Nucleophilic Displacement Reactions in Aromatic Systems. Part X.[1] Kinetics of the Reactions of Substituted α-Halogenopyridines with Aniline, *N*-Methyl-, and *N*-Ethyl-aniline in Ethanol or Ethyl Acetate, and of 1-Fluoro-2,4-dinitrobenzene with Aniline in Various Solvents. The Influence of Basic Catalysts

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Rate coefficients for the reactions of 2-chloro- or -fluoro-3- or -5-nitropyridine with *N*-methylaniline in ethanol at 80° and for the reactions of 2-chloro-3-cyano- or 3-cyano-2-fluoro-5-nitropyridine with aniline, *N*-methyl-, or *N*-ethyl-aniline in ethanol at 20° have been determined. The effect of the initial concentration of the amine and of the concentration of added potassium acetate, acetic acid, or sodium perchlorate has been extensively investigated. Catalysis of the reactions of the fluoro-compounds (but not the chloro-compounds) by acetate ion is typical. except with aniline as nucleophile. but catalysis by the amine is not usually observed. The acetate-ion catalysis and the relative mobility of fluorine and chlorine in the various reactions are discussed in terms of the two-stage mechanism of nucleophilic aromatic substitution. The role of the amine and the occurrence of side reactions (ethanolysis and acetolysis) are also examined. Rate coefficients for the reactions of 2-chloro-3-cyano- or 3-cyano-2-fluoro-5-nitropyridine with aniline, *N*-methyl-, or *N*-ethyl-aniline in ethyl acetate (at various convenient temperatures) have also been measured. The reactions of the fluoro-compound (but not of the chloro-compound) are subject to strong catalysis by the amine. Rate coefficients have also been measured for the reactions of 1-fluoro-2,4-dinitrobenzene with aniline or *N*-methylaniline in methanol, ethanol, benzyl alcohol, ethyl acetate, or toluene. In the less polar solvents, pyridine or triethylamine catalyses the amination strongly, and catalysis by the reactant amine is also observed. All these results are discussed in terms of the two-stage mechanism.

SINCE its discovery by Bunnett and his co-workers in 1958, the occurrence and form of base catalysis in nucleophilic aromatic substitution [2] has been of great importance in all discussions of the reaction mechanisms. The topic has been well reviewed [3,4] up to 1968, and only some recent work now calls for mention. This includes further contributions by Bunnett and his co-workers,[5] and by Kirby and Younas.[6] Moreover, nucleophilic substitution in heterocyclic aromatic compounds, which has been surveyed by Miller,[7] *e.g.* the studies of Zollinger and his co-workers,[8] and of Illuminati and his co-workers,[9] continues to attract attention. We therefore thought it of interest to investigate base catalysis in the reactions of aromatic

[1] Part IX, G. B. Barlin and N. B. Chapman, *J. Chem. Soc.*, 1965, 3017. *N.B.* Due to a change of plans there is no Part VIII.

[2] (*a*) J. F. Bunnett and K. M. Pruitt, *J. Elisha Mitchell Sci. Soc.*, 1957, **73**, 297; (*b*) J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020.

[3] J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1.

[4] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.

[5] (*a*) J. F. Bunnett, T. Kato, and N. S. Nudelman, *J. Org. Chem.*, 1969, **34**, 785; (*b*) J. F. Bunnett and C. F. Bernasconi, *ibid.*, 1970, **35**, 70; (*c*) J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1970, **92**, 2417.

[6] A. J. Kirby and M. Younas, *J. Chem. Soc.* (*B*), 1970, 1187.

[7] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, London, 1968.

[8] (*a*) P. Rys, A. Schmitz, and H. Zollinger, *Helv. Chim. Acta*, 1971, **54**, 163; (*b*) P. Caveng and H. Zollinger, *ibid.*, 1967, **50**, 866.

[9] G. B. Bressan, I. Giardi, G. Illuminati, P. Linda, and G. Sleiter, *J. Chem. Soc.* (*B*), 1971, 225, and previous papers in the series.

amines with 2-fluoro- and 2-chloro-3- or -5-nitropyridine and some of their derivatives, the uncatalysed reactions of some of which we had previously studied.[10] We have also investigated base catalysis in the reactions of 1-fluoro-2,4-dinitrobenzene with aromatic amines, utilising a wider range of solvents than heretofore.

EXPERIMENTAL

Preparation and Purification of Halogeno-compounds.—2-Chloro-3-nitropyridine (Koch–Light) was crystallised twice from methanol (charcoal) and twice from light petroleum (b.p. 60—80°) and had m.p. 102° (lit.,[11a] 102°). 2-Chloro-5-nitropyridine was prepared as described in Part I [11a] and had m.p. 107·5—108° (lit.,[11b] 108°).

2-Fluoro-3- and -5-nitropyridine. These were prepared by Finger and Starr's method [12] and had respectively b.p. 110° at 10 mmHg (lit.,[12] 109—109·5° at 10 mmHg), n_D^{25} 1·5282 (lit.,[12] 1·5278); and m.p. 16·5—17·5° (lit.,[13] 19—21°), b.p. 75—76° at 4 mmHg (lit.,[12] 86—87° at 7 mmHg), n_D^{25} 1·5247 (lit.,[12] 1·5243).

2-Chloro-3-cyano-5-nitropyridine. This was prepared as described in Part VII [10] and had m.p. 122—123° (lit.,[14] 121—122°) (Found: C, 39·4; H, 1·05; N, 23·0; Cl, 19·3. Calc. for $C_6H_2ClN_3O_2$: C, 39·25; H, 1·1; N, 22·9; Cl, 19·3%).

3-Cyano-2-fluoro-5-nitropyridine. Anhydrous potassium fluoride (10 g, 0·172 mol; dried over phosphoric oxide at 110° and 1 mmHg for several hours) was stirred with 2-chloro-3-cyano-5-nitropyridine (10 g, 0·054 mol) in dry *NN*-dimethylformamide [30 ml; n_D^{25} 1·4270 (lit.,[15] 1·4269)] at room temperature for 8—9 h (g.l.c. showed conversion was complete). *NN*-Dimethylformamide was removed at 50—55° and 4 mmHg, and the residue was shaken several times with cold, dry benzene. The solution was filtered and benzene was removed at 40° and 4 mmHg to give a pink solid (5·75 g, 63%), from which the product was extracted with hot light petroleum (b.p. 60—80°). The solvent was removed and the *residue* was repeatedly crystallised (charcoal) from light petroleum (b.p. 60—80°) and had m.p. 92·5—93·5° (Found: C, 43·2; H, 1·1; N, 24·8. $C_6H_2FN_3O_2$ requires C, 43·1; H, 1·2; N, 25·15%).

1-Fluoro-2,4-dinitrobenzene (Koch–Light) was distilled, b.p. 110—114° at 0·5 mmHg, and crystallised twice from dry ethanol, m.p. 25—26° (lit.,[16] 25·3°). No impurities were detected by g.l.c. in any of the halogeno-compounds.

Attempts to convert 6-chloro-5-cyano-2,4-dimethyl-3-nitropyridine into the corresponding fluoro-compound by the above method failed. The major product was a dark brown resin and during the reaction the mixture became intensely purple in colour. We ascribe these observations to deprotonation of the substrate by fluoride ion (a strong base in *NN*-dimethylformamide) and subsequent reaction of the purple anion to yield polymeric products.

