Kinetics of Reaction of Substituted Pyridines and Oxygen Anions with Methyl Chloroformate in Aqueous Solution

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The rate constants for nucleophilic reaction of nine substituted pyridines with methyl chloroformate gives a sharply curved Brönsted plot, the slope changing from β 0.93 to 0.15 with increasing reactivity. This contrasts with the straight line (β 0.93) observed with *p*-nitrophenyl acetate, and is shown to be quantitatively consistent with a change in rate-determining step. It is argued that this is from breakdown to formation of a zwitterionic tetrahedral intermediate which is only just stable enough to exist. The hydrolytic stabilities of some of the methoxycarbonylpyridinium ions produced by this reaction, and the nucleophilic reactivities towards methyl chloroformate of imidazole, of phenolate, *p*-nitrophenolate, and acetate anions, and of phosphate dianion are reported and discussed.

THE kinetics and mechanism of acyl transfer to amines in aqueous solution have been the subject of much research, and general acid and general base catalysed, as well as uncatalysed reaction pathways have been recognised. The uncatalysed pathway was for many years considered to involve rate-determining attack of amine (either to form a tetrahedral intermediate or in a displacement mechanism) and the reasons for this conclusion have been summarised.[1,2] One difficulty was the fact that very reactive acyl compounds such as the 1-acetoxy-4-methoxypyridinium ion show diminished sensitivity to the basicity of the amine with the most basic amines,[3] as can be seen from the curvature of the plot of log (rate constant) against the pK_a of the conjugate acid of the amine (Brönsted plot). The curvature suggests a change in the rate-determining step, but if amine attack is rate determining for most amines, it is hard to imagine what earlier step would be rate limiting for the most basic amines.

In order to investigate this point we chose to study the aminolysis of methyl chloroformate an acyl compound with a better leaving group (Cl^-) than that possessed by the 1-acetoxy-4-methoxypyridinium ion (4-methoxypyridine-1-oxide), but of similar overall reactivity. (The relative ease of acetyl and methoxycarbonyl transfer will be discussed in a later paper.) Results with primary amines[4] showed that the curvature of the Brönsted plot occurred at lower pK_a than with the 1-acetoxy-4-methoxypyridinium ion, which showed the importance of leaving group ability. The scatter of points (probably arising from the necessary use of amines of variable structural type) precluded quantitative consideration of the sharpness of the curvature. In this paper, part of which has previously been communicated,[5] we report the kinetics of reaction of substituted pyridines with methyl chloroformate, thus covering a range of pK_a units with the minimum of significant structural variation, and a consideration of the Brönsted plot which suggests that a two step mechanism through a tetrahedral intermediate quantitatively accounts for the observed curvature.

In the reaction of pyridines with methyl chloroformate, the formation of a tetrahedral intermediate is particularly unfavourable, since such an intermediate possesses two good leaving groups (pyridine and chloride ion) expulsion of either of which leads to a carbonyl compound stabilised by resonance between the carbonyl and methoxy-groups. The methoxy-group can also stabilise an incipient acylium ion in a displacement mechanism which bypasses the tetrahedral intermediate. The conclusion that nevertheless a tetrahedral intermediate is on the reaction path, formation or breakdown of which can be rate determining depending on the basicity of the nucleophile, suggests that the aminolysis of aryl acetates, where formation of the tetrahedral intermediate should be relatively more favourable, also proceeds through such an intermediate, breakdown to products of which must normally be rate determining. Satterthwait and Jencks[6] have recently produced strong evidence that this is the case, contrary to previous conclusions.

This paper also reports the reactivity of imidazole and of some oxygen bases towards methyl chloroformate.

RESULTS

The primary object of this work was to measure the specific rate constants k_n for reaction of methyl chloroformate with the free base forms of substituted pyridines. This reaction produces the corresponding methoxycarbonylpyridinium ion which then undergoes hydrolysis. The substrate is also subject to direct hydrolysis. With excess total pyridine over methylchloroformate and at constant pH, this gives three linked first-order processes (1)–(3) with first-order rate constants k_1—k_3. The desired rate constant

$$\mathrm{MeO{\cdot}CO{\cdot}Cl + XPy \xrightarrow{k_1} MeO{\cdot}CO{\cdot}\overset{+}{P}yX + Cl^-} \quad (1)$$

$$\mathrm{MeO{\cdot}CO{\cdot}\overset{+}{P}yX + H_2O \xrightarrow{k_2} MeOH + CO_2 + PyX + H^+} \quad (2)$$

$$\mathrm{MeO{\cdot}CO{\cdot}Cl + H_2O \xrightarrow{k_3} MeOH + CO_2 + H^+ + Cl^-} \quad (3)$$

SCHEME 1

k_n can be found, if k_1 can be measured, from the relationship $k_n = k_1/[\mathrm{XPy}]$ where [XPy] is the concentration of the substituted pyridine in the free base form.

