Kinetics of Hydrolysis and Aminolysis of 1-Methoxycarbonylpyridinium Ions

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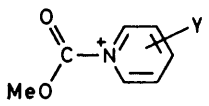
Rate constants are reported for reactions of 1-methoxycarbonylpyridinium ions in aqueous solution with water, hydroxide ion, and primary and secondary amines. The water reaction is general base-catalysed; solvent isotope effects are reported. Both the water and hydroxide reactions proceed with rate-determining formation of a tetrahedral intermediate. With the primary and secondary amines, either formation or breakdown of a tetrahedral intermediate is rate-determining, depending upon the ring substituent. Structure–reactivity plots lead to estimates of relative leaving-group abilities, which are compared with others in the literature. Hydroxide-ion catalysed aminolysis is observed in some cases, and occurs by a concerted mechanism.

THE reaction of substituted pyridines with methyl chloroformate [1] leads in the first instance to 1-methoxycarbonylpyridinium ions (1) [equation (i)] which react



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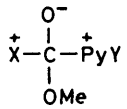


(2)

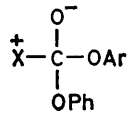
further by hydrolysis and (in the presence of a primary or secondary amine) aminolysis [equation (ii)]. The dependence of k_n upon the substituent Y has been studied, and

$$MeOCOCl + YPy \xrightarrow{k_n} MeOCO\overset{+}{P}yY + Cl \qquad (i)$$

$$MeOCO\overset{+}{P}yY \xrightarrow{k} Products \qquad (ii)$$

the change in slope of the Brønsted plot attributed to a change in rate-determining step from formation to breakdown of a tetrahedral intermediate (2; X = Cl^-). The bend of the Brønsted plot comes where the substituted pyridines have comparable leaving ability to chloride ion. A similar study [2] of the reaction of 2,4-dinitrophenyl methyl carbonate with substituted pyridines has permitted a comparison of the relative leaving-group abilities of 2,4-dinitrophenolate anion and substituted pyridines.

3- and 4-substituted pyridines offer a wide range of reactivities with the minimum of significant structural change, with which to explore relative leaving-group abilities. They can provide either a series of nucleophiles as just described, or a series of electrophilic reagents (ring-substituted 1-acylpyridinium ions) which react with a common nucleophile as in the work described in this paper. From either sort of study, changes in the slopes of structure–reactivity profiles can be used as shown below to give directly comparable measures of leaving-group abilities from (2) of various nucleophiles relative to a reference substituted pyridine (chosen as 4-dimethylaminopyridine). These can be compared with other measures of leaving-group ability. Gresser and Jencks [3,4] have demonstrated the intermediacy of (3) (X = substituted quinuclidine, 4-dimethylaminopyridine, or 1-methylimidazole) in the reaction of diaryl carbonates with these bases, or of aryloxycarbonylquinuclidinium ions with arylate anions, and assessed leaving group abilities of the amines relative to arylate anions. Leaving-group abilities relative to phenolate anion from intermediates like (3) (Me instead of OAr) have been estimated also by Ritchie.[5]



(3)

RESULTS

Reactions of Amines with Methyl Chloroformate.—Second-order rate constants are in Table 1 and supplement previous data.[1,6] The values for 3-acetyl- and 4-methoxypyridine fall near the curve of log k_n against pK_a previously drawn for other substituted pyridines.[1] The values for morpholine and piperidine are somewhat larger than those of both primary amines [6] and pyridines [1] of similar pK_a, but the Brønsted slope between them (0.23) is similar.

The Kinetics of Hydrolysis of Ring-substituted 1-Methoxycarbonylpyridinium Ions.—It was found that as with 1-acetylpyridinium ions [7] the observed first-order rate constant k for decomposition of the ion was given by

TABLE 1

Rate constants k_n for reaction of methyl chloroformate with amines in water at 25 °C and ionic strength 0.2 mol dm^{-3}

Amine	Total amine concentration / mol dm^{-3}	pH	Number of runs	k_n [a] / mol^{-1} dm^3 s^{-1}
3-Acetylpyridine	$1—8 \times 10^{-4}$	4.96	5	15.5 (±1)
4-Methoxypyridine	0.01	4.08—4.31	4	177 (±7)
Morpholine	0.02—0.2	3.93—4.61	13	990 (±30)
Piperidine	0.2	5.37—6.33	11	4 300 (±1 000)

[a] Errors are standard errors from the weighted mean.[6]

TABLE 2

Rate constants k_w, k_{OH}, and k_b for the hydrolysis of 1-methoxycarbonyl-Y-pyridinium ions in water at 25 °C and ionic strength 0.2 mol dm^{-3}

Substituent Y	pK_a [a]	pH	Total pyridine concentration / mol dm^{-3}	λ [b] / nm	Number of runs	k_w [c] / s^{-1}	k_{OH} [c] / mol^{-1} dm^3 s^{-1}	k_b [c] / mol^{-1} dm^3 s^{-1}	β [d]
3-Chloro	2.98	2.98	0.2	294	10	0.141 (±0.05)	*e*	*e*	
3-Acetyl	3.32	3.9	0.04 —0.1	358	8	0.073 (±0.003)	*e*	*e*	
No substituent	5.32	5.37—6.93	0.02 —0.38	275	20	0.035 (±0.001)	3.0 (±0.1) × 10^5	0.104 (±0.005)	0.31
4-Methyl	6.15	5.46—6.80	0.04 —0.40	285	8	0.0125 (±0.001)	1.1 (±0.1) × 10^5	0.12 (±0.01)	0.35
4-Methoxy	6.66	0.80—1.10 and 6.13—6.50	0.005—0.05	266	10	2.06 (±0.04) × 10^{-3}	2.78 (±0.06) × 10^4	0.038 (±0.004)	0.36
4-(2,2,2-Trifluoroethylamino)	8.55	1.0—2.0 and 8.27—8.62	0.005—0.02	304	18	9.4 (±0.4) × 10^{-5}	2 320 (±60)	0.12 (±0.04)	0.47
4-(4-Morpholino)	8.77	1.0—2.0 and 8.40—8.80	0.005—0.02	335	16	3.7 (±0.2) × 10^{-5}	1 110 (±50)	0.14 (±0.05)	0.51
4-Amino	9.15	0.92—1.41 and 8.58—9.31	0.003—0.03	296	15	3.3 (±0.1) × 10^{-5}	1 010 (±20)	*e*	
4-Dimethylamino	9.55	0.8—1.45 and 9.12—9.18	0.005—0.05	324	13	1.91 (±0.1) × 10^{-5}	750 (±40)	*e*	

