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Dibenzo[*b*,*g*]thiopyrano[3,2-*b*]thiopyran-6,12-dione (Thioepindolidione) (2). To a solution of 0.91 g (2.25 mmol) of crude **11** and 1.2 mL (9.5 mmol) of freshly distilled (over CaH_2) trimethylsilyl chloride in 30 mL of dry THF at −76 °C was added dropwise by syringe 1.3 equiv of lithium diisopropylamide (LDA) (freshly prepared from 0.41 mL of diisopropylamine and 1.2 mL of 2.5 M of *n*-BuLi in 1.5 mL of THF) under argon. The reaction mixture was kept at −75 °C for 30 min, equilibrated to ~3 °C (ice cooling), and stirred for 2 h. The brown solution was cooled with ice, and 35 mL of aqueous NH_4Cl was added dropwise (pot temperature was kept below 17 °C), followed by 3.2 mL (1 equiv) of 5.25% aqueous NaOCl bleach (Jones Chemicals, Inc., New York), and the mixture was stirred overnight under a nitrogen flush. The precipitated brownish yellow solid was filtered and washed with water and ether to give 245 mg of a light brown solid, which was shown by TLC to contain no thioindigo. The crude product was purified by boiling it in 50 mL of ethyl acetate. After cooling, the insoluble light brown solid was filtered and washed with ethyl acetate to give 205 mg (31%) of thioepindolidione (**2**): mp ~380 °C; electron-impact mass spectrum, *m/e* 296 (M^+), 268 ($M^+ - CO$), 240 ($M^+ - 2CO$); IR (KBr) and ^1H NMR ($CDCl_3$) (see Table I). Anal. Calcd. for $C_{16}H_8O_2S_2$: C, 64.8; H, 2.7; S, 21.6. Found: C, 64.7; H, 2.6; S, 21.7.

Thioepindolidione (2) and *trans*-Thioindigo (5). To a solution of 525 mg (1.3 mmol) of trimethylsilyl ether **11** in 60 mL of dry THF cooled to −76 °C was added by syringe 1.2 equiv of LDA (freshly prepared from 336 μL of diisopropylamine and 0.96 mL of 2.5 M *n*-BuLi in 2 mL of THF) under argon. The dark red reaction mixture was allowed to equilibrate to room temperature overnight and poured into a beaker containing aqueous NH_4Cl and Clorox. The precipitated red solid was filtered and washed thoroughly with water and ether, giving 250 mg (64%) of a dark red powder. TLC (silica gel, CH_2Cl_2) of this material showed only two spots corresponding to *trans*-thioindigo (**5**) (R_f 0.66) and thioepindolidione (**2**) (R_f 0.43). Electron-impact mass spectrum of this mixture showed the following: *m/e* 296 (M^+), 268 ($M^+ - CO$), 252 ($M^+ - CO_2$), 240 ($M^+ - 2CO$), 120. By integration over the ^1H NMR region where the peri H's adjacent to the carbonyl resonate (δ 7.95 for **5** and δ 8.62 for **2**), the ratio of **5** to **2** in this mixture was estimated as ~1:2.

Acknowledgment. We thank Dr. Joe L. Lippert and Karen E. Maskasky of the Analytical Sciences Division for obtaining the fluorescence spectra of thioepindolidione and thioindigo and Frank M. Michaels and Sandra M. Finn for helping on the high-field NMR spectra.

Registry No. **1**, 17352-37-3; **2**, 97634-87-2; **5**, 3844-31-3; **6**, 3528-17-4; **7**, 67220-30-8; **8**, 4892-02-8; **9**, 78880-71-4; **10**, 97634-84-9; **11**, 97634-86-1; **12**, 97634-85-0; pyrrolidine, 123-75-1.

Nonlinear Brønsted-Type Plot in the Pyridinolysis of 2,4-Dinitrophenyl Benzoate in Aqueous Ethanol

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From the kinetics of the title reaction in 44 wt% aqueous ethanol at 25 °C, ionic strength 0.2 M (KCl), a curved Brønsted-type plot is obtained. The curve is interpreted in terms of a zwitterionic tetrahedral intermediate in the reaction path and a change in the rate-determining step from breakdown to products of this intermediate to its formation as the pyridine becomes more basic. A semiempirical equation based on this hypothesis accounts for the experimental results. The center of the Brønsted-type curvature ($pK_a°$) is located at $pK_a = 9.5$, lower than the value found in the pyridinolysis of 2,4-dinitrophenyl *p*-nitrobenzoate in the same solvent, showing that electron withdrawal from the acyl group of the substrate favors amine expulsion relative to phenoxide from the tetrahedral intermediate. It is claimed that the influence of the acyl group of the substrate on the value of $pK_a°$ cannot be quantified when comparing similar reactions in water and aqueous ethanol since the $pK_a°$ value for a given reaction should be larger in the latter solvent. The activation parameters obtained support the hypothesis that for the title reactions, $pK_a° > 9$.

Structure–reactivity correlations for nucleophilic reactions have usually been expressed through Brønsted-type plots, log k_N against basicity of the nucleophile, where k_N is the second-order rate constant for the reaction of the nucleophile with a common substrate (electrophile).

