Nonlinear Structure–Reactivity Correlation in the Pyridinolysis of Acetic Anhydride

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Second-order rate constants are measured for the nucleophilic reactions (k_N) of acetic anhydride with a series of 3- and 4-monosubstituted pyridines in aqueous solution at 25 °C, ionic strength 0.2 M. The curved Brønsted-type plot (log k_N vs. basicity of nucleophile) obtained is explained through a semiempirical equation based on the existence of a tetrahedral intermediate and a change in rate-determining step from decomposition to formation of the intermediate. From the pK_a value at the center of the curvature (p$K_a{}^\circ$ = 6.1) acetate is deduced to be a poorer leaving group from the tetrahedral intermediate than a substituted pyridine of equal basicity. Acetate is a better leaving group than 2,4-dinitrophenolate as a result of a comparison between the p$K_a{}^\circ$ values for pyridinolysis of acetic anhydride and 2,4-dinitrophenyl acetate. The effect of the relative leaving abilities of oxygen anions and pyridines upon substitution of methyl by methoxy as the "nonleaving" group is also analyzed.

Introduction

The aminolysis reactions of carbonyl compounds with good leaving groups usually exhibit nonlinear structure–reactivity relationships. The Brønsted-type plots for these nucleophilic reactions clearly show two linear regions and a curvature between them. This is the case for two types of Brønsted plots: (i) the ones obtained for the reactions of a series of structurally similar carbonyl compounds with a common amine (log k vs. basicity of leaving group of electrophile); (ii) the ones obtained for the reactions of a series of structurally similar amines with a common electrophile (log k vs basicity of nucleophile).

The latter type of Brønsted plot shows a break from a large ($\beta \approx 0.8$–1.0) to a small ($\beta \approx 0.1$–0.3) dependence of the rate constant on basicity of the attacking amine as the basicity of the nucleophile increases. These plots were obtained, for example, in the reactions of primary, secondary, and tertiary amines with substituted phenyl acetates,[1] substituted quinuclidines with aryl phenyl carbonates,[2] primary and secondary amines with substituted acetylpyridinium ions,[3] amines with phthalic and succinic anhydrides,[4] primary amines with cyanic acid,[5] and substituted pyridines with methyl chloroformate,[6] 2,4-dinitrophenyl methyl carbonate,[7] and 2,4-dinitrophenyl acetate.[8]

The break of the above type of Brønsted plot has been attributed to a change in the rate-determining step from breakdown to formation of a tetrahedral intermediate in the reaction path, as the nucleophile increases its basicity. From the basicity value at the center of the curvature (p$K_a{}^\circ$), leaving abilities of nitrogen and oxygen bases have been assessed, and also the influence of the group that does not leave on the p$K_a{}^\circ$ value has been subject to study.[2,8,9]

The object of the present work is to obtain the Brønsted-type plot for the reactions of acetic anhydride with structurally similar substituted pyridines in order to get information on the leaving abilities of pyridines and acetates and to study the influence of the "nonleaving" group on the leaving abilities of pyridines and oxygen anions, by comparing our results with previous ones.[2,7-9]

Two of the reactions of acetic anhydride with substituted pyridines reported here have been studied previously (Scheme I, B is a general base) in somewhat different conditions,[10] but we wanted to get our Brønsted plot for a whole set of reactions under the same experimental conditions.

Scheme I

$$\mathrm{NC_5H_4X + CH_3COOAc} \underset{k_{-N}}{\overset{k_N}{\rightleftharpoons}}$$

$$\mathrm{CH_3CON^+C_5H_4X + AcO^-} \xrightarrow[\mathrm{H_2O,\ B}]{k_H} \mathrm{AcOH + HN^+C_5H_4X}$$

Experimental Section

Materials. The substituted pyridines, acetonitrile, and water were purified as previously described.[6,8] Acetic anhydride (AA), analytical grade, from Merck, was distilled.