[a] Of Y-pyridinium ion at an ionic strength of 0.2 mol dm^{-3}. [b] Wavelength used for kinetic studies. [c] Errors are standard errors. [d] Slope of the Brønsted plot for general base catalysis (see Discussion section). [e] Contributions from this term too small for rate constant determination under the conditions used.

equation (iii). The last term represents general base-catalysis by the free-base form of the pyridine, concentration $[Py]_{f.b.}$. The substituted pyridine was used as a

$$k = k_w + k_{OH}[OH^-] + k_b[Py]_{f.b.} \quad \text{(iii)}$$

buffer for the reaction. The initial concentration of methyl chloroformate was always at least 20-fold less than that of the buffer component present in the small concentration. The analysis to obtain the rate constants k_w, k_{OH}, and k_b varied with the ring substituent Y. With 3-chloropyridine and 3-acetylpyridine, only k_w was significant and was obtained directly. With pyridine, the $[OH^-]$ term was found to contribute negligibly at pH <5.4, and k_w and k_b were obtained from intercept and slope of a plot of k against $[Py]_{f.b.}$. The latter concentration was taken as high as practically possible (0.02 mol dm^{-3}) to check whether the general base-catalysis were limited in extent. The plot remained linear and no such limitation was found. The rate constant k_{OH} was then found using buffers of higher pH. With pyridine also, some studies were made of specific effects of various salts used to maintain constant ionic strength. The rate constants were found to be insensitive within experimental error to the cation (pyridinium, tetramethylammonium, potassium) but the use of perchlorate (as previously [1]) rather than chloride (as here) as the anion reduced k_w by *ca.* 10%. All rate constants reported in this paper refer to an ionic strength of 0.2 mol dm^{-3} with chloride as the predominant anion.

For the more basic pyridines equation (iii) was rearranged to equation (iv), plots of the left hand side of which against $([Py]_{f.b.}/[OH^-])$ gave k_{OH} and k_b from intercept and slope respectively. The value of k_w for each of these pyridines

$$(k - k_w)/[OH^-] = k_{OH} + k_b([Py]_{f.b.}/[OH^-]) \quad \text{(iv)}$$

was separately determined by pre-forming the ion in the pyridine buffer, then acidifying to render the contributions of the last two terms on the right of equation (iii) negligible. Close agreement between rate constants at different values of pH in the range 0.8—2.0 demonstrated the absence of acid catalysis, as expected from previous studies of the hydrolysis of 1-methoxycarbonylpyridinium ion in moderately concentrated aqueous sulphuric acid.[8] Experimental conditions and rate constants k_w, k_{OH}, and k_b are given in Table 2. When calculating the concentration of free-base pyridine or 4-methylpyridine account was taken of association by dimerisation using the association constants reported.[7]

Solvent Isotope Effects on k_w.—These were studied in the cases of the 1-methoxycarbonyl-3-chloro- and 1-methoxycarbonyl-4-dimethylamino-pyridinium ions. Rate constants and conditions are in Table 3.

The Kinetics of Aminolysis of Ring-substituted 1-*Methoxycarbonylpyridinium Ions*.—In the presence of a primary or secondary amine, the decomposition of the 1-methoxycarbonylpyridinium ion (1) is partly diverted to carbamate formation. The substituted pyridine was again used as a buffer, to which methyl chloroformate was added, but there

TABLE 3

Rate constants k_w for the hydrolysis of 1-methoxycarbonyl-Y-pyridinium ions in H_2O–D_2O mixtures at 25 °C and ionic strength 0.2 mol dm^{-3}

Atom fraction deuterium	(k_w/s^{-1}) [a]	(k_w/k_w^H) [b]	
	Y = 3-Chloro		
0	0.141	(1)	
0.25	0.122	0.86	
0.5	0.096	0.68	
0.75	0.079	0.56	
1.0	0.049	0.35	
	Y = 4-Dimethylamino		
0	1.91 × 10^{-5}	(1)	
0.2	1.56 × 10^{-5}	0.82	(0.82) [c]
0.5	1.10 × 10^{-5}	0.58	(0.59) [c]
0.8	0.81 × 10^{-5}	0.42	(0.39) [c]
1.0	0.54 × 10^{-5}	0.28	(0.28) [c]

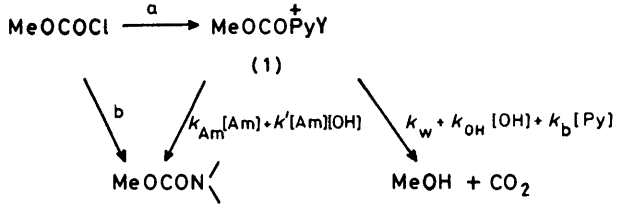
[a] Mean of two or three runs. [b] The value of k_w divided by that for H_2O. [c] Calculated values using the fractionation factors suggested by Schowen [12] (see Discussion section).

was present an appropriate concentration of the amine. Conditions were such that formation of (1) was much faster than its decomposition, and the decay of absorbance due to (1) was accurately first order giving an observed first-order rate constant k. Any direct reaction of amine with methyl chloroformate (step b in Scheme 1) was without effect on the observed kinetics, but it was known from the rate constants for steps a and b (Table 1 and refs. 1 and 6) that this was generally small in extent. The total concentration of amine was at least 20-fold in excess of the initial concentration of methyl chloroformate.

