

## 678. Nucleophilic Reactivity. Part V.<sup>1</sup> The Reaction between Amines and Ethyl Methanesulphonate.

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The rates of reaction between ethyl methanesulphonate and several amines in aqueous solution have been measured, and the influence of steric hindrance established. The dependence of the rate constant on the substituent in the nucleophile is related to the corresponding  $pK_a$  according to the Brønsted catalysis law, for the reaction of the ester with substituted pyridines and imidazoles. The magnitude of the exponential coefficient is discussed.

In previous Papers,<sup>2</sup> the selectivity coefficient,  $\alpha$ , of the Brønsted relation,  $\log_{10} k = pK_a + \text{constant}$ , was interpreted as a measure of the extent of bond formation and charge transfer in the transition state of a displacement reaction. This relation, originally limited to general acid- and base-catalysed reactions,<sup>3</sup> can be extended to other nucleophilic displacements, *e.g.*, the hydrolysis of *p*-nitrophenyl acetate catalysed by a series of substituted anilines, pyridines, imidazoles, and oxy-anions.<sup>4</sup> The separate lines obtained for each series of nucleophiles have a common slope of  $\alpha \simeq 0.8$ , attributed by us<sup>5</sup> to the high degree of charge transfer in the transition state, which probably resembles an addition intermediate.<sup>6</sup>

In view of the weaker bond energies in an  $S_N2$  transition state, and the consequent variation in its structure and charge distribution with the reaction conditions,<sup>7</sup> we have determined the values of  $\alpha$  for the reactions in water of a series of (a) pyridines and (b) imidazoles with ethyl methanesulphonate. This ester was chosen because it is known to solvolyse by an  $S_N1/S_N2$  borderline mechanism,<sup>8</sup> and because of its solubility in water.

The rate of reaction of alkyl halides with substituted pyridines and the role of steric hindrance have been discussed by Brown and his collaborators,<sup>9</sup> who reach the conclusion that steric interactions influence activation and thermodynamic equilibria similarly.

The rate constants for the reactions of pyridine and substituted pyridines with ethyl methanesulphonate in water are related to the  $pK_a$  in water of the corresponding protonated pyridine as shown in Fig. 1. It is observed that 3- and 4-substituted pyridines give a linear  $\log_{10} k$  vs.  $pK_a$  relationship with  $\alpha = 0.11 (\pm 0.01)$ . This value is significantly lower than those observed for other alkylating agents,<sup>2</sup> *e.g.*, 0.20 for the chloroacetate ion, 0.22 for 3-bromopropanol, and 0.32 for ethylene oxide, suggesting that the transition state has a greater " $S_N1$  character,"<sup>7</sup> like the corresponding solvolysis.<sup>8</sup>

Parallel lines can be drawn for the  $\alpha$ - and  $\alpha\alpha'$ -methyl substituted pyridines (Fig. 1), the successive displacements being attributed to the steric effect of the methyl groups. (The steric effect in the classical sense cannot be differentiated from the steric repression of solvation,<sup>10</sup> but the investigations of Brown *et al.*<sup>9</sup> suggest that this effect is small.) This separation of steric and electronic effects is similar in principle to the procedure widely developed by Taft,<sup>11</sup> and reference to Fig. 1 shows that the steric interactions of the  $\alpha$ -methyl groups are additive.

<sup>1</sup> Part IV, *J.*, 1964, 5.

<sup>2</sup> (a) Hudson and Klopman, *J.*, 1962, 1062; (b) Hudson and Loveday, *J.*, 1962, 1068.

<sup>3</sup> Bell, "The Proton in Chemistry," Cornell University, 1959, p. 155.

<sup>4</sup> Bruice and Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265.

<sup>5</sup> Hudson, *Chimia (Switz.)*, 1962, **16**, 173.

<sup>6</sup> Bender, *Chem. Rev.*, 1960, **60**, 53.

<sup>7</sup> Grunwald, Winstein, and Jones, *J. Amer. Chem. Soc.*, 1948, **70**, 846; Swain and Mosely, *ibid.*, 1955, **77**, 3727; Gold, *J.*, 1956, 4633; Hyne and Robertson, *Canad. J. Chem.*, 1956, **34**, 863.

<sup>8</sup> (a) Robertson, *Canad. J. Chem.*, 1953, **31**, 589; (b) Hudson, Timmis, and Marshall, *Biochem. Pharmacol.*, 1958, **1**, 48.

<sup>9</sup> Brown and Cahn, *J. Amer. Chem. Soc.*, 1955, **77**, 1715; Brown and Horowitz, *ibid.*, 1733.

<sup>10</sup> Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 34.

<sup>11</sup> Taft, "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 556.

On the other hand, the effect of a second alkyl group substituted at the nitrogen atom of a primary amine is considerably greater than the first, as shown by the data of Table 1.

TABLE 1.

Rate constants for the reaction of several amines with ethyl methanesulphonate in water at 35°.

	<i>n</i> -Butylamine	Diethylamine	Triethylamine
$10^5 k_2$ l.mole <sup>-1</sup> sec. <sup>-1</sup> .....	48.2	16.4	1.95
$\log_{10} k_2 + 5$ .....	1.68	1.21	0.29
$pK_a$ .....	10.61	11.01	10.81

The difference can be explained qualitatively by considering the optimum orientation in the transition states of the two systems. For pyridine, the position of minimum potential energy is the symmetrical structure (I), and the  $\alpha$ -mono- and  $\alpha\alpha'$ -di-methylpyridines will

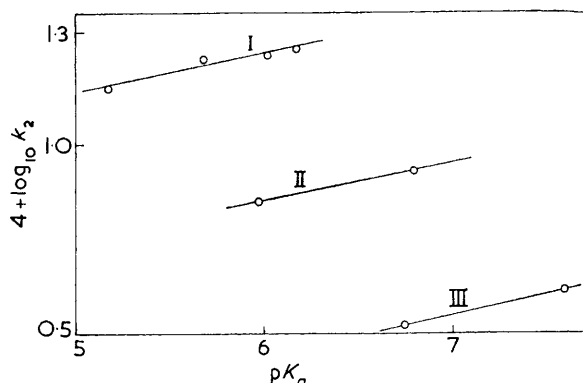
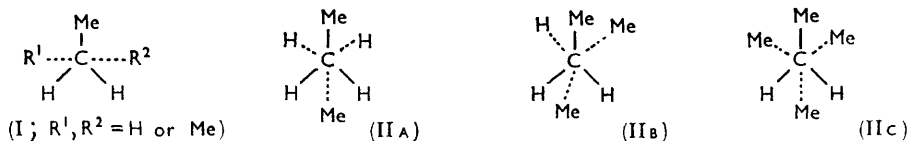


FIG. 1. The relationship between  $\log_{10} k_2$  and  $pK_a$  for the reaction between substituted pyridines and ethyl methanesulphonate in water at 61°. (I)  $\beta$ - and  $\gamma$ -substituted pyridines; (II)  $\alpha$ -substituted pyridines; (III)  $\alpha\alpha'$ -disubstituted pyridines.

assume the same configuration. Consequently the steric effects of the two methyl groups are approximately equal.

In the aliphatic series the repulsion due to a second alkyl group in the  $\alpha$ -position produces a change in orientation from (IIA) to (IIB), since the Me-H repulsion is considerably less than Me-Me repulsion.



The introduction of another  $\alpha$ -methyl group results in a reversion to the original orientation, with increased repulsion between the alkyl groups (IIc).

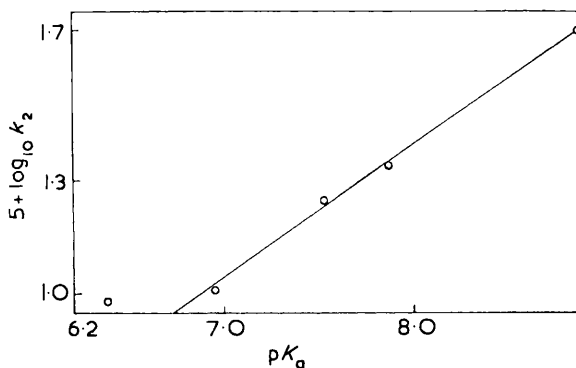
Steric effects are almost absent in the corresponding reactions of imidazoles, since the 2-substituted derivatives lie on the same plot of  $\log_{10} k$  against  $pK_a$  as the 3- and 4-substituted compounds (Fig. 2). This is no doubt due to the smaller angle of the imidazole ring and the greater distance between the interacting alkyl groups in the transition state.

Comparison of Figs. 1 and 2 shows that, in the absence of steric influences, the imidazoles show a much greater selectivity than the pyridines. Thus, if the value for the 4(5)-hydroxymethyl compound is neglected,\* the  $\log_{10} k$  against  $pK_a$  relation gives a value

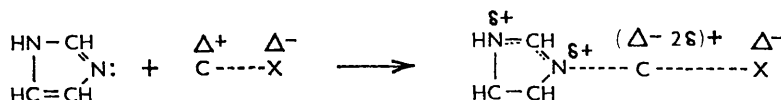
\* We prefer to neglect this point in the evaluation of  $\alpha$ , as the rate is of the same order of magnitude as that of a (hypothetical) substituted pyridine with the same  $pK_a$ , at the same temperature. If this point is included, an approximate value of  $\alpha \approx 0.30 \pm 0.05$  is found, which is considerably greater than the value obtained for the pyridines.

of  $\alpha = 0.35$ , compared with the value of  $\alpha = 0.11$  for the substituted pyridines. This difference may be due in part to the difference in temperature of the two sets of reactions. The Hammett  $\rho$ -factor for simple displacement reactions usually decreases with increase in temperature.<sup>12</sup> This effect is, however, in most cases relatively small,<sup>12</sup> and is unlikely to account for the large difference observed here.

FIG. 2. The relationship between  $\log_{10} k_2$  and  $pK_a$  for the reaction between substituted imidazoles and ethyl methanesulphonate in water at 35°.



A more likely explanation is an increase in reactivity produced by conjugation with the second nitrogen atom, which increases the charge transfer from the nucleophilic nitrogen atom to the reaction centre:



According to our previous discussions,<sup>2,5</sup> an increase in charge transfer of this kind (which corresponds to a decrease in "S<sub>N</sub>1 character" of the S<sub>N</sub>2 transition state) is reflected in a greater value of the coefficient,  $\alpha$ . These results suggest therefore that a change in the relative importance of bond-making and bond-breaking in the transition state is produced not only by a change in structure and solvent, but also by a change in the nucleophile.

## EXPERIMENTAL

**Materials.**—Ethyl methanesulphonate was prepared<sup>8b</sup> by the action of sodium ethoxide on methanesulphonyl chloride in ether (56%); it had b. p. 100°/24 mm.,  $n_D^{25}$  1.4182. Commercial primary aliphatic amines and substituted pyridines were distilled over potassium hydroxide pellets through a 2-ft. column packed with nickel Dixon rings. The boiling points and refractive indices agreed very closely with the values in the literature, and the purity was checked by gas chromatography. Imidazole and benzimidazole (Eastman Kodak analytical grade) were used without further purification; 2-methylimidazole, m. p. 141°, was prepared by Fargher and Pyman's method,<sup>13</sup> and 2,4,5-trimethylimidazole by Cowgill and Clarke's method<sup>14</sup> (m. p. of hydrochloride 316°). Pure samples of 4(5)-hydroxymethylimidazole (m. p. 93°) and 4(5)-methylimidazole (m. p. 55°) were supplied by Dr. R. M. Marshall.

**Kinetic Methods.**—Two methods were used to follow the reaction, depending on the basicity of the amine. With the aliphatic amines and the imidazoles, the reaction mixture contained a constant concentration of sodium hydroxide, to maintain the amine in the reactive form.

**Method (a).** A solution (100 ml.) of the amine in aqueous sodium hydroxide of known concentration was held in a thermostat bath and a few drops of ethyl methanesulphonate were added from a tared-weight pipette. The flask was vigorously shaken, and, at known intervals.

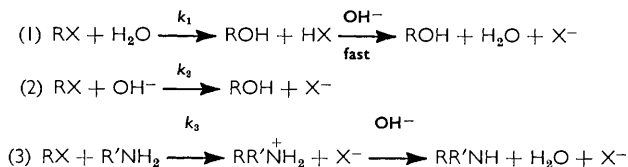
<sup>12</sup> Wells, *Chem. Rev.*, 1963, **63**, 183; Jaffé, *ibid.*, 1953, **53**, 191.

<sup>13</sup> Fargher and Pyman, *J.*, 1919, **115**, 217.

<sup>14</sup> Cowgill and Clark, *J. Biol. Chem.*, 1952, **198**, 33.

5.00-ml. portions were added to 100.0-ml. quantities of water at pH 4.6. The excess of base was titrated electrometrically with standard hydrochloric acid in a constant stream of nitrogen to eliminate absorption of carbon dioxide. The final readings were obtained after at least 10 half-lives, and also from the weight of the ester added.

The following reactions have to be considered:



The rate constants were obtained from the initial stages of the reaction, so that the further reaction with  $\text{RR}'\text{NH}$  could be neglected. In view of the observed rate sequence  $\text{R}'\text{NH}_2 > \text{R}'_2\text{NH}$ , the influence of this reaction must be very small.

The rate of reaction is then given by

$$-d[\text{OH}^-]/dt = k_1[\text{RX}] + k_2[\text{RX}][\text{OH}^-] + k_3[\text{RX}][\text{R}'\text{NH}_2]$$

If the initial concentrations of ester, hydroxide, and amine are  $a$ ,  $b$ , and  $c$ , respectively, the initial rate of reaction is given by

$$(dx/dt)_{t=0} = k_1a + k_2ab + k_3ac$$

where  $x$  is the decrease in  $[\text{OH}^-]$  in time  $t$ . The observed pseudo-unimolecular rate constant,  $k$ , is then given by

$$k = \frac{1}{a} \left( \frac{dx}{dt} \right)_{t=0} = (k_1 + k_2b) + k_3c = k^0 + k_3c$$

For a given solution of sodium hydroxide,  $b$  is constant, and the value of  $k^0$  can be determined in a separate experiment. The value of  $k_3$  can then be calculated from the experimental values of  $k$  and  $k^0$ . At least two separate experiments were made in each case, and the results plotted on the same graph, to give the mean values of  $k$  recorded in Table 2.

TABLE 2.

The reaction between ethyl methanesulphonate and various amines in water at 35°.

Amine	[Amine] (10 <sup>2</sup> M)	10 <sup>5</sup> $k$ (sec. <sup>-1</sup> )	10 <sup>4</sup> $k_3$ (l. mole <sup>-1</sup> sec. <sup>-1</sup> )	pK <sub>a</sub> <sup>14,15</sup>
n-Butylamine .....	2.46 4.49	2.64 3.53	4.82 4.39	10.61
Diethylamine .....	2.04	1.88	1.67	11.01
Triethylamine .....	2.25	1.59	0.19	10.81
4(5)-HO-CH <sub>2</sub> -Imidazole .....	4.50	1.97	0.95	6.38
Imidazole .....	2.02	1.75	1.03	6.95
4(5)-Me-Imidazole .....	2.10	1.92	1.78	7.52
2-Me-Imidazole .....	1.92	1.97	2.20	7.86
2,4,5-Me <sub>3</sub> -Imidazole .....	1.89	2.50	5.03	8.86

$$k_1 = 1.226 \times 10^{-5} \text{ sec.}^{-1}, b = 0.020\text{M}; k_2 = 1.60 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec.}^{-1}; k_0 = 1.546 \times 10^{-5} \text{ sec.}^{-1}.$$

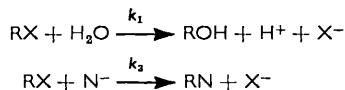
*Method (b).* With the less basic pyridines, the reaction could be followed by an automatic titrator,<sup>2b</sup> and the rate constant calculated from the final titration.

A known quantity of the amine was dissolved in 200 ml. of water and introduced into a specially-designed cylindrical glass cell. Three holes in the periphery of the cell allowed the glass and calomel electrodes and the delivery tube of an automatic burette to be introduced. The centrifugal stirrer was fitted through the centre of the vessel and a constant stream of nitrogen was bubbled through the solution. The cell and electrode assembly were maintained in a thermostat bath at 61°, until thermal equilibrium had been reached, and sodium hydroxide solution was added to give pH 9. About 14 drops of the ester, sufficient to give a 0.01M-solution, were added from a Lunge-Rey pipette, and the reaction was followed by using the

<sup>15</sup> Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146.

Pye automatic titrator as described previously.<sup>2b</sup> The concentration of the titrant was such that the total amount added during the course of the reaction was about 10% of the initial volume, which produced no temperature change.

Assuming that the reaction product is stable, the following reactions have to be considered



If [N] is considerably greater than [RX], then the ratio of the two pseudo-unimolecular rate constants,  $k_1$  and  $k_2$ , are related simply to the percentage of hydrolysis observed at the end of the reaction,  $y$ , as follows:

$$\frac{k_1}{k_2 c} = \frac{y}{(100 - y)}$$

Thus by taking the final readings in two experiments, one with no amine present and the other with amine and the same concentration of ester, values of  $k_2$  given in Table 2 were obtained. In order to obtain accurate values of  $y$ , several separate experiments were performed in each case, the mean values being recorded in Table 3.

TABLE 3.

Rate constants for the reaction of ethyl methanesulphonate with substituted pyridines in water at pH 9 and 61°.

Amine	[Amine] (10 <sup>2</sup> M)	Ester (10 <sup>2</sup> M)	Acid liberated at $t_{\infty}$ (%)	10 <sup>4</sup> $k_2$ (l. mole <sup>-1</sup> sec. <sup>-1</sup> )	pK <sub>a</sub> <sup>16</sup>
Pyridine .....	21.0	0.927	41.0	14.2	5.17
$\beta$ -Picoline .....	5.10	0.986	71.3	16.8	5.68
$\alpha$ -Picoline .....	5.36	0.987	84.8	7.13	5.97
$\gamma$ -Picoline .....	5.00	1.02	71.1	17.3	6.02
3,5-Lutidine .....	4.40	1.01	72.8	18.0	6.17
2,6-Lutidine .....	4.16	1.01	93.9	3.30	6.75
2,4-Lutidine .....	4.61	1.03	83.8	8.88	6.79
2,4,6-Collidine.....	2.28	0.937	95.6	4.09	7.59

*Determination of n-butylamine.* It is assumed that the rate constants  $k_2$  refer to substitution only, and that no  $\beta$ -elimination occurs. This was confirmed in the reaction with n-butylamine, by direct estimation of the amine before and after the reaction by the Van Slyke micro-method. The apparatus and procedure have been described by Hamilton.<sup>17</sup>

*Results.*—Ethyl methanesulphonate (0.0204M) was added to a solution of sodium hydroxide (0.0200N) and n-butylamine (0.02265M) in water at 35°.

*Initial solution.* 2.0 ml. gave (a) 1.084 ml. of nitrogen (3 detns.) at 20.9° and 766 mm.; calculated concentration of amine = 0.02266 mole l.<sup>-1</sup>.

*Final solution.* The mixture was left in the thermostat at 35° for 3 days (10 half-lives); 2.0 ml. gave 0.692 ml. N<sub>2</sub> at 21° and 758 mm.; calculated concentration of amine = 0.01429M. Concentration of amine alkylated = 0.00837M. Concentration of amine reacted (by titration) = (1.091 × 0.0204)/2.638 = 0.00843M. The two values are in very good agreement, showing that  $\beta$ -elimination due to the amine may be neglected. It is assumed that the less basic amines also give no olefin.

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<sup>16</sup> Braude and Nachod, "Determination of Organic Structures by Physical Methods," New York, 1955, pp. 594, 597.

<sup>17</sup> Hamilton, Analytical Methods of Protein Chemistry, 1960, 2, 62.