[1] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, London, 1969.
[2] T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Donzel, and N. G. Kundu, *J. Amer. Chem. Soc.*, 1970, **92**, 1370.
[3] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.
[4] E. A. Castro and R. B. Moodie, *J.C.S. Perkin II*, 1974, 658.
[5] E. A. Castro and R. B. Moodie, *J.C.S. Chem. Comm.*, 1973, 828.
[6] A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7018.

One of two methods was used to determine k_1, depending on the substituent. For the electron-withdrawing substituents X = 3-CN, 4-CN, 3-Cl, and 2-aza, the decomposition of the methoxycarbonylpyridinium ion was sufficiently rapid for the overall production of hydrogen ions to be a first-order process with rate constant $k_1 + k_3$. The pH-stat method [3] was used. The rate constant k_3, under the conditions used here of 25 °C and an ionic strength of 0.2M, has previously been shown [4,7] to be 5.6×10^{-4} s^{-1}.

With the other substituted pyridines (X = H, 3-Me, 4-Me, 4-NH_2, and 4-NMe_2) the hydrolysis of the methoxycarbonylpyridinium ion was slow enough for it significantly to accumulate during the progress of the reaction. The appearance and disappearance of this ion was followed spectrophotometrically.

Scheme 1 leads to equation (4) for the variation with time t of an absorbance A due to the methoxycarbonylpyridinium ion, in which E is the absorbance which would be observed if all the substrate were converted into the methoxycarbonylpyridinium ion.

$$A = \frac{k_1 E}{k_2 - k_1 - k_3} (e^{-(k_1 + k_3)t} - e^{-k_2 t}) \qquad (4)$$

Values of k_2 and k_3 were obtained as described below, and then the whole absorbance–time curve was used to compute 'best fitting' values of k_1[8] and E with the aid of a non-linear least squares method described elsewhere. The observed and calculated curves for the appearance and disappearance of the unsubstituted 1-methoxycarbonylpyridinium ion are compared in Figure 1. The rate constant k_2

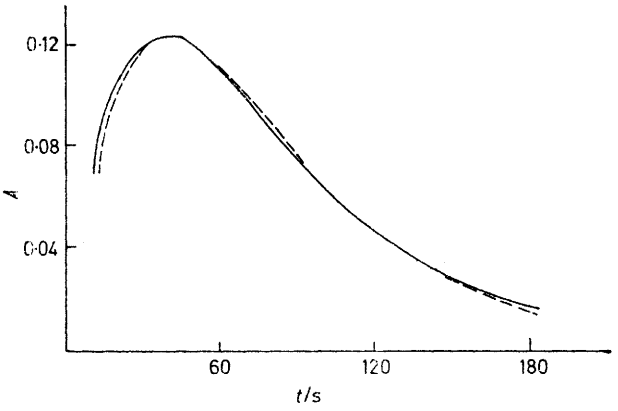


FIGURE 1 Observed (full line) and calculated (broken line) variation of absorbance A at 275 nm with time t for the reaction of methyl chloroformate with pyridine at pH 5.32

was determined independently from the normal first-order plot using the second, falling part of the absorbance–time curve. Results are in Table 1. To check that the derivation of the value of k_2 from the final portion of the curve was satisfactory, the latter part of the computed curve was used in the same way, and gave a good first-order plot and the same value of k_2 except in the case of unsubstituted pyridine. In this case k_2 had to be determined under conditions where the first, rising part of the absorbance–time curve was too fast to follow. Values of k_2 were determined for a range of conditions as shown in Table 1 and fitted equation (5) where [Py] is the concentration of free base pyridine. The value of k_2 appropriate for the conditions

$$k_2 = 0.0275 \text{ s}^{-1} + 0.47 \text{ l mol}^{-1} \text{ s}^{-1} [\text{Py}] \qquad (5)$$

used for the determination of k_1 was deduced from this equation. The second term is attributed to general base catalysis of the hydrolysis of the methoxycarbonylpyridinium ion by free base pyridine. Similar catalysis is reported in the case of the hydrolysis of the acetylpyridinium ion.[9]

