the conditions described above (130°C, 600 rpm), over three acidic zeolites with different structures, H-Y, H-Beta and H-Mor, respectively.

The consumption of 1,2-dimethoxybenzene as a function of time is presented in Fig. 1.

Fig. 1 first indicates that H-Y zeolite is the most active catalyst, both in terms of conversion (95% veratrole consumption after 3 h reaction) and in terms of initial rate (r_0 expressed in mol min^{-1} g^{-1}) of the reaction: $r_{0(H-Y)} = 0.125 > r_{0(H-Beta)} = 0.05 > r_{0(H-Mor)} = 0.015$, or in terms of turnover frequency (TOF expressed in mol min^{-1} (Al site (mol))$^{-1}$, i.e., in min^{-1}: TOF$_{(H-Y)} = 130 > $ TOF$_{(H-Beta)} = 44 > $ TOF$_{(H-Mor)} = 11$. Such an order of activity can be directly related to the microporous structure of the different samples, for which the pores of the tridimensional H-Y framework allow a readier diffusion of both substrate and product than those of the interconnected channels architecture of H-Beta [42,43] and those of the bidimensional H-mordenite framework. Another explanation could be that the reaction rate is also controlled by restricted transition state shape-selectivity.

Moreover, it can be seen from Fig. 1 that a fast deactivation occurs in all the cases after nearly 1-h reaction. Such a deactivation will be explained below.
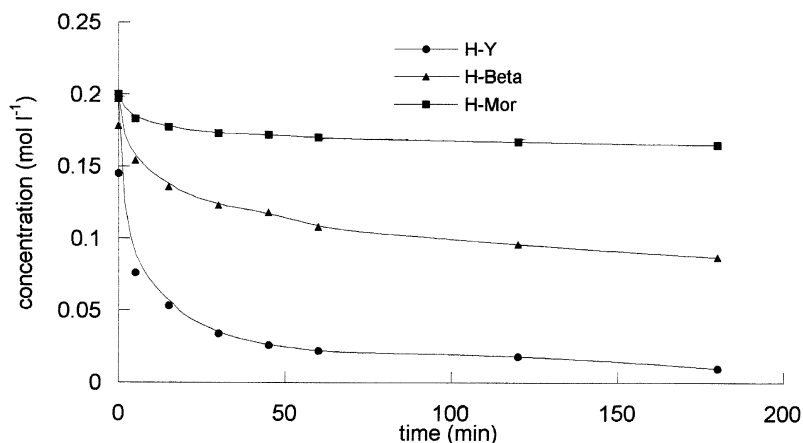

Fig. 1. Consumption of 1,2-dimethoxybenzene as a function of time in the acetylation reaction with acetic anhydride over zeolites (130°C, 600 rpm): ● H-Y (Si/Al = 15), ▲ H-Beta (Si/Al = 12.5), ■ H-Mor (Si/Al = 11).

As shown in Scheme 1, this acetylation reaction selectively leads to 3′,4′-dimethoxyacetophenone as the sole product, whatever the catalyst.

3.2. Acylation of 1,2-dimethoxybenzene with acetic anhydride: kinetic study

In order to gain a further understanding of the reaction mechanism, a kinetic study has been undertaken. The absence of external diffusion limitations has become evident under the experimental conditions described above (addition of acetic anhydride to the substrate in solution in chlorobenzene), for which it has been shown that the rate of reaction is unaffected by an agitation speed higher than 600 rpm and is proportional to the amount of catalyst until 1 g.

The experimental conditions have thus been set up at 600 rpm, with an amount of catalyst of 0.5 g.