The nucleophilic reactions of series of structurally similar amines with aryl acetate esters exhibit linear Brønsted-type plots when the leaving group of the substrate is moderately basic, but the plots are curved when the basicity of the leaving group decreases.[1] Primary and secondary amines also show curved Brønsted-type plots in their reactions with other reactive carboxylic acid derivatives.[2]

The nucleophilic reactions of quinuclidines with aryl phenyl carbonates show linear Brønsted-type plots for the substrates with more basic leaving groups; however the plots become nonlinear as the leaving ability of the aryl oxide group increases.[3]

The above picture is also obtained in the pyridinolysis of methoxycarbonyl and acetyl derivatives. The Brønsted-type plots are straight for leaving groups such as phenoxide[1,4] and *p*-nitrophenoxide[5,6] ions and curved for 2,4-dinitrophenoxide[4,7] and chloride[5,8] anions.

The nonlinear Brønsted-type plots described above have been explained through a tetrahedral intermediate along the reaction path (eq 1, N and L represent the substituted amine and the leaving group, respectively) and a change in the rate-determining step, from the second to the first one, as the nucleophile becomes more basic.[3-9] The slope

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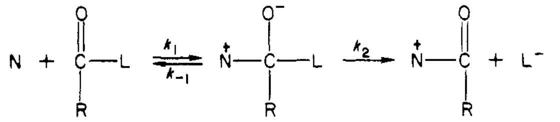
Table I. Experimental Conditions and Pseudo-First-Order Rate Constants (k_{obsd}) for the Pyridinolysis of 2,4-Dinitrophenyl Benzoate in 44 wt% Aqueous Ethanol, Ionic Strength 0.2 M (Maintained with KCl)[a]

substituent on pyridine	range of $[N]_T$, M[b]	F_N[c]	k_{obsd}, s^{-1}	no. of runs
3-chloro[d,e]	0.20–0.90	1.0	$(0.6–1.8) \times 10^{-5}$	8
3-carbamoyl[d,e]	0.20–0.90	1.0	$(1.5–5.6) \times 10^{-5}$	8
none	0.04–0.30	0.5	$(0.6–3.9) \times 10^{-4}$	10
	0.04–0.40	0.67	$(0.7–6.5) \times 10^{-4}$	9
	0.04–0.40	0.80	$(1.2–7.9) \times 10^{-4}$	9
3-methyl	0.04–0.40	0.50	$(0.2–1.5) \times 10^{-3}$	10
	0.04–0.40	0.67	$(0.2–1.9) \times 10^{-3}$	10
	0.04–0.40	0.80	$(0.3–2.2) \times 10^{-3}$	10
at 15.2 °C	0.04–0.40	0.80	$(0.1–1.0) \times 10^{-3}$	9
at 35.2 °C	0.04–0.40	0.80	$(0.6–4.9) \times 10^{-3}$	10
at 45.2 °C	0.04–0.40	0.50	$(0.7–6.2) \times 10^{-3}$	10
4-methyl	0.04–0.40	0.50	$(0.5–3.5) \times 10^{-3}$	10
	0.04–0.40	0.67	$(0.5–4.2) \times 10^{-3}$	9
	0.04–0.40	0.80	$(0.6–4.8) \times 10^{-3}$	9
3,4-dimethyl	0.04–0.40	0.50	$(0.9–6.7) \times 10^{-3}$	10
	0.04–0.40	0.67	$(1.2–8.2) \times 10^{-3}$	9
	0.04–0.40	0.80	$(0.2–1.0) \times 10^{-2}$	10
4-amino[d]	$(0.5–5.0) \times 10^{-3}$	0.035	$(0.3–3.0) \times 10^{-3}$	10
	$(0.5–5.0) \times 10^{-3}$	0.047	$(0.5–4.7) \times 10^{-3}$	10
	$(0.5–5.0) \times 10^{-3}$	0.067	$(0.7–6.4) \times 10^{-3}$	10
4-dimethylamino[d]	$(1.0–8.0) \times 10^{-3}$	0.030	$(0.9–7.2) \times 10^{-3}$	8
	$(0.5–5.0) \times 10^{-3}$	0.040	$(0.6–6.6) \times 10^{-3}$	9
	$(0.5–5.0) \times 10^{-3}$	0.060	$(0.9–9.9) \times 10^{-3}$	10
at 15.4 °C	$(0.1–1.0) \times 10^{-2}$	0.034	$(0.1–1.1) \times 10^{-2}$	10
at 35.4 °C	$(0.1–1.0) \times 10^{-2}$	0.035	$(0.1–1.3) \times 10^{-2}$	9
at 45.2 °C	$(0.5–5.0) \times 10^{-3}$	0.041	$(1.0–8.6) \times 10^{-3}$	10

[a] At 25 ± 0.1 °C, unless otherwise stated. Accuracy at other temperatures was ±0.1 °C, except 45.2 (±0.2 °C). [b] Molar concentration of total substituted pyridine. $[N]_T = [N] + [NH^+]$, where N and NH^+ represent the free and protonated forms of the amine, respectively. [c] Fraction of free amine. $F_N = [N]/[N]_T$. [d] In the presence of phosphate buffer ($H_2PO_4^- + HPO_4^{2-}$). Total concentration of buffer = 0.02 M. [e] For these reactions a plot of k_{obsd} vs. $[N]_T$ gave an intercept corresponding to $k_o \approx 3.3 \times 10^{-6}$ s^{-1}. Also, a few runs were carried out at F_N = 0.5 in the absence of phosphate buffer, where an intercept corresponding to $k_w \approx 1 \times 10^{-6}$ s^{-1} was obtained from a k_{obsd} vs. $[N]_T$ plot.

of these plots (β) changes from β_2 = 0.8–1.0 (second step limiting) to β_1 = 0.1–0.3 (first step limiting) reflecting the charge density on the nitrogen atom in the corresponding transition states, relative to reactants.[3-9]



$$\mathrm{N} + \mathrm{R{-}C({=}O){-}L} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{\overset{+}{N}{-}C(O^-)(R){-}L} \xrightarrow{k_2} \mathrm{\overset{+}{N}{-}C({=}O){-}R} + \mathrm{L^-} \qquad (1)$$

The pK_a value at the center of curvature of the Brønsted-type plot (p$K_a°$) is important since from this value relative leaving abilities of N and L can be determined. At this pK_a value, $k_{-1} = k_2$ (eq 1), i.e., a nucleophile of pK_a = p$K_a°$ has the same leaving ability from the tetrahedral intermediate as the leaving group of the substrate.