The rate constant k was found to be given by equation (v) ($[Am]_{f.b.}$ is the concentration of amine free-base). Plots of

$$k = k_w + k_{OH}[OH^-] + k_b[Py]_{f.b.} + k_{Am}[Am]_{f.b.} + k'[Am]_{f.b.}[OH^-] \quad (v)$$

($k_2 - k_w - k_{OH}[OH^-] - k_b[Py]_{f.b.}$) against $[Am]_{f.b.}$ for a series of runs at the same pH were straight lines through the origin.



SCHEME 1

In the cases where the amine was morpholine, and the pyridine ring substituent substituted amino, the slopes of these lines were detectably pH-dependent. The data in Figure 1 are representative. In these cases plots of slopes against $[OH^-]$ gave values of k_{Am} and k' from intercept and slope. The k' term made only a small contribution to the overall kinetics, and values are subject to larger errors than values of k_{Am} (Table 4).

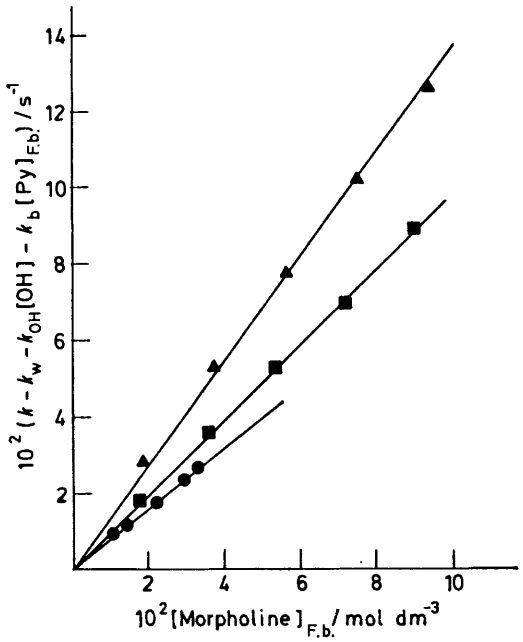


FIGURE 1 Plot of $10^2(k - k_w - k_{OH}[OH] - k_b[Py]_{f.b.})/s^{-1}$ against concentration of free-base morpholine in its reaction with 1-methoxycarbonyl-4-dimethylaminopyridinium ion at pH 8.91 (circles), 9.41 (squares), and 9.695 (triangles)

TABLE 4

Rate constants k_{Am} and k' for aminolysis of 1-methoxycarbonyl-Y-pyridinium ions in water at 25 °C and at ionic strength 0.2 mol dm^{-3}

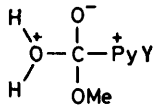
Substituent Y	pH	Total pyridine concentration / mol dm^{-3}	Total amine concentration / mol dm^{-3}	No. of runs	k_{Am} [a] / mol^{-1} dm^3 s^{-1}	k' [a] / mol^{-2} dm^6 s^{-1}
			Propylamine (pK_a 10.68) [b]			
None	5.93	0.05	0.05 —0.12	10	4.24 (±0.08) × 10^4	
4-Methyl	6.48	0.04	0.02 —0.07	10	1.85 (±0.07) × 10^4	
4-Methoxy	6.73	0.05	0.05 —0.13	10	5.66 (±0.08) × 10^3	
4-(2,2,2-Trifluorethylamino)	8.17—8.40	0.02	0.01 —0.05	8	530 (±20)	
4-(4-Morpholino)	8.53—8.68	0.02	0.007—0.028	10	250 (±10)	
4-Amino	8.96—9.57	0.05	0.002—0.024	14	220 (±10)	
4-Dimethylamino	8.95—9.16	0.10	0.005—0.015	5	95 (±7)	
			Morpholine (pK_a 8.47) [b]			
None	4.70	0.10	0.01 —0.05	8	1.32 (±0.08) × 10^4	
4-Methyl	5.48	0.10	0.01	5	6.3 (±0.5) × 10^3	
4-Methoxy	5.88—6.18	0.05	0.001—0.005	14	2 150 (±30)	
4-(2,2,2-Trifluoroethylamino)	8.15—8.57	0.02	0.002—0.01	18	18 (±2)	1.0 (±0.2) × 10^6
4-(4-Morpholino)	8.57—9.13	0.02	0.005—0.025	22	3.5 (±0.2)	8.5 (±1) × 10^4
4-Amino	8.56—9.29	0.05—0.10	0.007—0.05	30	2.2 (±0.3)	3.7 (±1.5) × 10^4
4-Dimethylamino	8.91—9.695	0.05—0.10	0.015—0.10	30	0.67 (±0.06)	1.0 (±0.1) × 10^4
			Piperidine (pK_a 11.26) [b]			
None	6.33	0.05	0.01 —0.03	10	3.58 (±0.05) × 10^5	
4-Methyl	5.83	0.04	0.05 —0.10	8	2.01 (±0.05) × 10^5	
4-Methoxy	6.08	0.05	0.01 —0.04	8	5.1 (±0.1) × 10^4	
4-(2,2,2-Trifluoroethylamino)	8.09	0.02	0.005—0.02	8	2 960 (±50)	
4-(4-Morpholino)	8.50	0.02	0.007—0.025	8	860 (±30)	
4-Amino	8.65	0.05	0.002—0.01	10	690 (±20)	
4-Dimethylamino	9.10—9.69	0.02—0.05	0.002—0.01	16	185 (±20)	
			Hydrazine (pK_a 8.15) [b]			
None	4.35	0.10	0.002—0.008	8	7.5 (±0.3) × 10^4	

[a] See equation (v). Errors are standard errors. [b] At ionic strength 0.2 mol dm^{-3}.