Purification of Amines.—Aniline and *N*-methylaniline were purified *via* the pure acetyl derivative as described in Part VII.[10] They had b.p. 62° at 7·5 mmHg, 79° at 16 mmHg (lit.,[16] 71° at 9 mmHg), n_D^{20} 1·5863 (lit.,[16] 1·5863), and b.p. 69° at 6 mmHg, 81° at 16 mmHg (lit.,[2b] 57° at 4 mmHg, 79° at 10 mmHg [16]), $n_D^{21.2}$ 1·5700 (lit.,[16] n_D^{20} 1·5702), respectively. *N*-Ethylaniline was purified either through its acetyl derivative or more conveniently through its toluene-*p*-sulphonyl derivative and had b.p. 64° at 3·5 mmHg, 82° at 8 mmHg (lit.,[16] 84° at 10 mmHg), n_D^{20} 1·5560 (lit.,[16] 1·5559). Pure triethylamine had b.p. 89·5° at 760 mmHg (lit.,[15] 89·35°), n_D^{20} 1·4012 (lit.,[15] 1·4010). Pyridine was purified by the method of Heap *et al.*[17] and had b.p. 115° at 760 mmHg (lit.,[17] 115°). No impurities were detected by g.l.c. in any of the amines.

Purification of Solvents.—Ethanol was dried by Smith's method [18a] and had b.p. 78·3° at 760 mmHg (lit.,[15] 78·3°), n_D^{20} 1·3611 (lit.,[15] 1·3614), and methanol by Lund and Bjerrum's method [18b] and had b.p. 64—65° at 760 mmHg (lit.,[15] 64·5°), n_D^{20} 1·3281 (lit.,[15] 1·3286). They were stored under dry nitrogen. The water content (Karl Fischer titration) rarely exceeded 0·01% and g.l.c. showed no impurities. Ethyl acetate was dried over freshly ignited potassium carbonate (14 days), then a molecular sieve (type 4A; 28 days) and distilled, b.p. 77·3° at 760 mmHg (lit.,[15] 77·1°), n_D^{20} 1·3722 (lit.,[15] 1·3724). Dry toluene was distilled from sodium, b.p. 110° at 760 mmHg (lit.,[15] 110·6°), n_D^{20} 1·4969 (lit.,[15] 1·4969). Benzyl alcohol was dried over potassium carbonate, then over a molecular sieve (type 4A) for a week. It was distilled under nitrogen and had b.p. 90° at 12 mmHg (lit.,[16] 93° at 10 mmHg), n_D^{20} 1·5400 (lit.,[15] 1·5403).

Products.—2-*N*-Methylanilino-5-nitropyridine had m.p. 101·5—102·5° [from light petroleum (b.p. 60—80°)] (lit.,[19] 102—104°), and the 3-nitro-isomer had m.p. 74—75° (lit.,[20] 73—74°).

2-Anilino-3-cyano-5-nitropyridine was prepared by interaction of the corresponding 2-chloro-compound with an excess of aniline in dry ethanol at room temperature overnight, and had m.p. 178—179° [from light petroleum (b.p. 60—80°)] (lit.,[10] 177—178°) (Found: C, 59·9; H, 3·3; N, 23·2. Calc. for $C_{12}H_8N_4O_2$: C, 60·0; H, 3·35; N, 23·3%).

3-Cyano-2-N-methylanilino- and *3-cyano-2-N-ethylanilino-5-nitropyridine* were similarly prepared and purified, and had m.p. 150° (Found: C, 61·4; H, 3·85; N, 22·05. $C_{13}H_{10}N_4O_2$ requires C, 61·4; H, 3·95; N, 22·05%), and m.p. 113—114° respectively (Found: C, 62·6; H, 4·4; N, 21·3. $C_{14}H_{12}N_4O_2$ requires C, 62·65; H, 4·5; N, 20·9%). 2,4-Dinitrodiphenylamine and its *N*-methyl derivative had m.p.s in agreement with those in the literature.

Miscellaneous Materials.—Pure crystalline sodium perchlorate was dried *in vacuo* at 110° over phosphoric oxide. Potassium acetate was crystallised from acetic acid and dried at 110° *in vacuo* over potassium hydroxide and phosphoric oxide. These salts were stored and manipu-

[10] N. B. Chapman, D. K. Chaudhury, and J. Shorter, *J. Chem. Soc.*, 1962, 1975.
[11] (*a*) R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 1952, 437; (*b*) W. T. Caldwell and E. C. Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1695.
[12] G. C. Finger and L. D. Starr, *J. Amer. Chem. Soc.*, 1959, **81**, 2674.
[13] W. Gruber, *Canad. J. Chem.*, 1953, **31**, 1020.
[14] P. E. Fanta and R. A. Stein, *J. Amer. Chem. Soc.*, 1955, **77**, 1045.
[15] A. Weissberger, E. S. Proskauer, J. A. Riddick, and E. E. Toops, 'Technique of Organic Chemistry,' Interscience, New York, 1955, 2nd edn., vol. 7.
[16] 'Dictionary of Organic Compounds,' eds. J. R. A. Pollock and R. Stevens, Eyre and Spottiswoode, London, 1965, 4th edn.
[17] J. G. Heap, W. J. Jones, and J. B. Speakman, *J. Amer. Chem. Soc.*, 1921, **43**, 1936.
[18] (*a*) A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 1956, 3rd edn., p. 168; (*b*) H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.
[19] R. G. D. Moore and R. J. Cox, B.P., 870,027/1961 (*Chem. Abs.*, 1961, **55**, 23,134c).
[20] R. A. Abramovitch, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.*, 1954, 4263.

lated in a dry atmosphere. AnalaR acetic acid was purified by fractional freezing and fractional distillation from potassium permanganate, and had b.p. 117·5° at 760 mmHg (lit.,[15] 117·7°), n_D^{20} 1·3716 (lit.,[15] 1·3716). Aniline hydrochloride was crystallised from dry ethanol to constant m.p. 194° (lit.,[21] 197—198°).

Kinetic Procedure.[22]—Some of the reactions of chloro-compounds were followed for almost two half-lives by the method described in Part VII,[10] involving Volhard determination of chloride ion. (The ferric alum indicator should be added only when the end-point has almost been reached, to avoid undesirable colouration of the solution.) Initial concentrations of chloro-compound were *ca.* 0·025M and of amine *ca.* 0·10 or 0·20M. Second-order rate coefficients were calculated as in Part VII,[10] any necessary corrections for solvent expansion or initial solvolysis of the chloro-compound being made.

All the reactions of the fluoro-compounds and some of those of the chloro-compounds, especially those involving added potassium acetate were studied spectrophotometrically[2] during *ca.* 10 half-lives, by the following method. A Unicam SP 600 spectrophotometer was used, with 1·00 cm silica cells. Standard solutions of the halogeno-compound (*ca.* 0·025—0·0005M) and the aromatic amine (in large excess, not less than 10-fold) in the appropriate solvent, with or without known concentrations of added base, or base and acetic acid, were prepared under nitrogen in individual reaction tubes (reactions at up to 40°) or sealed bulbs (higher temperatures) at thermostat temperature. Samples were taken at intervals, cooled if necessary, and quenched by the addition of 6M-nitric acid (2·50 or 5·00 ml) and diluted appropriately with a solvent (ethanol or 1 : 1 ethanol–water) in readiness for measurements of optical density, d, at the wavelength of maximum absorption in pure ethanol of the anilino-compound produced. Concentrations at 'zero' time were usually determined by analysis of a sample taken soon after the solutions had become homogeneous and had reached thermostat temperature.