From the above considerations it follows that for the aminolysis of similar substrates (same R, eq 1), the p$K_a°$ value should decrease as the leaving ability of L increases. This has been found in the reactions of quinuclidines with aryl phenyl carbonates, where quantification of the dependence of the basicity of L on p$K_a°$ was established,[3,10] and in the pyridinolysis of acetyl and methoxycarbonyl (L = aryloxy, Cl) derivatives.[4-8]

The influence of the nature of R on the p$K_a°$ value has received much less attention. It has been found that in the reaction of quinuclidines with aryl 3,4-dinitrophenyl carbonates, electron-withdrawing substituents on R favor amine expulsion relative to 3,4-dinitrophenoxide ion, i.e., the p$K_a°$ value increases as R becomes less basic.[10] A small dependence of the inductive effect of R[11] on the position of the center of the Brønsted curvature is inferred by comparison of the pyridinolyses of 2,4-dinitrophenyl methyl carbonate and 2,4-dinitrophenyl acetate. Substitution of methoxy for methyl as the R group of the tetrahedral intermediate (eq 1) increases the p$K_a°$ value (from 7.3 to 7.8),[4,7] reflecting the larger electron-withdrawing inductive effect of methoxy (σ_I = 0.25[11a]) compared to the methyl group (σ_I = −0.05[11a]).

In order to quantify the influence of R on the p$K_a°$ value we decided to study the pyridinolysis of a homogeneous series of substrates such as 2,4-dinitrophenyl *p*-substituted benzoates. The first substrate chosen was the *p*-nitro derivative, which showed a linear Brønsted plot up to pK_a = 9 (i.e., p$K_a°$ > 9).[12] Comparison with previous pyridinolyses of other substrates (same L, R = Me, MeO) is not accurate since the reactions with 2,4-dinitrophenyl *p*-nitrobenzoate were carried out in aqueous ethanolic media (due to solubility problems), instead of water. The change of solvent from water to ethanol–water should result in a larger k_{-1}/k_2 ratio (eq 1), and therefore a larger p$K_a°$ value, for a given tetrahedral intermediate.[10] In order to single out the influence of the nature of R we present in this work the Brønsted-type plot obtained in the pyridinolysis of 2,4-dinitrophenyl benzoate in aqueous ethanol and we compare it with the corresponding plot found in the pyridinolysis of the *p*-nitrobenzoate analogue in the same solvent mixture.

Experimental Section

Materials. Solvents and salts were analytical reagent grade. Monosubstituted pyridines were purified as previously.[5] 3,4-Dimethylpyridine was distilled, bp 174–175 °C (lit.[13] bp 175–176 °C). 2,4-Dinitrophenyl benzoate (DNPB) was prepared by a

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Table II. pK_a Values of Substituted Pyridinium Ions and Dihydrogen Phosphate Monoanion and Second-Order Rate Constants (k_N) for the Pyridinolysis of 2,4-Dinitrophenyl Benzoate, in 44 wt% Aqueous Ethanol, Ionic Strength 0.2 M (Maintained with KCl)[a]

ion	pK_a[b]	k_N, s^{-1} M^{-1}[c]
3-chloropyridinium	2.17	$(1.6 \pm 0.2) \times 10^{-5}$
3-carbamoylpyridinium	2.67	$(5.7 \pm 0.2) \times 10^{-5}$
pyridinium	4.63	$(3.6 \pm 0.5) \times 10^{-3}$
3-methylpyridinium	4.92	$(1.0 \pm 0.1) \times 10^{-2}$
at 15.2 °C	-	$(4.7 \pm 0.3) \times 10^{-3}$
at 35.2 °C	-	$(20.7 \pm 4.3) \times 10^{-3}$
at 45.2 °C	-	$(41.2 \pm 1.9) \times 10^{-3}$
4-methylpyridinium	5.35	$(2.3 \pm 0.2) \times 10^{-2}$
3,4-dimethylpyridinium	5.68	$(5.3 \pm 0.5) \times 10^{-2}$
4-aminopyridinium	8.98	18.7 ± 1.3
4-(dimethylamino)pyridinium	9.14	30.3 ± 2.3
at 15.4 °C	9.52	25.8 ± 0.8
at 35.4 °C	8.79	35.8 ± 1.6
at 45.2 °C	8.49	41.2 ± 2.6
dihydrogen phosphate	7.55	-
at 15.4 °C	7.62	-
at 35.4 °C	7.41	-
at 45.2 °C	7.33	-

[a] At 25 ± 0.1 °C unless otherwise stated. [b] These values were measured either potentiometrically or spectrophotometrically (see Experimental Section). The standard deviations for all these determinations are ±0.02. [c] Errors shown are standard deviations.

standard procedure[14,15] and identified by ^1H NMR: mp 131–132 °C (lit.[15] mp 130–131.5 °C).