Kinetic Measurements. A. pH-stat Method. The reactions of AA with 3-cyano-, 4-cyano-, 3-chloro-, 3-carbamoyl-(nicotinamide), and 4-methylpyridines and pyridine were followed by means of a pH-stat comprising a Radiometer PHM 62 pH meter, TTT60 titrator, REC 61 recorder, ABU 11 autoburet, and TT A60 titration assembly. The electrodes were Radiometer G 2040B (glass) and K 4040 (calomel). The titrant in the reservoir of the autoburet was an aqueous solution of sodium hydroxide (0.012–0.167 N). The maximum volume of titrant delivered in any kinetic run was 0.2 mL.

A Radiometer V-533 thermostatted vessel with 25 mL of the appropriate aqueous solution of the substituted pyridine at ionic strength 0.2 M (with sodium perchlorate) was thermally equilibrated at 25 ± 0.1 °C. A stock solution of AA in acetonitrile (83–200 μL) was then injected into the sample solution by means of a Unimetrics syringe, and the recording started at the same time. The initial concentration of AA was (0.5–5) $\times 10^{-4}$ M and the acetonitrile concentration never exceeded 0.8% in the kinetic runs.

At least a 20-fold excess concentration of the substituted pyridine over that of AA was used except in the cases of pyridine and 4-methylpyridine, where the concentration of the reactants were of the same order of magnitude. Nevertheless, good pseudo-first-order kinetics was obtained for all the substituted pyridines (Guggenheim plots were linear for at least three half-lives). This fact means that in the reactions with pyridine and 4-methylpyridine the concentration of the nucleophile remained approximately constant during the runs. This is reasonable since in the reactions of AA with these two pyridines, as well as in the ones with less basic pyridines, Scheme II holds under the experimental conditions; i.e., the substituted pyridines are released as soon as the intermediates are formed.

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(1) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

(2) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963.

(3) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442.

(4) Hall, W. E.; Higuchi, T.; Pitman, I. H.; Uekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153.

(5) Williams, A.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1754.

(6) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.

(7) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.

(8) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.

(9) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.

(10) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.

(11) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 658.

0022-3263/81/1946-2939$01.25/0

Table I. Experimental Conditions and k_{obsd} for the Reactions of Acetic Anhydride with Substituted Pyridines in Aqueous Solution at 25 °C, Ionic Strength 0.2 M (with Sodium Perchlorate)

nucleophile	total [pyridine], M	pH	10^3k_{obsd},[a] s^{-1}	no. of runs	method
3-cyanopyridine	0.015-0.33	5.5	2.7-7.3	6	pH-stat[b]
	0.015-0.33	6.0	2.7-7.3	6	
	0.015-0.33	6.5	2.8-7.5	6	
4-cyanopyridine	0.02-0.14	5.7	3.9-11.4	7	pH-stat[b]
	0.02-0.14	6.0	3.9-11.8	7	
	0.02-0.14	6.3	3.9-11.8	7	
3-chloropyridine	0.004-0.02	5.7	4.7-14.3	9	pH-stat[b]
	0.004-0.02	6.0	4.8-13.7	7	
	0.002-0.018	6.3	3.6-12.9	6	
nicotinamide	0.001-0.008	5.7	3.3-12.0	8	pH-stat[b]
	0.003-0.01	6.0	6.6-15.4	8	
	0.001-0.008	6.3	3.8-13.0	8	
pyridine	$(1-10) \times 10^{-5}$	5.7	3.0-7.7	10	pH-stat[b]
	$(1-10) \times 10^{-5}$	6.0	3.0-9.3	9	
	$(1-8) \times 10^{-5}$	6.3	3.3-7.5	8	
4-methylpyridine	$(1-7) \times 10^{-5}$	4.9	2.6-3.9	7	pH-stat[b]
	$(1-6) \times 10^{-5}$	5.2	2.8-4.5	6	
	$(1-6) \times 10^{-5}$	5.5	3.2-6.5	6	
4-aminopyridine	$(6-24) \times 10^{-4}$	5.9	3.2-5.6	7	spectro[c]
	$(5-17) \times 10^{-4}$	6.2	3.9-7.5	7	(290 nm)
	$(2-10) \times 10^{-4}$	6.5	3.5-8.1	7	
4-(dimethylamino)pyridine	$(1.2-2.4) \times 10^{-3}$	5.9	3.3-4.3	7	spectro[c]
	$(0.6-1.2) \times 10^{-3}$	6.2	3.6-4.5	7	(320 nm)
	$(0.6-2.4) \times 10^{-3}$	6.5	4.2-9.7	7	
water		5.7-8.2	2.4-3.9	10	pH-stat[b]

[a] Pseudo-first-order rate constant observed; kinetic form given by eq 1 (first six substituted pyridines) and by the equation $k_{obsd} = k_W + k_{Ph}[HPO_4^{2-}] + k_N[N]$ (the two most basic pyridines). [b] Reactions followed by automatic titration of the acid released. [c] Reactions followed spectrophotometrically at the fixed wavelengths shown. Total phosphate buffer concentration 0.002 M.

