Piperidino and Pyrrolidino Demethoxylation of 4-Methoxy-1-methyl-2,6-diphenylpyridinium Ion. Rate Parameters and Base Catalysis

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Abstract: The kinetics of pyrrolidino and piperidino demethoxylation of 4-methoxy-1-methyl-2,6-diphenylpyridinium ion have been studied in methanol in the presence of the corresponding amine/ammonium buffers, at 25 °C. The reactions display general base catalysis, as observed for the reactions with the nitroactivated benzene systems, and a kinetic pattern similar to that previously found when morpholine is used. A determination of a consistent set of pK_a values for the amines in methanol has been required and has allowed a clarification concerning morpholine in connection with some recent misleading reports. The kinetic analysis includes the evaluation of a number of significant parameters and is combined with the effect of the diverse basicity of the three amines. A specific base–general acid (SB–GA) mechanism is indicated as the most likely reaction path common to the investigated reactions.

Recently we have shown that the nucleophilic aromatic substitution reaction of 4-methoxy-1-methyl-2,6-diphenylpyridinium (**1**) and 4-methoxy-2,6-diphenylpyrylium (**2**) ions with morpholine in methanol follows a reaction mechanism closely related to that of the nucleophilic aromatic substitution of neutral activated aromatic compounds.[1] Both substrates are subject to general base catalysis, which is one of the most important features supporting the complex mechanism of S_NAr reactions involving an amine as the nucleophile.[2] Two interpretations are generally advocated in order to explain the general base catalysis. One of them requires catalysis to be a consequence of rapid equilibrium deprotonation of the intermediate adduct AH to give the adduct A, followed by a general acid catalyzed detachment of the leaving group. This mechanism is known as the SB–GA mechanism.[3] The second interpretation involves proton abstraction from AH in a rate-controlling step to form A followed by fast detachment of the leaving group[4] (Scheme I).

In this paper we wish to obtain further information toward a better understanding of the mechanism of base catalysis as observed in the reaction of **1**. To this end we have studied the effect of the basicity of the amine on the base catalysis phenomenon, and have carried out the reaction with piperidine and pyrrolidine. With respect to morpholine, these amines have comparable steric requirements, but different basicities and nucleophilicities.

Experimental Section

Materials. 4-Methoxy-1-methyl-2,6-diphenylpyridinium perchlorate was available from our previous work.[1] The 1-methyl-2,6-diphenyl-4-piperidinopyridinium cation was characterized in situ in MeCN by its ^1H NMR spectrum. The spectrum shows signals at δ 7.3 (C_6H_5, 10 H), 6.93 (s, pyridinium ring, 2 H), 3.31 (s, N–CH_3, 3H), besides the broad signals of the piperidino group.

The 1-methyl-2,6-diphenyl-4-pyrrolidinopyridinium cation shows a similar ^1H NMR spectrum in MeCN: δ 7.61 (C_6H_5, 10 H), 6.68 (s, pyridinium ring, 2 H), 3.33 (s, N–CH_3, 3 H), besides the broad signals of the pyrrolidino group.

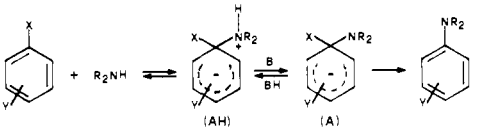
Methanol and methanol solutions of $HClO_4$ were prepared as previously described.[1] Piperidine and pyrrolidine were freshly distilled from sodium.

Kinetic Measurements. The kinetics were followed spectrophotometrically in methanol at 25 °C, under pseudo-first-order conditions ([**1**] in the order of 10^{-5} M), in the presence of an excess of amine, at 300 nm, in the thermostated compartment of a Cary 219 spectrophotometer. The measurements at low MeO^- concentrations were carried out in buffers prepared by partial neutralization of the amine with a solution of $HClO_4$ in methanol, whereas solutions for measurements at relatively higher MeO^- concentrations were obtained upon dilution of a concentrated sodium methoxide solution.

In methanol, cation **1** shows two absorption maxima, at 243 (log ϵ = 4.29) and 284 nm (log ϵ = 4.01). The piperidine derivative shows two absorption maxima at 250 (log ϵ = 4.15) and 300 nm (log ϵ = 4.3). The pyrrolidine derivative shows two absorption maxima at 250 (log ϵ = 4.2) and 300 nm (log ϵ 4.4).

