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Synthesis of nonsteroidal drugs with anti-inflammatory and analgesic activities with zeolites and mesoporous molecular sieve catalysts

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Abstract

A series of molecules with nonsteroidal anti-inflammatory and analgesic properties were synthesized through a chemical route involving the oximation of acetophenone derivatives, followed by the solid acid-catalyzed Beckmann rearrangement to give the corresponding amides. Microporous and mesoporous molecular sieves, as well as a delaminated (ITQ-2) zeolite, were studied as catalysts, and excellent activity and selectivity for amides were achieved when accessibility of the reactants to the active sites and the surface polarity of the catalyst were optimized. When the number and size of ring substituents increase in the product, only ITQ-2 and MCM-41 give high activities and selectivities. The order of activity observed, when the size of the oxime increases, can be reversed with respect to the obtained conventionally, because of a transition-state shape selectivity in the pores, where the bulkier substituents in the anti-position are impeded from migrating.

Keywords: Mesoporous molecular sieve fine chemical; Zeolite fine chemicals; Catalytic synthesis of nonsteroidal drugs; Beckmann rearrangement of zeolite catalyst; Beckman rearrangement of mesoporous catalyst

1. Introduction

The rearrangement of ketoximes to amides or lactams in the presence of acid catalysts is a process commonly used for the preparation of caprolactam, the monomer used in the production of nylon 6.

N-acetyl-*p*-aminophenol (acetaminophen or paracetamol) is one of the drugs most regularly prescribed because of its analgesic activity. Conventionally, it is prepared by acetylation of *p*-aminophenol with acetic anhydride. However, this reaction may cause problems because of the difficulty of mono acetylating the amine group and the possible oligomerization of the hydroxy aromatic amine. In the mid-1980s Davenport et al. [1] reported an innovative technology for the preparation of *N*-acetyl-*p*-aminophenol (**1**) that involves a two-step process. The first step involves reacting 4-hydroxyacetophenone with hydroxylamine hydrochloride to obtain the ketoxime (4-hydroxyacetophenone oxime, **1a**) followed by the Beckmann rearrangement in the presence of an acid catalyst, such as fuming sulfuric hydrochloride, trifluoroacetic, methanesulfonic, *p*-toluenesulfonic acids, Amberlyst, Nafion, or thionyl chloride in liquid sulfur dioxide. The use of homogeneous acid catalysts requires tedious workup procedures and the necessary neutralization of the strong media, producing undesired wastes. Thus when sulfuric acid is used as catalyst, *N*-acetyl-*p*-aminophenol (**1**) is recovered from the reaction mixture by neutralization of the oleum with aqueous ammonia. In this case a large amount of ammonium sulfate is formed. On the other hand, with an ion-exchange resin as catalyst and acetic acid as solvent under an inert atmosphere, only 66.7% of *N*-acetyl-*p*-aminophenol (**1**) is obtained. Although various catalysts can be used for this Beckmann rearrangement, thionyl chloride in liquid sulfur dioxide has been reported to be an excellent catalyst for the production of **1**, giving a yield of 88% [1]. Unfortunately the use of sulfur dioxide presents drawbacks due to its toxicity and corrosiveness. Moreover, it should be used

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as a liquid, and this requires more expensive and specialized equipment.

More recently Fritch et al. [2] have described an alternative to the above Beckmann rearrangement process that uses an alkyl alkanoate ester as a solvent and thionyl chloride or phosphorous oxytrichloride as an acid catalyst to give high conversions of **1**. Obviously, since *N*-acetyl-*p*-aminophenol (**1**) is an analgesic for human consumption, the product obtained from the above process requires extensive purification. The use of an insoluble acid catalyst will allow easy separation workup (no neutralization step required) and catalyst recycling and will avoid equipment corrosion and contaminant wastes. This has been largely attempted for the Beckmann rearrangement of cyclohexanone oxime to caprolactam in vapor or liquid phase, with the use of a larger number of heterogeneous catalysts such as alumina [3], silica [4], zeolites [5–8], and mesoporous molecular sieves (MCM-41) [9,10]. Concerning the Beckmann rearrangement of 4-hydroxyacetophenone oxime, only one example in liquid phase with Beta zeolites and different solvents has been reported [11], and the authors indicate that the performance of the reaction is strongly dependent on the nature of the solvent.

In this work we show that by with proper design of the topology, acidity, and adsorption characteristics of zeolites, it is possible to obtain, by Beckmann rearrangement, not only paracetamol from the corresponding 4-hydroxyacetophenone oxime (**1a**), but also a series of nonsteroidal drugs with anti-inflammatory (INSAID) and/or analgesic activities that show no gastrointestinal toxicity.

2. Experimental

2.1. Catalysts

Beta zeolites (Beta-1, Beta(F-15), Beta(F-30), Beta(F-50), Beta(F-100), and Beta(F-200)) were synthesized in our laboratory in fluoride media [12]. The acid form of mordenite (MOR) was obtained by calcination of the ammonium form (Conteka), followed by an acid treatment to extract the extraframework Al formed. MCM-41 with a Si/Al ratio of 15 was prepared with a method described in the literature [13]. A USY sample was obtained from PQ Zeolites B.V., and it was NH_4^+ exchanged, followed by calcination at 773 K for 3 h. The ITQ-2 delaminated material and the corresponding MCM-22 zeolite precursor were synthesized with a previously described method [14,15].