Experimental conditions and pseudo-first-order rate constants observed (k_{obsd}) for the reactions of AA with all these substituted pyridines are summarized in Table I.

B. Spectrophotometric Method. The reactions of AA with 4-amino- and 4-(dimethylamino)pyridines were followed by means of a Varian Super Scan 3 UV-vis spectrophotometer. For these reactions Scheme III holds under the experimental conditions used. The appearance and disappearance of the intermediates 1-acetyl-4-amino- and 1-acetyl-(4-dimethylamino)pyridinium ions were monitored at 290 and 320 nm, respectively. An aqueous solution (10 mL) consisting of the substituted pyridine, phosphate buffer (0.002 M), and sodium perchlorate (to give an ionic strength of 0.2 M) at a given pH was poured into a 4-cm cuvette placed in the thermostatted cell holder of the instrument. After temperature equilibration (25 ± 0.1 °C) a solution of AA in acetonitrile (40–120 μL) was injected by means of a Unimetrics syringe and the recording started. In the kinetic runs the initial concentration of the substrate was $(2-6) \times 10^{-5}$ M and the maximum acetonitrile concentration was 1%.

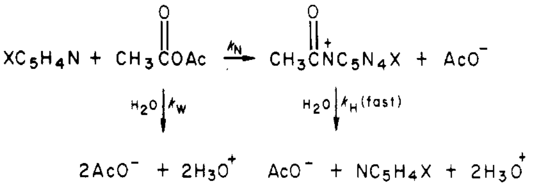
At least a 20-fold excess of substituted pyridine concentration over that of AA was used. The rate constants for these reactions were obtained by least-squares fitting to eq 2 (see Results). The experimental conditions and k_{obsd} for these reactions are summarized at the end of Table I.

Some of the reactions of AA with 3-cyano-, 3-chloro-, 4-methyl- and 4-aminopyridines were checked for reversibility (through k_{-N} of Scheme I) by injecting a second equal volume of the substrate solution into the reaction sample after the end of the first reaction, i.e., in the presence of an equal concentration of acetate. The new values of k_{obsd} were in agreement with the first ones within experimental error. This means that k_{-N} [AcO⁻] was negligible under the experimental conditions of the reactions.

Results

pH-stat Method. The reactions of acetic anhydride (AA) with all the substituted pyridines except 4-amino- and 4-(dimethylamino)pyridines can be satisfactorily described by Scheme II, under the experimental conditions of study. This results from Scheme I by ignoring the k_{-N} step (see end of Experimental Section) and assuming $k_H \gg k_N[N]$ (justified below), where N represents the free-base form of the substituted pyridine. The experimental pH values for these reactions (Table I) were higher than the pK_a values of both acetic acid and the corresponding substituted pyridinium ion (except for the reactions with 4-methylpyridine). Two protons were therefore produced from every molecule of substrate. In the reactions with 4-methylpyridine, however, less than two protons were produced since the pH values were comprised between the pK_a values of the two species involved.

Scheme II



$$\begin{tikzcd}
XC_5H_4N + CH_3\overset{O}{\overset{\|}{C}}OAc \arrow[r, "k_N"] \arrow[d, "H_2O" ', "k_w"] & CH_3\overset{O}{\overset{\|}{C}}\overset{+}{N}C_5N_4X + AcO^- \arrow[d, "H_2O" ', "k_H (fast)"] \\
2AcO^- + 2H_3O^+ & AcO^- + NC_5H_4X + 2H_3O^+
\end{tikzcd}$$

All these reactions were followed by automatic titration of the protons released by means of a pH-stat. Good pseudo-first-order kinetics was obtained for all of them. In the reactions with 4-methylpyridine protons are also released in the k_N step of Scheme II due to the pH values chosen for their study. The fact that good first-order kinetics was also obtained with this nucleophile means that $k_H \gg k_N[N]$ for these reactions under the conditions employed. This inequality must also hold for the reactions with less basic substituted pyridines where k_N should be smaller and k_H larger than the corresponding values for the reactions with 4-methylpyridine (the fact that higher concentrations of substituted pyridine were used in the reactions with less basic nucleophiles does not change significantly the above inequality).