In the reactions under spectrophotometric investigation the halogeno-compound (substrate, S) may in principle be consumed by several reactions, *viz.* amination, acetolysis, and ethanolysis, all reactants other than the substrate being in large and effectively constant excess. The reaction with aromatic amines, with first-order rate coefficient, k_1^a, is the reaction of principal importance. Hence equations (1) and (2) are obtained. Clearly $[S_0]$ and $[S_t]$

$$-d[S]/dt = k_1^a[S] + \sum_i k_1^i[S] = k_T[S] = (k_1^a + k_1^s)[S] = d[P^T]/dt \quad (1)$$

$$\log[S_0]/[S_t] = k_T t/2{\cdot}303 \quad (2)$$

may, if experimental methods require it, be replaced by by the same sub-multiple of each. Equation (2) leads to the usually applicable expression (3) where d is the optical

$$\log(d_\infty - d_0) - \log(d_\infty - d_t) = k_T t/2{\cdot}303 \quad (3)$$

density, provided that the 'background' optical density remains constant, and the proportions of the components in the product also remain constant throughout a run. This is almost certain, provided that, as observed, 'final' optical densities remain constant over many reaction half-lives. Values of k_T may be obtained graphically from plots of $\log(d_\infty - d_t)$ against t, or by the least squares procedure. The value of k_1^a is given by equation (4)

$$k_1^a = k_T[P^a{}_\infty]/[P^T{}_\infty] = k_T[P^a{}_\infty]/[S_0] \quad (4)$$

where P^a refers to the substituted anilinopyridine or diphenylamine, and P^T to the total product. Second-order rate coefficients are given by $k_2^a = k_1^a/[A_0]$ where A refers to the aromatic amine.

In the reactions of 2-chloro- and 2-fluoro-5-nitropyridine which are very slow (half-lives of 35—120 h), d_∞ could not be directly determined, as after the necessary time interval, significant decomposition of the reaction product had occurred. For these reactions the value of d_∞ (d_∞') which gives the best straight line, in the statistical sense, for plots of $\log(d_\infty - d_t)$ *vs.* t was calculated by an iterative procedure for which a computer program is available.* In some calculations of rate coefficients, the values obtained by using d_∞' differed by only 2—3% from those obtained by assuming that the sole absorbing product was the anilinopyridine ($d_\infty = [P^a{}_\infty]\varepsilon^a$), and the calculations were therefore made on the basis of this assumption. The values of k_2^a so obtained were reproducible to ±3%. (The number of independent runs was increased from 3 or 4 to 5 or 6.) For the reactions of 2-fluoro-5-nitropyridine without potassium acetate and of 2-chloro-5-nitropyridine in the presence of potassium acetate, d_∞' values were used, because of the significant occurrence of side-reactions in these systems.

To use equation (4) we need values of $[P^a{}_\infty]$. Moreover

$$[P^a{}_\infty]\varepsilon^a + \sum_i [P^i{}_\infty]\varepsilon^i = d_\infty{}^e \quad (5)$$

equation (5) applies where ε is an extinction coefficient, and $d_\infty{}^e$ is the experimental value of d at 'infinite' time, it now being assumed that 'background' optical density is negligible. (This was verified experimentally for the systems studied.) If the substituted anilinopyridine is the sole product absorbing at the chosen wavelength, $[P^a{}_\infty]\varepsilon^a = d_\infty{}^e$ and equation (6) is obtained where $d_\infty{}^c$ is

$$k_1^a = k_T d_\infty{}^e/\varepsilon^a[S_0] = k_T d_\infty{}^e/d_\infty{}^c \quad (6)$$

the final optical density corresponding to 100% yield of substituted anilinopyridine. This last circumstance was shown to pertain to the reactions of the 2-halogeno-3- and -5-nitropyridines with the relevant amines in ethanol, if measurements were made at 364 nm, and to those of 2-chloro-3-cyano-5-nitropyridine in the presence of acetic acid alone. Values of k_1^a for these reactions were calculated from equation (6), ε^a having been measured independently. If there is absorption due to by-products, with effective extinction coefficient, ε^b, when present in the proportions relevant to the reaction under consideration, equation (5) becomes (7) and hence (8) is

$$[P^a{}_\infty]\varepsilon^a + ([S_0] - [P^a{}_\infty])\varepsilon^b = d_\infty{}^e \quad (7)$$

$$k_1^a = k_T\{d_\infty{}^e/[S_0] - \varepsilon^b\}/(\varepsilon^a - \varepsilon^b) \quad (8)$$

obtained. Equation (8) was used for most of the reactions of 2-chloro-3-cyano- and 3-cyano-2-fluoro-5-nitropyridine, in which ethanolysis and acetolysis of the substrate are significant (see below). Values of ε^b were

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[21] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3875.

[22] See Ph.D. theses, University of Hull, of (*a*) D. M. Brewis, 1964; (*b*) D. J. Wright, 1968; (*c*) J. S. Paine, 1973.

obtained by suitable direct measurements. For these reactions, changing the wavelength at which measurements of optical density are made from 360 to 350 nm had no observable effect on measured values of k_2^a. In the reactions of 3-cyano-2-fluoro-5-nitropyridine in the absence of added acetate or acetic acid, ethanolysis is the sole side-reaction and the relevant value of ε^b is that of the corresponding ethoxy-compound, but this value is too low to be of significance and the effect of the side-reaction may be neglected. For reactions in ethyl acetate no side-reactions were detected, thus $k_1^a = k_T$.

Details of examples of individual experiments are in Table 1.

Ancillary Spectrophotometric Measurements.—The spectral properties of the products of interaction of 2-halogeno-

TABLE 1

2-Chloro-3-nitropyridine and *N*-methylaniline in ethanol at 70·0°

Initial [PhNHMe] 0·1009M, initial [chloro-compound] 0·0113M, initial [KOAc] 0·0968M. The reaction mixtures were diluted 10-fold before measurement of d_t.

Time (h)	23	45	69	93	113	147	185
d_t* (l mol^{-1} cm^{-1})	0·194	0·350	0·479	0·586	0·657	0·757	0·839

$d_\infty^e = 1{\cdot}067$ l mol^{-1} cm^{-1}; theoretical value (d_∞^c) = 1.111

For a plot of log ($d_\infty^e - d_t$) *vs.* t, gradient = $-3{\cdot}59 \times 10^{-3}$ h^{-1}, standard error of gradient = 0·6%, correlation coefficient = 0·9999.

$k_T = 2{\cdot}27 \times 10^{-6}$ s^{-1}, $k_1^a = 2{\cdot}18 \times 10^{-6}$ s^{-1}, $k_1^s = 0{\cdot}90 \times 10^{-7}$ s^{-1}, $k_2^a = 2{\cdot}16 \pm 0{\cdot}03 \times 10^{-5}$ l mol^{-1} s^{-1}

* Optical density at 400 nm corrected for reactant absorption.

2-Fluoro-5-nitropyridine and *N*-methylaniline in ethanol at 80·0°

Initial [PhNHMe] 0·0999M, initial [fluoro-compound] 0·000895M, initial [HOAc] 0·1033M. The reaction mixtures were diluted 20-fold before measurement of d_t.

Time (min)	0	184	419	661	900
d_t (l mol^{-1} cm^{-1})	0·092	0·121	$0{\cdot}157_5$	$0{\cdot}189_5$	0·220
Time (min)	1363	1619	1862		
d_t (l mol^{-1} cm^{-1})	$0{\cdot}277_5$	0·301	0·323		
Time (min)	2103	2339	2620	3062	3298
d_t (l mol^{-1} cm^{-1})	0·347	0·363	0·402	0·416	0·432
Time (min)	3541	3780	4263	4561	
d_t (l mol^{-1} cm^{-1})	0·445	0·455	0·480	0·490	

$d_\infty' = 0{\cdot}618$ l mol^{-1} cm^{-1}; theoretical value (d_∞^c) = 0·6755

For a plot of log ($d_\infty' - d_t$) *vs.* t, gradient = $-1{\cdot}359 \times 10^{-4}$ min^{-1}, standard error of gradient = 1·0%, correlation coefficient = 0·9992.