Acidity measurements were made by adsorption–desorption of pyridine by IR spectroscopy. The infrared spectra were recorded with a Nicolet 710 FTIR with the use of self-supported wafers of 10 mg cm^{-2}. The calcined samples were outgassed overnight at 673 K and 10^{-3} Pa dynamic vacuum; then pyridine was admitted into the cell at room temperature. After saturation, the samples were outgassed at 523 K for 1 h under vacuum and cooled to room temperature, and the spectra were recorded. The main characteristics of the catalysts are summarized in Table 1.

Table 1
Main structural characteristic of the catalysts

Zeolite	Si/Al	Brönsted acidity[a]		Area ($m^2\ g^{-1}$)	Crystallite size (μm)
		523 K	623 K		
USY	35	43	18	730	0.4–0.6
Beta-1	15	52	26	582	0.02–0.03
Beta(F-15)	15	45	22	536	0.3–0.5
Beta(F-30)	30	36	28	503	0.25
Beta(F-50)	50	19	8	452	0.50
Beta(F-100)	100	11	10	463	0.50
Beta(F-200)	200	8	1	460	0.50
ITQ-2	15	30	20	573	0.30
MCM-22	15	55	44	453	0.3–0.5
ZSM-5	40	30	26	420	1.0–3.0
Mordenite	10	80	47	507	0.15–0.20
MCM-41	15	41	25	909	0.10–0.15

[a] Acidity (μmol pyridine adsorbed per gram of catalyst) calculated using the extinction coefficients from Ref. [26].

2.2. Reagents

Oximes were synthesized from the corresponding ketones by reaction with hydroxylamine hydrochloride in a mixture of ethanol and pyridine at 358 K, by the general method reported in the literature [16]. The oximes were purified by recrystallization with ethanol. Their structures were confirmed by GC-MS (Hewlett–Packard 5988A) and ^{1}H-NMR (400 MHz Varian VXR-400S).

2.3. Reaction procedure

We activated the catalyst (100 mg) in situ by heating the solid under vacuum (1 Torr) for 2 h. After this, the system was left at room temperature, and then a solution of oxime (150 mg) and nitrobenzene (100 mg) as internal standard in the solvent (10 ml) was poured onto the activated catalyst. The resultant suspension was magnetically stirred and heated at the required temperature in a silicone oil bath with an automatic temperature control system. Samples were taken at regular time periods and analyzed by gas chromatography (GC). At the end of the reaction the catalyst was filtered and washed with dichloromethane, and the organic solution was concentrated under reduced pressure, weighed, and analyzed by ^{1}H-NMR and GC-MS. After reaction, the catalyst was submitted to continuous solid-liquid extractions with acetonitrile in a micro-Soxhlet device. After removal of the solvent the residue was also weighted and analyzed by GC-MS and ^{1}H-NMR spectroscopy. In all experiments the recovered material accounted for more than 90% of the starting oxime, and no significant differences were found between the relative percentages of each compound present in the reaction liquid phase and the zeolite extracted residue.

3. Results and discussion

The synthesis of paracetamol by Beckmann rearrangement of 4-hydroxyacetophenone oxime (**1a**) was performed in liquid phase in acetonitrile as a solvent, at 355 K and with zeolites with different topologies as solid acid catalysts (Scheme 1). In all cases the reaction proceeded cleanly, and the only compound observed was the amide *N*-acetyl-*p*-aminophenol (**1**), which is formed trough an anti-migration of the 4-hydroxyphenyl group of the oxime. It is known that the group that migrates in the Beckmann rearrangement is generally the one anti to the hydroxyl group, and this is often used as a method for determining the configuration of the oximes. Other products, such as *N*-methyl-*p*-hydroxybenzamide or *p*-aminophenol, which could be formed by a syn migration of the methyl group or by hydrolysis of **1**, respectively, were not detected under our reaction conditions.

According to the widely accepted reaction mechanism for the Beckmann rearrangement, the first step in the formation of paracetamol is the protonation of the oxime oxygen (O-protonated oxime), followed by the migration of the 4-hydroxyphenyl group and the removal of a water molecule, giving a nitrilium cation. The nitrilium cation reacts with one molecule of water to form the amide tautomer and finally the corresponding amide [17].

However, more recently it was proposed that the most energetically favorable path in the Beckmann rearrangement involves the protonation of the oxime, giving a N-protonated oxime. This is followed by a 1,2-H shift, giving the O-protonated oxime, which evolves toward the nitrilium cation and then gives the amide [18] (Scheme 2).

According to this, it is clear that the reaction involves relatively bulky intermediates with high polar character, and consequently one should be able to design and optimize the catalyst by controlling its pore dimensions, acidity, and adsorption properties. Since all of this can be achieved with zeolite catalysts, we investigate here how these different parameters influence the final catalytic behavior.

The Beckmann rearrangement of **1a** was carried out with 12-member-ring (MR) tridirectional zeolites (USY and Beta), a 12-MR monodirectional zeolite (Mordenite), a 10-MR bidirectional zeolite (ZSM-5), a MCM-22 zeolite that combines 10- and 12-MR, a delaminated ITQ-2 zeolitic material, and a mesoporous aluminosilicate (MCM-41).

