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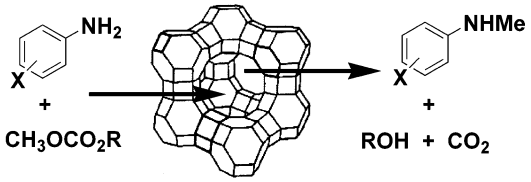
Mono-*N*-methylation of Functionalized Anilines with Alkyl Methyl Carbonates over NaY Faujasites. 4. Kinetics and Selectivity

Maurizio Selva,* Pietro Tundo, and Tommaso Foccardi

Dipartimento di Scienze Ambientali dell'Università Ca' Foscari, Calle Larga S. Marta 2137, 30123, Venezia, Italy

selva@unive.it

Received October 29, 2004



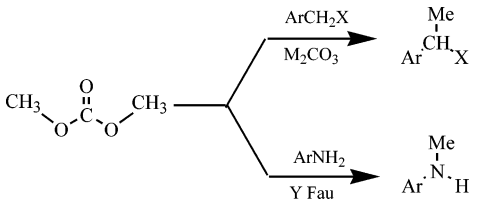
In the presence of NaY faujasite as the catalyst, the reaction of bifunctional anilines (**1**−**4**: $XC_6H_4NH_2$; X = OH, CO_2H, CH_2OH, and $CONH_2$) with methyl alkyl carbonates [$MeOCO_2R'$: R′ = Me or $MeO(CH_2)_2O(CH_2)_2$] proceeds with a very high mono-*N*-methyl selectivity (XC_6H_4NHMe up to 99%), and chemoselectivity as well, with other nucleophilic functions (OH, CO_2H, CH_2OH, $CONH_2$) fully preserved from alkylation and/or transesterification reactions. Aromatic substituents, however, modify the relative reactivity of amines **1**−**4**: good evidence suggests that, not only steric and electronic effects, but, importantly, direct acid−base interactions between substituents and the catalyst are involved. Weakly acidic groups (OH, CH_2OH, $CONH_2$, $pK_a \geq 10$) may help the reaction, while aminobenzoic acids (pK_a of 4−5) are the least reactive substrates. The solvent polarity also affects the reaction, which is faster in xylene than in the more polar diglyme. The mono-*N*-methyl selectivity is explained by the adsorption pattern of reagents within the zeolite pores: a $B_{Al}2$ displacement of the amine on methyl alkyl carbonate should occur aided by the geometric features of the NaY supercavities. Different factors account for the reaction chemoselectivity. Evidence proves that the polarizability of the two nucleophilic terms (NH_2 and X groups) of anilines is relevant, although adsorption and confinement phenomena of reagents promoted by the zeolite should also be considered.

Introduction

In the past decade, the need for safer and more selective processes has fueled a growing interest for dimethyl carbonate ($MeOCO_2Me$, DMC), as a methylating agent.[1] DMC, in fact, is a nontoxic compound[2] that allows an unprecedented high selectivity (up to 99%, at complete conversion) in the monomethylation of both CH_2-active compounds and primary aromatic amines (Scheme 1).[3,4]

In particular, we recently reported that the combined use of DMC and sodium-exchanged Y-zeolite (NaY) is also a valuable protocol for the *N*-methylation of functionalized anilines such as amino-phenols (**1**), -benzoic acids (**2**), -benzyl alcohols (**3**), and -benzamides (**4**) (Scheme 2).[5]

SCHEME 1. M = K, Na; X = CN, CO_2Me; Y Fau: Alkali Metal-Exchanged Y Faujasites



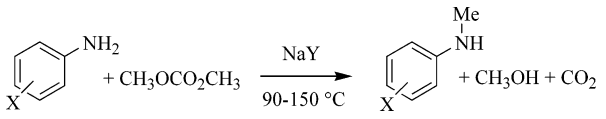
(1) (a) Shaik, A.-A. G.; Sivaram, S. *Chem. Rev*. **1996**, *96*, 951−976. (b) Tundo, P.; Selva, M. *Acc. Chem. Res*. **2002**, *35*, 706−716.

(2) (a) Romano, U.; Rivetti, F.; Di Muzio, N. U.S. Pat. 4,318,862, 1981, C.A. 80141, 1979. (b) Rivetti, F.; Romano, U.; Delledonne, D. In *Green Chemistry*: *Designing Chemistry for the Environment*; Anastas, P., Williamson, T. C., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1996; Vol. 626, pp 70−80.

(3) (a) Selva, M.; Marques, C. A.; Tundo, P. *J. Chem. Soc*., *Perkin Trans. I* **1994**, 1323−1328. (b) Fu, Z.-H.; Ono, Y. *J. Catal*. **1994**, *145*, 166−70. (c) Tundo, P.; Selva, M.; Bomben, A. *Org. Synth*. **1999**, *76*, 169−177. (d) Selva, M.; Tundo, P.; Perosa, A.; Memoli, S. *J. Org. Chem*. **2002**, *67*, 1071−1077.

10.1021/jo048076r CCC: $30.25
Published on Web 03/10/2005

SCHEME 2. **X = OH, CO_2H, CH_2OH, $CONH_2$**



This reaction not only shows a very high mono-*N*-methyl selectivity (up to 99%), but it proceeds with a complete chemoselectivity toward the amino group, with the other nucleophilic functionalities (OH, CO_2H, CH_2-OH, $CONH_2$) fully preserved from alkylation and/or transesterification reactions. Moreover, with respect to conventional methylation procedures, which require stoichiometric bases and harmful reagents (methyl halides or dimethyl sulfate), the reaction of Scheme 2 takes place with catalytic amounts of NaY and neither organic nor inorganic wastes need to be disposed of.[6]

With the aim of further exploring the features of this process, we wish to report here a kinetic analysis of the methylation of compounds **1**−**4** (Scheme 3) with either DMC or 2-(2-methoxyethoxy)methyl ethyl carbonate [$MeO(CH_2)_2O(CH_2)_2OCO_2Me$, MEC] as methylating agents, and NaY faujasite as a catalyst.

This study shows how the presence of aromatic substituents OH, CH_2OH, CO_2H and $CONH_2$ modifies the relative methylation rate of amines **1**−**4**, plausibly by altering the adsorption of these substrates within the pores of the zeolite used. Some general conclusions on the role of steric hindrance and of interactions of aniline substituents with the zeolite cages are also drawn from the reaction of some *O*-protected bifunctional amines ($XC_6H_4NH_2$: X = OMe, **6a**,**b**; CO_2Me, **7a**,**b**; CO_2Et, **8a**,**b**; Scheme 4) with DMC and MEC, in the presence of NaY.

The overall investigation has been developed through the following lines: (i) at first, the order and the regime of the reaction were evaluated to validate the kinetic examination; (ii) then, pseudo-first-order rate constants were obtained for the reaction of DMC with amines **1** and **3**,**4**, and for the reaction of MEC with amines **1**−**4** (including aminobenzoic acids **2a**,**b**), and with aminothiophenols (*ortho*- and *para*-isomers, respectively); (iii) finally, pseudo-first-order rate constants were obtained for the reaction of MEC with anisidines and esters of aminobenzoic acids (**6**−**8**).