The pseudo-first-order rate constants observed (k_{obsd}) for all the reactions followed by the pH-stat method are given in Table I and obey eq 1, where k_w is the first-order

$$k_{obsd} = k_w + k_{OH}[OH^-] + k_N[N] \qquad (1)$$

Table II. Rate Constants for the Nucleophilic Reactions of Substituted Pyridines with Acetic Anhydride in Aqueous Solution at 25 °C, Ionic Strength 0.2 M (with Sodium Perchlorate)

nucleophile	$pK_a{}^a$	$k,{}^b$ s^{-1} M^{-1}
3-cyanopyridine	1.62	0.014 ± 0.0005
4-cyanopyridine	1.98	0.066 ± 0.002
3-chloropyridine	2.98	0.57 ± 0.02
nicotinamide	3.46	1.29 ± 0.05
pyridine	5.32	76 ± 3
4-methylpyridine	6.15	370 ± 10
4-aminopyridine	9.15	2500 ± 50
4-(dimethylamino)pyridine	9.55	3200 ± 60
water	(−1.75)	$(4.4 \pm 0.05) \times 10^{-5}$
hydroxide anion	(15.75)	890 ± 30

[a] Of the conjugate acid of the base at 25 °C, ionic strength 0.2 M, measured as previously described.[6,11] (The figures for water and hydroxide anion are conventional.) [b] Second-order rate constants which correspond to k_N for the substituted pyridines, to k_{OH} for hydroxide anion, and to $k_w/55.56$ for water; hence $k_w = (2.44 \pm 0.03) \times 10^{-3}$ s^{-1}. The errors are standard errors, either of the slopes (k_N and k_{OH}) or intercepts (k_w) of appropriate plots, obtained by least-squares analysis (see Results).

rate constant for uncatalyzed hydrolysis of AA, k_{OH} and k_N are the second-order rate constants for hydroxide anion and substituted pyridine attack, respectively, and N is the free-base form of the latter. The second term of eq 1 was almost negligible under the experimental conditions used for the determinations of k_N. Plots of k_{obsd} vs. [N] at constant pH gave k_N as slopes and $k_w + k_{OH}[OH^-]$ as intercepts. Since the variation of the intercepts with pH was almost negligible under the conditions and k_N had no definite dependence on pH, a new single plot of k_{obsd} vs. [N] including all the experimental points at different pH values gave the final k_N value (Table II) as the slope of the above plot through the linear least-squares method.

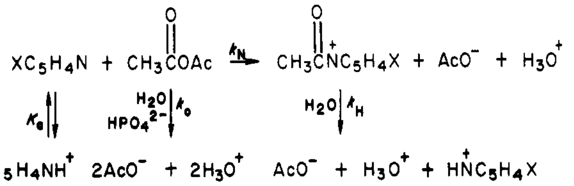
The values of k_w and k_{OH} were determined in the absence of substituted pyridine as the intercept and slope, respectively, of a plot of k_{obsd} vs. $[OH^-]$ at the pH range 5.7–8.2, by least-squares analysis.

The range of k_{obsd} values obtained is shown in Table I. The values of k_w and k_{OH} and their standard errors are shown in Table II.

Some of the reactions under study in the present work were examined by Jencks and co-workers under slightly different conditions (ionic strength 1 M maintained with potassium chloride).[10,12] Their values for pyridine (84 s^{-1} M^{-1}), 4-methylpyridine (490 s^{-1} M^{-1}), water (2.5×10^{-3} s^{-1}), and hydroxide anion (1.1×10^3 s^{-1} M^{-1}) agree reasonably with ours (Table II) when due account is taken of the difference in ionic strength.