Fig. 1 displays the kinetic behavior for the rearrangement of **1a** over different zeolites with acetonitrile as solvent at 355 K, and the yields and initial reaction rates (r_0) are summarized in Table 2. There it can be seen that the order of activity (r_0) is MCM-41 > ITQ-2 > MCM-22 > ZSM-5 ≅ USY > Beta(F-15) ≅ mordenite. On the other hand, when the activity per acid site of medium and high acid strength of the different zeolites, measured by pyridine adsorption and desorption at 523 K (Table 1), is compared, it can be observed that the activity of MCM-41 and ITQ-2 is much higher than that of the microporous cat-

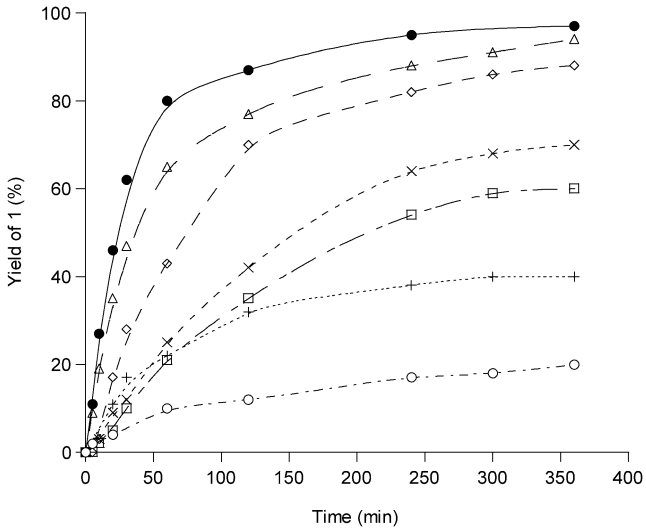
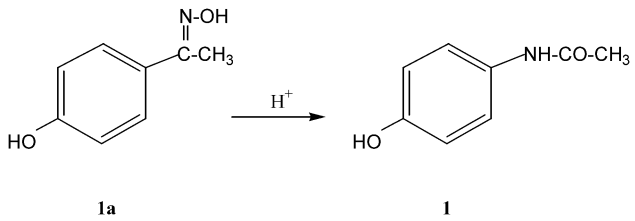
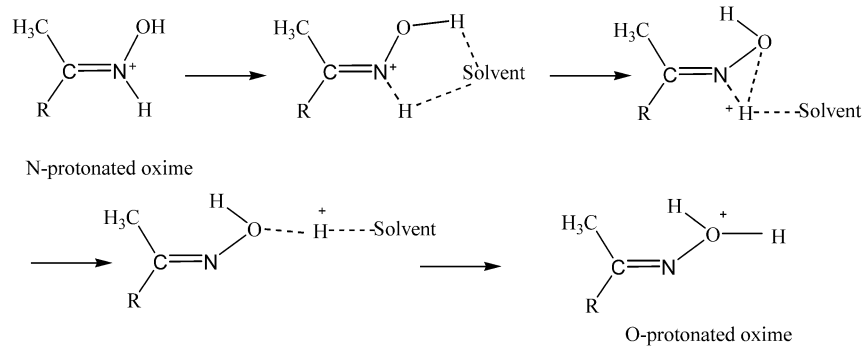


Fig. 1. Yield of paracetamol versus reaction time in the presence of MCM-41 (●), ITQ-2 (△), Beta(F-15) (□), MCM-22 (◊), USY (×), Mor (○), ZSM-5 (+).



1a **1**

Scheme 1.



Scheme 2.

Table 2
Results of the Beckmann rearrangement of oxime **1a** using different zeolites as catalysts[a]

Catalysts	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	r_0/B_a (min^{-1})	Yield (%)
USY	0.38	0.88	69
Beta(F-15)	0.19	0.42	60
MCM-22	0.65	1.18	88
Mordenite	0.20	0.25	16
ITQ-2	1.86	6.20	94
MCM-41	2.02	4.92	97
ZSM-5	0.40	1.33	40

[a] Reaction conditions: in acetonitrile as a solvent; 355 K; 6 h reaction time.

alysts (Table 2). These results appear to indicate that the mesoporous aluminosilicate MCM-41 and delaminated zeolite ITQ-2, the structure of which consists of thin sheets (≅2.5 nm thick), with a hexagonal array of "cups" with an aperture of ∼0.7 nm, exhibit the best accessibility of the reactant to the active sites. In the case of MCM-22 the sinusoidal 10-member ring channels and the 10-member ring windows, which connect to the 12-member ring cavities, can decrease the accessibility of the reagents to the active sites, decreasing the efficiency of this zeolite. In this case the reaction mainly takes place in the open cups at the external surface of the crystals. As we have seen in the case of ITQ-2, these external cups are quite effective for performing the reaction, by allowing the products to easily desorb. Indeed, results from Fig. 1 clearly show a lower catalyst deactivation rate for MCM-22 than for any of the other zeolites. The low activity of ZSM-5, a medium pore bidirectional zeolite, is probably related to diffusional limitations of the pores and geometrical constraints for the formation of the intermediates inside the pores. Consequently, an important relative contribution of the acid sites at the external surface can be expected with this zeolite. Indeed, a similar effect for the Beckmann rearrangement of acetophenone oxime with ZSM-5 as an acid catalyst in liquid [6] and vapor phase [7] has been observed.

Mordenite shows the largest number of potential active sites, but it appears that the unidirectional system of channels imposes either intrinsic diffusional limitations or pore blocking due to the strong adsorption of the reactant or products (see Fig. 1). This effect has also been observed for the vapor-phase Beckmann rearrangement of cyclohexanone oxime with mordenite [19]. It should be noted in this case that there are no geometrical restrictions for the diffusion of reactants through the pores.