TABLE 1

First-order rate constants k_2 for hydrolysis of substituted methoxycarbonylpyridinium ion at 25 °C, ionic strength 0.2M, produced *in situ* from the reaction of the substituted pyridine with methyl chloroformate

Substituent	pH	$10^2[B]_t$[a]/M	$10^4 k_2$/s^{-1}
None	4.7	2.0	283
None	4.8	2.0	287
None	5.0	2.0	295
None	5.1	2.0	302
None	5.3	2.0	308
3-Methyl	5.81	0.04	158
4-Methyl	6.20	0.04	120
4-Amino	6.38	1,1.5,2	2.63 [b,c]
4-Amino	6.67	1,1.5,2	3.05 [b,d]
4-Dimethylamino	6.40	1,1.5,2	1.28 [b,c]
	6.70	1,1.5,2	1.62 [b,d]

[a] Total concentration of the substituted pyridine. [b] Mean of three runs. [c] In the presence of 0.005M-Na_2HPO_4 and 0.01M-KH_2PO_4. [d] In the presence of 0.005M-Na_2HPO_4 and 0.005M-KH_2PO_4.

In the cases of 4-amino- and 4-dimethylamino-pyridine, phosphate buffers were used, and the values of k_3 varied with pH, reflecting varying extents of catalysis by phosphate ion and/or hydroxide ion. This was not further investigated. Phosphate also affected the value of k_3; this was investigated by potentiometric estimation of chloride ion release from methyl chloroformate in phosphate buffers, as described in the Experimental section. The appropriate value of k_3 in the above experiments was thus found to be 6.1×10^{-4} s^{-1}. The proportion of methyl chloroformate reacting with phosphate in these experiments never exceeded 3%, which justified our neglect of any complications which might arise from the intermediacy of methoxycarbonylphosphate species.

The values of k_n for all the pyridine bases are given in Table 2, together with values of the same quantity for imidazole and some anionic oxygen mucleophiles obtained either by the pH-stat method or by potentiometric estimation of chloride ion release.

p-*Nitrophenyl Acetate*.—For comparison the Brönsted plot for pyridinolysis of this compound was needed. Values of k_n at 25° and ionic strength 1M have been reported for pyridine, 4-methylpyridine, and nicotinamide; [3] we now report in Table 3 data for 4-dimethylamino-, 4-cyano-, 3-chloro-, and 2-aza-pyridine (pyridazine) under the same conditions. The two last mentioned have been studied [10] at an ionic strength of 0.5M; our results are in satisfactory agreement. Concentrations of free base pyridine were kept as low as possible to minimise the effects of self-association [9] of the free base pyridine. The fact that values of k_n showed no downward trend with increasing concentrations of pyridine shows that such effects were negligible.

[7] A. Queen, *Canad. J. Chem.*, 1967, **45**, 1619.
[8] E. A. Castro, Ph.D. Thesis, Exter, 1974.
[9] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432.

Errors.—The errors reported for values of k_n in Tables 2 and 3 are standard errors from the weighted mean with weights assigned as previously described,[4] except in the cases of the reactions of pyridine and 4-amino- and 4-dimethylamino-pyridine with methyl chloroformate, where results from curve fitting to equation (2) are unweighted. The rate constants for the methylpyridines (only two runs each) are assigned the same percentage error as that for pyridine.

General Acid and General Base Catalysis.—Most reactions were studied at various values of pH and over a range of substrate concentration, as shown in Table 2; in no case was there evidence of general catalysis.

TABLE 2

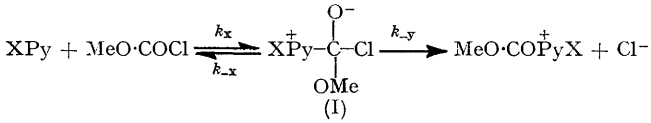
Second-order rate constants k_n for reactions of nucleophiles with methyl chloroformate at 25 °C and ionic strength 0.2M