We have then measured initial rates at different initial concentrations of acetic anhydride while the concentration of veratrole is kept constant, and vice versa, using H-Y (Si/Al = 15) as catalyst. Table 2 shows the results obtained (initial rate (r_0) of the reaction as a function of initial concentrations of veratrole and acetic anhydride, respectively). As can be seen from these values, when the initial concentration of veratrole is kept constant, the initial rate first increases with an increase of initial acetic anhydride concentration (first order towards acetic anhydride), and then reaches a level off (zero order); the same trend is obtained when the initial concentration of acetic anhydride is kept constant and the initial concentration of acetic anhydride is increased.
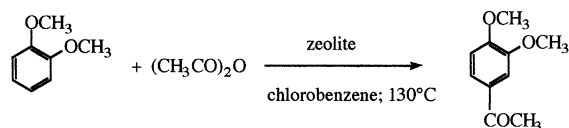
Table 2

Initial rates obtained in the reaction of 1,2-dimethoxybenzene with acetic anhydride over H-Y zeolite (Si/Al = 15) (experimental conditions described in the text)

Reactants		[Veratrole]$_0$ / [Ac$_2$O]$_0$	r_0^a
[veratrole]$_0^b$	[Ac$_2$O]$_0^b$		
10	5	2	0.03
10	10	1	0.12
10	20	0.5	0.10
5	10	0.5	0.04
10	10	1	0.12
20	10	2	0.12

$^a r_0$ in mol min^{-1} g^{-1}.
^{b}Initial concentration in millimole.

It is well-established that the acylation reaction proceeds through an acylium intermediate RCO$^+$, generated from the adsorption of the acylating agent (i.e., the anhydride) onto the Brönsted acidic sites of the zeolite catalyst, which then reacts with the aromatic substrate.

The latter can be adsorbed competitively on equivalent Brönsted sites of the surface; such a possibility is a characteristic of a Langmuir–Hinshelwood process, where the initial rate presents a maximum as a function of the initial concentration of each reactant. The reaction can also proceed through the attack of the acylium ion on the aromatic substrate in the liquid phase, which corresponds to a pure Eley–Rideal mechanism, where a first order is observed, whatever is the initial substrate concentration.

Our results do not correspond to any of these two possibilities. They suggest, in agreement with recent results from our group [44], a modified Eley–Rideal type process, where a molecule of the adsorbed acetic anhydride reacts with veratrole in the liquid phase, but in which veratrole is also adsorbed on the active sites of the catalyst, acting in a certain way as a poison and leading to the level off experimentally observed (zero order).

The corresponding rate equation can be written as follows: $r = k\Theta_{AA}[\text{VER}]$, with

$$\Theta_{\text{anhyd}} = \frac{\lambda_{AA}[\text{AA}]}{1 + \lambda_{AA}[\text{AA}] + \lambda_{\text{VER}}[\text{VER}]}$$

Scheme 1. Selective synthesis of 3′,4′-dimethoxyacetophenone from the acylation of 1,2-dimethoxybenzene with acetic anhydrides over zeolites.
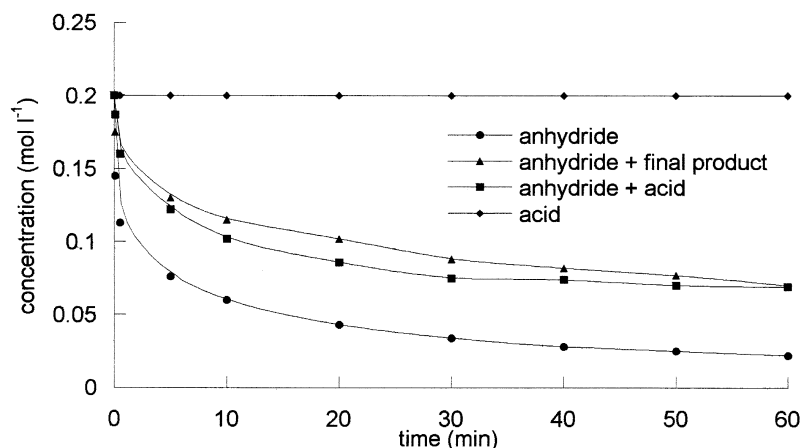
Fig. 2. Consumption of 1,2-dimethoxybenzene as a function of time in the acetylation reaction with acetic anhydride in the presence of reaction products over H-Y zeolite: ● standard conditions (acetic anhydride alone), ■ acetic anhydride + acetic acid (1:1 molar ratio), ▲ acetic anhydride + 3′,4′-dimethoxyacetophenone (1:1 molar ratio), ♦ acetic acid alone (consumption over 60 min).

where λ_{AA} and λ_{VER} are the adsorption coefficients of acetic anhydride and veratrole, respectively.