The most surprising observation was the low activity (r_0) shown by USY and Beta zeolites (Table 2). The lower activity exhibited by the tridirectional zeolites (USY and Beta) compared with MCM-41 and ITQ-2 can be attributed not only to differences in accessibility of reactant and/or products to active sites (see molecular size in Scheme 4 and activity in Table 2), but to a strong adsorption of the reactants and/or products in the pores of the catalyst. In fact, when the influence of time on stream on conversion is analyzed, the results presented in Fig. 1 indicate that in most cases conversion does not reach 100%, but stops after a certain reaction time. This can be explained by assuming that a catalyst deactivation exists, which is probably generated by the strong adsorption of the reactants and/or products that block the pores or active sites. When the ratio of the external to the internal surface in zeolite Beta was increased by the production of a sample with a crystal size of 20–30 nm (Beta-1), the conversion at a reaction time of 6 h was 81% and continued to increase with time, compared with 60% for the Beta with 0.3–0.5 μm. Since the initial rates were similar for the two samples, this result supports the important role of the strong adsorption within the pores, on catalyst deactivation. Even if a batch reactor is not the best-suited reactor for the study of catalyst deactivation, if we look at the shape of the curves in Fig. 1, it could be said that the order of catalyst deactivation is Mor > ZSM-5 > Beta(F-15) > USY > MCM-22 > ITQ-2 > MCM-41.

If catalyst decay is related to a strong adsorption of reactant and/or products, and since adsorption is an exothermic process, we have to expect that when the reaction temperature is increased, the adsorption constant, and therefore the amount of reactants and products adsorbed, should decrease, decreasing the catalyst decay. Thus the reaction was performed with ITQ-2 and USY zeolites in benzonitrile as a solvent at 383 K. The results were compared with those obtained with acetonitrile as a solvent at 355 K (Figs. 2a and 2b). Indeed, conversion increases with increasing reaction temperature; the increase in activity is more pronounced in the case of USY zeolite, which was the one presenting a higher rate of deactivation. These results would be consistent with a larger heat of adsorption of reactants and/or products responsible for catalyst deactivation on USY than on ITQ-2. Nevertheless, we have to take into account that in these experiments we have changed not only the reaction temperature but also the solvent. Therefore, even if the solvents were nitriles in both cases, we have to determine whether replacing acetonitrile with benzonitrile, while working at the same reaction temperature, has an effect on catalyst activity. Then, working in both solvents at 355 K (Fig. 3), we could see that conversion was lower with benzonitrile than with acetonitrile. These results provide two pieces of information. One is that the effect on desorption–deactivation observed with increasing reaction temperature was indeed due to temperature and not to the solvent; the other is that the polarity of the solvent may play an important role in the final catalyst activity observed. The polarity effect can be associated with the removal by the solvent of the polar molecules adsorbed to the catalyst and with the stabilization of the transition state, which leads to the 1,2-H shifts (Scheme 2) and the migration of the OH_2^+ group from the nitrogen to the carbon atom [11]. Thus, the more polar acetonitrile would be a more suitable solvent than benzonitrile for carrying out the Beckmann rearrangement to produce paracetamol (Fig. 3).

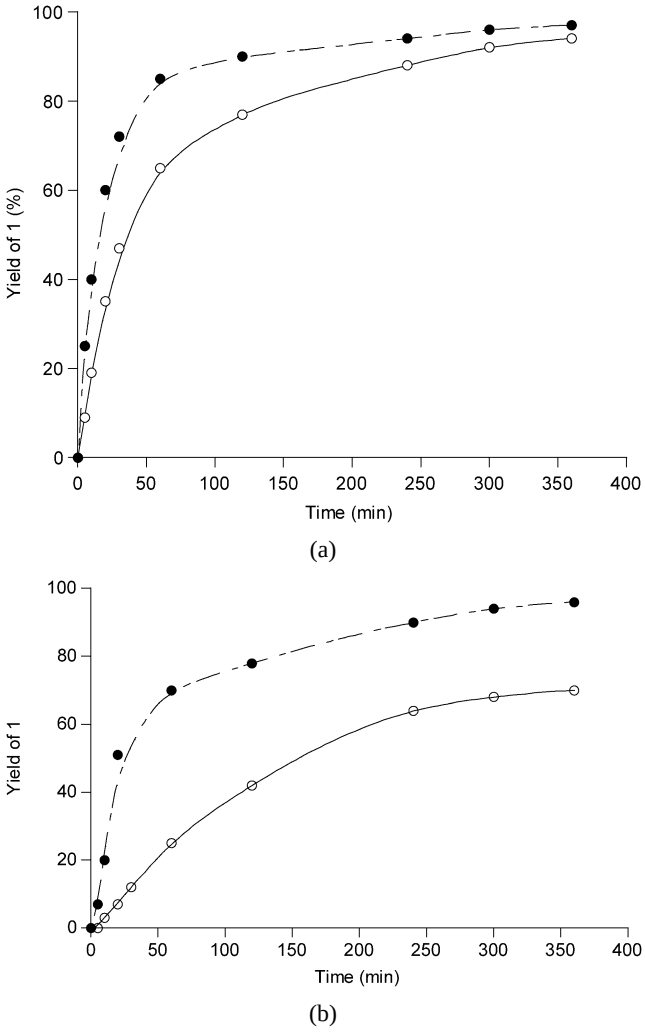


Fig. 2. (a) Yield of **1** versus time obtained using ITQ-2 zeolite as a catalyst at different temperatures: (○) at 355 K in acetonitrile as a solvent; (●) at 383 K in benzonitrile as a solvent. (b) Yield of **1** versus time obtained using USY zeolite as a catalyst at different temperatures: (○) at 355 K in acetonitrile as a solvent; (●) at 383 K in benzonitrile as a solvent.