The concentration of free-base morpholine was taken as high as practically possible in some cases, to check for the presence of a second-order term in morpholine, but no such term was found.

DISCUSSION

The Hydrolysis of Ring-substituted 1-*Methoxycarbonylpyridinium Ions.*—log (k_w/s^{-1}) *versus* pK_a of the conjugate acid of the leaving pyridine is plotted in Figure 2. There is scatter and apparent curvature in the plot. The possibility was considered that the curvature was due to a change, with decreasing leaving-group ability of the substituted pyridine, from rate-determining formation to rate-determining breakdown of the intermediate (4).



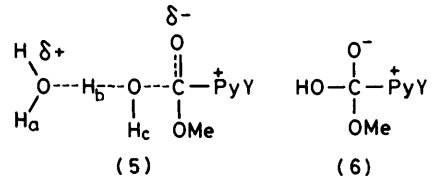
(4)

Such an intermediate might not live long enough for proton equilibration among its basic sites, as in the aminolysis of reactive acyl compounds.[9] The rate-determining step would depend upon whether water or substituted pyridine were expelled from it more easily. It is now known that from several electrophilic centres oxygen bases are much poorer leaving groups than nitrogen bases of the same pK_a,[3-5,10] so that comparable leaving-group ability of water and a substituted pyridine of pK_a *ca.* 5, as the region of curvature of the Brønsted plot (Figure 2) would suggest, is not wholly unreasonable. However, we reject the conclusion that (4) is an intermediate for three reasons.

(1) If such an intermediate were involved, then the general base-catalysis by free-base pyridine would have to be due to proton removal from the intermediate (4), preventing water expulsion and regression to reactants. Such catalysis should be limited in extent, the maximally enhanced rate being that where formation of (4) has become rate-determining. For the unsubstituted pyridine there was no sign of such limitation (see Results section).

(2) The slope of the plot of the log (k_{OH}/mol^{-1} dm ^{3}s^{-1}) *versus* pK_a, also shown in Figure 2 would be expected, since OH^- is a worse leaving group than H_2O, to be similar to that part of the plot of log (k_w/s^{-1}) where formation of (4) is supposed to be rate-limiting. In fact the slope is much closer to that of the right-hand portion.

(3) The solvent isotope effect is considerable (Table 3) and similar for the decomposition of 1-methoxycarbonyl-3-chloro- and 1-methoxycarbonyl-4-dimethylamino-pyridinium ions, the most and the least reactive ions studied, respectively. The values of k_w^H/k_w^D are 2.9 and 3.6, respectively. The similarity of the effect suggests a common rate-determining step for both compounds and its magnitude suggests that in it there is a proton ' in flight '. The variations of the rate constants with the atom fraction of deuterium in the case of the 3-chloro-compound is within experimental error linear, but the experimental errors were large because of the short half-life (5—15 s) of the reaction. In the case of the 4-dimethylamino-compound the deviations from a linear dependence are significant. Both the overall magnitude of the effect and the dependence upon the atom fraction of deuterium [11,12] are wholly in accord with a transition state of structure (5) for the water reaction. Using the

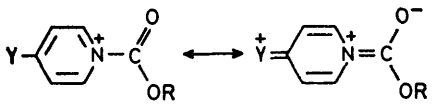


(5) (6)

fractionation factors suggested by Schowen [12] for this type of transition state (ϕ_a 0.83, ϕ_b 0,4, ϕ_c 1) the values of k_w/k_w^H in parentheses in Table 3 were calculated, and are seen to be very close to the observed values.

We therefore conclude that the reaction with water does not proceed through the intermediate (4) but through transition state (5) to form intermediate (6). Reactions of water with many other electrophilic centres are thought to proceed in the same way.[11-14]

The curvature of the Brønsted plot for water (Figure 2) remains unexplained. Fersht and Jencks [7] suggested in the case of 1-acetylpyridinium ions that electron-releasing substituents in the 4-position can stabilise such ions by an interaction not available for the stabilisation of the protonated pyridines and therefore not reflected in the pK_a (Scheme 2). This gives a more satisfactory explanation for the curvature in Figure 2.



SCHEME 2

The general base-catalysis arises because the substituted pyridine can play the role of the left-hand water molecule in (5). It is not possible to study general base-catalysis with other bases, because nucleophilic reaction would interfere. (Nucleophilic reaction by the substituted pyridine regenerates the same ion.) From the water reaction and the substituted pyridine general

$$\beta = [\log (55.5 \text{ mol dm}^{-3}\ k_b/k_w)]/(pK_a + 1.74) \quad \text{(vi)}$$

base reaction it is possible to calculate a Brønsted β value for the general base catalysis using equation (vi). These are in Table 2. β Increases with decreasing reactivity, suggesting that transfer of proton (b) in transition state (5) is more complete with less reactive 1-methoxycarbonylpyridinium ions. A similar effect is found in the hydration of triarylcarbonium ions.[14] In each case the value of k_{OH} is too great to fit on the Brønsted plot for k_w and k_b, showing that the hydroxide ion acts as a nucleophile and not as a general base.

TABLE 5

Values of log $K^{\ddagger}$ for several leaving groups X

X	pK_a [a]	log ($k_{Am}°$/mol^{-1} dm^3 s^{-1}) [b]	log ($k_{OH}°$/mol^{-1} dm^3 s^{-1}) [b]	log $K^{\ddagger}$
4-Dimethylaminopyridine	9.55	—		(0) [c]
Morpholine	8.47	2.36	3.57	2.3
Piperidine	11.26	3.59	3.26	1.3
Propylamine	10.68	2.42	3.04	0.5
Phenolate [d]	9.81			<-1.3
4-Nitrophenolate [d]	7.09			(−0.6)
2,4-Dinitrophenolate [e]	4.00			1.2
Chloride [f]				3.4

[a] Of the conjugate acid of X at 0.2 mol dm^{-3} ionic strength. [b] See equation (viii). [c] By definition. [d] From ref. 4. [e] From ref. 2. [f] From ref. 1.