Nucleophile	pK_a [a]	Method [b]	pH	$10^2[B]_t$ [c]/M	Number of runs	kn/l mol^{-1} s^{-1}
3-Cyanopyridine	1.62	A	5.0—5.5	0.10—0.40	14	1.1 (±0.02)
4-Cyanopyridine	1.98	A	4.0—6.0	0.05—0.17	18	2.4 (±0.1)
3-Chloropyridine	2.98	A	5.0	0.01—0.05	8	10.6 (±0.3)
Pyridazine	2.44	A	5.0	0.02—0.10	8	9.9 (±0.5)
Pyridine	5.32 [d]	B (275 nm)	2.2—5.3	0.04—15	12	107 (±16)
3-Methylpyridine	5.81	B (278 nm)	5.8	0.04	2	220 (±30)
4-Methylpyridine	6.15	B (268 nm)	6.2	0.04	2	180 (±30)
4-Aminopyridine	9.15	B (296 nm)	6.4—6.77	0.25—2.0	9	480 (±15) [e]
4-Dimethylaminopyridine	9.55	B (324 nm)	6.4—6.7	0.25—1.5	9	520 (±20) [e]
Imidazole	7.09 [d]	A	4.7—5.6	0.6—5.0	7	11 (±0.3)
Phenolate anion	9.74	A	6.4—6.7	2.5—2.0	9	65 (±2)
p-Nitrophenolate anion	7.00 [d]	C	7.0	0.04—0.05	6	2.7 (±0.1)
Acetate anion [f]	4.61 [d]	C	4.6	0.02—0.20	5	0.0134 (±0.0006)
Phosphate anion	6.77 [d]	C	6.4—6.9	1.9—5.0	12	0.0098 (±0.0002)

[a] Of the conjugate acid of the nucleophile at an ionic strength of 0.2M, measured as described in the experimental section unless otherwise noted. [b] A, pH-stat method. B, Spectrophotometric method (wavelength used for observation). C, Potentiometric estimation of chloride ion release. [c] Total concentration of nucleophile (free base + conjugate acid). [d] Literature value after correction for ionic strength (see Experimental section). [e] These values are 8 and 30% lower, respectively than those previously measured by method A and reported graphically.[5] The possibility of a minor degree of reaction through the conjugate acid [5] was ruled out by the absence of nucleophilic activity at pH 1. The reason for the discrepancy is unknown. [f] We thank A. D. Hamilton for these measurements.

DISCUSSION

Pyridinolysis.—The Brönsted plot for pyridinolysis of methyl chloroformate is sharply curved, in contrast to the good straight line obtained for *p*-nitrophenyl acetate (Figure 2). The latter suggests that if attention is restricted to substituted pyridines, the pK_a of the conjugate acid is a satisfactory measure of nucleophilic reactivity, and the curvature of the plot for methyl chloroformate is then reasonably ascribed to a change in rate-determining step. This is a reaction in which proton transfer steps are not involved, the change in rate determining step can only be from uncatalysed breakdown to



SCHEME 2

uncatalysed formation of a zwitterionic tetrahedral intermediate [(I) in Scheme 2]. The observed rate constant for such a section is given by equation (6). It is clear that with increasing pK_a the magnitude of k_{-x} will fall

$$k_n = k_x/[1 + (k_{-x}/k_{-y})] \quad (6)$$

relative to that of k_{-y}, and that this could lead to a change in rate-determining step from breakdown (k_{-y} step) to formation (k_x step) of (I). If the slope of the plot of log k_n *versus* pK_a has a constant slope β_2 when breakdown to products of (I) is rate determining, and a constant slope β_1 when formation of (I) is rate determining, then it can be shown that the equation of the whole curve will be as in equation (7), in which k_n^0 and pK_a^0 refer to the (hypothetical) pyridine for which $k_{-x} = k_{-y}$.

$$\log(k_n/k_n^0) = \beta_2(pK_a - pK_a^0) - \log\left[\frac{1 + 10^{(\beta_2-\beta_1)(pK_a-pK_a^0)}}{2}\right] \quad (7)$$

This equation was used to draw the solid curve in Figure 2, with β_1 0.15, β_2 0.93, pK_a^0 3.60, and log k_n^0 1.55, and can be seen to give a satisfactory account of the curvature. The value taken for β_2 is the slope of the plot for *p*-nitrophenyl acetate (Figure 2), the pyridinolysis of which is believed to be limited in rate by breakdown of the tetrahedral intermediate for all the pyridines

TABLE 3

Second-order rate constants k_n for reactions of substituted pyridines with *p*-nitrophenyl acetate at 25 °C and ionic strength 1.0M maintained with KCl