We have learned from the previous experiments that, for the reaction under study, the controlling step was probably the desorption of polar molecules that may block active sites and channels. Furthermore, it appears that we may favor the product desorption by controlling the polarity of the catalyst, the polarity of the solvent, and the reaction temperature. It is known that zeolite polarity can be modified by a change in the framework composition [20]. In the case of the other two variables, reaction temperature and solvent polarity, we must keep in mind that selectivity may decrease with increasing reaction temperature, and that some solvents can inhibit the Beckmann rearrangement by competitive adsorption [11,21].

3.1. *Influence of the zeolite polarity*

We have shown by working with several reactants and catalysts that maximizing activity and selectivity not only involves optimization of the number and strength of the acid sites; one should also take into account the adsorption properties (hydrophobicity and hydrophilicity) of the zeolite catalysts [22].

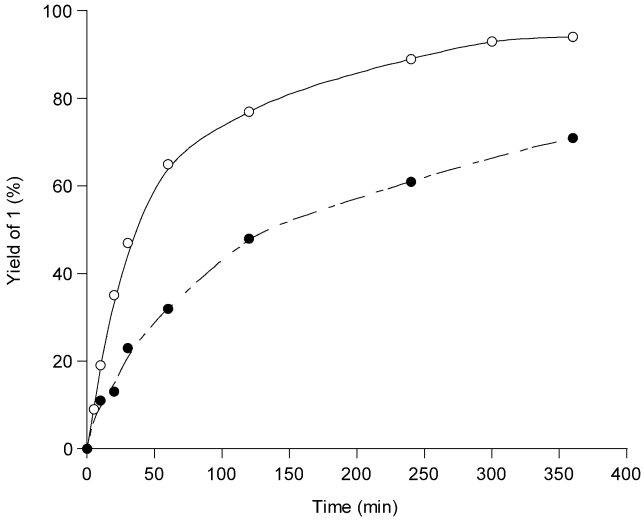


Fig. 3. Yield of **1** versus time reaction when the Beckmann rearrangement was carried out at 355 K using acetonitrile (○) and benzonitrile (●) in the presence of ITQ-2 zeolite.

Thus, with increasing framework Si/Al ratio, the catalyst becomes more hydrophobic, the number of acid sites decreases, and the acid strength of the remaining sites increases up to a constant value when the framework Si/Al ratio reaches approximately 10 [23]. According to the results and conclusions presented above, we could expect that less polar zeolites should favor the desorption of the adsorbed polar products, and therefore an optimum between activity (number of active sites) and catalyst life (catalyst polarity) should be found with a change in the framework Si/Al ratio of the zeolite. In order to check this, the Beckmann rearrangement of **1a** was performed in the presence of Beta zeolite samples with different framework Si/Al ratios: 15, 30, 50, 100, and 200. The samples were prepared in fluoride media, to minimize internal defects and decrease, even further, the polarity of the surface.

The results from Fig. 4 show a maximum in activity for a sample with a Si/Al ratio of 30, which presents a much lower concentration of acid sites than the sample with a lower Si/Al ratio (Si/Al = 15) (see Table 1). From these results it appears that a larger number of acid sites does not guaranty a higher catalyst activity, because of the inhibiting adsorption effect of reactant and products. Thus, in the present case, a less polar sample with a lower concentration of active sites performs better. In fact, an 85% yield of **1** was obtained with Beta(F-30) after 6 h. Of course, if the concentration of active sites is still further reduced, it reaches a point where this becomes the controlling parameter. It has to be noticed that the reaction does not proceed in the presence of the pure siliceous Beta sample under our reaction conditions.

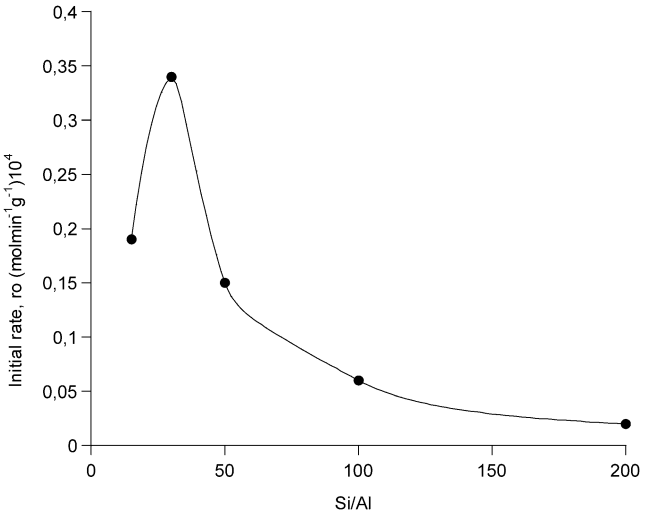


Fig. 4. Influence of Si/Al ratio of different Beta zeolites on the initial reaction rate of **1**.