The rate constants observed for hydrolysis of acetylpyridinium and 1-acetyl-4-methylpyridinium ions (k_H, Scheme I) have been reported to consist of an uncatalyzed and two general base catalyzed (acetate and pyridine) terms, under given experimental conditions.[10] Similar expressions for k_H have been reported for ring-substituted 1-(methoxycarbonyl)pyridinium ions.[13,14] In the reactions followed by a pH-stat in the present report general base catalyzed terms for hydrolyses of the substituted acetylpyridinium ions could not be observed under the experimental conditions since the rate determining steps were the formation of the intermediates (k_N step, Scheme II).

Scheme III



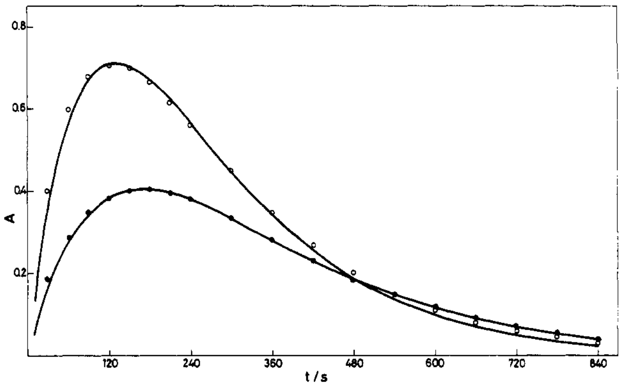


Figure 1. Curves of absorbance at 320 nm (4-cm cells) vs. time, calculated from eq 2 and "best-fitting" parameters of Table III, for the reactions of acetic anhydride with 4-(dimethylamino)pyridine at pH 6.5 (phosphate buffer) and at total amine concentration values of 0.0024 (upper curve) and 0.0009 M (lower curve). The points are experimental.

Spectrophotometric Method. The reactions of AA with 4-amino- and 4-(dimethylamino)pyridines can be described by Scheme III under the experimental conditions employed. In this scheme $k_0 = k_w + k_{Ph}[HPO_4{}^{2-}]$ and $k_H \approx k_N[N] + k_0$. In these reactions the appearance and disappearance of the substituted acetylpyridinium ion intermediates were followed by UV spectrophotometry. The intermediate 1-acetyl-4-(dimethylamino)pyridinium ion has also been observed in similar reactions in nonaqueous solvents.[15] The dependence of the intermediate absorbance at the wavelength chosen with time is shown in eq 2, where A and ϵ are the absorbance and the molar

$$A = \frac{k_N[N]\epsilon[S]_0 l}{k_H - k_N[N] - k_0}\left[l^{-(k_N[N]+k_0)t} - l^{-k_H t}\right] \tag{2}$$

extinction coefficient of the intermediate, respectively, $[S]_0$ is the initial concentration of AA and l is the light-path length of the UV cell.

The rate constants involved in Scheme III were determined by fitting the experimental to the theoretical absorbances given by eq 2, through nonlinear least-squares analysis. Once best fitting values of ϵ and $k_N[N]$ for given values of k_H and k_0 were obtained, the two latter values were then varied in order to find the best fitting values for the four variables (best correlation coefficient). The "best" values obtained for the set of parameters in eq 2 for all the reactions of AA with 4-amino- and 4-(dimethylamino)pyridines are shown in Table III. The k_0 calculated values agree with those obtained from the equation $k_0 = k_w + k_{Ph}[HPO_4{}^{2-}]$, where k_w has the experimental value (Table II) and $k_{Ph} = 0.15$ s^{-1} M^{-1}.[12]

Figure 1 shows two curves calculated from eq 2 and the best fitting values of the four parameters shown in Table III, for the reactions with 4-(dimethylamino)pyridine at two different concentrations of the nucleophile. The ex-

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(12) Kirsh, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

(13) Guillot-Edelheit, G.; Laloi-Diard, M.; Guibé-Jampel, E.; Wakselman, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1123.

(14) Battye, P. J.; Ihsan, E. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 741.

(15) Guibé-Jampel, E.; Le Corre, G.; Wakselman, M. *Tetrahedron Lett.* **1979**, 1157. Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

Table III. "Best-Fitting" Values of Four Parameters in Eq 2 for the Reactions of Acetic Anhydride with Substituted Pyridines in Aqueous Solution at 25 °C, Ionic Strength 0.2 M (with Sodium Perchlorate)

substituent	$10^4[N]_{tot}$,[a] M	pH	$10^3k_N[N]$, s^{-1}	$10^{-4}\epsilon$[b]	10^3k_H,[c] s^{-1}	10^3k_0,[d] s^{-1}
4-amino	6.0–24.0	5.9	0.8–3.1	4.8–5.8	10.8–11.0	2.45–2.50
	5.0–17.0	6.2	1.3–4.9	5.1–6.3	12.1–12.8	2.55–2.60
	2.0–10.0	6.5	0.9–5.5	3.5–4.0	11.8–12.5	2.55–2.60
4-dimethylamino	12.0–24.0	5.9	0.8–1.8	3.0–3.2	4.8–5.0	2.45–2.50
	6.0–12.0	6.2	1.0–1.9	1.5–3.2	6.0–7.0	2.55–2.60
	6.0–24.0	6.5	1.6–7.1	1.7–2.0	6.0–6.5	2.55–2.60

[a] Concentration of total substituted pyridine = $[N] + [NH^+]$. [b] The molar extinction coefficients apparently show some variation with pH. Nevertheless, the mean values and standard errors including all the reactions are ϵ_{290}(4-aminopyridine) = 47 000 ± 6000 and ϵ_{320}[4-(dimethylamino)pyridine] = 25 000 ± 4000. [c] No dependence of this rate constant either on [N] or on pH was found. Mean values and standard errors including all runs are k_H(4-aminopyridine) = 0.012 ± 0.001 s^{-1} and k_H[4-(dimethylamino)pyridine] = 0.006 ± 0.0007 s^{-1}. [d] This rate constant increases slightly with pH as expected and agrees with the experimental value (see Results).

perimental points shown fit satisfactorily to the calculated curves.

The values of k_N for the reactions described by Scheme III were determined as slopes of plots of $k_N[N]$ (Table III) vs. [N], including all experimental points, by the least-squares method. The final values of k_N and their standard errors for the reactions of AA with 4-amino- and 4-(dimethylamino)pyridines are shown in Table II.

The rate constants for the hydrolyses of the substituted acetylaminopyridinium ions (k_H, Scheme III) did not show general base catalyzed terms under the experimental conditions used (as seen in Table III). This can be explained in terms of negligible values of the acetate and substituted pyridine catalyzed terms compared to the uncatalyzed (water catalyzed) one. the uncatalyzed terms can be estimated from Jencks' data on the hydrolysis of acetylpyridinium, 1-acetyl-4-methylpyridinium, 1-acetyl-3,4-lutidinium, and 1-acetyl-4-methoxypyridinium ions.[10] A Brønsted plot based on these four points (β(leaving group) ≈ 0.8) gives values of 0.013 and 0.008 s^{-1} for the rate constants of the uncatalyzed hydrolyses of the 4-amino and 4-dimethylamino derivatives, respectively. These figures are in accord with our experimental k_H values (Table III). A similar Brønsted slope was found for the hydrolyses of substituted 1-(methoxycarbonyl)pyridinium ions.[14] The rate constants for the substituted pyridine-catalyzed hydrolysis of the corresponding substituted acetylpyridinium ions do not change significantly with the basicity of the pyridine;[10] therefore, values of 10–20 s^{-1} M^{-1} can be deduced for the 4-amino and 4-dimethylamino derivatives. The acetate-catalyzed rate constants for the hydrolyses of the above ions can be estimated[10] smaller than 1 s^{-1} M^{-1}. According to these values and the ones for the concentrations of acetate and free substituted pyridine during the reactions (Table I), the uncatalyzed terms for the hydrolyses of the above ions result with values much larger than the ones for the base-catalyzed terms.

Discussion

The Brønsted-type plot obtained (from the data of Table II) for the reactions of substituted pyridines with AA in aqueous solution is curved (Figure 2). For the present reactions the Brønsted curve can best be explained in terms of a tetrahedral intermediate in the reaction path and a change in the rate-determining step from breakdown to formation of the intermediate as the nucleophile increases its basicity (Scheme IV).

Application of the steady-state treatment to the tetrahedral intermediate gives eq 3, where k_N is the overall second-order rate constant.

$$k_N = \frac{k_1k_2}{k_{-1} + k_2} \qquad (3)$$

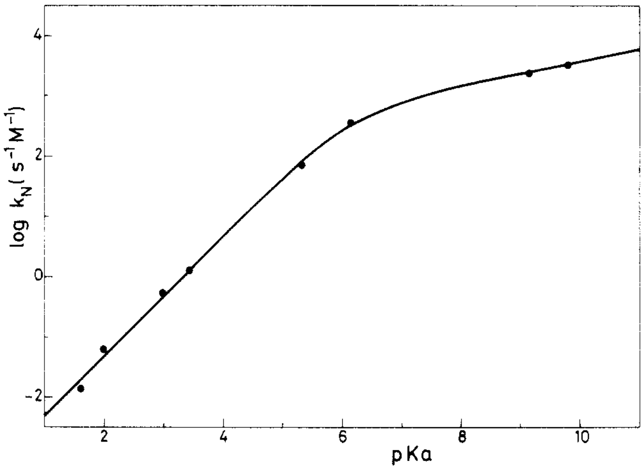
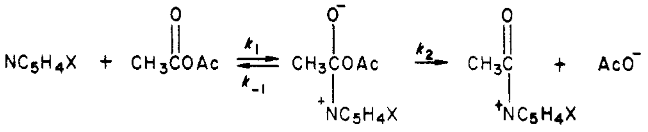


Figure 2. Dependence on basicity of the rate constants for amine attack for the reactions of acetic anhydride with a series of substituted pyridines in aqueous solution at 25 °C, ionic strength 0.2 M ($NaClO_4$). The solid line was calculated by eq 4 and the points are experimental. The pK_a value at the center of the curvature (pK_a°) is 6.1.

Scheme IV



$$NC_5H_4X + CH_3C(=O)OAc \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3C(O^-)(OAc)(\overset{+}{N}C_5H_4X) \xrightarrow{k_2} CH_3C(=O)\overset{+}{N}C_5H_4X + AcO^-$$

Three limiting cases can occur. (i) For the less basic nucleophiles $k_{-1} \gg k_2$, and according to eq 3 $k_N = K_1k_2$, where K_1 is the equilibrium constant for the first step, and the second is the rate-determining step. (ii) For nucleophiles of intermediate basicities $k_{-1} \approx k_2$ and eq 3 holds without approximations. (iii) For the most basic nucleophiles $k_{-1} \ll k_2$, eq 3 gives $k_N = k_1$, and the first is the rate-determining step. Linear Brønsted relationships are expected for cases i and iii, but a nonlinear one for case ii. The higher sensitivity of the rate to amine basicity for the less basic nucleophiles (β_N = 1.0, Figure 2) compared to the smaller one for the most basic nucleophiles (β_N = 0.2, Figure 2) has been explained in terms of the transition-state structures for cases i and iii. In the former there is full bond formation between the amine nitrogen and carbonyl carbon, whereas in the latter only a "loose" bond occurs between these atoms.

A semiempirical equation based on the above assumptions can be derived[6] (eq 4). In this equation β_2 and β_1

$$\log (k_N/k_N°) = \beta_2(\mathrm{p}K_a - \mathrm{p}K_a°) + \log 2 - \log [1 + 10^{(\beta_2-\beta_1)(\mathrm{p}K_a-\mathrm{p}K_a°)}] \qquad (4)$$

are the Bønsted slopes when the second and the first step are rate-determining, respectively, and k_N° and pK_a° refer to the (hypothetical) nucleophile for which $k_{-1} = k_2$.

The solid curve of Figure 2 was calculated by eq 4 with the following values for the empirical parameters: $\beta_2 = 1.0$, $\beta_1 = 0.2$, $pK_a° = 6.1$, $\log k_N° = 2.5$. The calculated line shows a satisfactory fit to the experimental data.

Recently, a sharply curved Brønsted plot obtained for the hydrolysis of substituted 1-(methoxycarbonyl)pydidinium ions was shown not to be due to the tetrahedral intermediate, probably because of the high instability of the possible intermediate.[14] We believe that the Brønsted plot found in the present work does reflect the presence of a tetrahedral intermediate and a change in the rate-determining step because this was proved in the similar pyridinolysis reactions of 2,4-dinitrophenyl acetate[8] (DNPA). Furthermore, in the reactions of *p*-nitrophenyl acetate with a series of similar substituted pyridines a straight Brønsted plot was obtained, which was attributed to the breakdown to products of the tetrahedral intermediate being the rate-determining step along the series.[6]

The magnitudes of the Brønsted slopes found for the present reactions are similar to the ones found for aminolysis of other reactive acyl compounds.[1-8] Fersht and Jencks obtained a straight Brønsted plot for the reactions of AA with four substituted pyridines of $pK_a = 5.3$–6.8 ($\beta = 0.87$),[10] but they considered that these pyridines might fall near the break point of this structure–reactivity correlation, since for primary amino acids there is a much smaller dependence of reactivity upon basicity ($\beta = 0.25$).[16]

The fact that in Figure 2 the curvature is centered at $pK_a = 6.1$ means that 4-methylpyridine ($pK_a = 6.15$) and acetate ($pK_a = 4.62$) have approximately equal leaving abilities from the tetrahedral intermediate formed in the reactions (Scheme IV). In other words, acetate is a poorer leaving group from the tetrahedral intermediate than a substituted pyridine of the same basicity. This is confirmed by the high Brønsted slope found in the reactions of some pyridines with AA[10] but is not in accord to the scale of Ritchie for leaving abilities by which acetate leaves the tetrahedral intermediate more than 50 times as readily as 4-methylpyridine.[17] Many authors have discussed the factors affecting the larger leaving abilities of nitrogen bases compared to oxygen anions.[2,9,18,19]

The fact that $pK_a°$ values of 7.3 and 6.1 were obtained for the Brønsted plots for the pyridinolyses of DNPA and AA, respectively, means that 2,4-dinitrophenolate is a worse leaving group from the tetrahedral intermediate than acetate. This is confirmed by the Brønsted plot obtained for the reactions of anionic oxygen nucleophiles with DNPA, where the point for acetate falls on the linear portion of the plot where the expulsion of the phenolate is rate determining; i.e., the expulsion of acetate from the intermediate is faster than 2,4-dinitrophenolate.[1]

DNPA is a little more reactive toward substituted pyridines than 2,4-dinitrophenyl methyl carbonate (DNPMC); this must be due to a slightly higher electron-releasing effect of the methoxy compared to the methyl group. The $pK_a°$ values found for the Brønsted plots obtained for these reactions are 7.3 (DNPA)[8] and 7.8 (DNPMC),[7] which means that replacement of methyl by methoxy as the "nonleaving" group of the tetrahedral intermediate favors pyridine expulsion relative to phenolate; i.e., the electron-donating effect from the acyl group favors pyridine release from the intermediate. If this applies to partitioning of the tetrahedral intermediate formed in the reactions of this work, replacement of methyl by methoxy as the acyl group should result in a $pK_a°$ value higher than 7.3.

The above effect is the opposite of the one found on partitioning of the tetrahedral intermediate formed in the reactions of [(3,4-dinitrophenoxy)carbonyl]quinuclidinium ions with arylate anions; i.e., electron withdrawal from the "nonleaving" aryl oxide group favors amine expulsion relative to 3,4-dinitrophenolate.[9] The discrepancy may be due to the different nature of both the "nonleaving" and the amino groups of the corresponding tetrahedral intermediates involved which makes difficult a comparison of the effects on partitioning of the two intermediates.

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Registry No. Acetic anhydride, 108-24-7; 3-cyanopyridine, 100-54-9; 4-cyanopyridine, 100-48-1; 3-chloropyridine, 626-60-8; nicotinamide, 98-92-0; pyridine, 110-86-1; 4-methylpyridine, 108-89-4; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3.

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(16) Brouver, D. M.; Vlugt, M. J.; Havinga, E. *Proc. Kon. Ned. Akad. Wetensch., Ser. B* **1958**, *61*, 141.

(17) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170.

(18) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 489, 499, 507.

(19) Suh, J.; Lee, B. H. *J. Org. Chem.* **1980**, *45*, 3103.