$k_T = 5{\cdot}20 \times 10^{-6}$ s^{-1}, $k_1^a = 4{\cdot}76 \times 10^{-6}$ s^{-1}, $k_1^s = 4{\cdot}43 \times 10^{-7}$ s^{-1}, $k_2^a = 4{\cdot}77 \pm 0{\cdot}08 \times 10^{-5}$ l mol^{-1} s^{-1}

1-Fluoro-2,4-dinitrobenzene and aniline in ethanol at 30·0°

Initial [$PhNH_2$] 0·1000M, initial [fluoro-compound] 0·000500M, initial [KOAc] 0·2000M. The reaction mixtures were diluted 20-fold before measurement of d_t.

Time (min)	3·50	5·50	7·65	9·63
d_t (l mol^{-1} cm^{-1})	0·065	0·166	0·232	0·276
Time (min)	11·67	13·77	15·72	17·78
d_t (l mol^{-1} cm^{-1})	0·306	0·331	0·347	0·366

$d_\infty^e = 0{\cdot}406$ l mol^{-1} cm^{-1}; theoretical value (d_∞^c) = 0·442 l mol^{-1} cm^{-1}.

For a plot of log ($d_\infty^e - d_t$) *vs.* t, gradient = $-6{\cdot}28 \times 10^{-2}$ min^{-1}, standard error of gradient = 2·0%, correlation coefficient = 0·9988.

$k_T = 2{\cdot}41 \times 10^{-3}$ s^{-1}, $k_1^a = 2{\cdot}21 \times 10^{-3}$ s^{-1}, $k_1^s = 0{\cdot}20 \times 10^{-3}$ s^{-1}, $k_2^a = 2{\cdot}21 \pm 0{\cdot}06 \times 10^{-2}$ l mol^{-1} s^{-1}

TABLE 1 (*Continued*)

3-Cyano-2-fluoro-5-nitropyridine with *N*-methylaniline in ethanol at 20·0°

Initial [PhNHMe] 0·0999M, initial [fluoro-compound] 0·000675M, initial [KOAc] 0·01006M. The reaction mixtures were diluted five-fold before measurement of d_t^i or d_t^f (see below † for definitions).

Time (s)	89·0	137·0	190·0	243·0
d_t^i (l mol^{-1} cm^{-1})	$0{\cdot}171_5$	0·285	0·365	0·417
Time (s)	299·0	354·0	407·0	
d_t^i (l mol^{-1} cm^{-1})	0·469	$0{\cdot}506_5$	$0{\cdot}530_5$	

$d_\infty^e = 0{\cdot}602$ l mol^{-1} cm^{-1}; theoretical value (d_∞^c) = 2·564 l mol^{-1} cm^{-1}.

For a plot of log ($d_\infty^e - d_t^i$) *vs.* t, gradient = $-2{\cdot}426 \times 10^{-3}$ s^{-1}, standard error of gradient = 1·4%, correlation coefficient = 0·9995.

$k_T = 5{\cdot}59 \times 10^{-3}$ s^{-1}, $k_1^a = 7{\cdot}28_5 \times 10^{-4}$ s^{-1}, $k_1^s = 4{\cdot}86 \times 10^{-3}$ s^{-1}, $k_2^a = 7{\cdot}29 \pm 0{\cdot}20 \times 10^{-3}$ l mol^{-1} s^{-1}.

Time (s)	89·0	137·0	190·0	243·0
d_t^f (l mol^{-1} cm^{-1})	0·344	$0{\cdot}411_5$	0·458	$0{\cdot}489_5$
Time (s)	299·0	354·0	407·0	
d_t^f (l mol^{-1} cm^{-1})	$0{\cdot}520_5$	0·543	0·557	

$d_\infty^e = 0{\cdot}602$ l mol^{-1} cm^{-1}.

For a plot of log ($d_\infty^e - d_t^f$) *vs.* t, gradient = $-2{\cdot}364 \times 10^{-3}$ s^{-1}, standard error of gradient = 1·3%, correlation coefficient = 0·9996.

$k_T = 5{\cdot}45 \times 10^{-3}$ s^{-1}.

2-Chloro-3-cyano-5-nitropyridine with aniline in ethanol at 20·0°

Initial [$PhNH_2$] 0·0927M, initial [chloro-compound] 0·0215M; titrimetric procedure.

Time (s)	331	477	636	698	850	971	1130
Reaction (%)	22·0	29·9	36·9	40·1	45·4	49·3	53·8
$10^3 k_2^a$ (l mol^{-1} s^{-1})	8·53	8·67	8·62	8·80	8·71	8·67	8·61
Time (s)	1240	1369	1616	1750	2109	2435	
Reaction (%)	57·3	60·3	64·9	68·0	72·6	78·2	
$10^3 k_2^a$ (l mol^{-1} s^{-1})	8·79	8·72	8·55	8·71	8·78	8·84	

Mean $k_2^a = 8{\cdot}69 \pm 0{\cdot}08 \times 10^{-3}$ l mol^{-1} s^{-1}.‡

2-Chloro-5-nitropyridine with *N*-methylaniline in ethanol at 80·0°

Initial [PhNHMe] 0·1988M, initial [chloro-compound] = 0·0248M; titrimetric procedure.

Time (min)	1046	1550	2420	2996
Reaction (%)	18·1	25·5	36·7	43·2
$10^5 k_2^a$ (l mol^{-1} s^{-1})	1·64	1·65	1·67	1·68
Time (min)	3815	4912	6350	8518
Reaction (%)	51·5	60·8	69·7	8·7
$10^5 k_2^a$ (l mol^{-1} s^{-1})	1·72	1·76	$1{\cdot}76_5$	1·86

Mean $k_2^a = 1{\cdot}72 \pm 0{\cdot}06 \times 10^{-5}$ l mol^{-1} s^{-1}.‡

Value of k_2^a extrapolated to zero time $1{\cdot}60 \pm 0{\cdot}02 \times 10^{-5}$ l mol^{-1} s^{-1}.

Determined spectrophotometrically, $k_2^a = 1{\cdot}62 \pm 0{\cdot}03 \times 10^{-5}$ l mol^{-1} s^{-1}.

The most likely explanation of the upward trend in values of k_2^a is autocatalysis arising from *N*-protonation of the substrate by $PhN\overset{+}{H}_2Me$ (*cf.* ref. 11*a*).

† In some experiments the optical densities of samples taken in a kinetic run changed from an 'initial' value, d_t^i to a 'final' value, d_t^f, observed after the samples had been kept until there was no further change. As can be seen from this example, the differences in values of k_T arising from the use of d_t^i or d_t^f in their evaluation, amounts only to a few percent, comparable to the usual measure of reproducibility of k_2^a (Table 4). ‡ Error given is the average error.

or 3-cyano-2-halogeno-5-nitropyridines with aniline, *N*-methyl-, or *N*-ethyl-aniline are in Table 2. The solutions were found to obey the Beer–Lambert law. The reactants and relevant additives have very small extinction coefficients in the range 350—400 nm. It appears that 2-*N*-methylanilino-5-nitropyridine is protonated by low concentrations of nitric acid in aqueous ethanol, with consequent reductions in values of ε, but the less basic 3-cyano-2-*N*-methyl(or ethyl)anilino-5-nitropyridine or 2-*N*-methylanilino-3-nitropyridine are not protonated and values of ε are independent of [HNO_3] within the range studied.