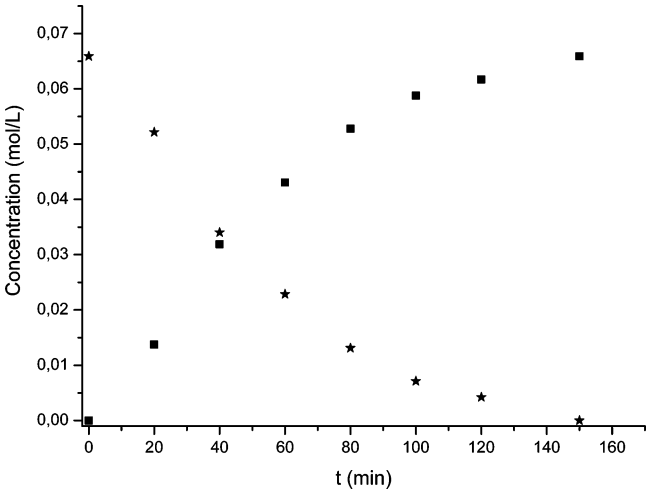


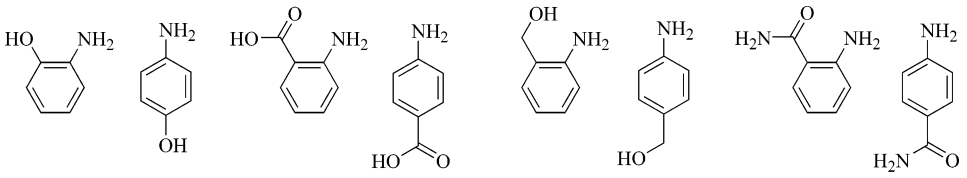
FIGURE 1. The mono-*N*-methylation of *o*-aminophenol with DMC, at 90 °C (*Q* = 2): disappearance of **1a** (★) and formation of its mono-*N*-methyl derivative (■).

Results

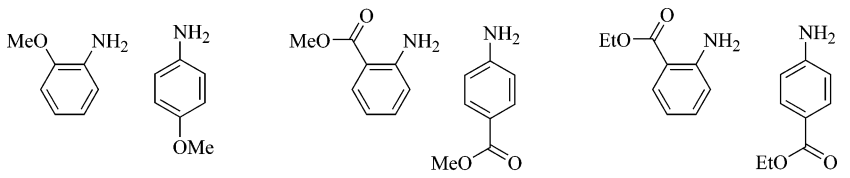
1. Mono-*N*-methylation of *o*-Aminophenol (1a). Order and Regime. *o*-Aminophenol (**1a**) was initially chosen as a model compound. Solutions of **1a** in DMC (6.5×10^{-2} M, 42 mL; DMC serving both as the methylating agent and as the solvent) were made to react at 90 °C, under a N_2 atmosphere, in the presence of different amounts of the faujasite NaY as the catalyst [weight ratio NaY:**1a** (*Q*) in the range of 0.5−3], and of triglyme [$CH_3O(CH_2O)_2(CH_2)_2OCH_3$, 0.56 mmol] as the internal standard. Both the disappearance of *o*-aminophenol and the formation of its *N*-methyl derivative (*o*-HOC_6H_4-NHMe) were monitored by GLC and GC/MS. In all cases, no other products were observed, except for traces (<1%) of *o*-(*N*,*N*-dimethylamino)phenol at conversions >90%. As an example, Figure 1 reports the reaction run with *Q* = 2.

From these data, in accordance with the treatment already described by us for the methylation of aniline over NaY zeolite,[4d] pseudo-first-order rate constants (k_{obs}) for the decay of **1a** could be evaluated at different *Q* ratios.[7] The results are reported in Table 1.

SCHEME 3



SCHEME 4



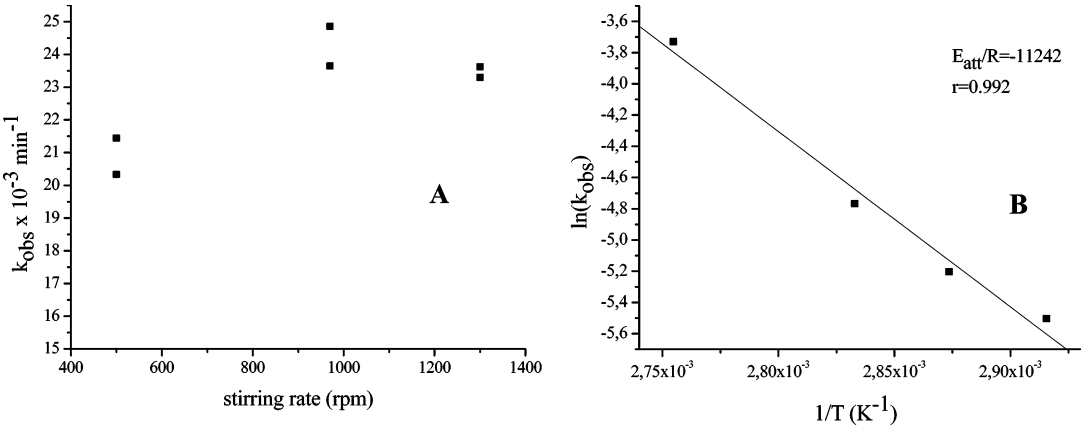


FIGURE 2. Mono-*N*-methylation of **1a** with DMC and NaY ($Q = 2$): (A) the effect of the stirring rate on k_{obs}; (B) apparent activation energy from the Arrhenius equation.

TABLE 1. Pseudo-First-Order Rate Constants for the Mono-*N*-methylation of *o*-Aminophenol with DMC in the Presence of Different Amounts of NaY (*Q*)

entry	Q[a]	$k_{obs} \times 10^{-3}$ (min^{-1})
1	0.5	6.7
2	1.0	13.6
3	1.6	20.7
4	2.0	24.5
5	3.0	34.0

[a] *Q*: weight ratio NaY:**1a**.

General criteria recommended for heterogeneously catalyzed processes[8] were then applied to evaluate the regime under which the reaction occurred: both the effect of the catalyst weight and of the stirring rate on the kinetic constant (k_{obs}), and the activation energy of the reaction were considered.

In particular, it was noted that: (i) a linear relationship held between k_{obs} of Table 1 and the *Q* ratio,[9] and, under the conditions of Figure 1, (ii) the reaction rate (k_{obs}) tended to an asymptotic value provided that the stirring rate was above 970 rpm (Figure 2A), and (iii) the apparent activation energy calculated from the Arrhenius equation ($\ln k_{obs} = \ln A - E_{att}/RT$; Figure 2B) was 93.5 kJ mol^{-1}. The *A* factor was of 2.68×10^{-2} (see Experimental Section for details).

2. a. Mono-*N*-methylation of *ortho*- and *para*-Isomers of Aminophenols (1a,b), Aminobenzyl Alcohols (3a,b), and Aminobenzamides (4a,b) with DMC. Two sets of experiments (a and b) were performed.

(a) In the first, the reactivity of *ortho*-substituted compounds (**3a** and **4a**) was explored under the conditions above-described for *o*-aminophenol.[10] Solutions of **3a** and **4a** in DMC (6.5×10^{-2} M, 42 mL) were made to react at 90 °C in the presence of the faujasite NaY [for convenience, the weight ratio NaY:substrate (*Q*) was set at 2, see Experimental Section]. Triglyme [$CH_3O(CH_2O)_2$-$(CH_2)_2OCH_3$, 0.63 and 0.47 mmol for **3a** and **4a**, respectively] was the internal standard.

(b) In the second, to compare rate constants for both *para*- and *ortho*-derivatives, reaction conditions were slightly modified: because *p*-aminophenol (**1b**) and *p*-aminobenzamide (**4a**) were sparingly soluble in DMC, 1,2-dimethoxyethane (DME) was used as a cosolvent.[11] Accordingly, solutions of compounds **1a**,**b**, **3a**,**b**, and **4a**,**b** in a mixture of DMC/DME (4.2×10^{-2} M, 42 mL, DMC:DME = 4 v:v), were made to react at the reflux of DME (84 °C), under a N_2 atmosphere, in the presence of NaY ($Q = 2$) and of an internal standard (triglyme, **1a**,**b**, **3a**, and **4a**,**b**; hexadecane, **3b**).

The disappearance of the reagents and the formation of the corresponding *N*-methyl derivatives (XC_6H_4NHMe; X = OH, CH_2OH, $CONH_2$) were monitored by GLC and GC/MS. In all cases, pseudo-first-order rate constants (k_{obs}) for the decay of the substrates were obtained as described for **1a** in Table 1.[12]

(4) (a) Fu, Z.-H.; Ono, Y. *Catal. Lett.* **1993**, *22*, 277−81. (b) Selva, M.; Bomben, A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1041−1045. (c) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677−680. (d) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2002**, *67*, 9238−9247.