Such a rate law has been previously proposed by Corma et al. [7] on one side and Richard et al. [11] on the other side to explain the results obtained respectively in the acylation of anisole with phenylacetyl chloride and the acetylation of benzofurane with acetic anhydride.

In terms of competitive adsorption, the results expressed in Table 2 are indicative of similar effects of veratrole and acetic anhydride on the reaction rate, which appears to indicate that the adsorption of both reactants is very close.

3.3. Acylation of 1,2-dimethoxybenzene with acetic anhydride: deactivation of the catalyst

As already said above and as shown in Fig. 1, a fast deactivation occurs in all the cases.

Such a loss of the catalytic activity can be due to the saturation of the active sites of the catalyst by the products formed, acetic acid and (or) the aromatic ketone.

In order to confirm such a possibility, the acetylation reaction of 1,2-dimethoxybenzene has been carried out, under the same conditions as described above, in the presence of initially added acetic acid and 3′,4′-dimethoxyacetophenone. The corresponding consumption of the substrate as a function of time, under these new conditions, is presented in Fig. 2, and compared with those obtained under standard conditions.

When the reaction is carried out with acetic anhydride in the presence of 3′,4′-dimethoxyacetophenone (in a 1:1 ratio with veratrole), the initial rate of the reaction is decreased by a factor 1.7 ($r_0 = 0.071$ mol min^{-1} g^{-1}), while the presence of acetic acid in a 1:1 ratio with acetic anhydride leads to a decrease by a

Table 3
Initial rates (r_0, mol min^{-1} g^{-1}) and TOF (min^{-1}) of the consumption of dimethoxybenzenes in the acetylation reaction with acetic anhydride over zeolites (solvent: chlorobenzene, temperature: 130°C)

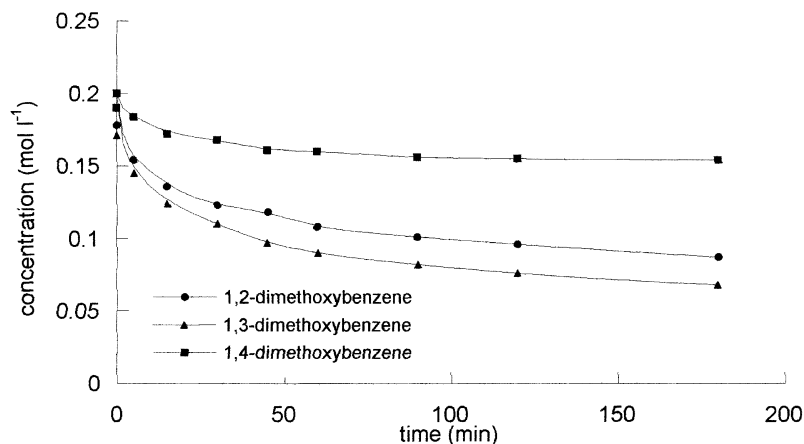|	H-Y (Si/Al = 15)		H-Beta (Si/Al = 12.5)		H-Mor (Si/Al = 11)	
	r_0	TOF	r_0	TOF	r_0	TOF
1,2-diMeO	0.125	130	0.05	44	0.015	11
1,3-diMeO	0.125	130	0.062	55	0.05	38
1,4-diMeO	0.047	49	0.021	19	/	/

Fig. 3. Consumption of 1,2- (●), 1,3- (▲) and 1,4- (■) dimethoxybenzenes as a function of time in the acetylation reaction with acetic anhydride over H-Beta zeolite.

factor 8.5 ($r_0 = 0.0146$ mol min^{-1} g^{-1}) (Fig. 2). A corresponding decrease of the maximum conversion is observed in both cases, which indicates that the product of the reaction and acetic acid are also adsorbed on the zeolite, the latter being the most strongly adsorbed. This phenomenon leads to a significant loss of activity of the catalyst. Such an adsorption thus explains the fast deactivation of the catalyst as soon as the products are formed. Unfortunately, it cannot be avoided in our batch conditions [40].