Substituent	pK_a [a]	pH	$10^2[B]_t$ [b]/M	Number of runs	k_n/l mol^{-1} s^{-1}
4-CN	2.21	4.85 [c]	0—15	5	4.6 (±0.2) × 10^{-6}
3-Cl	3.20	3.10, 3.01	10, 30	2	1.66 (±0.2) × 10^{-5}
2-Aza [d]	2.52	6.2 [e]	5—26	5	1.12 (±0.05) × 10^{-4}
4-NMe$_2$	9.82	9.4—9.6	0.02—0.06	9	55 (±2)

[a] Of the conjugate acid at 1.0M ionic strength, measured as described in the Experimental section. [b] Total concentration of substituted pyridine. [c] In the presence of 0.01M-acetate buffer. [d] Pyridazine. [e] In the presence of 0.014M-phosphate buffer.

[10] J. A. Zoltewicz and L. W. Deady, *J. Amer. Chem. Soc.*, 1972, **94**, 2765.

studied, as with other amines.[6] β_2 Is not expected to vary much with reactivity,[11] and indeed the pyridinolysis of acetic anhydride,[9] a much more reactive electrophile, has (for the restricted range of pyridines studied) a very similar value of β (0.87). The value of β_1 is within the range expected for reactions in which tetrahedral intermediate formation is rate limiting.[6]

In a recent paper Ritchie [12] has extended the use of his nucleophilic parameters N^+ to embrace acyl transfer reactions in which uncatalysed formation or breakdown

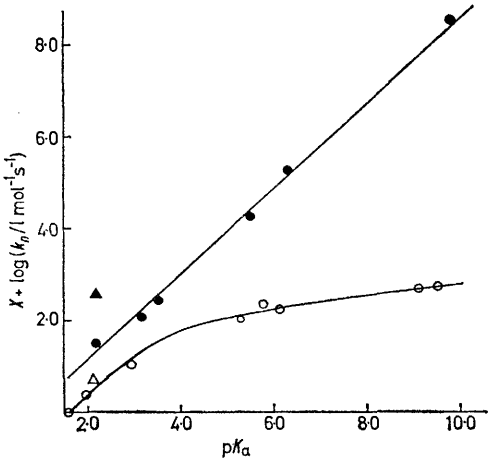


FIGURE 2 Brönsted plot of $X + \log (k_n/\text{l mol}^{-1}\text{ s}^{-1})$ against pK_a of the conjugate acid, for substituted pyridines reacting with methyl chloroformate (open symbols, $X = 0$, ionic strength 0.2M) and with *p*-nitrophenyl acetate (full symbols, $X = 6.8$, ionic strength 1.0M). The points for pyridazine (triangles) are statistically corrected [20]

of a tetrahedral intermediate can be rate-determining, as in Scheme 1. In equation (8), $\log k_0$ is characteristic only of the acyl compound and N^+ only of the nucleophile. It

$$\log k_n = \log k_0 + N^+ - \log(1 + k_{-x}/k_{-y}) \qquad (8)$$

is noteworthy that equation (8) requires β values to be independent of reactivity whilst a given step is rate determining. In order to reduce the number of fitting parameters, relative values of $\log k_{-x}$ and $\log k_{-y}$ are assessed on the necessary but extreme assumption that they are characteristic of the leaving group and independent of the acyl compound from which they depart. (It follows that k_{-x} and k_{-y} are equal for the same leaving group.) The reasonably smooth curve of $\log k_n$ against pK_a (Figure 2) suggests that if equation (7) is applicable here, the two limiting slopes $\beta_1(= 0.15)$ and $\beta_2(= 0.93)$, corresponding to $k_{-x} \ll k_{-y}$ and $k_{-x} \gg k_{-y}$ respectively, lead to equations (9) and (10).