Determination of pK_a Values. These were measured in the same experimental conditions of the kinetics (Table I). The pK_a values of the three more acidic pyridinium ions (less basic pyridines) were determined spectrophotometrically, and those of the other pyridinium ions and dihydrogen phosphate monoanion were measured potentiometrically by the methods and instruments described previously.[12] The pK_a values obtained are shown in Table II.

Kinetic Measurements. These were carried out as previously.[12] The initial concentration of substrate was (4–5) × 10^{-5} M.

The reactions of DNPB with pyridine, 3- and 4-methylpyridines, and 3,4-dimethylpyridine were carried out without external buffer, whereas in the other reactions phosphate ($H_2PO_4^-$ + HPO_4^{2-}) was used as external buffer. Generally, the kinetics were studed at three different free amine fractions (F_N). The F_N values for the reactions of the aminopyridines were calculated from the following equations:

$$F_N = [N]/[N]_T$$

$$[N]_T = [N] + [NH^+]$$

$$[H]_T = [NH^+] + [H_2PO_4^-]$$

$$K_a = [N]a_{H^+}/[NH^+]$$

$$K_a' = [HPO_4^{2-}]a_{H^+}/[H_2PO_4^-]$$

where N and NH^+ are the free amine and its conjugate acid, $[H]_T$ is the total concentration of HCl added to partially protonate both the amine and HPO_4^{2-} (the solutions were prepared from the free amine and Na_2HPO_4), and a_{H^+} is the activity of H^+ as measured by the glass-calomel electrode. K_a and K_a' are "mixed" ionization constants,[16] and their values were determined as described above. Due to the relative large concentrations of NH^+ and $H_2PO_4^-$ and to the fact that the "pH" was ca. 8 for the reactions of the aminopyridines, the terms $[OH^-]$ and $[H^+]$ were omitted from the third equation.

Most of the reactions were carried out in large excess of total amine over the substrate. Pseudo-first-order rate constants (k_{obsd}) were obtained from least-squares analysis of "infinity" plots. These remained linear for at least three half-lives. The values of k_{obsd} found and the experimental conditions of the reactions are shown in Table I.

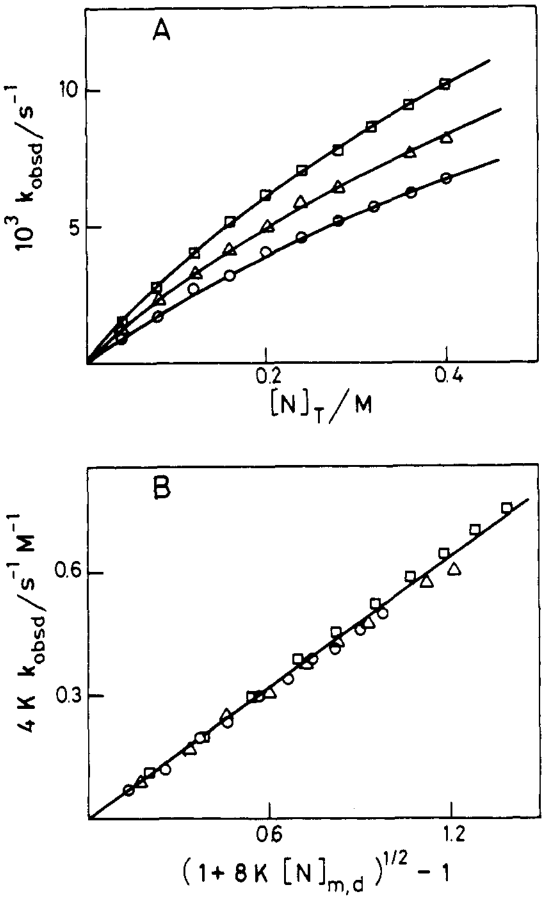

Figure 1. Plots of eq 2 (A) and eq 4 (B) for the reactions of 2,4-dinitrophenyl benzoate with 3,4-dimethylpyridine in 44 wt% aqueous ethanol at 25 °C, ionic strength 0.2 M (KCl), at three free amine fractions (F_N): F_N = 0.50 (○), F_N = 0.67 (△), F_N = 0.80 (□). The points are experimental and the lines calculated through eq 3 (plot A) and eq 4 (plot B) with k_N = 0.053 s^{-1} M^{-1} and K = 1.85 M^{-1}.

Product Studies. Benzoate and 2,4-dinitrophenoxide anions were the only products found in the reactions of DNPB with 4-amino-, 3-methyl-, and 3-carbamoylpyridines ("pH" > 5.6) as shown by comparison of the final UV–vis spectra (200–500 nm) of the reactions with those of authentic samples of equimolar amounts of benzoic acid and 2,4-dinitrophenol at the same experimental conditions of the reactions.

1-Benzoyl-4-aminopyridinium ion, a possible intermediate in the reaction of DNPB with 4-aminopyridine, was not observed by repetitive UV scannings (250–350 nm) but the fact that an isosbestic point was not found suggests its existence.

Results

The second-order rate constants (k_N) for the reactions under study were obtained from k_{obsd} vs. $[N]_T$ plots at constant F_N. In most cases, k_N was obtained at three different values of F_N, and no dependence of k_N on F_N was noted.