When the acetylation reaction of veratrole is performed, under the same conditions, with acetic acid instead of anhydride, no reaction occurs, as already observed in previous works [4,24,29]. Such a result confirms the special behaviour of acetic acid in acylation reactions under heterogeneous conditions, compared not only with acetic anhydride but also to other aliphatic carboxylic acids.

Moreover, the use of the regenerated catalyst (used zeolite washed and reactivated at 550°C to eliminate organic products) leads to the same activity and initial rate as for the fresh catalyst. This shows that a modification of the zeolite structure, in particular a possible dealumination by acetic acid, did not occur during the reaction under the conditions used (batch conditions, liquid phase, 130°C).

3.4. Acylation of dimethoxybenzene isomers with acetic anhydride over zeolites

The catalytic activities of the three previous zeolite samples were investigated in the acetylation of the two isomers of 1,2-dimethoxybenzene, 1,3- and 1,4-dimethoxybenzenes, respectively, under the standard conditions. A significant difference in the behaviour of the three isomers is observed. As shown in Table 3, which gives the initial rates of the consumption of the three isomers under the same conditions, it appears that 1,3-dimethoxybenzene (*meta* isomer) is more reactive than its 1,2- (*ortho*) and 1,4- (*para*) isomers, respectively, whatever is the zeolite used.

Fig. 3 shows, as an example, the consumption of the substrates as a function of time over the H-Beta zeolite sample.

Such a result, together with the selective formation of only one isomer in each case, is in
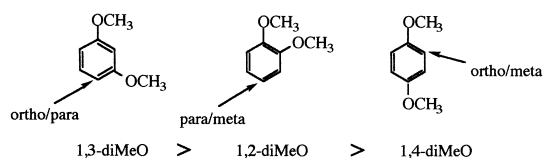
Scheme 2. Orientation substitution effect and reactivity of dimethoxybenzene isomers in the acetylation reaction with acetic anhydride over zeolites.

agreement with the orientation substituent effect of methoxy groups in aromatic electrophilic substitution [45]. These methoxy groups are *ortho-* and *para*-directing activators; it is thus logic that 1,3-dimethoxybenzene, which can give only acetylation at *ortho* and *para* positions to each methoxy group, is more reactive than its 1,2- and 1,4- isomers for which the substitution orientation are *para/meta* and *ortho/meta*, respectively (Scheme 2).

4. Conclusion

Large pore zeolites, such as H-Y and H-Beta, have been shown to be efficient catalysts in the acetylation reaction of activated aromatic derivatives, such as 1,2-, 1,3- and 1,4-dimethoxybenzenes, with acetic anhydride, under liquid phase conditions. Whatever the substrate is, H-Y was generally more active than H-Beta, an order of activity that can be directly related to the microporous structure of the different samples. The kinetic study of the reaction of the 1,2-isomer (veratrole) with acetic anhydride over H-Y $(Si/Al = 15)$ zeolite allowed to establish a modified Eley–Rideal type mechanism, where the adsorbed acetic anhydride reacts with veratrole in the liquid phase, but in which veratrole is also adsorbed on the active sites of the catalyst, acting in a certain way as a poison of the reaction. The evidence of a competitive adsorption of both reactants and products has been demonstrated. Thus, a significant inhibiting effect of the reaction product $(3',4'$-dimethoxyacetophenone in the case of 1,2-dimethoxybenzene as the substrate) and of the acetic acid formed in the reaction has been especially shown, leading to a certain loss of activity of the catalyst. Despite such a deactivation, the use of zeolites in the acetylation of dimethoxybenzenes allows the development of a selective procedure for the preparation of the corresponding dimethoxyacetophenones in convenient yields.

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