The Uncatalysed Aminolysis of Ring-substituted 1-Methoxycarbonylpyridinium Ions.—The pK_a of the conjugate acid of the leaving pyridine is an unsatisfactory basis for the comparison of the reactivity of these ions (see above). Values of log (k_{Am}/mol^{-1} dm^3 s^{-1}) and log k_w/s^{-1} are plotted instead against log (k_{OH}/mol^{-1} dm^3 s^{-1}) in Figure 3. The plot of log (k_w/s^{-1}) is linear. In contrast the plots of log (k_{Am}/mol^{-1} dm^3 s^{-1}) show sharp curvature for each of the amines studied. This suggests a change with increasing reactivity of the 1-methoxycarbonylpyridinium ion from rate-determining breakdown to rate-determining formation of intermediate (2) (Scheme 3).

For the more reactive 1-methoxycarbonylpyridinium ions, $k_{-1} \ll k_2$ and $k_{Am} = k_1$ [see equation (vii)]. The

$$k_{Am} = k_1k_2/(k_{-1} + k_2) \qquad \text{(vii)}$$

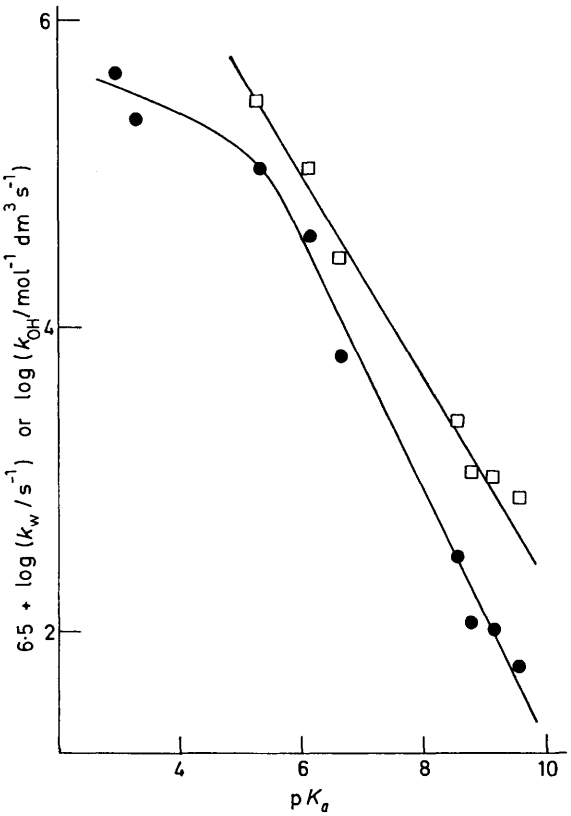
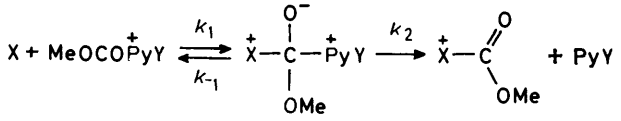


FIGURE 2 Plots of 6.5 + log (k_w/s^{-1}) (full circles) and log (k_{OH}/mol^{-1} dm^3 s^{-1}) (open squares) against pK_a of the conjugate acid of the substituted pyridine for the hydrolysis of 1-methoxycarbonyl-Y-pyridinium ions

slope of the plot of log (k_{Am}/mol dm^{-3} s^{-1}) against log (k_{OH}/mol^{-1} dm^3 s^{-1}) is called γ_1 (slope of the upper linear parts of the curves in Figure 3). For the less reactive ions $k_{Am} = k_1k_2/k_{-1}$, and the slope is γ_2. The equation of



(2)

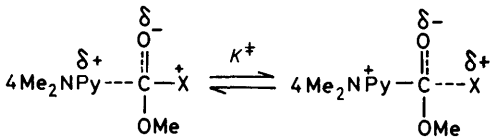
SCHEME 3

the whole curve is then (viii). A similar equation was used previously.[1]

$$\log (k_{Am}/k_{Am}°) = \gamma_2 \log (k_{OH}/k_{OH}°) - \log\left[\frac{1 + 10^{(\gamma_2-\gamma_1)\log(k_{OH}/k_{OH}°)}}{2}\right] \qquad \text{(viii)}$$

This equation was used to generate the solid lines in Figure 3, and γ_1 and γ_2 were taken as 0.77 and 4.09, respectively, for all the amines. Rate constants $k_{Am}°$ and $k_{OH}°$ refer to the hypothetical substituted 1-methoxycarbonylpyridinium ion for which $k_{-1} = k_2$. Values are in Table 5. The fit to equation (viii) is seen to be very satisfactory, suggesting that the mechanism (Scheme 3) is correct. Species (2) is too short-lived for proton loss, gain, or transfer.[9]

Leaving-group abilities from (2) relative to 4-dimethylaminopyridine can be measured as log (k_{-1}/k_2) which is the vertical gap between the extrapolated linear extremes of the curves at the value of k_{OH} for the 1-methoxycarbonyl-4-dimethylaminopyridinium ion ($k_{OH}^{4NMe_2}$). This is indicated for piperidine by the pecked vertical line in Figure 3. This quantity is [4] the logarithm of the equilibrium constant $K^{\ddagger}$ between the transition states (7) and (8) for breakdown and formation