Determination of pK_a Values in Methanol. The pK_a values for the amines were determined at 25 °C from half-neutralization protentials of amine solutions in methanol. The titrations of these solutions ($\sim 10^{-3}$ M) were carried out with $HClO_4$ in methanol. The measurements were performed with a PHM 22 Radiometer pH meter in conjunction with a Radiometer high-pH glass electrode and a Radiometer calomel electrode filled with saturated KCl methanolic solution, as described by Ritchie.[5]

Scheme I



Scheme II

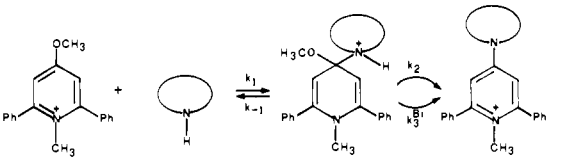


Table I. Kinetic Data for the Piperidino Demethoxylation of Pyridinium Cation [1] in MeOH, at 25 °C

[piperidine], M	[piperidine]/[piperidinium]	[MeO^-], $M \times 10^3$	k_{obsd}, $s^{-1} \times 10^4$	k_{obsd}/[piperidine], $s^{-1} M^{-1} \times 10^3$
0.16	43	0.06	4.55	2.88
0.24	43	0.06	10.2	4.3
0.39	43	0.06	26	6.7
0.55	43	0.06	50	9.1
0.02		2.7	0.8	4.0
0.02		5.4	1.56	7.8
0.02		8.1	2.1	10.0
0.02		10.8	2.54	12.7
0.02		13.5	2.9	14.5

(1) Aveta, R.; Doddi, G.; Illuminati, G.; Stegel, F. *J. Am. Chem. Soc.* **1981**, *103*, 6148.
(2) Bernasconi, C. F. *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **1973**, *3*, 33.
(3) (a) Bunnett, J. F.; Cartaño, A. V. *J. Am. Chem. Soc.* **1981**, *103*, 4861. (b) Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *Ibid.* **1981**, *103*, 4865.
(4) (a) Bernasconi, C. F.; Hoyos de Rossi, R.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.
(5) Ritchie, C. D.; Heffley, P. D. *J. Am. Chem. Soc.* **1965**, *87*, 5402.

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Table II. Kinetic Data for the Pyrrolidino Demethoxylation of Pyridinium Cation [1] in MeOH, at 25 °C

[pyrrolidine], M × 10²	[pyrrolidine]/[pyrrolidinium]	[MeO⁻], M × 10³	k_{obsd}, s⁻¹ × 10⁴	k_{obsd}/[pyrrolidine], s⁻¹ M⁻¹ × 10³
0.83	6.2	0.015	0.21	2.48
1.04	6.2	0.015	0.31	2.95
2.08	6.2	0.015	1.10	5.29
3.12	6.2	0.015	2.19	7.02
7.28	6.2	0.015	11.2	15.4
2.3		2.75	6.3	27.5
2.3		5.5	9.0	39.3
2.3		8.25	11.3	49.1
2.3		11.0	12.6	54.8
2.3		13.0	14.1	61.3

Table III. Summary of Kinetic Results of the Reactions of Piperidine, Pyrrolidine, and Morpholine with [1] in MeOH, at 25 °C

	piperidine	pyrrolidine	morpholine[a]
k_1, s⁻¹ M⁻¹	3.3×10^{-2}	8.3×10^{-2}	2.8×10^{-3}
k_3^{am}/k_{-1}, M⁻¹	0.74	3.0	0.28
k_3^{MeO}/k_{-1}, M⁻¹	57	177	106
k_2/k_{-1}	*b*	*b*	3.8×10^{-3}
k_3^{am}/k_3^{MeO}	1.3×10^{-2}	1.7×10^{-2}	2.7×10^{-3}

[a] Data from ref 1. [b] The experimental data do not allow a safe evaluation of this ratio.

The pH meter was calibrated by using tribenzylamine (pK_a 6.40[6]), Dabco (pK_a 8.99[7]), and ethylenediamine (pK_a 10.90[7]) buffers in methanol.