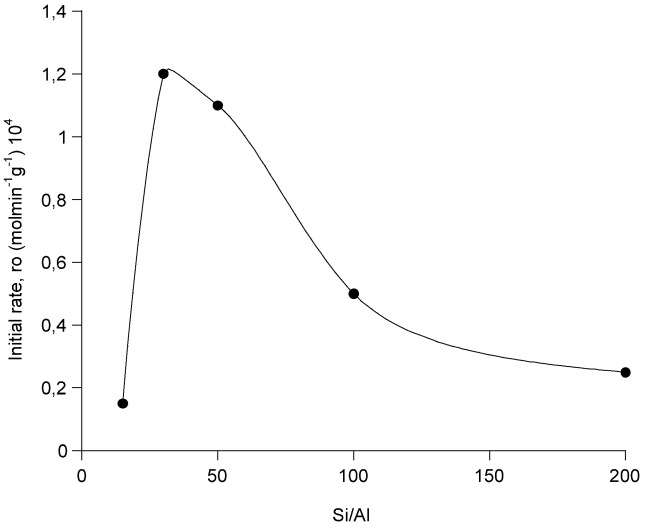


Fig. 5. Influence of Si/Al ratio of different Beta zeolites on the initial reaction rate of **2**.

Similar behavior was observed when the transposition of 4-ethoxy acetophenone oxime (**2a**) was carried out with the Beta(F) zeolites (Fig. 5). However, in this case the presence of an ethoxy group instead of the OH group in the *para* position of the aromatic ring decreases the polarity of the substrate **2a** with respect to **1a**. As can be seen from Fig. 5, this change in the oxime polarity, and therefore in the adsorption/desorption characteristics, is reflected by a shift of the maximum in the activity of the Si/Al curve toward more hydrophobic surfaces (Si/Al ratios between 30 and 50). A related effect of the catalyst hydrophobicity on the acetalization reaction by acid zeolites has recently been reported [24].

In conclusion, we have found that the Beckmann rearrangement of 4-hydroxyacetophenone oxime can be performed in liquid phase at 355 K in the presence of delaminated ITQ-2 and MCM-41 zeolites, giving paracetamol in high yields and selectivities in short rection times. USY and Beta zeolites, in spite of their tridirectional structure, exhibit lower activity, which is due to a fast deactivation of the catalyst as a consequence of the strong adsorption of organic compounds. The study of the influence of the Si/Al ratio of Beta zeolite on the catalytic activity has shown that the hydrophobic–hydrophilic character of the catalyst surface has an impact on the catalytic activity. This parameter should be optimized according to the polarity of the substrate involved in the process.

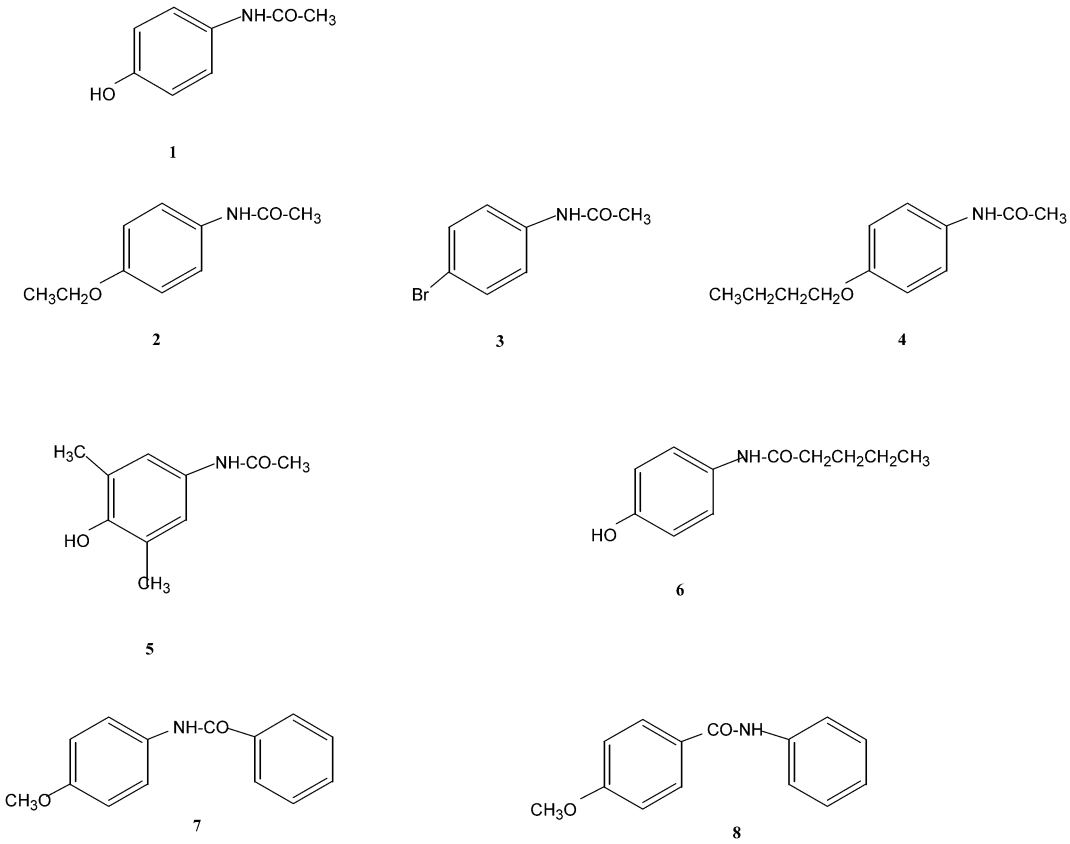
3.2. Catalyst deactivation and regeneration

In order to study the catalyst deactivation occurring during the synthesis of paracetamol, we carried out the Beckmann rearrangement with MCM-41 and ITQ-2 zeolite. After the reaction was complete, the catalyst sample was filtered, washed with acetone, and subjected to a Soxhlet extraction with dichloromethane. The resultant sample was used again in a second experiment. In both cases little deactivation of the catalysts was observed, achieving yields of paracetamol of 85 and 77% after a reaction time of 6 h for MCM-41 and ITQ-2, respectively.