TABLE 2

Spectral properties at 20·0° of substituted 2-anilino-5-nitropyridines (all values of $\lambda_{max.}$ and ε^a are means of two independent measurements)

Exocyclic *N*-substituent	3-Substituent	Solvent *	$\lambda_{max.}$ (nm)	ε (l mol^{-1} cm^{-1})	
Me	None	EtOH	364	19,635 †	
Me	None	1	374	18,170 ‡	
Me	None	2		17,530 ‡	
Me	None	3		12,290 ‡	
None	CN	EtOH	356	18,620 §	18,470 ¶
None	CN	1	356	17,690 §	17,455 ¶
None	CN	4	356	17,690 §	17,455 ¶
None	CN	5	356	17,690 §	17,455 ¶
None	CN	6	356	17,910 §	17,645 ¶
Et	CN	EtOH	355	20,245 §§	19,910 ††
Me	CN	EtOH	354	19,425 **	19,360 ††
Me	CN	1	359	19,035 **	18,485 ††
Et	CN	1	361	19,595 §§	18,790 ††

* Solvents are as follows: 1, 52·5% EtOH–H_2O; 2, 1 containing 0·5% 6N-HNO_3; 3, 1 containing 5% 6N-HNO_3 [in the range 0—5% 6N-HNO_3, ε^a is approximately related to the percentage (p) of 6N-HNO_3, by the equation $\varepsilon^a = 18{,}170 - 1191p$]; 4, 1 containing 2·5% 6N-HNO_3; 5, 1 containing 10% 6N-HNO_3; 6, 1 containing 5% EtOAc and 2·5% 6N-HNO_3. All percentages by volume. † At 364 nm. The corresponding 2-chloro- and 2-fluoro-compound, respectively, have ε 88·9 and 61·0 l mol^{-1} cm^{-1} at 364 nm in ethanol. 2-*N*-Methylanilino-3-nitropyridine has ε 1974 l mol^{-1} cm^{-1}, and the corresponding 2-chloro- and 2-fluoro-compound, respectively, have ε 11·1 and 15·8 l mol^{-1} cm^{-1} at 400 nm in ethanol. The value for 2,4-dinitrodiphenylamine in 1 : 1 ethanol–water is 17,680 l mol^{-1} cm^{-1} at 361 nm, and that for 1-fluoro-2,4-dinitrobenzene is negligibly small. ‡ At 374 nm. § At 356 nm. ¶ At 350 nm. ** At 354 nm. †† At 350 nm. §§ At 335 nm. The last four values of ε^a were unchanged by addition of up to 10% of 6N-HNO_3.

For the calculation of rate coefficients, values of ε^a and ε^b at the appropriate wavelength are necessary, with conditions as to solvent the same as those pertaining in spectrophotometric measurements made during kinetic runs. It is particularly necessary to take care over the nitric acid concentration in reactions of 2-halogeno-5-nitropyridines. Relevant values of ε^a are assembled in Table 2. Side-reactions influencing observed optical densities in reactions of chloro-compounds in the presence of acetate (with or without added acetic acid) and in all the reactions of fluoro-compounds must occur, because the observed optical density at ' infinite ' time is less than that calculated from the initial substrate concentration and the relevant extinction coefficient, except for reactions of 2-halogeno-5-nitropyridines. The necessary effective extinction coefficients were measured in standard fashion and the results are assembled in Table 3.

Products.—Solutions of potassium acetate in ethanol contain both ethoxide and acetate ions and react with the halogeno-compounds studied to yield a mixture of the corresponding ethoxy- and acetoxy-compound. It is readily shown that the percentage of acetoxy compound f^{ac}, is given by $f^{ac} = 100 - f^{et} = 100(\varepsilon^b - \varepsilon^{et})/(\varepsilon^{ac} - \varepsilon^{et})$

TABLE 3

Spectral properties of products of the reactions at 20·0° of 3-cyano-2-halogeno-5-nitropyridine * with ethanol or with solutions (A) of potassium acetate and/or acetic acid in ethanol

No.	Halogen	A	Extinction coefficient † ε^b (l mol^{-1} cm^{-1}) at 350 nm	354 nm	355 nm	356 nm
1	F		492	378	357	336
2	F	KOAc (0·010M)	3470	2305	2050	1835
3	F	KOAc (0·10M)	3505	2330	2070	1855
4	F	KOAc (0·011M) + HOAc (0·011M)	3645	2420	2150	1925
5	F	HOAc (0·011M)	671	494	459	426
6	F	HOAc (0·10M)	963	683	625	573
7	Cl	KOAc(0·10M)	2650	1775	1585	1425
8	Cl	KOAc (0·12M)	2675	1795	1600	1440
9	Cl	KOAc (0·10M) + HOAc (0·10M)	3610	2395	2130	1905

* The 2-chloro-compound has ε 113·0, 110·2, and 106·5 l mol^{-1} cm^{-1} in ethanol at 354, 355, and 356 nm, and in ethyl acetate 126·2, 122·3, and 118·6 l mol^{-1} cm^{-1} respectively. For the fluoro-compound in ethyl acetate the values are 74·8, 72·5, and 70·3 l mol^{-1} cm^{-1} respectively (all values are for 20·0°). † Measured at 20·0° in ethanol containing 2·5—10% (v/v) 6N-HNO_3. The values are independent of the concentration of added HNO_3. Extinction coefficients measured without added HNO_3 vary with the degree of dilution of the reaction mixture, suggesting the conversion, under these conditions, of the first formed product into a more strongly absorbing product which is destroyed by strong acids.

where superscripts ac and et refer to acetoxy- and ethoxy-compound and ε^b is the mean extinction coefficient of the product [$=d_\infty/(c^{ac} + c^{et})$]. For reactions of the fluoro-compound, f^{ac} is *ca.* 95% and for those of the chloro-compound, *ca.* 69%. Addition of an equimolar concentration of acetic acid can be shown by consideration of the relevant equilibria to reduce the ethoxide ion concentration in the above solutions by a factor of *ca.* 5×10^3. Because spectrophotometric measurements show only a small (6—45%) increase in proportion of acetoxy-compound when acetic acid is added as above, we conclude that in the presence of acetic acid, ether formed by reaction of the substrate with ethoxide ions is only a very small proportion of the product. Also that formed by reaction with ethanol is very small, as can be seen from the relevant rate coefficients (Table 5). Hence the extinction coefficients in items 4 and 9 of Table 3 are essentially those of the acetoxy-compounds.

Addition of an aromatic amine to solutions of potassium acetate in ethanol may in principle cause a very small increase in ethoxide ion concentration, but mainly because of the much higher rate of acetolysis than ethanolysis in the prevailing conditions, the overall effect of this addition on the composition of the product is negligible In the presence of acetic acid this effect is smaller still.

Addition of an aromatic amine to solutions of acetic acid in ethanol causes a substantial increase in the acetate concentration, with consequential increase in the proportion of acetoxy-compound in the product. The value of the relevant extinction coefficient can be calculated by an iterative procedure, the details of which are given in ref. 22*c*. In practice only two repetitions are necessary to obtain a satisfactory value.

DISCUSSION

General Comments on the Kinetics of Amination of 2-Halogeno-3- or -5-nitropyridines.—The results are in Tables 4 and 5.

Items 2 and 7 in Table 4 show that for 2-halogeno-5-nitropyridines reacting with *N*-methylaniline in ethanol at 80°, the specific rate for the fluoro- relative to that for the chloro-compound is *ca.* 1·14. The corresponding value for 2-halogeno-3-nitropyridines reactions are of the second order, first order in substrate and in nucleophile, and that there is no measurable catalysis by the amine acting as a base. The one exception is the reaction of 3-cyano-2-fluoro-5-nitropyridine with *N*-methylaniline, for which k_2^a is increased by *ca.* 70% when the initial amine concentration is increased from 0·05 to 0·2M (Table 5, item 17 and footnote ¶). The corresponding reaction of *N*-ethylaniline seems scarcely affected in this way.