$$\text{d} \log N^+/\text{d } pK_a = 0.15 \qquad (9)$$

$$\text{d} \log k_{-x}/\text{d } pK_a = -0.78 \qquad (10)$$

From these equations the values of N^+ and relative $\log k_{-x}$ for all the pyridines can be deduced, starting from the reported [12] values for pyridine itself, 5.00 and 4.94, respectively. Furthermore, chloride ion has leaving group ability comparable to a substituted pyridine of pK_a 3.60 (see earlier) from which one obtains a relative $\log k_{-y}$ value for chloride ion of 6.3 on Ritchie's scale. This makes it a better leaving group, by a factor of *ca.* 10, than 4-methoxypyridine 1-oxide.[12] The latter is estimated to depart from the tetrahedral intermediates formed by attack of hydrazine or methylamine on 1-acetoxy-4-methoxypyridinium ion with a rate constant of *ca.* 10^{10} s^{-1}. If rate constants really are almost independent of the group from which they depart,[12] then the lifetime of the tetrahedral intermediate formed in the reaction of methyl chloroformate with nucleophiles which are worse leaving groups than chloride ion is *ca.* 10^{11} s, and if the nucleophile departs more readily than chloride ion, as for instance with the cyanopyridines, the lifetime must be even shorter and approach the time for one C–N vibration (*ca.* 10^{-13} s). In other words the tetrahedral intermediates produced in these reactions must be near the limit of instability.

Anionic Oxygen Nucleophiles.—We believe that the reactions of acetate, phenolate, and *p*-nitrophenolate with methyl chloroformate are reactions in which formation of the tetrahedral intermediate is rate limiting for the following reasons. (a) Gravitz and Jencks [13] have shown that alkoxide ions are much poorer leaving groups (from the *NO*-trimethylenephthalidinium ion) than anions of the same basicity. It is likely that the same applies to aryloxide ions. (b) Acetate is deduced to be a poorer leaving group than unsubstituted pyridine (and therefore than chloride ion) because the Brönsted plot for the pyridinolysis of acetic anhydride has a relatively high slope. This casts doubt on the conclusion [12] that acetate is an exceptionally good leaving group.

A reasonably good linear correlation between values of $\log k_n$ for aminolysis of methyl chloroformate and 1-acetoxy-4-methoxypyridinium ion has previously been noted.[4] The anionic oxygen nucleophiles deviate by 1.2—1.8 log units, consistent with there being a favourable electrostatic interaction only with the cationic acyl compound. The values of $\log k_n$ for the reactions of water, phosphate dianion, phenolate, and *p*-nitrophenolate anion with methyl chloroformate correlate excellently with those for reaction with acetic anhydride at 5 °C.[14]

Imidazole.—The value of k_n for this compound is much lower than that of pyridines of similar pK_a (Table 2). Its exalted reactivity [15] is manifest only when tetrahedral intermediate breakdown is rate determining, which suggests that it arises from poor leaving group ability rather than inherently high nucleophilicity.[12]

Pyridazine.—Enhanced reactivity, attributed to the ' α-effect ', towards *p*-nitrophenyl acetate has previously been noted,[10] and our results (Table 3 and Figure 2)

[11] C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, 1973, **95**, 270.
[12] C. D. Ritchie, *J. Amer. Chem. Soc.*, 1975, **97**, 1170.
[13] N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 499.
[14] S. Leppänan, L. Strandman, S. Jakala, P. Pajunen, and J. Koskikallio, *Acta Chem. Scand.*, 1973, **27**, 3572.
[15] S. L. Johnson in 'Advances in Physical Organic Chemistry,' ed. V. Gold, Academic Press, London, 1967, vol. 5.

confirm this. It is interesting that the effect is not observed with methyl chloroformate (Table 2 and Figure 2) in view of the similar Brönsted slopes in this region.[16]

EXPERIMENTAL

Materials.—Methyl chloroformate, acetonitrile, 3-chloropyridine, pyridine, 3-methylpyridine, 4-methylpyridine, and pyridazine were purified by distillation. 3-Cyanopyridine (light petroleum), 4-cyanopyridine (light petroleum), 4-aminopyridine (benzene), 4-dimethylaminopyridine (light petroleum), imidazole (benzene), and *p*-nitrophenol (dilute aqueous HCl) were recrystallised from the indicated solvents. Phenol (AnalaR) was used directly.

Kinetic Methods.—Method A utilised a pH-stat apparatus comprising a Radiometer 26A pH meter, TTT11 titrator, SBU/1a syringe burette. The glass electrode was Radiometer type G202B for which sodium ion corrections are negligible under the conditions used. The concentration of sodium hydroxide used as titrant was in the range 5×10^{-3}—0.1M. Solutions (final volume 25 cm^3) were brought to the correct pH and ionic strength with hydrochloric acid and sodium perchlorate, and to 25°C. Methyl chloroformate was then added as a solution in acetonitrile (10—20 μl) such that its initial concentration was 10^{-4}—10^{-3}M. Method B involved spectrophotometric observation, with a Unicam SP 1800, of the appearance and disappearance of a u.v. adsorption due to the 1-methoxycarbonylpyridinium ion at the wavelengths given in Table 2. Reactions were initiated by injecting 1.5—30 μl of an acetonitrile solution of methyl chloroformate into 10 cm^3 of the reactant solution in a thermostatted u.v. cell.