(7) (8)

of (2). It may be evaluated algebraically using equation (ix). Values are in Table 5. Those for X = 2,4-dini-

$$\log K^{\ddagger} = \log(k_{-1}/k_2) = (\gamma_2 - \gamma_1)\log (k_{OH}°/k_{OH}^{NMe_2}) \qquad \text{(ix)}$$

trophenolate and chloride ions are deduced in a similar manner but using the (bent) Brønsted plots for nucleophilic attack of a series of substituted pyridines on methyl 2,4-dinitrophenyl carbonate [2] and methyl chloroformate.[1] The limiting value for phenolate comes from the observation [4] that (2) (X = ÕPh, Y = 4-NMe_2),

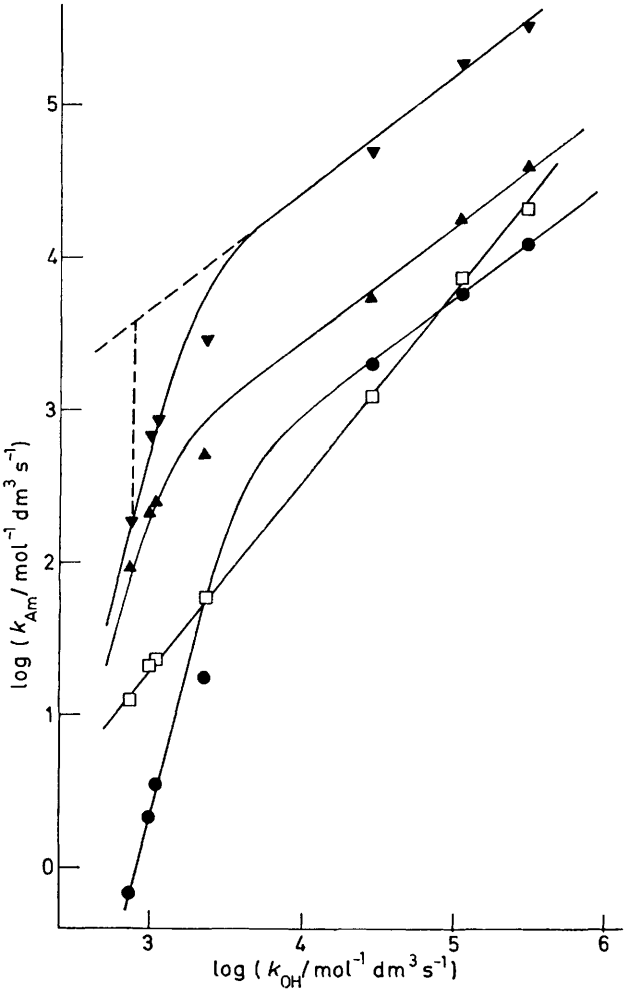


FIGURE 3 Plots of log (k_{Am}/mol^{-1} dm^3 s^{-1}) against log (k_{OH}/mol^{-1} dm^3 s^{-1}) for the aminolysis of 1-methoxycarbonyl-Y-pyridinium ions by morpholine (circles), propylamine (upright triangles), and piperidine (inverted triangles). The open squares are for 5.8 + log (k_w/s^{-1}) against log (k_{OH}/mol^{-1} dm^3 s^{-1})

generated by attack of methoxide ion on 1-phenoxycarbonyl-4-dimethylaminopyridinium ion, partitions >95% in favour of methyl phenyl carbonate. The value for 4-nitrophenolate obtained similarly [4] is not strictly comparable because it relates to transfer of phenoxycarbonyl rather than methoxycarbonyl.

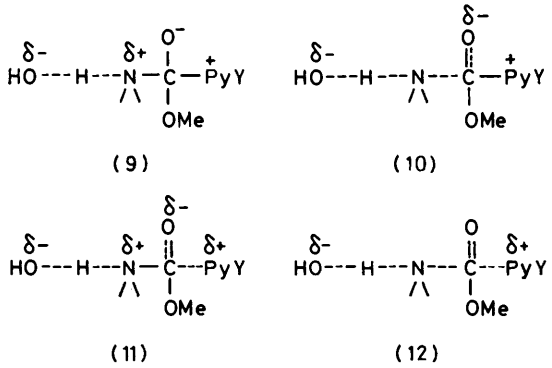
Comparing first morpholine and piperidine because of their close structural similarity, it is evident that the difference in pK_a (*ca.* 3 units) produces a much smaller difference (*ca.* 1 unit) in log $K^{\ddagger}$. This is expected since (2) is an unstable intermediate which transition states (7) and (8) should both resemble. The charge changes on the nitrogen atoms are expected to be fractional.

Piperidine is a better leaving group (bigger log $K^{\ddagger}$) than propylamine in spite of its higher pK_a. This may be a steric effect. The relative leaving-group abilities of propylamine, piperidine, and morpholine are similar to those deduced by Ritchie [5] by empirical fitting of data for several ester aminolyses. [Ritchie's values of (log k_{-x}) are those for log $K^{\ddagger}$ for the equilibrium between transition states (7) and (8) (PhÕ in place of 4-NMe_2Py, Me in place of MeO).] Both piperidine and propylamine are better leaving groups than 4-dimethylaminopyridine though their pK_a values would suggest otherwise. 4-Dimethylaminopyridine is a worse leaving group also than an aliphatic tertiary amine of similar pK_a.[4] This may be because [4] in transition state (8) there is some development of the type of resonance stabilisation depicted in Scheme 2.

log $K^{\ddagger}$ for 2,4-dinitrophenolate is like that for piperidine, though their pK_a values differ by >7 units. The poor leaving group ability of aryloxide anions relative to amines is well documented,[3-5,10] but the effect is greater in the present case possibly because the expulsion of aryloxide from (2, X = ÕAr) involves charge separation whereas it does not for instance from (3).[3,4]

The pK_a of the conjugate acid of the leaving group is clearly a very poor guide to leaving-group ability unless attention is restricted to groups of closely similar structure. There can be no unique scale or order of leaving group abilities but comparisons amongst various measures help to show the factors which govern relative leaving group abilities in particular circumstances.