(5) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2003**, *68*, 7374−7378.

(6) The coproduct MeOH (Scheme 2) can, in principle, be recycled to the preparation of the carbonate itself.

(7) If one considers that the concentration of the DMC (reagent/solvent) is a constant during the reaction, a simplified rate law equation for the disappearance of **1a** can be used: $v = -(d[\mathbf{1a}]/dt) = k\cdot[\mathbf{1a}]^p\cdot[\mathbf{DMC}]^q = k'[\mathbf{1a}]^p$, where $k' = k[\mathbf{DMC}]^q$. We observed that, throughout the range of *Q*, the concentration profiles of **1a** (determined by GC) fitted the integrated rate law with $p = 1$ ($\ln[\mathbf{1a}]_o/[\mathbf{1a}] = k't$, where $[\mathbf{1a}]_o$ and $[\mathbf{1a}]$ were the concentrations of **1a** at $t = 0$ and at a later time *t*, respectively). The resulting plots gave straight lines ($r > 0.99$), whose slopes were the pseudo-first-order rate constants k_{obs}, for the disappearance of the substrate. According to the above equation, the evaluation of the order with respect to DMC is not possible: this would require a large excess of the amine and, consequently, the presence of a solvent. Under such conditions, compound **1a** as well as all the other amines **1**−**4** would dissolve only in polar solvents (i.e., alcohols, DMF, DMSO, sulfolane, etc.), which strongly adsorb on the zeolite and deactivate it (see ref 4d and references therein, as well as the discussion section).

(8) (a) Boudart, M.; Diega-Mariadasson, G. In *Kinetics of Heterogeneous Catalytic Reactions*; Prausnitz, J. M., Brewer, L., Eds.; Princeton University Press: Princeton, NJ, 1984. (b) Alcorn, W. R.; Sullivan, T. J. In *Catalysis of Organic Reactions*; Kosak, J. R., Ed.; Marcel Dekker Inc.: New York, 1984. (c) Satterfield, C. N. *Mass Transfer in Heterogeneous Catalysis*; MIT Press: Cambridge, MA, 1970.

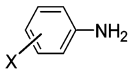
(9) See Figure 1 in the Supporting Information. It should be noted, however, that saturation effects of the catalyst by both aromatic amines and dialkyl carbonates should be expected. We already observed these effects in (i) the reaction of aniline with MEC (ref 4d), and (ii) the reaction of aniline with a large excess of DMC (ref 4b).

(10) At 90 °C, both anthranilic and *p*-aminobenzoic acids (**2a**,**b**) did not react with DMC in the presence of NaY (ref 5). Therefore, they were not considered at this stage.

(11) The choice of DME was based on results previously reported by us (refs 4d and 5).

(12) The Supporting Information reports the example of the mono-*N*-methylation of *p*-amino benzamide (**4b**).

TABLE 2. Mono-*N*-methylation of *o*- and *p*-Aminophenols (1a,1b), *o*- and *p*-Aminobenzyl Alcohols (3a,3b), and *o*- and *p*-Aminobenzamides (4a,4b)

Entry [a]		solvent	t (min)	Conv.'n (%) [b]	$S_{M/D}$ (%) [c]	k_{obs} 10^{-3} (min^{-1})
1	**1a**: X = *o*-OH	DMC	150	100	99	24.5
2	**3a**: X= *o*-CH_2OH		405	63	99	1.9
3	**4a**: X = *o*-$CONH_2$		540	85	94	4.8
4	**1a**: X = *o*-OH	DMC / DME	240	88	99	8.9
5	**1b**: X = *p*-OH		315	79	94	4.9
6	**3a**: X= *o*-CH_2OH		600	67	89	1.6
7	**3b**: X = *p*-CH_2OH		570	79	92	2.9
8	**4a**: X = *o*-$CONH_2$		480	88	99	3.9
9	**4b**: X= *p*-$CONH_2$		570	78	89	2.0

[a] Entries 1−3: experiments were carried out at 90 °C using DMC as a solvent. Entries 4−9: experiments were carried out at 84 °C using a mixture of DMC/DME (4:1 v/v) as a solvent. [b] Reaction conversion, % by GC. [c] $S_{M/D}\% = XC_6H_4NHCH_3/(XC_6H_4NHCH_3 + XC_6H_4N(CH_3)_2) \times 100$ is the mono-*N*- to *N*,*N*-dimethyl selectivity.

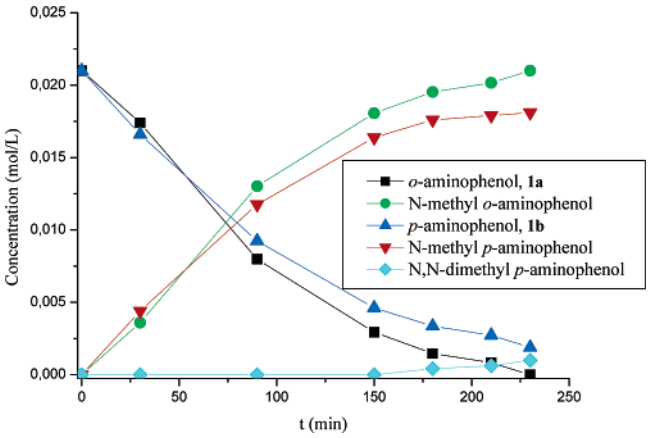


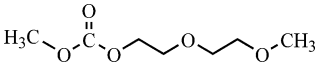
FIGURE 3. Competitive mono-*N*-methylation of *o*- and *p*-aminophenols with DMC/DME.

Table 2 reports k_{obs} for the investigated compounds. The table also shows the mono-*N*- to *N*,*N*-dimethylselectivity ($S_{M/D}$%), which is always very high (from 89% to 99%) even at substantially quantitative conversions. $S_{M/D}$% defines also the overall reaction selectivity because no other products were observed except XC_6H_4NHMe and $XC_6H_4NMe_2$.

To further compare the reactivity between *ortho*- and *para*-isomers, also a competitive reaction between *o*- and *p*-aminophenol (**1a**,**b**) was carried out using a solution of equimolar amounts of the two isomers (2.1×10^{-2} M in each substrate) in DMC/DME (42 mL; DMC/DME = 4 v/v), in the presence of NaY [NaY/(**1a** + **1b**) = 2 weight ratio]. The result is reported in Figure 3.

2. b. Mono-*N*-methylation of *ortho*- and *para*-Isomers of Aminophenols (1a,b), Aminobenzoic Acids (2a,b), Aminobenzyl Alcohols (3a,b), and Aminobenzamides (4a,b) with 2-(2-Methoxyethoxy)-methylethyl Carbonate (MEC). To complete the kinetic analysis for amines **1**−**4**, the mono-*N*-methylation of acids **2a**,**b** had to be explored. Compounds **2a**,**b**, however, reacted with DMC only at $T \geq 130$ °C, in autoclaves with internal pressures up to 6−7 bar.[5,10] Because these conditions were not suitable for a kinetic study, an asymmetrical alkyl methyl carbonate, 2-(2-methoxyethoxy)methylethyl carbonate (MEC, Scheme 5), was chosen as the methylating agent.

SCHEME 5. 2-(2-Methoxyethoxy)methylethyl Carbonate, MEC



MEC in fact, was easily prepared from DMC, and it allowed us to run both *O*- and *N*-methylation reactions with 99% chemoselectivity, at temperatures up to 160 °C, and at atmospheric pressure.[4c,d,13]

Two sets of experiments (c and d) were performed.

In (c), solutions of *ortho*-substituted compounds **1a**−**4a** in xylene[14] (7×10^{-2} M, 30 mL) were made to react at 135 °C, in the presence of MEC (in a 10 molar excess with respect to the reactant amine), of the faujasite NaY [weight ratio NaY:substrate (*Q*) of 2], and of octadecane as the internal standard (Scheme 6a).