TABLE 4

Kinetics of the reactions of 2-halogeno-3- or -5-nitropyridines with *N*-methylaniline in ethanol

No.	Halogen	[KOAc](M)	[HOAc](M)	*Y* *	$10^5k_2^a$ (l mol^{-1} s^{-1}) †	$10^6k_1^s$ (s^{-1}) †	$10^5k_1^s$/[KOAc] (l mol^{-1} s^{-1}) †
			5-Nitro-compounds at 80·0°				
1	Cl ‡			100·0	1·60 § ‖		
2	Cl ¶			100·0	2·04		
3	Cl	0·106		45·7	1·84	2·19	2·05
4	Cl	0·104	0·104	81·6	1·85	0·42	0·40
5	Cl		0·106	100·0	1·62		
6	F			92·7 **	1·82 §‖	0·25	
7	F ¶			87·6	2·15	0·30	
8	F	0·0204		12·8	5·61	38·3	188
9	F	0·0403		12·5	9·52	66·6	165
10	F	0·0601		11·8	13·4	100	166
11	F	0·0818		12·2	17·9	130	159
12	F	0·101		11·7	21·9	167	166
13	F	0·121		11·9	25·6	190	158
14	F	0·141		12·1	29·5	217	154
15	F	0·160		11·8	33·9	253	158
16	F	0·180		11·3	36·6	289	161
17	F	0·204		11·7	41·3	314	154
18	F	0·0530	0·0530	26·9	12·5	34·2	64·4
19	F	0·0825	0·0819	24·3	17·6	55·3	67·0
20	F	0·111	0·111	26·0	23·2	65·8	59·3
21	F	0·153	0·154	24·6	31·4	95·7	62·4
22	F		0·1040	91·8	4·73	0·43	
			3-Nitro-compounds ‡ at 70·0°				
23	Cl			100·0	2·16		
24	Cl	0·0968		96·0	2·16		
25	Cl ¶			100·0	2·17		
26	F			100·0	3·79		
27	F	0·0508		51·4	12·7		
28	F	0·122		46·9	29·2		
29	F ¶			100·0	3·98		

* Percentage yield of substituted anilinopyridine. † Rate coefficients are, unless otherwise stated, mean values from three independent determinations, with a maximum deviation from the mean of ±2%. Where necessary values were obtained by extrapolation to zero time. Most separate values of k_2^a were reproducible to ±3 or 4%, except when KOAc alone was added when they were reproducible to ±5%. Values of k_1^s are reproducible to ±4% except for the reactions of 2-fluoro-5-nitropyridine without added KOAc (±25%) and for those of the 2-chloro-compound in the presence of KOAc (±10—15%). ‡ For the reaction with aniline at 70·0°, $k_2^a = 2·76 \times 10^{-5}$ l mol^{-1} s^{-1}. § Mean of four separate values. ‖ Unaffected by a 3-fold variation (from *ca.* 0·1 to *ca.* 0·3M) in [PhNHMe]. ¶ In the presence of 0·1065M-$NaClO_4$ (no. 2) or 0·1016M-$NaClO_4$ (no. 7), or 0·1030M-$NaClO_4$ (no. 25), or 0·1170M-$NaClO_4$ (no. 29). ** Mean value from 3 determinations when the initial [PhNHMe] varies from 0·0997 to 0·299M: range 87·9—95·6%.

at 70° (items 23 and 26) is 1·75. For 2-halogeno-3-cyano-5-nitropyridines reacting with aniline at 20° (Table 5, items 1 and 6) the relative reactivity is much larger, *ca.* 12, but for the reactions with *N*-methylaniline (items 12 and 17) and *N*-ethylaniline (items 25 and 30) the fluoro-compound is less reactive than the chloro-compound, the relative reactivities being 0·93 † and 0·74 respectively.

For most of the above mentioned reactions, k_2^a is in each case, within experimental error, independent of the initial amine concentration over a two- or three-fold change. There can be little doubt that these

† At [amine] = 0·10 M; allowing for catalysis by the amine (see later) the ratio is *ca.* 0·60.

For the reactions of chloro-compounds with *N*-methylaniline (Table 4, items 1—5 and 23—25; Table 5, items 12—16), or aniline (Table 5, items 1—5) or *N*-ethylaniline (Table 5, items 25—29) the results show that k_2^a is only slightly affected by added potassium acetate, sodium perchlorate, or acetic acid. A small, rate-enhancing effect of potassium acetate is comparable with that produced by sodium perchlorate, and this is undoubtedly the medium effect of an ' inert salt '. This influence of potassium acetate on k_2^a is not affected by the addition of acetic acid, which also has no effect when it is the sole additive. It is clear that these reactions, like those of analogous homocyclic compounds,[2b] are not subject to catalysis by

TABLE 5

Kinetics of the reactions of 2-halogeno-3-cyano-5-nitropyridines with aniline, *N*-methyl-, or *N*-ethyl-aniline (PhNHR) in ethanol at 20·0°

No.	R	Halogen	[KOAc](M)	[HOAc](M)	*Y* *	$10^3k_2^a$ (l mol^{-1} s^{-1}) †	$10^5k_1^s$ (s^{-1})	$10^4k_1^s$/[KOAc] (l mol^{-1} s^{-1})
1	H	Cl			100·0	8·64 ‡§		
2	H	Cl ‖			100·0	9·51		
3	H	Cl	0·1005		96·3	10·5	4·1	4·1
4	H	Cl	0·1007	0·1007	97·7	10·5	2·5	2·5
5	H	Cl		0·1008	100·0	8·56		
6	H	F			99·0	104 ‡§	2·2	
7	H	F ‖			98·2	106	2·2	
8	H	F	0·01164		21·9	128	539	4630
9	H	F	0·01253	0·01132	22·3	132	541	4320
10	H	F		0·01104	97·9	104	2·6	
11	H	F		0·1010	96·8	106	4·0	
12	Me	Cl			99·8	1·35 ‡§		
13	Me	Cl ‖			99·7	1·50		
14	Me	Cl	0·09892		80·9	1·64	3·9	3·9
15	Me	Cl	0·1009	0·1013	85·5	1·63	2·8	2·7
16	Me	Cl		0·1016	99·6	1·35		
17	Me	F ¶			83·4	1·25	2·5	
18	Me	F ‖			85·6	1·37	2·3	
19	Me	F	0·01010		13·1	7·20	483	4780
20	Me	F	0·01493		12·5	9·80	687	4600
21	Me	F	0·02021		12·3	12·9	928	4590
22	Me	F	0·01013	0·01092	14·4	7·37	440	4350
23	Me	F		0·01106	76·3	1·33	4·1	
24	Me	F		0·1012	67·4	1·77	8·5	
25	Et	Cl			99·3	0·337 §		
26	Et	Cl ‖			99·0	0·378		
27	Et	Cl	0·1221		45·0	0·420	5·13	4·20
28	Et	Cl	0·1005	0·1000	63·5	0·405	2·34	2·32
29	Et	Cl		0·1044	99·2	0·336		
30	Et	F ¶			50·9	0·248	2·4	
31	Et	F ‖			50·7	0·251	2·4	
32	Et	F	0·01004		3·2	1·67	5·15	5260
33	Et	F	0·01490		3·1	2·30	7·19	4830
34	Et	F	0·0202		3·05	3·08	9·79	4850
35	Et	F	0·0102	0·01106	3·5	1·74	4·79	4690
36	Et	F		0·01106	40·2	0·264	0·040	
37		F **					1·82	
38		F ††		0·011			1·94	
39		F ††		0·100			2·12	
40		F ††	0·0102				514	5050
41		F ††	0·0114	0·0109			547	4800