Results

The reaction of **1** with both amines in methanol is remarkably accelerated by MeO^- ion. According to the mechanism of nucleophilic aromatic substitution of activated benzene systems with amines[2] these reactions may generally be described by Scheme II, where $k_{-1} \geq k_2 + k_3^{Bi}[B_i]$. In this scheme k_2 is the kinetic constant for the uncatalyzed decomposition of MH to the final product, whereas k_3^{Bi} is referred to the same process as catalyzed by a base B_i. By using procedures reported in the literature[8] from the observed rate constants (Tables I and II) we have calculated k_1 and other significant parameters that are collected in Table III together with the related data for the morpholine reaction.

The kinetic analysis to be dealt with in the Discussion required a consistent set of pK_a values of the amines, which were obtained by a potentiometric method. Such values were found to be 11.3, 11.1, and 9.5 for pyrrolidine, piperidine, and morpholine, respectively. The value for piperidine was found to be in good agreement with that reported by Izmailov and Mozharova.[9] In contrast, while this work was in progress, we realized that the much lower value quoted by Ritchie et al.[7] and used, successively, by ourselves for morpholine[1] was mistakenly taken from that originally reported for morphine by the Russian group.[9] The kinetic parameters obtained for the reaction of **1** with morpholine[1] to be used in the following Discussion were not affected by the change in pK_a value of the amine.[10]

Discussion

The reactivity order observed for the nucleophilic attachment at position 4 (k_1 values), i.e., pyrrolidine > piperidine > morpholine, is analogous to the one reported for the substitution reactions of activated aromatic substrates[11] and for the attachment reactions to tri-*p*-anisylmethyl cation,[12] 1,3,5-trinitrobenzene,[13] and activated alkenes.[14] A plot of the log k_1 vs. the pK_a values of the amines in methanol is approximately linear with slope $\beta_{nuc} = 0.8$ (see Figure 1). This value indicates that in the transition state for the nucleophilic attachment a significant amount of the positive charge is transferred on the nitrogen of the attacking amine.

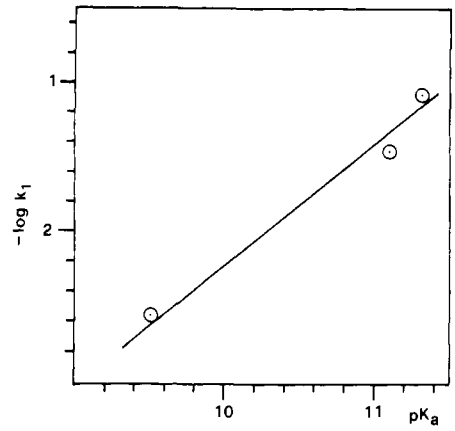
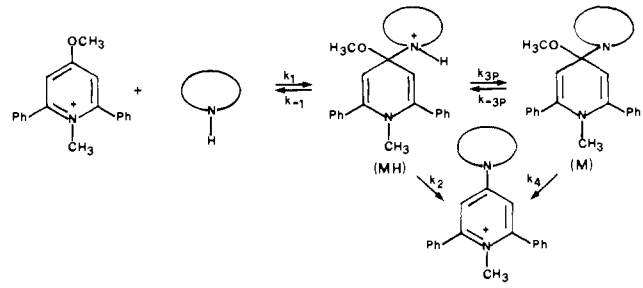


Figure 1. Effect of the basicity (pK_a) on the nucleophilic reactivity (log k_1) of the amine.

Scheme III



Mechanism of Substitution. Scheme III gives a more detailed description of the aromatic substitution reactions with amines. Owing to the presence of two bases, MeO^- and amine, and the corresponding conjugated acids, the rate constants k_{3p}, k_{-3p}, and k_4 are defined as:

$$k_{3p} = k_{3p}^{MeO}[MeO^-] + k_{3p}^{am}[am] \quad (1)$$

$$k_{-3p} = k_{-3p}^{MeOH} + k_{-3p}^{amH}[amH^+] \quad (2)$$

$$k_4 = k_4^{MeOH} + k_4^{amH}[amH^+] \quad (3)$$

The rate constants k_{3p}^{MeO} and k_{3p}^{am} refer to the deprotonation of MH to M by MeO^- and amine, respectively; k_{-3p}^{MeOH} and k_{-3p}^{amH} refer to the protonation of M to MH by MeOH and the conjugate acid of the amine, respectively; k_4^{MeOH} refers to the solvent assisted leaving group departure from M, and k_4^{amH} correponds to the same process as catalyzed by the conjugate acid of the amine.

If the proton-transfer mechanism is operating, i.e., the leaving group departure is faster than protonation of M, the deprotonation

(6) Ritchie, C. D.; Skinner, G. A.; Badding, V. G. *J. Am. Chem. Soc.* **1967**, *89*, 2063.
(7) Ritchie, C. D.; Minasz, R. J.; Kamego, A. A.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3747.
(8) (a) Bunnett, J. F.; Garst, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 3879. (b) Bunnett, J. F.; Bernasconi, C. F. *Ibid.* **1965**, *87*, 5209. (c) Bernasconi, C. F. *J. Org. Chem.* **1967**, *32*, 2947.
(9) Izmailov, N. A.; Mozharova, T. B. *Zh. Phys. Khim.* **1960**, *34*, 1709.
(10) This is not so for the kinetic parameters for the much faster reaction of 4-methoxy-2,6-diphenylpyrylium ion (compound **2**, see introduction) which required the use of the pK_a of morpholine for the assessment of the MeO^- contribution to the observed rate. As reported in ref 1, such contribution is absent in the reaction of **1**. A correction concerning compound **2** will be reported elsewhere in connection with further work on the pyrylium system.
(11) Miller, J. "Aromatic Nucleophilic Substitution"; Elsevier Publishing Co.: Amsterdam, 1968.
(12) Bunton, C. F.; Huang, S. K. *J. Am. Chem. Soc.* **1974**, *96*, 515.
(13) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.
(14) (a) McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 343. (b) Rappoport, Z.; Topol, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1823. (c) Rappoport, Z.; Peled, P. *Ibid.* **1973**, 616. (d) Schreiber, B.; Martinek, H.; Wolscham, P.; Schuster, P. *J. Am. Chem. Soc.* **1979**, *101*, 4708. (e) Bernasconi, C. F.; Carrē, D. J. *Ibid.* **1979**, *101*, 2698. (f) Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *Ibid.* **1980**, *102*, 2810. (g) Bernasconi, C. F.; Fornarini, S. *Ibid.* **1980**, *102*, 5329.

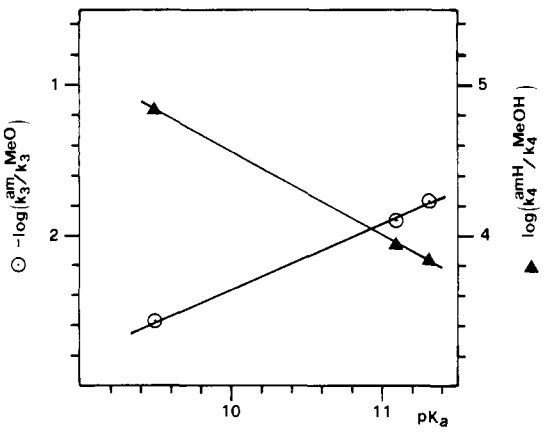


Figure 2. Effect of the basicity (pK_a) of the amine on some kinetic parameters related to the base-catalyzed, log (k_3^{am}/k_3^{MeO}) (open circles), and acid-catalyzed, log (k_4^{amH}/k_4^{MeOH}) (solid triangles), steps.

of MH becomes rate controlling and the $k_{3p}^{B_i}$ terms coincide with the overall $k_3^{B_i}$ terms of Scheme II. On the other hand, in the SB–GA mechanism the rate-controlling step is the decomposition of M into the product and any $k_3^{B_i}$ term coincides with the product of $K_{3p}^{B_i}$, the equilibrium constant between MH and each base B_i, by $k_4^{BH_i}$, i.e., $k_3^{MeO} = K_{3p}^{MeO}\, k_4^{MeOH}$ and $k_3^{am} = K_{3p}^{am}\, k_4^{amH}$. Since $K_{3p}^{am}/K_{3p}^{MeO} = K_s^{MeOH}/K_a^{amH}$ the relative effectiveness of different acids as catalysts is given by eq 4, where K_a^{amH} is the

$$k_4^{amH}/k_4^{MeOH} = k_3^{am}K_a^{amH}/k_3^{MeO}K_s^{MeOH} \qquad (4)$$

dissociation constant of the conjugated acid of the amine and K_s^{MeOH} is the autoprotolysis constant of methanol (1.2×10^{-17} at 25 °C).[15] We now want to verify whether the rate data for base catalysis fit one of the mechanistic models, if any.

Let us first assume that the proton-transfer mechanism is operating for the examined amines. Under this hypothesis we can evaluate the k_{-1} ratio for any two different amines, $k_{-1,am}/k_{-1,am'}$, from the k_3^{MeO}/k_{-1} ratios ($\equiv k_{3p}^{MeO}/k_{-1}$), since the rate constants for the deprotonation of the MH intermediates by MeO^- are diffusion controlled and, therefore, $k_{3p,mor}^{MeO} \simeq k_{3p,pip}^{MeO} \simeq k_{3p,pyrr}^{MeO}$. The ratios thus obtained are as follows: $k_{-1,mor}/k_{-1,pip} \simeq 0.5$; $k_{-1,mor}/k_{-1,pyrr} \simeq 2$; $k_{-1,pip}/k_{-1,pyrr} \simeq 3$. These values may be compared with those observed in related reactions where the amine detachment from a carbon atom leads to a $sp^3 \rightarrow sp^2$ change of the reaction center.[13,14e-g,16] This comparison shows that the last ratio is an acceptable one, as piperidine has a steric hindrance larger than pyrrolidine. However, the first ratio shows a remarkable disagreement with the literature data whereby the morpholino group expulsion is faster than that of piperidino by one or more orders of magnitude.

The k_3^{am}/k_3^{MeO} ratios may also give some indications as to whether the proton-transfer mechanism is operating. If the H^+ transfer is rate controlling, we should expect comparable values of these ratios for piperidine and morpholine. The rate of a proton transfer from the intermediate MH to the corresponding amine is expected to be diffusion controlled since the proton transfer is thermodynamically favored by more than 2 pK units, owing to the presence of the electron-withdrawing 1,4-dihydro-4-methoxy-4-pyridyl group.[17] However, such a process can be slowed down by steric factors, as observed in the attachment reactions of amines to activated alkenes,[14e,16b] to 1,3,5-trinitrobenzene,[13,18] and to the 2,4,6-triphenylthiopyrylium ion.[19] Morpholine and piperidine have the same steric situation. Moreover, the corresponding K_{3p}^{am} constants for the reaction between MH_i and the corresponding amines are expected to be independent of the nature of the amines, because $K_{3p}^{am} = K_a^{MH}/K_a^{amH}$ and both electronic and steric effects are essentially constant for each MH_i intermediate, so that we should have similar values for the k_{3p}^{am} terms for both amines. However, the observed values show a fivefold variation of the k_3^{am}/k_3^{MeO} ratios for piperidine and morpholine.

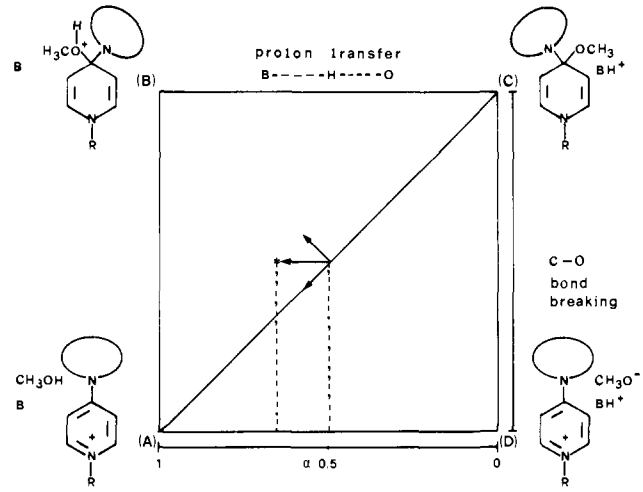


Figure 3. A More O'Ferrall diagram to illustrate the effect of changing the amine moiety on the acid and solvent assisted methoxy group detachment, assuming a diagonal reaction coordinate.

Whereas the above arguments weaken the proton-transfer hypothesis as a common mechanism for these amines, the SB–GA mechanism seems to be more consistent with the kinetic parameters. Thus there is a regular trend between the log (k_3^{am}/k_3^{MeO}) for the base-catalyzed decomposition of MH_i and the pK_a^{amH} (see Figure 2). This result would support a SB-GA mechanism whereby the expulsion of the leaving group is acid assisted in the rate-controlling step. In order to test this mechanism, with the aid of eq 4 we have evaluated the k_4^{amH}/k_4^{MeOH} ratios concerning the acid-catalyzed step. Clearly the log (k_4^{amH}/k_4^{MeOH}) also shows a regular dependence on pK_a^{amH} (see Figure 2).