The Hydroxide-ion-catalysed Aminolysis of Ring-substituted 1-Methoxycarbonylpyridinium Ions.—Possibilities for the transition state for the k' pathway [equation (v)] are (9)—(12). In (9), the rate-determining step is the loss of a proton from the tetrahedral intermediate (2). This should occur at or close to the diffusion-limited rate either to hydroxide or to a second molecule of amine, and the latter is present in greater concentration. The absence of a term second-order in amine rules out this pathway. In (9) and (10) departure of the leaving group has not begun and the sensitivity of



k' to the pyridine substituent Y should be like that of k_w and k_{OH} (Table 2). In fact k' for morphinolysis (Table 4) is more sensitive even than k_{Am} to the substituent Y under conditions where the latter represents rate-determining breakdown of (2) through (8). This makes

(9) and (10) unlikely as transition states for the k' pathway.

Transition state (11), in which expulsion of PyY from (2) is catalysed by hydroxide ion, can also be excluded. Since (2) does not live long enough to encounter a second molecule of amine even when the concentration of the latter is 0.1 mol dm^{-3}, its uncatalysed expulsion of amine must have a rate constant of greater than *ca.* 10^9 s^{-1}. Even when Y = 4-NMe_2, the expulsion of the substituted pyridine is not more than *ca.* 10^2 slower than that of the amine (Table 5). Transition state (11) could not therefore be formed at pH 9 by encounter of (2) with hydroxide, it would require the formation of (2) to have hydroxide as a 'spectator'.[14] The probability that OH^- replaces H_2O in the solvent cage of (2) at pH 9 is $<10^{-6}$, so that the rate constant for hydroxide-ion-catalysed breakdown of (2) through (11) would need to be greater than 10^{13} s^{-1} to compete with the uncatalysed breakdown of (2), which is unrealistic.

The most reasonable mechanism therefore appears to be the fully concerted process through transition state (12), which bypasses any form of tetrahedral intermediate. A similar conclusion has been reached concerning the general base-catalysed hydrazinolysis of the 1-acetylimidazolium ion.[15] The absence of a detectable k' term for piperidine and propylamine indicates that it is much less sensitive to the nature of the amine than is k_{Am}, in accord with transition state (12).

EXPERIMENTAL

Materials.—Methyl chloroformate, acetonitrile, 3-chloro-, 4-methyl-, 4-amino-, and 4-dimethylamino-pyridines were purified as previously. Morpholine piperidine and propylamine were purified by distillation. Because of traces of pyridine in the commercial piperidine, the hydrochloride was used for the studies of the reaction of piperidine with methyl chloroformate and purified by recrystallisation (3×) from ethanol. 4-Methoxypyridine was prepared from its 1-oxide by the method of Ochiai [16] and purified by distillation. Hydrazinium hydrogen sulphate (B.D.H. AnalaR) was used as supplied.

4-(4-Morpholino)pyridine.—Chloropyridine-1-oxide (46 g) (prepared from 4-nitropyridine-1-oxide [16]), morpholine (46 g) and water (70 cm^3) were heated together in a sealed tube at 160 °C for 5 h, then cooled to 0 °C. The mixture was made alkaline with solid Na_2CO_3 and filtered. The filtrate was extracted continuously for 16 h with chloroform. Removal of chloroform from the dried ($MgSO_4$) extract left 4-(4-morpholino)pyridine 1-oxide (12 g) which was recrystallised from acetone, m.p. 74—77 °C (lit.,[16] 75—78 °C). Treatment with PCl_3 [16] gave 4-(4-morpholino)pyridine (8 g) which was recrystallised [light petroleum (b.p. 60—80 °C)] as white crystals, m.p. 103—106 °C (lit.,[16] 101—104 °C) (Found: C, 65.6; H, 7.1; N, 16.9. Calc. for $C_9H_{12}N_2O$: C, 65.8; H, 7.4; N, 17.1%).

4-(2,2,2-Trifluoroethylamino)pyridine.—This was prepared similarly from 4-chloropyridine 1-oxide (15 g) 2,2,2-trifluoroethylamine hydrochloride (20 g), sodium hydroxide (6 g), and water (35 g), by heating in a sealed tube at 150 °C for 90 h. Extraction as above and vacuum sublimation gave 4-(2,2,2-trifluoroethylamino)pyridine 1-oxide, δ ($CDCl_3$) 3.90 (2 H, m, CH_2), 5.10br (1 H, s, N-H), 6.76 (2 H, d, aromatic), and 8.50 (2 H, d, aromatic). On addition of D_2O the signal at δ 5.10 disappeared and the multiplet at δ 3.90 collapsed to a quartet. Treatment with PCl_3 [16] and crystallisation of the product from light petroleum (60—80 °C)–acetone (10 : 1) gave white crystals of 4-(2,2,2-*trifluoroethylamino*)*pyridine* (3.7 g), m.p. 156—158 °C (Found: C, 47.8; H, 4.2; N, 15.8. $C_7H_7F_3N_2$ requires C, 47.7; H, 4.0; N, 15.9%); δ ($CDCl_3$) 3.78 (2 H, m, CH_2), 5.30br (1 H, s, N-H), 6.56 (2 H, d, aromatic), and 8.30 (2 H, d, aromatic). On addition of D_2O the signal at δ 5.30 disappeared and the multiplet at δ 3.78 collapsed to a quartet, *m/e* 176, 107, and 78.