The general rate law obtained for these reactions is given by eq 2, where k_o is the rate constant in the absence of amine.

$$k_{obsd} = k_o + k_N[N] \qquad (2)$$

The reactions of DNPB with 3-chloro-, 3-carbamoyl-, 4-amino-, and 4-(dimethylamino)pyridines showed linear k_{obsd} vs. $[N]_T$ plots and the k_N values were obtained by dividing the slopes of these plots by F_N. The values of k_N

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Table III. Thermodynamic Parameters for the Dissociation Equilibria of 4-(Dimethylamino)pyridinium Cation and Dihydrogen Phosphate Monoanion and Activation Parameters for the Reactions of Two Substituted Pyridines with 2,4-Dinitrophenyl Benzoate[a]

ion	ΔH°, kcal mol^{-1}	ΔS°, cal K^{-1} mol^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$, cal K^{-1} mol^{-1}
dihydrogen phosphate	4.3 ± 0.8	-20.2 ± 2.5		
4-(dimethylamino)pyridinium	14.5 ± 1.0	6.7 ± 1.9	2.3 ± 1.0	-44.2 ± 1.5
3-methylpyridinium			13.0 ± 1.0	-24.3 ± 2.0

[a] In 44 wt% aqueous ethanol, ionic strength 0.2 M (KCl), temperature range 15–45 °C.

found for these reactions are shown in Table II.

The reactions of DNPB with pyridine, 3-methyl-, 4-methyl-, and 3,4-dimethylpyridines exhibited nonlinear k_{obsd} vs. $[N]_T$ plots (Figure 1 part A). This type of behavior has been attributed to dimerization of these pyridines. Pyridine, methylpyridines, and most notably 3,4-dimethylpyridine are known to dimerize at relatively low amine concentration in aqueous solutions.[17] The unreactive nature of the dimer due to involvement of the lone electron pair of the nitrogen atom of the pyridine either with the solvent or with another pyridine molecule[18] must be responsible for the leveling off shown by k_{obsd} vs. $[N]_T$ plots. The concentration of free monomeric substituted pyridine has been expressed as a function of the total concentration of monomeric plus dimeric species, $[N]_{m,d}$.[12] Replacing this in eq 2 and ignoring k_o,[19] one gets eq 3,

$$k_{obsd} = \frac{k_N}{4K}\left(\sqrt{1 + 8K[N]_{m,d}} - 1\right) \qquad (3)$$

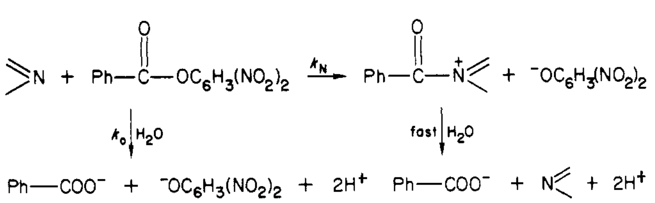
where K is the equilibrium constant for the dimerization process. Rearranging the above relationship, one gets eq 4. A plot of eq 4 is shown in Figure 1 part B. The values of K and k_N were found by iterative fitting of the rate and concentration data to eq 4, through linear least-squares analysis. Neither k_N nor K showed any dependence on

$$4Kk_{obsd} = k_N\left(\sqrt{1 + 8K[N]_{m,d}} - 1\right) \qquad (4)$$

the free amine fraction. The final values of these parameters were obtained as average of the ones at each free amine fraction. The values of k_N are given in Table II and those of K at 25 °C were 1.03, 1.07, 1.09, and 1.85 M^{-1} for pyridine, 3-methyl-, 4-methyl-, and 3,4-dimethylpyridines, respectively. There is only a small increase in the K values at 25 °C in going from pyridine to 3,4-dimethylpyridine in aqueous ethanol compared to aqueous solution.[17] The curves shown in Figure 1 part A were calculated with the aid of eq 3 (with $[N]_{m,d} = F_N[N]_T$) and with the values of k_N and K determined above. The three curves merge into one when one plots k_{obsd} vs. $[N]_{m,d}$, instead of $[N]_T$, confirming the independence of k_N and K on the free amine fraction.

Values of pK_a. The values for pyridinium and 4-methylpyridinium ions (Table II) agree reasonably well with those reported in aqueous methanol.[20] The values shown in Table II were not corrected for the pH meter readings,[12] but even if corrected they show significant differences with those obtained in the same conditions of solvent, temperature, and ionic strength, but the latter maintained with sodium perchlorate.[12] These differences (from 0.3 pK_a units up to 0.6 for 3-chloropyridine) highlight the importance of specific salt effects on the values of these equilibrium constants.

Scheme I



It was also necessary to determine the pK_a of 4-(dimethylamino)pyridinium ion and dihydrogen phosphate monoanion at temperatures other than 25 °C in order to obtain the F_N values (see Experimental Section) and hence, those of k_N and activation parameters for the reaction with DNPB. These pK_a values at various temperatures are shown at the bottom of Table II.

Ionization and Activation Parameters. For the equilibrium ionization of 4-(dimethylamino)pyridinium ion our ΔH° and ΔS° values (Table III) are higher than those reported in water, in the absence of ionic strength.[21] The solvent change from water to aqueous ethanol, which should decrease both values, must be counterbalanced by the increase in ionic strength, which tends to enlarge the values of ΔH° and ΔS°.

The values of ΔH° and ΔS° for the ionization of dihydrogen phosphate monoanion (Table III) are higher than those in water at zero ionic strength.[22] In this case, the decrease of solvent polarity (in going from water to aqueous ethanol) should increase both ΔH° and ΔS° values due to the relative decrease of solvation of products compared to the reactant. The change in ionic strength (from zero to 0.2 M) should result in lower ΔH° and ΔS° values; therefore, this change only partially offsets the solvent change, in view of the higher values of ΔH° and ΔS° found in this work.