If detachment of the methoxy group is not affected by particular factors such as steric or stereoelectronic effects, as observed in the acid-catalyzed ethoxy group departure in amino deethoxylation of 2,4-dinitro-1-naphthyl ethyl ether,[3b] the breakdown of M_i intermediates should be correlated with the acid strength of the catalysts by a Brønsted relationship. Steric or stereoelectronic effects are expected to be unimportant in our reactions because of the absence of substituents flanking the sp^3-hybridized carbon atom. Therefore the presence of a regular trend between the rate constants for the leaving group departure and the acid strength of the ammonium ions is conceivable. However, it should be noted that the observed trend is the result of two processes, namely, the acid catalyzed and the solvent assisted leaving group detachment. Such processes may occur by different mechanisms, as observed in the alkoxy departure from Meisenheimer[20] and phthalimidium adducts.[21] The acid-catalyzed departure of the methoxy group should be made easier in the morpholine reaction by the presence of the morpholinium ion, a stronger acid with a respect to piperidinium and pyrrolidinium ions, and by a change from the pyrrolidino and piperidino to the morpholino moieties. In contrast, the solvent assisted leaving group detachment is expected to be slowed down in going from the pyrrolidino to the morpholino adduct.

This may be better visualized with the aid of a More O'Ferrall energy diagram,[20,22,23] assuming that the acid-catalyzed breakdown of the M_i adducts follows a Brønsted relationship. Figure 3 shows such a diagram where corners C and A refer to the M_i adduct

(15) Koskikallio, *J. Suom. Kemistil. B.* **1957**, *30*, 111.
(16) (a) Gravitz, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 499. (b) Bernasconi, C. F.; Carrè, D. J.; Fox, J. P. "Techniques and Applications of Fast Reactions in Solution"; Getting, W. J., Wyn-Jones, E., Eds.; Reidel: Dordrecht, Holland, **1979**; p 453.
(17) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818.
(18) Crampton, M. R.; Gibson, B. *J. Chem. Soc., Perkin Trans. 2* **1981**, 533.
(19) Doddi, G.; Ercolani, G. Abstracts, XIII Convegno Nazionale di Chimica Organica; Società Chimica Italiana: Milano, Sept, 1982.
(20) Bernasconi, C. F.; Gandler, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 8117.
(21) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 507.
(22) More O'Ferrall, R. A. *J. Chem. Soc. B.* **1970**, 274.
(23) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7498.

and the product respectively, corners B and D to intermediates of stepwise processes, the vertical axes to C–O bond breaking/formation, and the horizontal axes to proton transfer (as measured by the Brønsted α parameter). The reaction coordinate for an idealized concerted mechanism will be represented by the diagonal C–A.

Upon making the amino moiety more electron withdrawing (morpholine) the energy of the lower edge is raised with respect to that the upper edge by a decreased conjugative effect of the amino group. The energy of corner B should also be raised but the effect is expected to be lower than that at corner D.

This will produce both a perpendicular effect that shifts the transition state toward corner B (Thornton effect) and a shift along the reaction coordinate toward corner A (Hammond effect). The overall effect will be a shift of the transition state toward the new position as indicated by an asterisk, whose horizontal component indicates an increase in the proton transfer and hence in the α value. However, we do not expect a large increase of α because the amino moiety is not directly involved in the proton-transfer bond-breaking process.[24]

As Jencks has pointed out a concerted mechanism would no longer be possible if the proton transfer is thermodynamically strongly disfavored.[25] Therefore the methanol assisted methoxy group departure, as shown for the water assisted alkoxy group expulsion from phthalimidium[21] and Meisenheimer[20] adducts, should proceed by a stepwise mechanism through the intermediate of corner D (BH^+ = methanol). The incipient conjugation between the amino group and the partially positive charged ring should be a major factor in the stabilization of the transition state of this process. Therefore the pyrrolidino moiety is expected to favor the reaction with respect to morpholino.

In short, the observed trend between k_3^{am}/k_3^{MeO} and pK_a of amines is the result of both an increase of k_4^{amH} and a decrease of k_4^{MeOH} values with pK_a on going from pyrrolidine to morpholine.