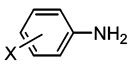
In (d), both *ortho*- and *para*-substituted compounds (**1a**,**b**, **2a**,**b**, and **4a**,**b**, respectively) were made to react with MEC under the same conditions described for set c, except for the solvent used: because *p*-aminobenzoic acid (**2b**) and *p*-aminobenzamide (**4b**) were not soluble in xylene, a glycol-derived dimethyl ether (DME-like) such as diglyme [$CH_3O(CH_2)_2O(CH_2)_2OCH_3$, bp 162 °C] was chosen (Scheme 6b).

For both sets c and d, in accordance to the procedure described for Tables 1 and 2,[7,15] pseudo-first-order rate

(13) Perosa, A.; Selva, M.; Tundo, P.; Zordan, F. *Synlett* **2000**, *1*, 272−274.

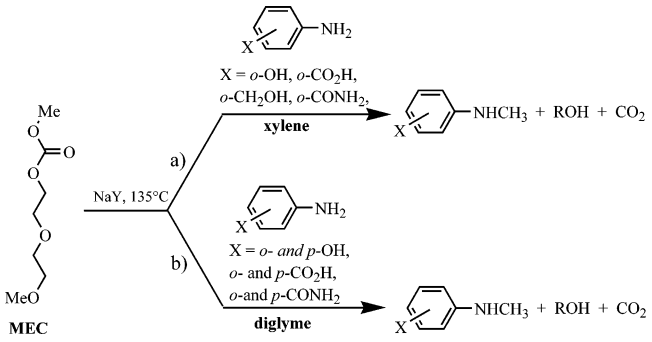
(14) The adsorption of hydrocarbons over zeolites takes place to a much lesser extent with respect to more polar compounds. Thus, when possible, apolar media (i.e., xylene) are excellent solvents for liquid-phase reactions catalysed by faujasites. See refs 4d and: (a) Espeel, P. H. J.; Vercruysse, K. A.; Debaerdemaker, M.; Jacobs, P. A. *Stud. Surf. Sci. Catal.* **1994**, *84*, 1457. (b) Jayat, F.; Sabater Picot, M. J.; Guisnet, M. *Catal. Lett.* **1996**, *41*, 181.

TABLE 3. The Reactions of Amines 1−4 with MEC in the Presence of NaY

Entry [a]		Solvent	t (min)	Conv.'n (%) [b]	$S_{M/D}$% [b]	k_{obs} 10^{-3} (min^{-1}) [b]
1	**1a**: X = *o*-OH	xylene	10	100	100	-
2	**2a**:X = *o*-CO_2H		540	72	100	2.3
3	**3a**: X = *o*-CH_2OH		80	100	96 [c]	-
4	**4a**: X = *o*-$CONH_2$		80	95	90	36.9
5	**1a**: X = *o*-OH	diglyme	80	87	100	34.3
6	**1b**: X = *p*-OH		50	98	92	49.2
7	**2a**: X = *o*-CO_2H		2880	66	97	0.41
8	**2b**: X = *p*-CO_2H		600	77	91	1.6
9	**4a**: X = *o*-$CONH_2$		300	86	93	6.2
10	**4b**: X = *p*-$CONH_2$		50	84	86	39.3

[a] Entries 1−4: experiments were carried out at 135 °C using xylene as a solvent. Entries 5−10: experiments were carried out at 135 °C using diglyme as a solvent. [b] Conversions, $S_{M/D}$% (as defined in Table 2), and k_{obs} were averaged over two runs. [c] The overall selectivity toward the wanted product (*o*-$CH_2OHC_6H_4NHMe$) was of only 62% due to the occurrence of side-reactions.

SCHEME 6. The Methylation of Amines 1−4 with MEC

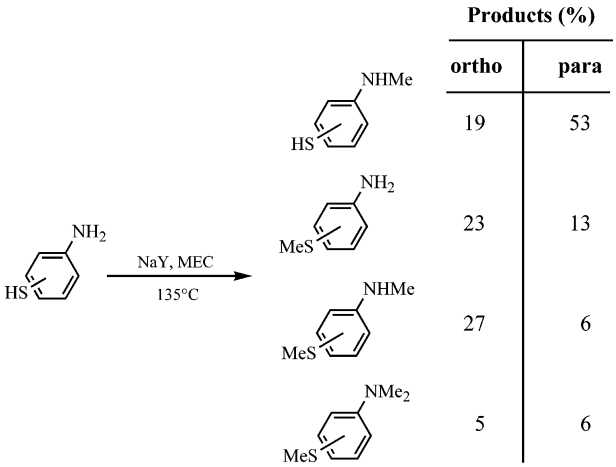


constants (k_{obs}) were evaluated for the disappearance of reagents **1**−**4**. Results are reported in Table 3.

It should be noted that in xylene as a solvent, k_{obs} values related to *o*-aminophenol and *o*-aminobenzyl alcohol (**1a** and **3a**, respectively) are missing (entries 1 and 3). In these cases, the kinetic investigation was precluded because of two different reasons: (i) the reaction of **1a** took place too rapidly (10 min, entry 1), and (ii) the concentration profile of **3a** was altered with respect to a first-order decay, by the onset of side-reactions. In particular, the formation of three high-boiling byproducts in a total amount of 35% was observed at complete conversion of the substrate: two of them reasonably derived from the N-alkylation of **3a** [HO-$CH_2C_6H_4NHR$ and $HOCH_2C_6H_4N(CH_3)R$, R = CH_3O-$(CH_2)_2O(CH_2)_2$: molecular ions M^+ of 225 and 239, respectively], while the structure of the third compound (M^+ = 281) was not assigned. This lack of selectivity suggested to us that we not investigate the reactivity of aminobenzyl alcohols (**3a**,**b**) in diglyme.

(15) The concentration of MEC (molar ratio MEC:substrate = 10) was assumed to be constant during the reactions.

SCHEME 7. The Reaction of Aminothiophenols with MEC: Distribution (%) of Products Determined by GC/MS

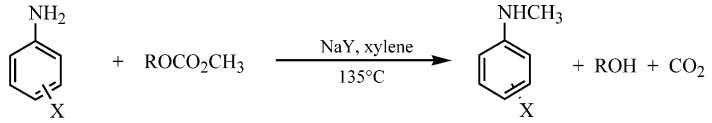


5a: conversion of 74% after 8h
5b: conversion of 78% after 4h

2. c. Methylation of *ortho*- and *para*-Isomers of Aminothiophenols (5a,b) with MEC. Under the condition of Table 3 (entries 1−4), also the reaction of other ambident nucleophiles such as aminothiophenols ($HSC_6H_4NH_2$; *ortho* and *para*, compounds **5a** and **5b**, respectively) with MEC was explored. The results are reported in Scheme 7.

3. The Reaction of MEC with Anisidines and Methyl and Ethyl Aminobenzoates. Finally, to further examine the role of aromatic substituents, the methylation of some *O*-protected bifunctional aromatic amines (**6a**,**b**, **7a**,**b**, and **8a**,**b**) with MEC was investigated (Scheme 8). All reactions were carried out under the conditions of entries 1−4 of Table 3. At 135 °C, solutions of compounds **6**−**8** in xylene (7×10^{-2} M, 30 mL) were made to react with MEC (in a 10 molar excess

SCHEME 8. Methylation of Protected Anilines 6−8 with MEC over NaY



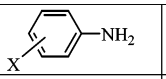
6a and **6b**: X = *o*- and *p*-OCH_3; **7a** and **7b**: X = *o*- and *p*-CO_2CH_3; **8a** and **8b**: X = *o*- and *p*-$CO_2CH_2CH_3$

R = $CH_3O(CH_2)_2O(CH_2)_2$

with respect to the reactant amine), in the presence of the faujasite NaY [weight ratio NaY:substrate (*Q*) of 2], and of an internal standard (0.35 mmol: dodecane for **6a**,**b**, tetradecane for **7a**,**b**, hexadecane for **8a**,**b**).

The course of reactions was monitored by GLC-GC/MS: only mono-*N*- and di-*N*,*N*-methyl derivatives of compounds **6**−**8** were observed. According to the procedure described for Tables 1−3, pseudo-first-order rate constants (k_{obs}) were evaluated for the disappearance of reagents. The results are reported in Table 4.

TABLE 4. The Reaction of Compounds 6−8 with MEC over NaY

Entry		t (min)	Conv.'n (%) [a]	$S_{M/D}$ (%)[b]	$k_{obs} \cdot 10^{-3}$ (min^{-1})
1	**6a**: X = *o*-OMe	1320	85	84	2.0
2	**6b**: X = *p*-OMe	210	88	77	10.9
3 [c]	**1a**: X = *o*-OH	6	100	100	nd [d]
4	**7a**: X = *o*-CO_2Me	660	44[e]	97	1.0
5	**7b**: X = *p*-CO_2Me	270	95	90	10.3
6 [c]	**2a**: X = *o*-CO_2H	540	72	100	2.2
7 [c]	**4a**: X = *o*-$CONH_2$	80	95	90	37.0
8	**8a**: X = *o*-CO_2Et	4680	57	88	0.1
9	**8b**: X = *p*-CO_2Et	540	78	82	2.9

[a] Reaction conversion, % by GC. [b] $S_{M/D}$ (%) as defined in Tables 1−3. [c] Already reported in Table 3. [d] nd: not determined (see entry 1 of Table 4). [e] After 33 h, a conversion of 73% was obtained with a $S_{M/D}$ of 94%.

For a direct comparison, Table 4 also indicates the rate constants for the methylation of *o*-aminophenol, anthranilic acid, and anthranilamide (compounds **1a**, **2a**, and **4a**, respectively) obtained under the same reaction conditions (entries 1, 2, and 4, Table 3).

Discussion

The Regime of the Reaction. Data of Table 1 and Figure 2A, and **t**he apparent activation energy of 93.5 kJ mol^{-1} (Figure 2B) well above the threshold of 25 kJ mol^{-1} accepted for chemically controlled reactions,[16] allow us to conclude that the model reaction of compound **1a** with DMC is not diffusion-limited under the examined conditions. Therefore, the kinetic investigation is validated.

Steric and Electronic Effects. At 90 °C, in either DMC [set a: entries 1−3, Table 2] or DMC and DME as a cosolvent [set b: entries 4−9, Table 2], aminophenols (1) are the more reactive substrates, and a general reactivity scale can be recognized (Scheme 9).

SCHEME 9

Phenols (**1a-b**) > Amides (**4a-b**) ≥ Alcohols (**3a-b**)

The same trend holds at 135 °C with MEC as the methylating agent (Table 3). For instance, in either xylene or diglyme as solvents, the reaction of **1a** proceeds 6−8 times faster with respect to amide **4a** (entries 1 and 4, 5 and 9).[17] Phenols **1a**,**b** are also more reactive than acids **2a**,**b** (entries 1 and 4, 5 and 7, 6 and 8).

Reasonably, the electron-donating and steric properties of the OH substituent may account for both an increase in the nucleophilicity and a reduced hindrance around the NH_2 group, of **1** with respect to compounds **2**, **3**, and **4** as well.

The role of steric hindrance seems readily appreciable also from data of Table 4: for both anisidines (entries 1 and 2) and methyl and ethyl esters of aminobenzoic acids (entries 4,5 and 8,9, respectively), *para*-isomers are by far more reactive than the *ortho* ones; also, k_{obs} values of methyl *p*-aminobenzoate and methyl anthranilate (entries 4 and 5) are higher than those of the corresponding ethyl esters (entries 8 and 9).

The Role of H-Bonding. Steric and electronic effects, however, do not explain other relevant aspects of the reactivity of amines **1**−**4**. In particular, (i) although the $CONH_2$ group shows a higher electron-withdrawing capacity,[18] and a moderately larger bulkiness with respect to the CH_2OH substituent (Table 3 of SI), the reaction of DMC with amides is faster than with alcohols, especially in the case of *o*-substituted compounds ($k_{4a} \approx 2k_{3a}$, entries 2 and 3, Table 2); and (ii) more surprisingly, a striking difference of reactivity is evident between acids **2** and amides **4**: at 135 °C with MEC, the ratio of rate constants for *ortho*-derivatives (k_{4a}/k_{2a}) is 16 (entries 2 and 4, Table 3), and it is even higher for *para*-reagents **2b** and **4b** ($k_{4b}/k_{2b} = 24$; entries 8 and 10, Table 3). This, despite CO_2H and $CONH_2$ substituents possess medium-to-strong electron-withdrawing effects and a similar steric hindrance (Table 3 of SI).

To discuss this kinetic evidence, the knowledge of adsorption phenomena of reagents over the catalyst becomes mandatory. Model cases of aniline and phenol are suitable to this scope.

According to Czjiek et al.,[19] the steric requisites of aniline allow it to diffuse into the pores of NaY (super-

(16) Bond, G. C. *Heterogeneous catalysis principles and applications*, 2nd ed.; Clarendon Press: Oxford, 1987.

(17) The relative reactivity for compounds **1a** and **4a** (entries 1 and 4) is estimated from the time required for both reactions to be completed.

(18) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1991. (b) Hansh, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(19) Czjiek, M.; Vogt, T.; Fuess, H. *Zeolites* **1991**, *11*, 832.

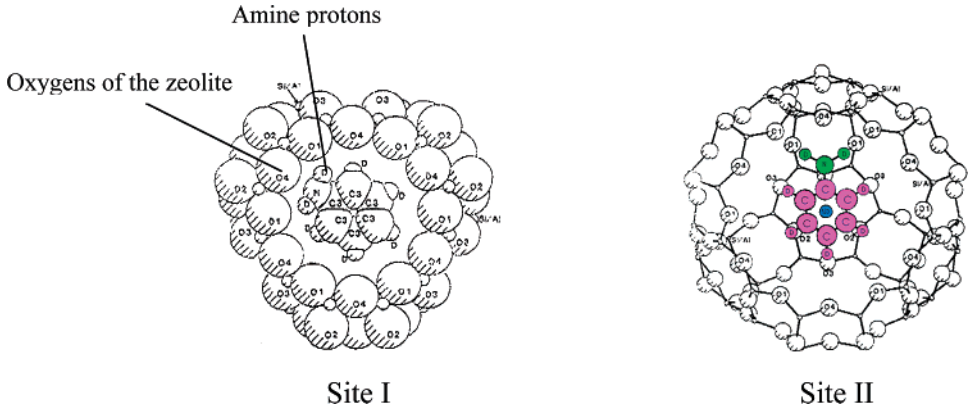


FIGURE 4. Two adsorption sites for $PhND_2$ in the NaY faujasite. Site II: Na^+ is the blue dot.

cages), where two sites of adsorption have been identified through diffraction techniques (Figure 4): on the first (site I), the amine is held through H-bonds between amine protons and basic oxygen atoms of the zeolite framework; on the second (site II), the amine is pinned to the lattice, forming a π complex between the aryl ring and a Lewis-acid cation (e.g., Na^+).

Different authors reported that also the hydroxyl group of a phenol adsorbed into an alkali metal-exchanged faujasite (i.e., NaX) is predominantly H-bonded to basic oxygen atoms of the cavity of the zeolite.[20,21]

H-bond interactions should be expected to play an important role also in the adsorption of amines **1**−**4** within NaY. In fact, as supported by the comparison of the molecular size of compounds **1**−**4**[22] with the dimensions of the zeolite channels and cavities (diameters of 7.4 and 11.8 Å, respectively[23]), also amines (**1**−**4**) may have a relatively free access to the faujasite supercages. If so, the kinetic outcome of Tables 2 and 3 has to be affected by specific interactions of aromatic substituents such as OH, CO_2H, CH_2OH, and $CONH_2$, with the catalyst itself.

Aminophenols (**1a**,**b**). The OH group of aminophenols can exert a 2-fold favorable effect: (a) because of its moderate steric hindrance and its electron-donating properties, it can help the interaction of the amino group with the catalyst (particularly on site I, Figure 4); (b) it may stabilize the adsorption of reagents **1a**,**b** through a direct H-bond with the zeolite (ArO−H····O−zeolite).

Aminobenzyl Alcohols (**3a**,**b**). Like phenols, also the OH group of benzyl alcohols undergoes H-bonding with oxygen atoms of alkali metal-exchanged faujasite.[24] However, a poorer interaction with respect to phenols (pK_a of 10) is expected because of the poorer acidity of alcohols (pK_a of 16). Along with the steric hindrance and the moderate electron-withdrawing properties of the CH_2-OH functionality, this fact offers a rationale for the relative reactivity of compounds **1** and **3**.

Aminobenzoic Acids (**2a,b**) and Aminobenzamides (**4a**,**b**). Weakly acid amidic protons ($pK_a = 17$) should go through H-bonds of intensity comparable to that of alcohols **3**, while a strong acid−base interaction between carboxylic functions of acids **2a**,**b** ($pK_a = 4-5$) and oxygen atoms of the zeolite may plausibly block the reagents over the catalytic sites (slowing the reaction).[25] The relative rates of methylation of compounds **2** and **4** with both DMC and MEC (Table 4) may be so explained.

Overall, the balance between steric/electronic effects and the acidity associated with the aromatic substituents of amines **1**−**4** appears as one of the key factors accounting for the kinetic results of Tables 2 and 3. This seems confirmed also from the reactions of *O*-protected anilines (**6**−**8**) with MEC (Table 4). Data show that: (i) the reaction of *o*-aminophenol (**1a**, entry 3) is much faster with respect to *o*-anisidine and even more surprisingly, with respect to *p*-anisidine too (entries 1 and 2); and (ii) anthranilammide (**4a**, entry 7) is more reactive than methyl anthranilate (entry 4) and, despite the *ortho* substitution, also than methyl *p*-aminobenzoate (entry 5). These remarkable differences reflect the positive effect of H-bonding interactions between the catalyst and OH or $CONH_2$ groups of **1a** and **4a**, which is missing for *O*-protected anilines (**6a**,**b** and **7b**). On the other hand, when acid−base interactions between the zeolite and the substrate become too strong, then reactivity drops: the reaction of anthranilic acid (**2a**, entry 6) is only slightly faster with respect to that of the corresponding methyl ester (entry 5). Like compounds **1**−**4**, also amines **6**−**8** should be hosted by the zeolite supercavity (Table 3 of SI).

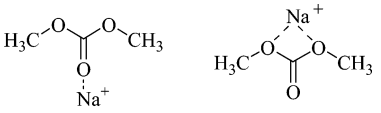
The Reaction Mechanism: Mono-*N*-methyl Selectivity. To formulate a mechanistic hypothesis for the investigated reaction, the methylation of aniline with DMC over NaY is a suitable model. Again, the role of the adsorption of reagents over the catalyst should be considered, and having already described the behavior of aniline (see above), only the case of DMC is detailed.

The adsorption of DMC on faujasites has been investigated via IR experiments carried out by us over NaY[26] and by others over NaX zeolites:[21] two modes of interac-

(20) Fu, Z. H.; Ono, Y. *Catal. Lett.* **1993**, *21*, 43.
(21) Beutel, T. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 985.
(22) The molecular size of amines **1**−**4** was estimated with both semiempirical and ab initio methods: see Table 3 of SI.
(23) Schwochow, F.; Puppe, L. *Angew. Chem., Int. Engl. Ed.* **1975**, *14*, 620.
(24) Bezoukhanova, C. P.; Kalvachev, Y. A. *Catal. Rev.-Sci. Eng.* **1994**, *36*, 125.
(25) Although the proposed interactions between substrates **2** and **4** with NaY are plausible, to our knowledge, investigations of adsorption modes of carboxylic acids and/or amides over Y zeolites have not been reported so far.
(26) Damin, A.; Bonino, F.; Bordiga, S.; Tundo, P.; Selva, M.; Zecchina, A. EuroConference on Guest-Functionalized Molecular Sieve Systems, Hattingen (Germany), March 20−25, 2004.

tions can be envisaged where DMC acts as a base to form an acid−base complex with the Lewis acidic sites of the catalyst (Scheme 10).

SCHEME 10. Modes of Adsorption (III and IV) of DMC over Na-Exchanged Faujasites

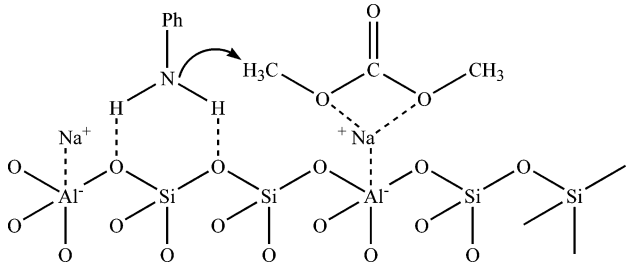


III IV

It should be noted that the formation of both complexes (III and IV) implies a lengthening of the O−CH_3 bond of DMC, meaning that DMC undergoes an electrophilic activation within the pores of the solid.

Based on Figure 4 and Scheme 10, the mono-*N*-methyl selectivity of the reaction of aniline and DMC can be discussed through a mechanism which involves the geometric features of the catalyst (shape selectivity) and its amphoteric properties as well. In particular, once the amine and DMC diffuse into the supercages of NaY, they may approach each other only according to the steric requisites of their adsorption patterns. Scheme 11 gives a pictorial description where, for simplicity, only one adsorption mode is considered for both reagents (sites I and IV, respectively).[27]

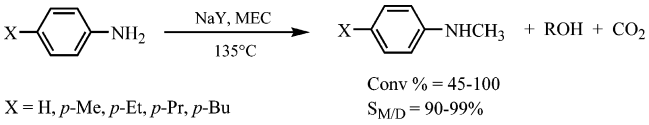
SCHEME 11. $B_{Al}2$ Displacement of Aniline on DMC within the NaY Supercage



Contrary to our previous hypothesis,[4b] the reaction then proceeds via a $B_{Al}2$ displacement of aniline on DMC. The product, mono-*N*-methyl aniline (PhNHMe), plausibly adsorbs into the zeolite in a different way with respect to aniline, because different H-bonds (N−H····O−zeolite) take place with the solid. Moreover, as recently reported by Su et al.,[28] *N*-methyl amines may also interact with NaY by H-bonding between the protons of the methyl group and the oxygen atoms of the zeolite. It may be so imagined that the NHMe group forces the molecule a bit far from the catalytic surface in a fashion less suitable to meet DMC and react with it. This behavior can account for the mono-*N*-methyl selectivity observed, which is peculiar to the use of DMC: in the presence of alkali metal-exchanged faujasites, in fact, the bis-*N*-methylation of primary aromatic amines occurs easily with conventional methylating agents (i.e., dimethyl sulfate).[29]

According to Scheme 11, the key requisite for selectivity is that the reactant amine can migrate through the zeolite channels, to reach the catalytic supercavity. We already noticed that this condition was crucial also in the methylation of *p*-alkylanilines with MEC (Scheme 12).[4d]

SCHEME 12. Mono-*N*-methylation of *p*-Alkyl Anilines with MEC



As far as the size of *p*-substituents allowed the diffusion of reagents into the catalyst, good mono-*N*-methyl selectivities (up to 99%) and conversions (45−100%) were observed, while the bulky 3,5-di-terbutylamine gave a modest selectivity of 82%, even at a low conversion of 9%.

In line with this observation, the mechanism of Scheme 10 is plausibly validated also for amines **1**−**8**: in fact, the molecular size estimation of these substrates indicates that they are all expected to be hosted by the catalytic supercavity of NaY (see Table 3, SI). For compounds **6**−**8**, however, the mono-*N*-methyl selectivity ($S_{M/D}$) is somewhat unsatisfactory: for instance, in the case of *p*-anisidine, $S_{M/D}$ is of only 77% at a conversion of 88% (entry 2, Table 4). The alteration of the adsorption geometry, induced by OR groups, into the catalytic cages seems the most probable reason for this result.

The Chemoselectivity. According to the principle of hard and soft acids and bases,[30] in a S_N2-type reaction involving a soft electrophilic center (i.e., a carbon atom), an ambident nucleophile becomes more likely to attack with its less electronegative atom.[31] This statement fits the investigated reaction: the methylation takes place exclusively at the aminic N-atom of anilines **1**−**4**, with both DMC and MEC.

The role played by the nature of the substrate clearly emerges also from results of Scheme 7: for aminothiophenols (**5a**,**b**), the higher polarizability of the thiol group (with respect to OH) does not allow one to discriminate between the N- and S-nucleophilic terms of reagents, and both N- and S-methylations are observed.

In addition to the hard−soft character of the nucleophile, "solvation effects" induced by the zeolite should also be considered. Zeolites, in fact, may behave as solid solvents, which, beyond the adsorption of organic molecules, allow other noncovalent host−guest interactions (of the van der Waals type) able to confine preferably some molecules versus others, within their intracrystalline volume.[32] These adsorption and confinement phenomena should contribute to the reaction chemoselectivity observed for amines **1**−**4**. In fact, when other catalysts are used, the N,O-chemoselectivity is elusive even with DMC as a methylating agent. Scheme 13 exemplifies the

(27) According to Beutel (ref 21), in the coadsorption of phenol and DMC over a NaX zeolite, DMC would be forced into a preferential adsorption state corresponding to complex IV of Scheme 10.

(28) Docquir, F.; Toufar, H.; Su, B. L. *Langmuir* **2001**, *17*, 6282−6288.

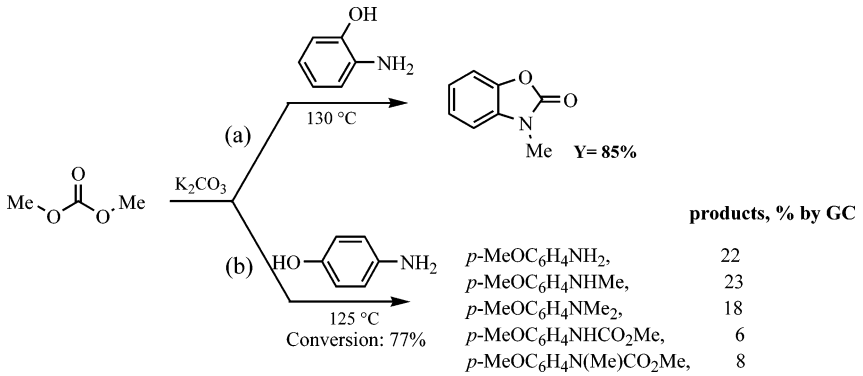
(29) Onaka, M.; Ishikawa, K.; Izumi, Y. *Chem Lett*. **1982**, 1783.

(30) Pearson, R. G.; Songstand, J. *J. Am. Chem. Soc*. **1967**, *89*, 1827.

(31) March, J. *Advanced Organic Chemistry*, *Reactions*, *Mechanisms*, *and Structures*, 4th ed.; Wiley: New York, 1992; Chapter 10, pp 367−368.

(32) Derouane, E. G. *J. Mol. Catal. A* **1998**, *134*, 29.

SCHEME 13



behavior of reactions of DMC with *o*- and *p*-amino phenol **1a**,**b**, both catalyzed by K_2CO_3.[5,33]

In the case of **1a**, *N*-methylbenzoxazolinon-2-one forms through a *O*-methoxycarbonylation/*N*-methylation sequence followed by a cyclization reaction; for **1b**, a plethora of products are obtained from simultaneous *N*-/*O*-methylation and *N*-methoxycarbonylation reactions.

The Influence of Solvent Polarity. The activity of faujasites is rather affected by the solvent polarity: in particular, the competitive adsorption between solvent and substrates over the catalyst is more and more important as the media polarity increases, and, as a consequence, reactions are slowed.[4d,14] This behavior plausibly accounts for some of the kinetic results reported in Tables 1−4.

In Table 3, for instance, methylations with MEC are much faster in xylene (ϵ of 2.4) than in diglyme (ϵ of 7.2; see also ref 14) (compare entries 1 and 5, 2 and 7, 4 and 9), at the point that k_{obs} can be evaluated for aminophenols **1a**,**b** only in diglyme (entries 5 and 6).

Also, the relative differences of k_{obs} change with the solvent.

In Table 2, for example, the comparison between phenols and alcohols shows that in DMC alone, the ratio k_{1a}/k_{3a} (∼12, entries 1 and 2) doubles that achievable in DMC/DME (∼5.5, entries 4 and 6).

The most striking evidence, however, seems the alteration of the *ortho*/*para* reactivity.

In the presence of DME as a cosolvent (Table 2), the reactions of DMC with *ortho*-isomers of phenols and amides proceed faster than with *para*-ones (entries 4,5 and 8,9), while the reverse is true for alcohols **3a**,**b** (entries 6 and 7). This is also confirmed by the competitive reaction between *o*- and *p*-aminophenol (**1a**,**b**) with DMC/DME (Figure 3),[34] which shows that the *ortho*-substituted compound (**1a**) react more rapidly than the *para*-isomer **1b**. In all cases, the selectivity ($S_{M/D}$%) is moderately better for the more reactive isomers: also in Figure 3, the *N*,*N*-dimethyl derivative is observed only for **1b** ($S_{M/D}$% for **1b** of 93% at a conversion of 91%).

In diglyme solvent instead (Table 3), less hindered *p*-substituted compounds exhibit a reactivity higher than the corresponding *o*-isomers within all three couples of *ortho*/*para* isomers investigated (k_{1b}/k_{1a} = 1.4, entries 5 and 6; k_{2b}/k_{2a} = 4.0, entries 7 and 8; k_{4b}/k_{4a} = 6.3, entries 9 and 10). Overall, neither the temperature (from 90 to 135 °C) nor the use of two different carbonates (DMC and MEC) show appreciable effects on the mono-*N*-methyl selectivity (except for the alcohol **3a**, $S_{M/D}$% ranges from 86% to 100% also for the experiments of Table 3).

The lower reactivity of *ortho*- with respect to *para*-isomers in Table 3 may partly be ascribed to the steric hindrance and the occurrence of intramolecular H-bonds on *ortho*-compounds; if so, however, the role of the same effects is not appreciable in the reactions with DMC (Table 2), which show the opposite behavior.

Conclusions

This study demonstrates that several factors can account for the trend of reactivity/selectivity shown by amines **1**−**4** in their mono-*N*-methylation with DMC and MEC.

The selectivity of mono-*N*-methylation is explained through a $B_{Al}2$ mechanism assisted by the steric requites of the supercavities of the NaY catalyst: accordingly, the estimate of the molecular size of the reactant amines is in good agreement with the general premise that all of these compounds can be hosted into the zeolite pores.

The kinetic analysis shows that the reactivity of compounds **1**−**4** toward *N*-methylation is largely modified by the properties of aromatic substituents (X = OH, CO_2H, CH_2OH, $CONH_2$). Both steric and electronic effects on the reaction site (NH_2 group) and the establishment of direct acid−base interactions between substituents X and the catalyst must be simultaneously considered to explain the observed scheme of rate constants. Weakly acid groups (CH_2OH, $CONH_2$, up to OH: pK_a of 16−17 up to 10), may help the adsorption of amines **1** and **3**,**4** (particularly of **1**) over the NaY surface, and so favor the reaction. In fact, *O*-protected anilines (anisidines and esters of aminobenzoic acids, **6**−**8**), where RO-substituents cannot undergo H-bond interactions with the zeolite, show lower *N*-methylation rates with respect to aminophenols and aminobenzamides.

Acids **2a**,**b** (pK_a of 4−5), however, are the least reactive substrates among compounds **1**−**4**, presumably because carboxylic groups go through strong acid−base interactions with the catalyst.

The solvent polarity also plays a role: methylations of amines **1**−**4** with MEC are faster in xylene rather than in the more polar diglyme, and, particularly, the relative reactivity of *ortho*/*para* isomers changes when reactions

(33) Selva, M. *Synthesis* **2003**, *18*, *2872*−*76*.

(34) In Figure 3, both isomers **1a** and **1b** react more rapidly with respect to entries 4 and 5 of Table 2; this should be ascribed to the different reaction conditions used.

in DMC/DME or diglyme solvents are compared. The competitive adsorption between solvent and substrates over the catalyst can account for this behavior.

Finally, the reaction chemoselectivity is explained through the different polarizability of the two nucleophilic terms (NH_2 and X groups) of amines **1**−**4** and solvation effects promoted by the zeolite.

Experimental Section

Compounds **1**−**4**, anisidines **6a**,**b**, methyl anthranilate (**8a**), and DMC were ACS grade and were employed without further purification. The zeolite NaY was from Aldrich (art. 33,444-8), and, before each reaction, it was dried under vacuum (65 °C; 8 mbar) overnight.

2-(2-Methoxyethoxy)methylethyl carbonate [$MeO(CH_2)_2O(CH_2)_2OCO_2Me$, MEC], methyl and ethyl *p*-aminobenzoates (**7b** and **8b**), and ethyl anthranilate (**8a**) were prepared according to already described procedures:[4c,35] their physical and spectroscopic data were in agreement with those reported in the literature (**7b**,[36] **8a**,[37] **8b**,[38] MEC[4c]). MEC was also compared to an authentic sample.

GLC and GC/MS (70 eV) analyses were run using CPSil24, FFAP, and HP5/MS capillary columns (30 m), respectively. HPLC analyses were carried out with an inverse-phase C18 column ("Aqua", 250 × 4.5 mm, length × thickness; size particles, 5 μm): *p*-aminobenzoic acid (**2b**) and its mono-*N*- and di-*N*,*N*-methyl derivatives (whose structures were assigned by comparison to authentic samples) were eluted with a binary mixture of MeCN/H_2O (gradient: 20−100% MeCN, 20 min) buffered to pH = 3, and then revealed by an UV detector.

^1H NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ with TMS as the internal standard.

The kinetic results of Tables 1−4 were gathered through procedures a and b, described below. To check for repeatability, each data point should be considered as an average value of at least two subsequent runs whose corresponding k_{obs} values deviated ≤10% from each other.

(a) The Reaction of *o*-Aminophenol with DMC. Figure 1 and Table 1. A three-necked, jacketed, 50 mL round-bottomed flask fitted with a stopcock, an adapter for the withdrawal of samples, a reflux condenser capped with a N_2-containing rubber reservoir, and a magnetic bar was loaded with a solution of *o*-aminophenol (**1a**, 6.5×10^{-2} M, 42 mL) in dimethyl carbonate. Triglyme (0.56 mmol) as the internal standard and the faujasite NaY (weight ratio NaY:**1a** in the range of 0.5−3) were added to the mixture, which was then degassed under vacuum (10 mmHg) and kept under a N_2 atmosphere. The flask was heated at the reflux temperature (90 °C), while the mixture was vigorously stirred. At intervals, samples (0.1 mL) were withdrawn and were analyzed by both GC and GC/MS.

Figure 2A. Under the conditions of Figure 1, kinetic constants were measured at different stirring rates of 500, 970, and 1350 rpm.

Figure 2B. Under the conditions of Figure 1, kinetic constants (k_{obs}) were also measured at different temperatures (T) of 343, 348, 353, and 363 K (70, 75, 80, and 90 °C, respectively), and a plot of ln k_{obs} versus $1/T$ was built up. An apparent activation energy of 93.5 kJ mol^{-1} was then calculated from the Arrhenius equation ($\ln k_{obs} = \ln A - E_{att}/RT$; Figure 2B).

Table 2, Entries 1−3: Amines 1a, 3a, and 4a. The above-described procedure (a) was followed also for the experiments of entries 1−3 in Table 2. The Q ratio (weight ratio NaY: substrate) was set equal to 2 to allow most reactions to proceed near to (or at) completion in a working day.

Table 2, Entries 4−9: Amines 1a,b, 3a,b, and 4a,b. The above-described procedure a was followed for the experiments of entries 4−9 in Table 2, with the following modifications: (i) solutions of compounds **1a**,**b**, **3a**,**b**, and **4a**,**b** (4.2×10^{-2} M, 42 mL) in a mixture of DMC/DME (DMC:DME = 4 v:v) were made to react at the reflux of DME (84 °C); (ii) a constant weight ratio NaY:amine of 2 was always used; and (iii) the internal standards were triglyme (amines **1a**,**b**, **3a**, and **4a**,**b**) and hexadecane (compound **3b**).

(b) Table 3, Entries 1−4: Amines 1a−4a. A three-necked, jacketed, 50 mL round-bottomed flask fitted with a stopcock, an adapter for the withdrawal of samples, a reflux condenser capped with a N_2-containing rubber reservoir, and a magnetic bar was loaded with a solution of the given amine (7.0×10^{-2} M, 30 mL) in xylene as the solvent, and *n*-octadecane as the internal standard.

2-(2-Methoxyethoxy)methylethyl carbonate [$MeOCO_2(CH_2)_2O(CH_2)_2OMe$, MEC] and the faujasite NaY were added to the mixture (MEC:amine = 10 molar ratio, NaY:amine = 2 weight ratio), which was then degassed under vacuum (10 mmHg) and left under a N_2 atmosphere. The flask was heated at the desired temperature (135 °C), while the mixture was vigorously stirred. At intervals, samples (0.1 mL) were withdrawn and were analyzed by both GC and GC/MS.

Table 3, Entries 5−10: Amines 1a,b, 2a,b, and 4a,b. The above-described procedure b was followed for the experiments of entries 5−10 in Table 3, with the following modifications: (i) solutions of compounds **1a**,**b**, **2a**,**b**, and **4a**,**b** (7.0×10^{-2} M, 30 mL) in diglyme [$CH_3O(CH_2)_2O(CH_2)_2OCH_3$] as the solvent were made to react at 135 °C. In the case of **4b**, the reaction mixture was analyzed by HPLC.

Scheme 7 and Table 4. The above-described procedure (b) was followed for the reactions of amines **1a**, **2a**, **4a**, **5a**,**b**, **6a**,**b**, **7a**,**b**, and **8a**,**b**.

Except for the acid **2b**, calibration curves were built for each substrate and were used to follow the reaction by GC. The amount and the type of internal standards used for any given substrate in the different solvents are specified in the Supporting Information.

The structures of mono-*N*- and di-*N*,*N*-methyl derivatives of the investigated amines were assigned through GC/MS analyses. A synoptic table of GC/MS spectra is available in the Supporting Information.

In the case of amines **1**−**4**, the structure of the corresponding mono-*N*-methyl derivatives was confirmed also by comparison to authentic samples previously prepared by us.[5]

Acknowledgment. MIUR (Italian Ministry of University and Research) and INCA (Interuniversity Consortium Chemistry for the Environment) are gratefully acknowledged for financial support.

Supporting Information Available: GC/MS spectra of mono-*N*- and di-*N*,*N*-dimethyl derivatives of amines **1**−**8**, details of some kinetic results, and a synoptic table of internal standards. The estimation of molecular size of amines **1**−**8** is also given. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048076R

(35) Hosangadi, B.; Dave, R. *Tetrahedron Lett*. **1996**, *37*, 6375−6378.
(36) Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem*. **1995**, *60*, 768.
(37) Herweh, J. E.; Hoyle, C. E. *J. Org. Chem*. **1980**, *45*, 2195.
(38) Zafar, A.; Melendez, R.; Geib, S. J.; Hamilton, A. D. *Tetrahedron* **2002**, *58*, 683.