Activation parameters for the reactions of DNPB with 3-methyl- and 4-(dimethylamino)pyridines are shown in Table III. The values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were obtained from the slope and intercept, respectively, of Eyring plots, by least-squares analysis. The activation parameters for the reaction of DNPB with 3-methylpyridine are similar to those obtained in the reaction of 3-chloropyridine with 2,4-dinitrophenyl acetate in aqueous medium.[4]

Discussion

Considering the kinetic results and product studies, the general mechanism found for the pyridinolysis of DNPB, at the reaction conditions is shown in Scheme I, where *N*≡ represents the substituted pyridine. Ethanol was omitted from this scheme since no products such as ethyl benzoate were detected during the kinetic runs. This is under-

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[17] Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209. Fersht, A. R.; Jencks, W. P. *Ibid.* **1970**, *92*, 5432.

[18] Sacconi, L.; Paoletti, P.; Ciampolini, M. *J. Am. Chem. Soc.* **1960**, *82*, 3828. Huykens, P. L.; Smets, R. S.; Mas, D. H. *Bull. Soc. Chim. Belg.* **1977**, *86*, 741 and references therein.

[19] The value of k_o was negligible compared to $k_N[N]$, except in the reactions with 3-chloro- and 3-carbamoylpyridines (see footnote e of Table I).

[20] Tissier, M. C.; Tissier, M. *CR Acad. Sci. Paris, C* **1975**, *281*, 749. The pK_a values were interpolated at molar fraction 0.24, which is the equivalent of 44 wt% aqueous ethanol.

[21] Essery, J. M.; Schofield, K. *J. Chem. Soc.* **1961**, 3939. Aue, D. H.; Webb, H. M.; Bowers, M. T.; Liotta, C. L.; Alexander, C. J.; Hopkins, H. D. *J. Am. Chem. Soc.* **1976**, *98*, 854.

[22] Dickerson, R. E. "Molecular Thermodynamics", 1st ed.; Benjamin: New York, 1969; p 442. The ΔH° and ΔS° values, derived from the data, are 1 kcal mol^{-1} and -30 cal K^{-1} mol^{-1}, respectively.

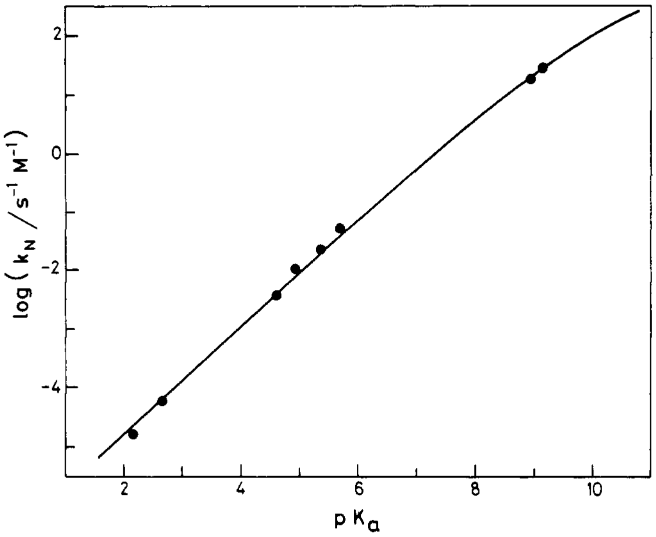
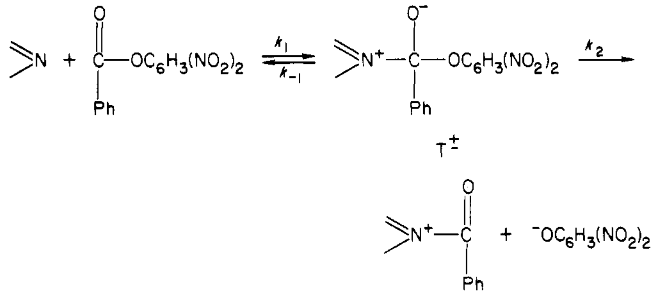


Figure 2. Brønsted-type plot for the pyridinolysis of 2,4-dinitrophenyl benzoate in 44 wt% aqueous ethanol at 25 °C, ionic strength 0.2 M (KCl). The points are experimental and the line was calculated by means of eq 5 with log $k_N^\circ = 1.7$, $pK_a^\circ = 9.5$, $\beta_1 = 0.4$, and $\beta_2 = 0.9$.

Scheme II



standable in terms of both the lower concentration of ethanol compared to water (8.6 M and 27.8 M, respectively) and also the lower basicity of the former in aqueous media.[23] No accumulation of the substituted benzoylpyridinium ion was observed, indicating that the decomposition of this intermediate must be much faster than its formation. This is reasonable in view of the electron-withdrawing effect of the acyl phenyl group which destabilizes the ion. Substitution of phenyl by electron-donating groups such as methoxy or methyl renders the cation less unstable.[2a,5,24]

The Brønsted-type plot obtained in the pyridinolysis of DNPB (with the data of Table II) is shown in Figure 2. The curved plot can be interpreted through the existence of a tetrahedral intermediate in the reaction pathway[3-9] ($T^\pm$ in Scheme II). Applying the steady-state treatment to $T^\pm$ gives $k_N = k_1k_2/(k_{-1} + k_2)$, where k_N is the macroscopic rate constant defined in Scheme I. The curved Brønsted-type plot arises from a change in the rate-determining step from the second one to the first (Scheme II) as the nucleophile becomes more basic.[3-9] Inclusion of 3,4-dimethylpyridine in the Brønsted-type plot (Figure 2), the only disubstituted pyridine in the series, is justified since this pyridine correlates nicely with monosubstituted analogues in linear Brønsted-type plots.[2a,25]