We have already pointed out that the hypothesis of a proton-transfer mechanism leads with our data to an unsatisfactory prediction of the $k_{-1,am}/k_{-1,am'}$ ratio for the morpholine/piperidine pair. We now are able to show that the hypothesis of an SB–GA mechansim yields much better estimates. In particular, for a satisfactory comparison with the already mentioned data in the literature, we ought to expect the $k_{-1,mor}/k_{-1,pip}$ ratio to be appreciably greater than 1. We can easily show that such a ratio must indeed be comprised between 3 and 20. The first of these limits can be derived from the k_3^{am}/k_{-1} ratios for morpholine and piperidine reported in Table III. If an SB–GA mechanism is assumed, we obtain eq 5. Since the $K_{3p}^{mor}/K_{3p}^{pip}$ ratio is ap-

$$\frac{k_3^{mor}}{k_3^{pip}} = \frac{0.28}{0.74}\frac{k_{-1,mor}}{k_{-1,pip}} = \frac{K_{3p}^{mor}}{K_{3p}^{pip}}\frac{k_4^{morH}}{k_4^{pipH}} \quad (5)$$

proximatively unity (see above) and k_4^{morH}/k_4^{pipH} must be greater than 1 (catalytic effectiveness order), from eq 5 we derive the condition that $k_{-1,mor}/k_{-1,pip}$ be greater than $0.74/0.28 \simeq 3$. The second limit is derived from the $k_{3,am}^{MeO}/k_{-1,am}$ ratios for morpholine and piperidine (Table III) again under the assumption of an SB–GA mechanism. We obtain eq 6.

$$\frac{k_{3,mor}^{MeO}}{k_{3,pip}^{MeO}} = \frac{106}{57}\frac{k_{-1,mor}}{k_{-1,pip}} = \frac{K_{3p,mor}^{MeO}}{K_{3p,pip}^{MeO}}\frac{k_{4,mor}^{MeOH}}{k_{4,pip}^{MeOH}} \quad (6)$$

In this equation we note that $K_{3p,mor}^{MeO}/K_{3p,pip}^{MeO}$ is expected to be essentially equal to $K_a^{morH}/K_a^{pipH} = 40$ because of the common effect of additivity of the pyridyl moiety in both equilibria. Furthermore, $k_{4,mor}^{MeOH}/k_{4,pip}^{MeOH}$ must be somewhat less than unity (see discussion on the More O'Ferrall diagram above) so that the $k_{-1,mor}/k_{-1,pip}$ ratio will be less than $(57 \times 40)/106 \simeq 20$.

When a similar treatment is applied to the $k_{-1,am}/k_{-1,am'}$ ratios for other pairs of amines, such as piperidine and pyrrolidine, the estimated values are also consistent with the SB–GA mechanism, the estimates being in the order observed in the literature when they are worked out under the assumption of the SB–GA mechanism.

Concluding Remarks

Such general features as base catalysis in the reaction of **1** with amines and the leaving group ability order observed in the hydroxydehalogenation of the 1-methyl-4-halogenopyridinium ion[26] suggest that the nucleophilic aromatic substitution reactions of pyridinium salts and the corresponding reactions of activated benzene systems have similar behavior in spite of the different charge type of reaction. The present data show that the mechanism of the reaction of **1** with amines is most likely of the SB–GA type. This is borne out by the examination of the kinetic behavior as a function of the basicity of the amine and corrects the interpretation previously given for the reaction with morpholine[1] as based on a comparison of the pyridinium vs. pyrylium systems.[10]

Registry No. 1·perchlorate, 79038-32-7; MeO^-, 3315-60-4; 1-methyl-2,6-diphenyl-4-piperidinopyridinium, 47442-34-2; 1-methyl-2,6-diphenyl-4-pyrrolidinopyridinium, 86129-82-0; piperidine, 110-89-4; pyrrolidine, 123-75-1.

(24) $\Delta\alpha \simeq 0.3$ is observed in the acid-catalyzed alkoxy group detachment from phthalimidium[21] and Meisenheimer[20] adducts, where the substitution with electron-withdrawing groups has been accomplished directly on the alkoxy leaving group. A lower variation of the α parameter was reported for the latter reaction when the substitution has been accomplished on the ring, the effect being indirectly relayed by the conjugative effect.

(25) Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.

(26) O'Leary, M. H.; Stach, R. W. *J. Org. Chem.* **1972**, *37*, 1491.