In method C, chloride ion released was monitored potentiometrically by a null method.[17] The glass cell was H shaped, the vertical limbs being each of volume 35 cm^3 and magnetically stirred. The horizontal limb contained a sintered glass disc to prevent mixing but provide electrical contact. The buffer solution in which the reaction of methyl chloroformate was to be studied, also containing 5×10^{-4}M-NaCl, was allowed to fill the cell and sinter so that there was 30 cm^3 on either side. This was brought to 25 °C. Each limb was equipped with a silver–silver chloride electrode; these were connected to a potentiometer which was balanced to give zero deflection on the galvanometer. The delivery tube of a syringe burette containing 0.02M HCl solution was immersed in one limb and 0.1 cm^3 delivered, causing a deflection on the galvanometer. A portion (usually 0.1 cm^3) of an acetonitrile solution of methyl chloroformate was added to the other limb, and the stop-clock started when the galvanometer deflection became zero. A further portion of HCl was added to the first limb, and the time recorded when the galvanometer deflection again became zero. In this way volumes V_t at times t added to maintain zero deflection were recorded, corresponding to adding chloride ion to one limb equal to that produced by reaction in the other. Plots of $-\ln(V_\infty - V_t)$ against t, where V_∞ was the total volume (usually *ca.* 1 cm^3) of HCl solution added, were linear over 2—3 half-lives; the slope was the observed first-order rate constant.

The silver–silver chloride electrodes, prepared as described in the literature,[18] were found to be inexplicably variable in response time; those that were sluggish in response were rejected. When not in use the electrodes were stored in shorted pairs in 1M-HCl solution.

Product Studies.—The methoxycarbonylpyridinium ions were unstable, and no attempt was made to isolate their salts. Unsubstituted methoxycarbonylpyridinium ion was found to have $\lambda_{max.}$ 275 nm and by back extrapolation of the first-order plot for its decomposition a molar absorptivity of 4 100 cm^{-1} mol^{-1} dm^3 at this wavelength. These are very close to the reported figures (272 nm; 4 400 cm^{-1} mol^{-1} dm^3) for the acetylpyridinium ion.[9] 4-Amino- and 4-dimethylamino-pyridine were presumed to react through their ring nitrogens because (a) this is the most basic site [19] and (b) they both react at similar rates with methyl chloroformate to give initial products of similar stability and spectral properties. Phenyl methyl carbonate was identified as the product of the reaction of phenolate anion with methyl chloroformate by t.l.c. comparison with an authentic sample.

Determinations of pK_a.—These were as previously described [4] except in the case of the 3-cyanopyridinium ion, for which a spectrophotometric method was employed. The ionisation ratio was found from equation (11) in which A

$$[BH^+]/[B] = (A - A_B)/(A_{BH} - A) \qquad (11)$$

is the absorbance of the mixture, A_B that of the free base B, and A_{BH} that of the conjugate acid BH^+, all at the same wavelength, with the same stoicheiometric concentration of 3-cyanopyridine, and with an ionic strength of 0.2M maintained with $NaClO_4$. Wavelengths of 226 and 265 nm were employed. The plot of $-\log [BH^+]/[B]$ against pH was linear with unit slope and intercept (=pK_a) of 1.62. The addition of −0.14 for the logarithm of the activity coefficient of 0.2M-sodium perchlorate gives a thermodynamic pK_a of 1.48 (lit.,[19] 1.39, 1.45). The solutions were kept at at 25 °C for these measurements.

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[16] F. Filippini and R. F. Hudson, *J.C.S. Chem. Comm.*, 1972, 522; J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2052.

[17] C. G. Swain and S. Ross, *J. Amer. Chem. Soc.*, 1946, **68**, 658.

[18] R. G. Bates, ' Determination of pH,' Wiley, London, 1954.

[19] K. Schofield, ' Hetero-aromatic Nitrogen Compounds,' Butterworths, London, 1967.

[20] R. P. Bell and P. G. Evans, *Proc. Roy. Soc.*, 1966, *A*, **219**, 297.