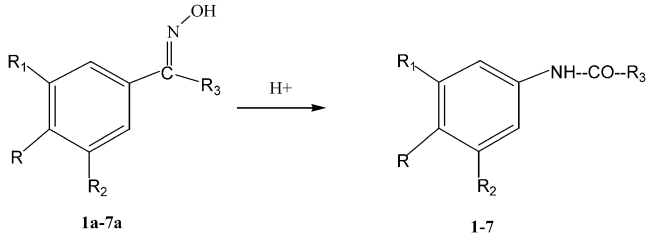
3.3. Beckmann rearrangement of different oximes

Nonsteroidal anti-inflammatory drugs are used for the treatment of inflammatory disorders such as arthritis, spondylitis, etc. Although these types of drugs are regularly prescribed, the gastrointestinal side effects (diarrhea, ulcer formation, etc.) make their use questionable, particularly for patients requiring long-term therapy. Recently, paracetamol derivatives demonstrating anti-inflammatory activity but without gastric toxicity have been reported [25]. A series of these paracetamol derivatives is presented in Scheme 3; we have attempted their synthesis here with the Beckmann rearrangement of the corresponding oximes (Scheme 4), with the use of zeolites as catalysts.

The yields and initial reaction rate (r_0) over different catalysts are summarized in Tables 3 and 5. For comparative purposes, in Table 3 the results of the Beckmann rearrangement of **2a**–**5a** oxime derivatives are also included. In all cases the corresponding acetamide derivatives **2**–**5** were obtained with selectivities greater than 98%. MCM-41, ITQ-2, MCM-22, and Beta(F-30), zeolites exhibited excellent activity for these transformations. These results are in good agreement with those found for the rearrangement of 4-hydroxyacetophenone oxime **1a**. On the other hand, the differences in activity found for the different oximes should also be related to the electron donor or acceptor character of the different substituents present in the aromatic ring. According to the reaction mechanism described before, the presence of different substituents in the aromatic ring should have an influence on the stabilization of the protonated-oxime intermediate. The electron acceptor character of the halogen atom in 4-bromo-acetophenone oxime **3a** would explain the lower



Scheme 3.



Amide	R_1	R_2	R_3	R	Oxime size (Å)	Amide size (Å)
1	H	H	CH_3	OH	10.50 × 7.16 × 6.00	11.02 × 7.17 × 4.53
2	H	H	CH_3	OC_2H_5	13.06 × 7.16 × 6.00	13.38 × 7.17 × 4.53
3	H	H	CH_3	Br	11.65 × 7.16 × 5.18	11.98 × 7.17 × 4.53
4	H	H	CH_3	OC_4H_9	15.79 × 7.16 × 6.00	15.92 × 7.17 × 4.53
5	CH_3	CH_3	CH_3	OH	11.01 × 8.79 × 5.77	10.46 × 7.90 × 4.53
6	H	H	C_4H_9	OH	13.68 × 7.16 × 5.69	15.09 × 7.17 × 4.53
7	H	H	C_6H_6	OCH_3	12.02 × 7.16 × 7.45	12.21 × 7.17 × 8.66

Scheme 4.

activity shown by this oxime in the Beckmann rearrangement.

For comparative purposes, the transposition of 4-ethoxyacetophenone (**2a)**, 4-Br-acetophenone (**3a**), 4-buthoxyacetophenone (**4a**), and 4-hydroxy-3,5-dimethylacetophenone (**5a**) oximes was also carried out under the same reaction conditions, with *p*-toluenesulfonic acid (pTSA) as a homogeneous acid catalyst. The initial rates for the Beckmann rearrangement under these reaction conditions follows the order **5a** > **4a** > **2a** ≫ **3a** (see Table 4). Taking into account the good accessibility of oximes to the active sites of pTSA, this order could be explained by a consideration of the electronic effects that control the activity of the different oximes. Then, if we consider the intrinsic reactivity of the different oximes given in Table 3, it is interesting to note that as the size of the substituent, or the number of them in the aromatic

Table 3
Results for the Beckmann rearrangement of oxime derivatives **2a**–**5a**[a]

Catalysts	**2**		**3**		**4**		**5**	
	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)
USY	0.67	90	0.02	13	0.35	61	0.75	76
Beta(F-30)	1.10	88	0.01	10	0.90	92	1.50	93
MCM-22	1.51	97	0.18	49	0.76	79	0.90	90
ITQ-2	1.84	98	0.25	47	2.22	99	2.26	98
MCM-41	1.70	97	0.30	50	1.80	95	3.94	98[c]
ZSM-5	0.04	13	0.01	5	0.18	25	0.27	47

[a] Reaction conditions: in acetonitrile as a solvent at 355 K.
[b] Yields given at 6 h reaction time.
[c] At 3 h reaction time.

Table 4
Beckmann rearrangement of **1a**–**7a** oxime derivatives in homogeneous phase using *p*-toluenesulfonic acid as catalyst[a]

Oximes	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)	Selectivity to amides (**1**–**8**) (%)
1a	2.1	85	88
2a	2.6	80	88
3a	0.3	8	30
4a	3.0	78	86
5a	4.4	88	94
6a	4.0	87	92
7a	2.8	80[b]	50[b]

[a] Reaction conditions: 1 mmol oxime; 0.2 mmol p-TSA, 10 ml acetonitrile; 355 K; 4 h reaction time.
[b] The mixture of oxime isomers leads to the corresponding benzamides *N*-(4-methoxyphenyl) benzamide (**7**) and *N*-phenyl-4-metoxybenzamide (**8**) in a 80% yield, where each isomer is 50%.