The line in the plot of Figure 2 was calculated by means of a semiempirical relation based on the existence of a tetrahedral intermediate (eq 5),[4,5,7] with the values log k_N°

$$\log (k_N/k_N^\circ) = \beta_2(pK_a - pK_a^\circ) - \log \frac{1+a}{2} \qquad (5)$$

$$\log a = (\beta_2 - \beta_1)(pK_a - pK_a^\circ)$$

$= 1.7$, $pK_a^\circ = 9.5$, $\beta_1 = 0.4$, and $\beta_2 = 0.9$, where pK_a°, β_1, and β_2 were defined in the Introduction, and k_N° is the value of k_N for a (hypothetical) pyridine of $pK_a = pK_a^\circ$. Similar relations have been reported which account for curved Brønsted-type plots.[3,8,24,26] Since the center of the Brønsted curvature is located at $pK_a = 9.5$, it follows that for the reactions of all the substituted pyridines studied in this work the rate-determining step is the second (k_2 of Scheme II), i.e., $k_{-1} > k_2$, although the inequality is not so large for the two aminopyridines.

The Brønsted-type slope obtained (Figure 2) when the second step is rate determining (β_2) is similar to the corresponding ones obtained in the pyridinolyses of 2,4-dinitrophenyl acetate,[4] methyl chloroformate,[5] 2,4-dinitrophenyl methyl carbonate,[7] acetyl chloride[8], and 2,4-dinitrophenyl *p*-nitrobenzoate,[12] and also in the aminolyses of phenyl acetates,[1] acylpyridinium ions,[2a] phthalic and succinic anhydrides,[2b] and aryl phenyl carbonates.[3]

For the reactions under study in this work, the value of the Brønsted-type slope calculated when the first step of Scheme II is rate limiting ($\beta_1 = 0.4$) is slightly higher than the corresponding slopes obtained in most aminolyses reactions,[3-9] but it is similar to those obtained in the aminolyses of acetic anhydride ($\beta_1 = 0.46$)[27] and diethyl pyrocarbonate ($\beta_1 = 0.4$).[28] The higher value of β_1 found in this work compared to the pyridinolyses of 2,4-dinitrophenyl acetate and methyl carbonate may be due to a solvent effect, since the latter reactions were studied in water.

The points corresponding to the six less basic pyridines in the plot of Figure 2 are best fitted to a line of slope $\beta_2 = 1.0$, instead of $\beta_2 = 0.9$. Nevertheless with $\beta_2 = 1.0$ the best fitting parameters to eq 5 for all the eight points are $pK_a^\circ = 8$ and $\beta_1 = 0.4$, but the calculated curve obtained with these parameters has a much smaller slope at $pK_a = 9$ than the experimental one.[29] Moreover, the activation parameters found for the reaction of DNPB with 4-(dimethylamino)pyridine show (as discussed below) that the kinetically important step for this pyridine is the second one (Scheme II), excluding, therefore, the possibility that the center of the Brønsted-type curve be at $pK_a = 8$ and confirming that $pK_a^\circ = 9.5$ for this plot is a more reasonable value.

The Brønsted-type plot obtained in the pyridinolysis of 2,4-dinitrophenyl *p*-nitrobenzoate under the same experimental conditions of the reactions presented in this work is linear.[12] This means that if a tetrahedral intermediate is present in these reactions, the breakdown of this intermediate to products (k_2, Scheme II) is the rate-deter-

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(23) Newall, C. E.; Eastham, A. M. *Can. J. Chem.* **1961**, *39*, 1752. Deno, N. C.; Wisotsky, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 1735.

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(25) Skoog, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 3356. Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.

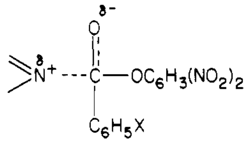
(26) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. Kluger, R.; Hunt, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 5667.

(27) Hartley, B. S.; Shotton, D. M. In "The Enzymes", 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1971; Vol. III, p 371.

(28) Osterman-Golkar, S.; Ehrenberg, L.; Solymosy, F. *Acta Chem. Scand., Ser. B* **1974**, *28*, 215.

(29) Unfortunately, the lack of pyridines more basic than 4-(dimethylamino)pyridine precludes verification of eq 5 in the region where the k_1 step is rate determining. Nevertheless, as pointed out in the text, the "best" fitting parameters to the eight experimental points were those reported in the legend of Figure 2 and which were used to draw the line shown in the plot. No satisfactory fit was observed with other reasonable values for β ($\beta_2 = 0.8, 1.1$; $\beta_1 = 0.1, 0.2, 0.3$).

mining step for all the series of pyridines, and the change in the rate-determining step should occur at $\mathrm{p}K_a >> 9$. The $\mathrm{p}K_a{}^\circ$ value for these reactions obviously cannot be determined with certainty, but it must be $\mathrm{p}K_a{}^\circ > 10$. Comparison of this value with the one found in the pyridinolysis of DNPB ($\mathrm{p}K_a{}^\circ = 9.5$) shows that electron withdrawal from the nonleaving aryl group (R) favors pyridine expulsion from the tetrahedral intermediate relative to 2,4-dinitrophenoxide release, i.e., k_{-1}/k_2 (Scheme II) increases as R becomes more electron withdrawing. This means that the transition state for the k_{-1} step (**1**) is more stabilized by electron withdrawal from R than that for the k_2 step (**2**). The same is found in the reactions of quinuclidines with aryl 3,4-dinitrophenyl carbonates[10] and by comparison of the pyridinolyses of 2,4-dinitrophenyl acetate[4] and methyl carbonate.[7] The electronic effects of the R group in the tetrahedral intermediate are mainly inductive,[11] and the fact that methoxy has an inductive effect more electron withdrawing than methyl[11a] is in agreement with the findings that the $\mathrm{p}K_a{}^\circ$ value for the former reactions is higher than that for the latter (7.8 and 7.3, respectively). Nevertheless, in the reactions of quinuclidines with 2,4-dinitrophenyl phenyl carbonate a value of $\mathrm{p}K_a{}^\circ = 7.5$ was found.[3] This value is not in accord with the above results since the phenoxy group is more electron withdrawing ($\sigma_I = 0.39$)[11a] than methoxy. The discrepancy may be due to the different nature of the amine attached to the tetrahedral intermediate.



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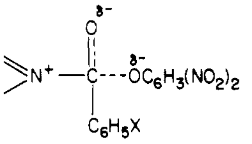
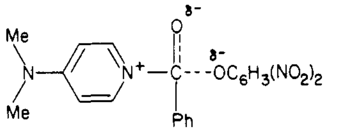


2

The reactions carried out in aqueous ethanol cannot be compared to similar ones (same amine and leaving group in the tetrahedral intermediate) studied in water if the magnitude of the electronic effect of R on $\mathrm{p}K_a{}^\circ$ is to be assessed. The change of solvent from water to aqueous ethanol should increase amine expulsion from the tetrahedral intermediate relative to phenoxide, leading to higher $\mathrm{p}K_a{}^\circ$ values.[10,12] In order to test this point we plan to carry out the pyridinolysis of 2,4-dinitrophenyl acetate and methyl carbonate in aqueous ethanol, in order to compare the Brønsted-type plots obtained with those found in the corresponding reactions in water.[4,7]

Activation Parameters. The values shown for the reaction of DNPB with 3-methylpyridine (Table III) can be explained by assuming that **2** (3-methylpyridine) is the kinetically important transition state. There is full C–N bond formation in **2**, and therefore, large charge development on the pyridine nitrogen atom in going from reactants to **2**, which should result in a rather well solvated transition state relative to reactants. This leads to a rather low $\Delta S^{\ddagger}$ value. Higher values (less negative) are expected for $\Delta S^{\ddagger}$ when the first step of Scheme II is rate determining in view of the partial C–N bond formation and charge development on nitrogen in the corresponding transition state (**1**), leading to a poorly solvated structure compared to **2**.[4]

The activation parameters for the reaction of 4-(dimethylamino)pyridine (Table III) can be accounted for by assumption of the k_2 step of Scheme II being rate determining and considering the two main cannonical forms of the transition state involved (**3** and **4**). Structure **3** should be less solvated than **4** for steric reasons. The proximity of the acyl phenyl group to the positively charged pyridine nitrogen in **3** should hinder solvation by ethanol and water around this charge. This solvation hindrance is confirmed by comparison of the $\Delta S^{\ddagger}$ values found in the reactions of 3-chloro- and 3-methylpyridines with 2,4-dinitrophenyl acetate[4] and benzoate (this work), respectively, when the k_2 step is rate determining. The former reaction, studied in water, has $\Delta S^{\ddagger} = -28.5$ cal K^{-1} mol^{-1}, which is lower than the second one, carried out in aqueous ethanol (Table III). Considering that $\Delta S^{\ddagger}$ for aminolysis reactions are, in general, more negative in the less polar solvents,[30] the $\Delta S^{\ddagger}$ value for the reaction of the acetate derivative should be even smaller in aqueous ethanol. This means that the transition state for the acetate reactions should be more solvated (relative to reactants) than the corresponding structures for the benzoate reactions (**2** or **3**). According to this, **4** should be more solvated than **3** since for the former the main solvation site is at the exocyclic nitrogen atom, far from the phenyl group. The higher solvation of **4** and the contribution of this structure to the hybrid transition state should be responsible for the lower $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values found in the reaction of DNPB with 4-(dimethylamino)pyridine compared with that of 3-methylpyridine. We believe that the activation parameters for the former reaction confirm that the center of the curvature of the Brønsted-type plot obtained in this work lies at basicity values higher than that of 4-(dimethylamino)pyridine, i.e., for the reaction of this pyridine with DNPB the rate-determining step is still the decomposition of the tetrahedral intermediate to give products.



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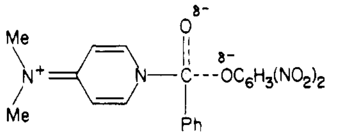

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Registry No. 2,4-Dinitrophenyl benzoate, 1523-15-5; 3-chloropyridine, 109-09-1; 3-carbamoylpyridine, 98-92-0; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; 3-chloropyridinium, 53760-42-2; 3-carbamoylpyridinium, 38719-50-5; pyridinium, 16969-45-2; 3-methylpyridinium, 17203-41-7; 4-methylpyridinium, 16950-21-3; 3,4-dimethylpyridinium, 66881-16-1; 4-(dimethylamino)pyridinium, 55277-36-6; 4-aminopyridinium, 33825-39-7; dihydrogen phosphate, 14066-20-7.

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(30) Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; p 138.