* Percentage yield of substituted anilinopyridine. † Rate coefficients are, unless otherwise stated, the mean values from three independent determinations, with a maximum deviation from the mean of ±2%. Most separate values of k_2^a were reproducible to ±4%. For reactions carried out in the presence of KOAc, mean values of k_2^a from 6—10 independent determinations are given, and these have mean deviations of ±3 to ±6%. ‡ Mean of three separate values with different initial [amine]. § Almost unaffected by a 2-fold variation in [$PhNH_2$] (no. 1), and a 3-fold variation in [$PhNH_2$], [PhNHMe], or [PhNHEt] (nos. 6, 12, and 25). ‖ In the presence of 0·1006M-$NaClO_4$ (no. 2), 0·01174M-$NaClO_4$ (no. 7), and of 0·01008M-$NaClO_4$ (nos. 13, 18, 26, and 31). ¶ No. 17, initial [PhNHMe] = 0·1010M. For initial [PhNHMe] = 0·05180, 0·1524, and 0·2014M, the values of $10^3k_2^a$ are 1·03, 1·47, and 1·70 l mol^{-1} s^{-1} respectively, of *Y* 67·4, 89·3, and 91·8% respectively, and of $10^5k_1^s$ 2·6, 2·7, and 3·0 s^{-1} respectively. No. 30, initial [PhNHEt] 0·1015M. For initial [PhNHEt] = 0·2010 or 0·3006M, the values of $10^4k_2^a$ are 2·58 and 2·60 l mol^{-1} s^{-1} respectively, and of $10^5k_1^s$ 2·5 s^{-1}. ** Solvolysis by pure ethanol. †† Solvolysis by pure ethanol or by ethanol containing KOAc and/or AcOH.

acetate ion acting as a base. On the other hand the reactions of the fluoro-compounds, like those of their homocyclic counterparts,[2b] show marked catalysis by added acetate ion. For 2-fluoro-3-nitropyridine (which we have not investigated extensively) reacting with *N*-methylaniline (Table 4, items 26—29) *ca.* 0·05M-KOAc causes a *ca.* 3·5-fold increase in k_2^a, and the catalytic effect shows signs of being linear in acetate concentration. For 2-fluoro-5-nitropyridine, which has been more extensively investigated (Table 4, items 6—22), there is again a marked catalytic effect, unaffected by an equimolar concentration of acetic acid, and as Figure 1 shows, clearly linear in acetate concentration: *ca.* 0·05M-KOAc causes a *ca.* 6-fold increase in k_2^a. Acetic acid alone (*ca.* 0·1M) gives rise to a *ca.* 2·5-fold increase in k_2^a (item 22). Sodium perchlorate has only a feeble salt effect (Table 4, items 6, 7; 26, 29).

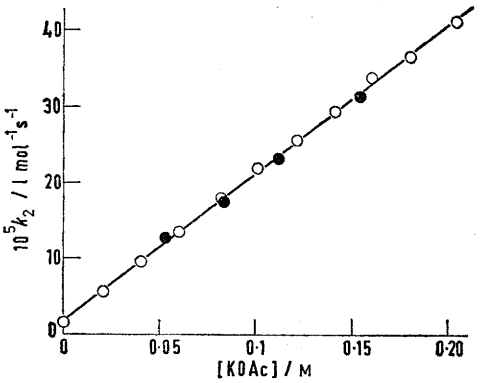
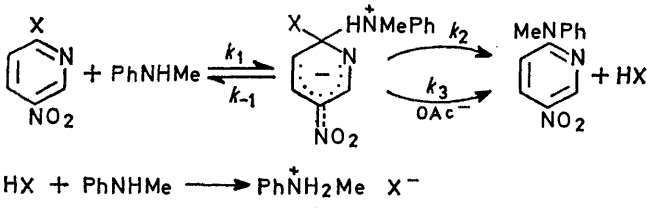


FIGURE 1 The effect of potassium acetate on k_2^a for the reaction of 2-fluoro-5-nitropyridine with *N*-methylaniline in ethanol at 80·0°. Data in Table 4, items 7—21: ○ KOAc alone; equimolar KOAc and AcOH

The reactions of 3-cyano-2-fluoro-5-nitropyridine with *N*-methyl- or *N*-ethyl-aniline are even more sensitive to the addition of acetate ion (Table 5, items 17—24, 30—36), *ca.* 0·02M-KOAc producing *ca.* 9- and 12-fold increases in k_2^a respectively. Again the catalytic effect appears to be linear, and to be uninfluenced by the addition of an equimolar concentration of acetic acid, which by itself has a small, rate-enhancing effect. The reaction of this fluoro-compound with aniline, however, shows only a slight indication of catalysis by acetate ions (Table 5, items 6—11). All this behaviour is, in the main, analogous to the corresponding reactions of the homocyclic analogue, 1-fluoro-2,4-dinitrobenzene.[21]

For the reactions of 2-halogeno-3-cyano-5-nitropyridines, the rate coefficients vary markedly with the nucleophile. For both the chloro- and the fluoro-compound the reactivity order is aniline > *N*-methylaniline > *N*-ethylaniline (Table 5, items 1, 12, 25; 6, 17, 30) but the spread of rate coefficients is much the greater for the fluoro-compounds. 2-Chloro-5-nitropyridine also shows the order aniline > *N*-methylaniline (Table 4, item 1 and footnote).

Acetate Ion Catalysis and F/Cl *Mobility.*—Following Bunnett and Randall [2b] we relate the acetate ion catalysis of the reactions of the 2-fluoropyridine compounds to the two-stage, intermediate-complex mechanism for nucleophilic aromatic substitution (*e.g.* Scheme 1),* despite the fact that in the past [10] we have had reservations about the universal applicability of this mechanism. Most of these reservations we no longer



SCHEME 1

retain. In the second step acetate ions, and conceivably other bases, may assist the removal of the proton in the elimination of HX from the intermediate. Mechanistic details of this catalysis are considered later, but we can at once dispose of the possibility that the acetate ion catalysis is indirect, *i.e.* exerted through equilibrium (9) with the actual basic catalyst being

$$EtOH + OAc^- \rightleftharpoons EtO^- + AcOH \quad (9)$$

the ethoxide ion. Later we have to consider this equilibrium in connection with the competitive solvolytic reactions of the halogeno-compounds, but the observed kinetics do not conform with its being involved in acetate ion catalysis, for this would require a linear dependence of k_2^a on $[OAc^-]^{\frac{1}{2}}$ and a suppression of the catalysis by the addition of acetic acid (*cf.* Figure 1). The intervention of $Ph\bar{N}Me$ through (10) may likewise be discounted.

$$PhNHMe + OAc^- \rightleftharpoons Ph\bar{N}Me + AcOH \quad (10)$$

There is also the alternative possibility of *nucleophilic* (rather than base) catalysis by acetate ion, *i.e.* catalysis might involve the displacement of fluorine by acetate ion to form the 2-acetoxypyridine derivative, and its rapid conversion into the *N*-methylanilino-product by reaction with the amine. This interpretation is ruled out by the fact that for the reactions of 2-fluoro-5-nitropyridine in the presence of acetate ion and acetic acid, in which the ethoxide ion (from $EtOH + OAc^- \longrightarrow EtO^- + HOAc$) is suppressed, and therefore acetolysis is the main side-reaction (see p. 1797), the value of *Y*, the yield of substituted anilinopyridine, is only *ca.* 25%. Rapid conversion of the acetoxy-compound into the anilino-compound is not compatible with these observations. This conclusion is similar to that reached by Bunnett and Randall [2b] for reactions of 1-fluoro-2,4-dinitrobenzene with *N*-methylaniline in ethanol.

In Scheme 1, if the concentration of the intermediate complex is always very small compared with the concentrations of the reactants, a stationary state treatment [2b] may be used to give equation (11). If

$$k_2^a = k_1(k_2 + k_3[OAc^-])/(k_{-1} + k_2 + k_3[OAc^-]) \quad (11)$$

$(k_2 + k_3[OAc^-])$ $(=z) \ll k_{-1}$, (11) becomes (12). This accords with the linear dependence of k_2^a on $[OAc^-]$

$$k_2^a = k_1k_2/k_{-1} + k_1k_3[OAc^-]/k_{-1} \quad (12)$$

observed for certain reactions of the 2-fluoro-compounds.