Table 5
Results for the Beckmann rearrangement of oxime derivatives **6a**–**7a**[a]

Catalysts	**6**		**(7 + 8)**	**7**	**8**
	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield (%)	$r_0 \times 10^4$ (mol min^{-1}g^{-1})	Yield[b] (%)	Yield[b] (%)
USY	1.21	84 (3)[c]	1.07	34	37
Beta(F-30)	1.90	99	1.36	38	50
MCM-22	1.82	93 (4)[c]	0.98	28	30
ITQ-2	2.14	99[b]	1.90	40	45
MCM-41	3.60	99[b]	1.97	43	45
ZSM-5	0.80	58 (7)[c]	1.41	38	47

[a] Reaction conditions: acetonitrile as a solvent at 355 K; 6 h reaction time.
[b] Yield at 3 h reaction time.
[c] In parentheses the yield of *N*-buthyl-4-hydroxybenzamide is given.

ring, increases (i.e., from ethoxy to butoxy group), the activities of the USY, Beta, and MCM-22 decrease or remain constant, whereas the activity of the ITQ-2 and MCM-41 increases according to the intrinsic reactivity of the oxime, regardless of the molecular size of the substrate.

With the purpose of studying the influence of the substituent R_3 (Scheme 4) on the Beckmann rearrangement, the transposition of 4-hydroxyvaleroacetophenone (**6a**) and *p*-methoxybenzophenone (**7a**) oximes was performed in the presence of these acid catalysts. The results obtained are summarized in Table 5. The results show that when the size of the group in the R_3 position increases (from CH_3 to Ph–), the effect of the zeolite pore topology on the Beckmann rearrangement has a lower impact than in the case of **2a**, **4a**, and **5a** oxime derivatives. This effect can be explained by a consideration of the reaction mechanism; that is, the group that migrates in the Beckmann rearrangement is generally the one anti to the hydroxyl group. Moreover, during the synthesis of oximes the most stable oxime is preferentially formed, that is, the oxime that possesses the aromatic ring in the *anti* position with respect to the hydroxyl group. Then in the case of **2a**, **4a**, and **5a** oxime derivatives, one has to expect that as the aromatic part of the molecule increases in size with the introduction of substituents, the migration of this group will be controlled by geometrical constraints in the pores of the zeolites. This certainly occurs in the case of Beta, MCM-22, and USY zeolites, whereas with the mesoporous MCM-41 and delaminated ITQ-2, such geometrical constraints do not exist, and the activity of the catalysts remains the same regardless of the size of the reagents involved in the process. In this case the reactivity is mainly controlled by electronic effects. For instance, this effect can be clearly seen when we compare the activities of Beta and USY catalysts for the rearrangement of **5a** and **6a** with those obtained with MCM-41 and ITQ-2. As can be observed in Tables 3 and 5, activities of Beta and USY are lower for **5a** (bearing a three-substituted aromatic ring) than for **6a** (in spite of the fact that the two oximes exhibit similar activity in the homogeneous phase; see Table 4). However, in the case of MCM-41 and ITQ-2, the two oximes exhibit similar activities. These results appear to indicate that the order of activity observed for oximes **2a**, **4a**, and **5a** (i.e., ITQ-2, MCM-41 $\gg$ Beta $>$ MCM-22 $>$ USY) when the size of the oxime is increased should be due not only to diffusional restrictions, but to transition-state geometrical constraints imposed by the zeolite structure, which impedes the migration of the bulkier substituent in the anti position.

On the other hand, it is interesting to note that during the synthesis of *p*-methoxybenzophenone oxime (**7a**) with hydroxylamine hydrochloride, two oximes with a 50% yield

were obtained. One of them possesses the *p*-methoxyphenyl group anti to the hydroxyl group and the other the phenyl group. This result is not surprising if we consider that the two geometrical oxime isomers should have similar thermodynamic stabilities. The Beckmann rearrangement of this mixture of oxime isomers leads to the corresponding benzamides, *N*-(4-methoxyphenyl) benzamide (**7**) and *N*-phenyl-4-metoxybenzamide (**8**), in good yields. In both cases the group that migrates is a methoxyphenyl or a phenyl ring that, as in the case of **1a**, does not show geometrical restrictions for the migration.

4. Conclusions

Zeolites present clear advantages over the conventional homogeneous acid catalysts used commercially for the preparation of paracetamol and other nonsteroidal anti-inflamatory drugs.

MCM-41, ITQ-2, Beta, and MCM-22 zeolites are very active and selective for the preparation of paracetamol and its derivatives by Beckmann rearrangement, and it is possible to achieve good conversion of oximes in relatively short reaction times.

It has been found that the adsorption properties (polarity) of the catalyst can be more important than the total number of acid sites when catalyst deactivation is also considered.

It was found that for 4-hydroxyacetophenone oxime the nature of the solvent has a strong effect on the activity of the catalysts.

Finally, delaminated ITQ-2 zeolite and the mesoporous aluminosilicate MCM-41 are suitable catalysts for carrying out the Beckmann rearrangement of large oximes such as **4a** and **5a**, giving interesting anti-inflammatory drugs.

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