Kinetics.—Rate constants k_n [equation (i)] were determined by the pH-stat method previously described. Rate constants k for decomposition of the substituted 1-methoxycarbonylpyridinium ions were determined spectrophotometrically, using a wavelength at which absorption was due only to that species. The ion was formed *in situ* by the addition of methyl chloroformate dissolved in acetonitrile (15—20 μl) to the aqueous pyridine buffer, in a silica gel, in the thermostatted cell compartment of an SP 1800 spectrophotometer. Conditions were always such that $k_n[Py] \gg k$. Formation of the ion was therefore much more rapid than its decay, and the latter was accurately first-order in all cases. The uncatalysed reactions with water of the 1-methoxycarbonyl-4-Y-pyridinium ions (Y = amino, dimethylamino, 4-morpholino, 2,2,2-trifluoroethylamino, and methoxy) were studied by pre-forming the ions in the pyridine buffer in the sample cell of the pH meter at 25 °C, then adding acid to bring the pH to 1—2. Spectrophotometric observation was then as above. A non-linear least-squares computer program was used to obtain the first-order rate constants.

Product Studies.—The reaction of methyl chloroformate with amines in aqueous solution was previously shown to give the expected carbamate. The following experiment chosen as representative, shows that the reaction of the amine with the 1-methoxycarbonylpyridinium ion also gives the carbamate. To an aqueous solution containing pyridine (0.085 mol dm^{-3}), morpholine (0.047 mol dm^{-3}), and hydrochloric acid (0.1 mol dm^{-3}) was added methyl chloroformate (0.17 g). The resulting solution after 5 min was mixed with solutions of sodium chloride (2 mol dm^{-3}, 50 cm^3) and hydrochloric acid (0.2 mol dm^{-3}, 50 cm^3). A solution of methyl *N*-phenylcarbamate in dichloromethane (0.14 mol dm^{-3}, 5 cm^3) was then added as an internal standard. The solution was extracted with dichloromethane (10 × 20 cm^3), dried ($MgSO_4$), and solvent removed by distillation to reduce the volume to 5 cm^3. The residue was analysed by g.l.c. (Pyre 104 instrument with flame-ionisation detector, 15% SE 30 on Chromosorb W, nitrogen carrier gas at 40 cm^3 min^{-1}, 154 °C). The retention times of 4-methoxycarbonylmorpholine and methyl *N*-phenylcarbamate (332 and 779 s, respectively) and the relative response factor (1.72) were determined separately. The yield of 4-methoxycarbonylmorpholine was 63%. The yield predicted from the rate constants reported in this paper (determined with rather lower concentrations of reactants) is 87%. It is possible that extraction was incomplete. The time of reaction was insufficient for any significant extent of direct reaction of methylchloroformate with morpholine to have occurred.

The u.v. spectrum of the pyridine buffer was shown in several cases to be identical before and after the reaction. In the case of hydrazine and 4-dimethylaminopyridine, a slow reaction between these two reactants at pH 9.3 in the

absence of methylchloroformate was observed and this is under investigation.

Determinations of pK_a.—A solution containing 0.05—2 mol dm^{-3} of the pyridine, exactly neutralized with hydrochloric acid, was titrated with sodium hydroxide. The ionic strength was maintained at 0.2 mol dm^{-3} with potassium chloride and the temperature was 25 °C. Several measurements of pH between one-quarter and three-quarters neutralization were made. The values obtained for pK_a values at this ionic strength were 8.55 for 4-(2,2,2-trifluoroethylamino)pyridine, 8.77 for 4-(4-morpholino)-pyridine, and 6.66 for 4-methoxypyridine. Thermodynamic pK_a values can be estimated by subtracting 0.14 from these values.

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REFERENCES

[1] P. M. Bond, E. A. Castro, and R. B. Moodie, *J.C.S. Perkin II*, 1976, 68.
[2] E. A. Castro and F. J. Gil, *J. Amer. Chem. Soc.*, 1977, **99**, 7611.
[3] M. J. Gresser and W. P. Jencks, *J. Amer. Chem. Soc.*, 1977, **99**, 6963.
[4] M. J. Gresser and W. P. Jencks, *J. Amer. Chem. Soc.*, 1977, **99**, 6970.
[5] C. D. Ritchie, *J. Amer. Chem. Soc.*, 1975, **97**, 1170.
[6] E. A. Castro and R. B. Moodie, *J.C.S. Perkin II*, 1974, 658.
[7] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432, 5442.
[8] R. B. Moodie and R. Towill, *J.C.S. Perkin II*, 1972, 184.
[9] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622; A. C. Satterthwaite and W. P. Jencks, *ibid.*, 1974, **96**, 7018, 7031.
[10] N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 489, 499, 507.
[11] V. Gold, *Adv. Phys. Org. Chem.*, 1969, **7**, 259. A. J. Kresge *Pure. Appl. Chem.*, 1965, **8**, 243. W. J. Albery, ' Solvent Isotope Effects ', eds. E. Caldin and V. Gold, Chapman and Hall, London, 1975; F. M. Menger and K. S. Venkatusubban, *J. Org. Chem.*, 1976, **41**, 1868.
[12] R. L. Schowen, Isotope Effects in Enzyme Catalysed Reactions, Proc. 6th Annual Harry Steinbeck Symp., 1976, p. 64.
[13] R. B. Moodie, K. Schofield. and P. G. Taylor, *J.C.S. Perkin II*, 1979, 133; L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Amer. Chem. Soc.*, 1978, **100**, 5444; P. J. Sansom and R. B. Moodie, unpublished work on the hydrolysis of phenyl isocyanate.
[14] C. D. Ritchie, D. J. Wright. Der-Shing Huang, and A. A. Kamego, *J. Amer. Chem. Soc.*, 1975, **97**, 1163; J. N. Ride, P. A. H. Wyatt, and Z. M. Zochowski, *J.C.S. Perkin II*, 1974, 1188.
[15] M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**. 8828.
[16] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534.