If $(k_2 + k_3[OAc^-]) \gg k_{-1}$ or if $k_2 \gg k_{-1}$, then equation (11) is reduced to (13), *i.e.*, the first step of Scheme 1

$$k_2^a = k_1 \quad (13)$$

becomes rate-determining, and k_2^a is then largely unaffected by the addition of acetate ions, as observed for the reactions of the 2-chloro-compounds.

Thus the above scheme explains the different behaviour of the fluoro- and the chloro-compound with respect to base catalysis in terms of a shift from the situation $z \gg k_{-1}$ to $z \ll k_{-1}$ when the leaving group is changed from chlorine to fluorine. This explanation is consistent with the facility of the two halogens ($F \ll Cl$) for separating heterolytically from carbon.[23]

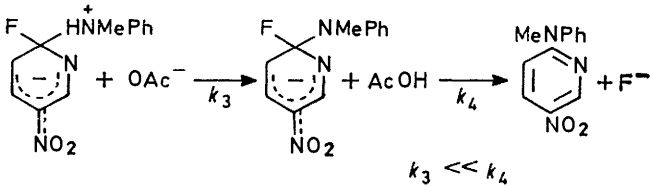
The observed relative reactivities of fluoro- and chloro-compounds are also consistent with a change in the rate-limiting step. The rate coefficient of the first step, k_1, will show the order $F \gg Cl$, because the more powerful $-I$ effect of fluorine will facilitate the addition of the nucleophile by reducing the electron density at the seat of substitution. As indicated already, k_2 values will show the order $F \ll Cl$. The comparable values of k_2^a for certain reactions of fluoro- and chloro-compounds observed in the present work arise from the moderation of the k_1 order ($F \gg Cl$) by the rate-limiting participation of the second (k_2) stage with the fluoro-compound. For 2-fluoro- or -chloro-3- or -5-nitropyridine reacting with *N*-methyl-

* For details of the reaction governed by k_2, see p. 1795.

[23] K. A. Cooper and E. D. Hughes, *J. Chem. Soc.*, 1937, 1183.

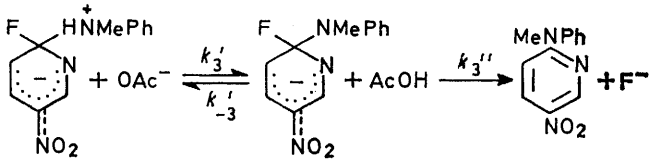
aniline the order is still F > Cl, but for 2-fluoro(or -chloro)-3-cyano-5-nitropyridine reacting with *N*-methylaniline or *N*-ethylaniline the order is reversed, *viz.* F < Cl. On the other hand, for the reactions of aniline with 2-fluoro(or -chloro)-3-cyano-5-nitropyridine, in both of which the rate of formation of the intermediate dominates (acetate ion catalysis for the fluoro-compound is fairly small), the order is F ≫ Cl.

We now consider the details of the mechanism by which the acetate ion catalyses the transformation of the intermediate complex into stable products. The simplest view is that of Bunnett and Randall [2b] who suggested that the proton is removed by the acetate ion in a rate-limiting attack (k_3), the subsequent loss of fluoride ion having $k_4 \gg k_3$. For 2-fluoro-5-nitropyridine the mechanism would be as in Scheme 2.



SCHEME 2

This formulation, however, has various unsatisfactory aspects. Proton transfer processes in hydroxylic media are usually regarded as very fast.[24] Scheme 2 not only postulates such a step as rate determining, but implies that the reprotonation (even in the presence of added acetic acid) would be much slower than the heterolysis of the carbon–fluorine bond in the final step, an unlikely hypothesis. Bunnett and Garst [25] suggested an alternative formulation, and for the present case the modified mechanism is shown in Scheme 3. Assuming that the proton-transfer step

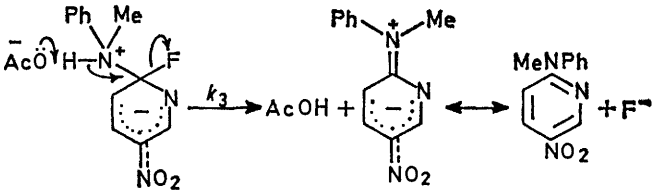


SCHEME 3

rapidly attains equilibrium, *and that the slow loss of the fluoride ion is catalysed by acetic acid,* the catalytic coefficient, k_3, of Scheme 1 and equations (11) and (12) is now equivalent to $k_3'k_3''/k_{-3}'$.

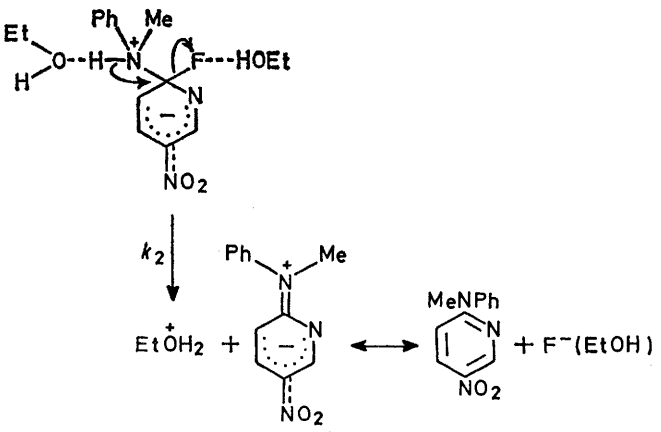
The difficulty about Scheme 3 is that there seems to be no reason why other base–acid pairs in the system should not participate in the proton transfer equilibrium and final step, each with characteristic rate coefficients corresponding to k_3', k_{-3}', and k_3'' for OAc^-–AcOH. Such pairs would be OEt^-–EtOH, PhNHMe–$PhN\overset{+}{H}_2Me$, F^-–HF, or EtOH–$Et\overset{+}{O}H_2$. The resulting kinetic expression is complicated,[22c] and implies that k_3 is liable to vary with the potassium acetate concentration, with the concentration of acetic acid, and during the course of each kinetic experiment. None of these is observed. For Scheme 3 to be valid it is necessary to suppose either that the relative reactivities for the reprotonation and for the loss of fluoride are the same for the various possible acid catalysts, or that the acetic acid component completely dominates the situation. The former condition seems inherently improbable. One of us has dealt elsewhere [22c] in detail with the latter condition and has concluded that it would be unlikely to be valid under all experimental conditions.

These difficulties are avoided if it is supposed that the acetate ion effects the removal of the proton and the detachment of the leaving group in a single concerted act. Such a mechanism has been considered by Bunnett and Garst,[25] and by Kirby and Jencks [26] as an alternative to the mechanisms already described, and for 2-fluoro-5-nitropyridine reacting with *N*-methylaniline is as in Scheme 4. Now k_3 is a simple rate coefficient, the value of which is not directly affected by the intervention of other species (*cf.* above), and which should therefore remain effectively constant as the acetate concentration is varied, when acetic acid is added, and



SCHEME 4

during the course of each kinetic experiment. The expulsion of the fluoride ion may well be assisted by hydrogen bonding to the solvent ethanol. Such a process may also participate in the uncatalysed reaction (k_2 stage), with the ethanol also acting as a base to receive the proton from the intermediate (Scheme 5).



SCHEME 5

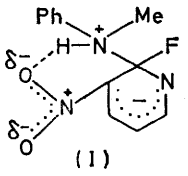
In the plot of k_2^a *vs.* [OAc^-] (Figure 1), the ratio of the slope to the intercept at [OAc^-] = 0 gives k_3/k_2,

[24] M. Eigen, *Angew. Chem. