

# Zeolites as Base Catalysts: Condensation of Benzaldehyde Derivatives with Activated Methylenic Compounds on Germanium-Substituted Faujasite

A. CORMA,<sup>\*,1</sup> R. M. MARTÍN-ARANDA,<sup>\*</sup> AND F. SÁNCHEZ<sup>†</sup>

<sup>\*</sup>Instituto de Tecnología Química, CSIC-UPV, Universidad Politécnica de Valencia, Camino Vera S/N, Valencia, and <sup>†</sup>Instituto de Química Orgánica, CSIC, Juan de la Cierva 3 28006 Madrid, Spain

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The condensation of benzaldehyde, 2-nitrobenzaldehyde, and 2-trifluoromethylbenzaldehyde with ethyl cyanoacetate and ethyl malonate to obtain intermediates for the production of dihydropyridine derivatives has been carried out on NaX-type zeolites. The substitution of Si by Ge during the zeolite synthesis results in a strong increase in activity, which has been related to changes in basicity. High activities and selectivities are obtained with the NaGeX zeolite when operating in a batch reactor at moderate temperatures. This zeolite is more active than pyridine and less active than piperidine. © 1990 Academic Press, Inc.

## INTRODUCTION

It has been shown (1, 2) that zeolites have basic sites, which are able to catalyze reactions needing weak and medium basic strength (3-5). It has been seen that the basicity of the zeolite depends on the average electronegativity of the framework (6), being stronger when the electronegativity is lower. Therefore, the influence of the framework Si/Al ratio and the type of counter-cation on the final basicity and catalytic activity has been studied (1, 5). It appears that the introduction into the framework of atoms other than Si and Al can change the basicity of the zeolite and, therefore, the catalytic activity for base-catalyzed reactions.

Bases are active and selective catalysts for the formation of C-C bonds through the reaction of a carbonyl with an activated methylene group. This type of condensation reaction is widely used to prepare  $\alpha,\beta$ -unsaturated esters and nitriles. In this work we have studied the condensation of benz-

aldehyde and benzaldehyde derivatives with ethyl cyanoacetate and ethyl malonate which support methylene groups with different acidities ( $pK_b$ ). Through this reaction it is possible to prepare intermediate products for the synthesis of dihydropyridines of the type shown in Scheme 1, which are of interest clinically as potent calcium channel blockers, and against hypertension (7).

In the present work, a NaX zeolite and a NaX zeolite in which the Si has been substituted by Ge during synthesis were used as catalysts, the activity for the condensation reactions being on the order of 20 times higher on GeX than on NaX.

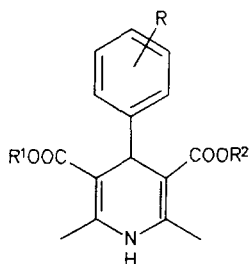
## EXPERIMENTAL

### Materials

A NaGe faujasite with a Ge/Al ratio of 1.03, a unit cell parameter of 25.57 Å, and 5.3 meq · g of Na<sup>+</sup> was prepared following the procedure described by Poncelet *et al.* (8, 9).

A NaX zeolite from Union Carbide (13-X, Si/Al = 1.20) with a unit cell size of 24.95 Å was also used as a catalyst.

<sup>1</sup> Author to whom correspondence should be addressed.



SCHEME 1

### Reaction Procedure

An equimolar solution of the two reactants, without any solvent, was kept in a batch reactor under stirring, while being heated to reaction temperature (90–170°C). Then, 1–2 wt% catalyst was added and the reaction started. Samples were taken periodically, and the evolution of the reaction between 1 and 480 min was followed by GLC using a 60-m phenylsilicone capillary column. <sup>1</sup>H-NMR spectra of the products were recorded with a 90-MHz spectrometer using CDCl<sub>3</sub> as solvent and TMS as an internal reference.

## RESULTS AND DISCUSSION

### Influence of External and Internal Diffusion

In liquid phase–solid catalyzed reactions special care should be taken to avoid the reaction to be controlled by the diffusion of reactants. To check this, the condensation of benzaldehyde with ethyl cyanoacetate was carried out at 140°C, while stirring the

TABLE 1

Influence of Stirring Speed on the Conversion during the Condensation of Benzaldehyde and Ethyl Cyanoacetate

Catalyst	T (°C)	Stirring speed (rpm)	Yield <sup>a</sup> (%)
NaGeX	140	1000	83
		3500	86
NaSiX	140	1000	41
		3500	42

<sup>a</sup> Reaction time = 1 h.

TABLE 2

Influence of Catalyst Particle Size on the Conversion during the Condensation of Benzaldehyde and Ethyl Cyanoacetate

Catalyst	T (°C)	Particle size (mm)	Yield <sup>a</sup> (%)
NaGeX	140	0.074	85
		0.140	85
		0.250	86
NaSiX	140	0.074	42
		0.140	42
		0.250	41

<sup>a</sup> Reaction time = 1 h. Stirring speed = 3500 rpm.

solution at 1000 and 3500 rpm. After 1 h of reaction the same conversion was obtained independently of the stirring speed (Table 1), indicating that under these conditions the reaction is not controlled by the external diffusion.

The reaction was repeated under the same conditions using catalyst pellets 0.074, 0.140, and 0.250 mm in diameter, prepared by pressing, crushing, and sieving the zeolite. The same conversion was observed (Table 2) in all cases, irrespective of the catalyst particle size; therefore, we can assume that if a catalyst with a particle size in the range studied is used, the results will not be affected by the so-called internal diffusion.

### Influence of Reaction Conditions

In Fig. 1, the conversion at different reaction times for the condensation of benzaldehyde (14.0 mmol) with ethyl cyanoacetate (14.0 mmol) using 0.031 g of the NaGe faujasite and NaX zeolite at 90, 120, and 140°C is given. Figure 2 shows the results for the same type of experiment at 130, 150, and 170°C reaction temperatures, but using benzaldehyde (7 mmol) and ethyl malonate (7 mmol) as reactants and 0.19 g of the NaGe faujasite and NaX zeolite. The NaX zeolite has a Si/Al ratio of 1.20, only slightly higher than the Ge/Al ratio of the NaGe faujasite. From the conversion results (Figs. 1 and 2) it is possible to see

that the activity of the Ge sample for both reactions is much higher than that of the parent silicon faujasite. The differences in activity indicate a higher basicity of the Ge faujasite. It has been reported (6) that the basicity of the zeolite increases as the negative charge on the framework oxygen atoms increases. This being higher when lower is the average Sanderson's electronegativity (10). Calculation of the average Sanderson electronegativity of the two zeolite samples does not reveal a significant difference, 3.28 and 3.25, between the germanium and the silicon faujasites, respectively. Therefore, the higher basicity shown by the Ge zeolite may be related to possible differences in the T-O-T bond angles of this sample (unit cell size 25.57 Å) with respect to NaX (unit cell size 24.95 Å).

### Kinetics of the Reaction

To study the kinetics of the condensation reactions, and thus to be able to estimate the kinetic rate constants and activation energies for the two catalysts, the following reaction model has been assumed.

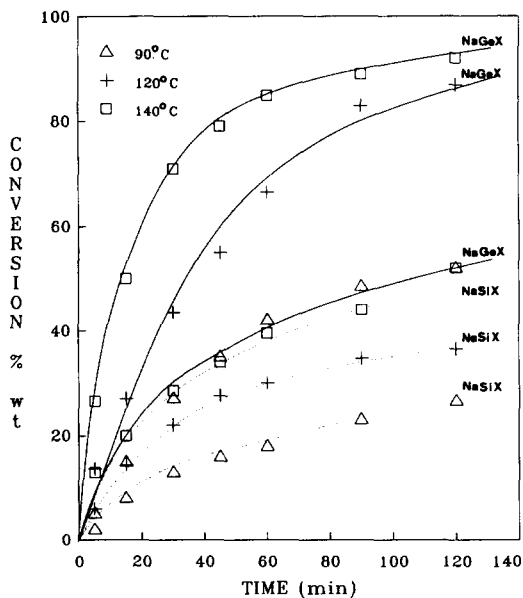


FIG. 1. Condensation of benzaldehyde (14 mmol) and ethyl cyanoacetate (14 mmol) at 90, 120, and 140°C using NaGe faujasite and NaX zeolite (0.031 g).

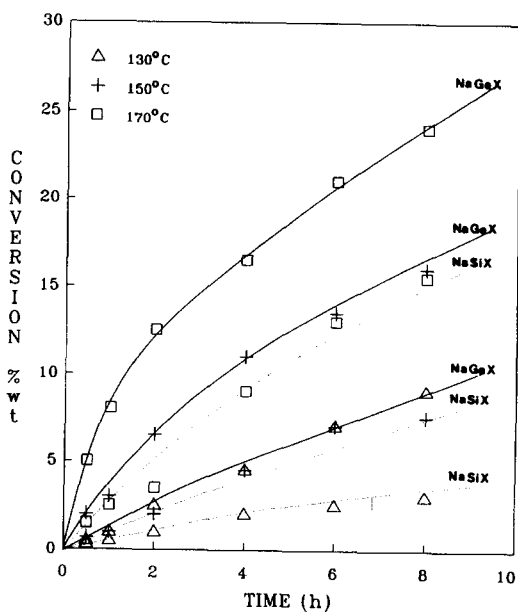
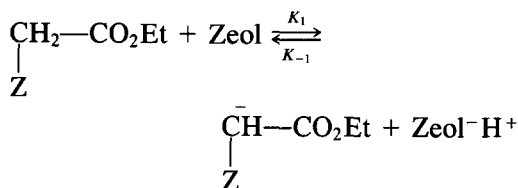
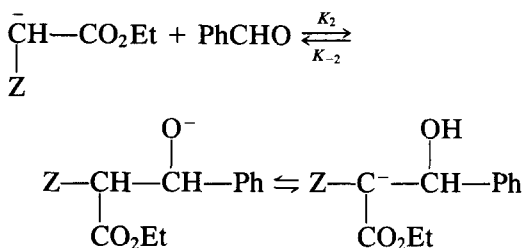


FIG. 2. Condensation of benzaldehyde (7 mmol) and ethyl malonate (7 mmol) at 130, 150, and 170°C using NaGe faujasite and NaX zeolite (0.19 g).

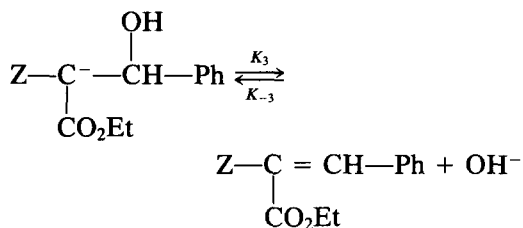
### Step 1



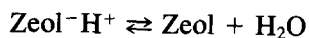
### Step 2



### Step 3



## Step 4



In the first step, the basic catalyst abstracts a proton from the methylenic group of the ethyl malonate or ethyl cyanoacetate, forming a stabilized enolate anion, which in the second step adds on to the carbonyl group of benzaldehyde, forming a new carbon-carbon bond. The adduct so constituted is in quick equilibrium with its C-anion tautomeric form, which, in the third step, by elimination of the hydroxyl group as hydroxide ion, gives the condensation product. Finally, water is formed from the hydroxide anion and the active site of the catalyst is restored. Two kinetic rate expressions, i.e., first and second order, have been considered assuming that the controlling step is either the proton abstraction (step 1),

$$r = K_0[S_0] \text{ [derivative of malonic ester]}, \quad (1)$$

or the attack to the carbonyl group of the aldehyde (step 2),

TABLE 3

Kinetic Rate Constants for the Condensation of Benzaldehyde (14 mmol) and Ethyl Cyanoacetate (14 mmol) Using NaGeX Faujasite (0.031 g) and NaX Zeolite (0.031 g)

Model	Zeolite	$T$ (°C)	$K \times 10^{13}$ (mol s <sup>-1</sup> unit cell <sup>-1</sup> )	C.C. <sup>a</sup>
1	NaGeX	90	14.2	0.99
		120	71.8	0.99
		140	143.6	0.98
2	NaGeX	90	14.5	0.99
		120	80.6	0.99
		140	159.2	0.99
1	NaX	90	2.8	0.98
		120	4.6	0.99
		140	6.5	0.99
2	NaX	90	3.4	0.98
		120	5.8	0.99
		140	10.3	0.99

<sup>a</sup> Linear correlation coefficient.

TABLE 4

Kinetic Rate Constants for the Condensation of Benzaldehyde (7 mmol) and Ethyl Malonate (7 mmol) Using NaGeX Faujasite (0.19 g) and NaX Zeolite (0.19 g)

Model	Zeolite	$T$ (°C)	$K \times 10^{16}$ (mol s <sup>-1</sup> unit cell <sup>-1</sup> )	C.C. <sup>a</sup>
1	NaGeX	130	89.8	0.99
		150	164.6	0.99
		170	243.1	0.98
2	NaGeX	130	93.5	0.99
		150	179.5	0.99
		170	284.2	0.98
1	NaX	130	24.8	0.99
		150	63.0	0.98
		170	147.0	0.99
2	NaX	130	25.3	0.98
		150	66.0	0.98
		170	153.0	0.99

<sup>a</sup> Linear correlation coefficient.

$$r = K_0[S_0] \text{ [derivative of malonic ester]} \text{ [benzaldehyde]}, \quad (2)$$

where  $r$  is the reaction rate,  $K_0$  is the rate constant,  $[S_0]$  is the concentration of basic sites and [derivative of malonic ester] is the concentration of either ethyl cyanoacetate or ethyl malonate.

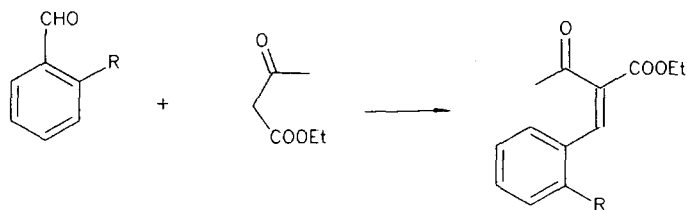
Since the concentrations of the derivative of malonic ester and of benzaldehyde are the same, the integrated rate expressions for the first- and second-order models are

$$\ln \frac{1}{1-X} = K_0[S_0]t, \quad (3)$$

$$\frac{X}{1-X} = K_0[S_0]t, \quad (4)$$

where  $X$  is the concentration of the unreacted reactant, and  $t$  is the reaction time.

The results shown in Figs. 1 and 2 have been arranged to fit these two kinetic expressions, and both models give comparable fits (Tables 3 and 4). In these tables, the kinetic rate constants per unit cell of zeolite for the condensation of benzaldehyde with ethyl cyanoacetate and ethyl malonate, on



a: R = NO<sub>2</sub>; b: R = CF<sub>3</sub>

SCHEME 2

NaGeX and NaSiX are given. It appears that the turnover number of the basic sites is on the order of 20 times higher for the Ge faujasite than for the Si-containing faujasite. Moreover, the NaGe faujasite shows that the kinetic rate constant for the condensation with ethyl malonate ( $pK = 13.3$ ) is  $\sim 15$  times lower than the kinetic rate constant for the condensation with ethyl cyanoacetate ( $pK = 8.6$ ). On the other hand the same ratio is 30 for the NaX zeolite, indicating that indeed, the introduction of Ge instead of Si increases the relative proportion of stronger basic sites.

We have also used these two zeolites to catalyze the condensation of 2-nitrobenzaldehyde and 2-trifluoromethylbenzaldehyde with ethyl acetoacetate (Scheme 2).

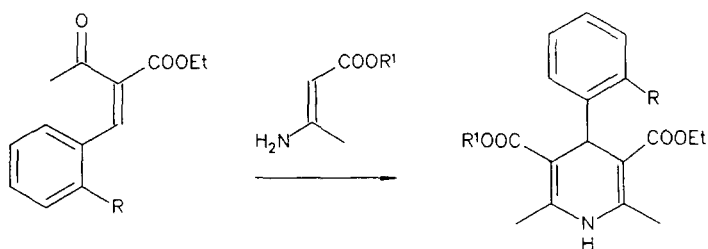
These two products can be now converted into dihydropyridine derivatives by reacting with an aminocrotonic derivative (Scheme 3).

Both reactions were carried out at 100 and 140°C, with 2 wt% catalyst and follow-

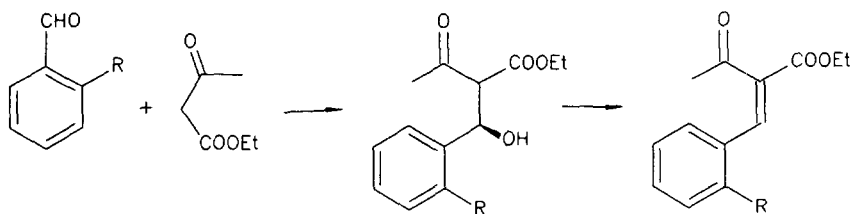
ing the same reaction procedure described previously. With both zeolites, traces of the hydroxylic intermediate were observed (Scheme 4).

Results in Figs. 3 and 4 show that NaGe faujasite is about three times more active than NaX zeolite; the selectivity is the same in both cases.

To compare the activity and selectivity of these zeolites with other base catalysts commonly used, we carried out the reaction using pyridine and piperidine as catalysts, in quantities equivalent to the number of moles of Na present when carrying out the reaction on the zeolite. The same products and in the same proportions as when the zeolites were used as catalysts were observed with both pyridine ( $pK_b = 8.8$ ) and piperidine ( $pK_b = 11.12$ ), indicating that the reactions take place through the same mechanism on both types of catalyst. However, Figs. 3 and 4 show that the order of activity is piperidine > NaGe faujasite > pyridine > NaX.



SCHEME 3



a: R = NO<sub>2</sub>; b: R = CF<sub>3</sub>

SCHEME 4

### CONCLUSIONS

Na faujasites are active and selective catalysts for the condensation of benzaldehyde and benzaldehyde derivatives with ethyl cyanoacetate and ethyl malonate at moderate temperatures. Therefore, they are of interest as catalysts for the preparation of intermediates in the manufacture of dihydropyridines. The substitution of Si by Ge in the framework of an X-type faujasite

strongly increase the activity of the zeolite for these base-catalyzed reactions. The increase in activity cannot be related to an increase in base strength due to a decrease in the average Sanderson electronegativity calculated by taking into account only the electronegativity of the compositional elements, but the T-O-T bond angle should be considered. Finally, the selectivity of

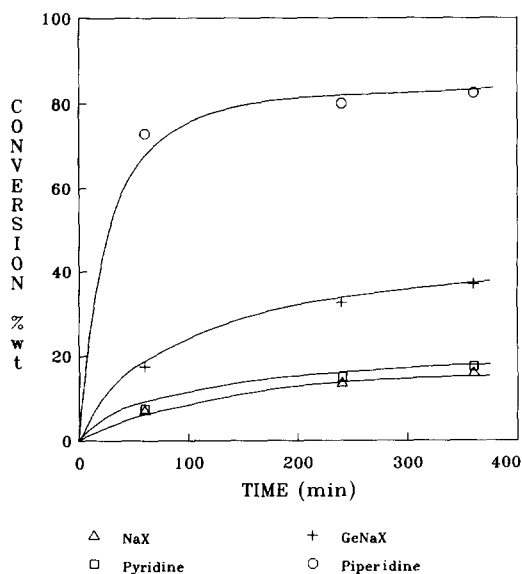


FIG. 3. Condensation of 2-nitrobenzaldehyde (5 mmol) and ethyl acetoacetate (5 mmol) at 100°C using NaGe faujasite (0.0280 g), NaX zeolite (0.0280 g), piperidine (0.0038 g), and pyridine (0.0035 g).

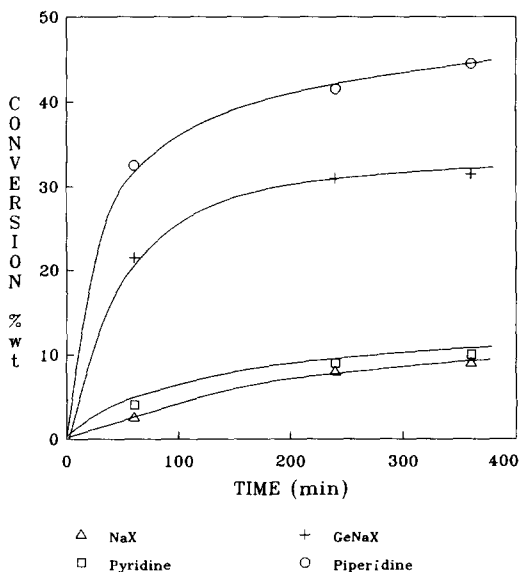


FIG. 4. Condensation of 2-trifluoromethylbenzaldehyde (4.3 mmol) and ethyl acetoacetate (4.3 mmol) at 100°C using NaGe faujasite (0.0262 g), NaX zeolite (0.0262 g), piperidine (0.0036 g), and pyridine (0.0033 g).

these zeolites for the condensation reaction studied is the same as that obtained when pyridine or piperidine was used as base catalyst. The activity of the NaGe faujasite is higher than that of pyridine and lower than that of piperidine, indicating that most of the basic sites on the NaGeX zeolite have a  $pK_b \approx 11.2$ . Nevertheless, sites with strength on the order of  $pK_b = 13.3$  must exist, since these zeolite catalysts are able to abstract protons from ethyl malonate.

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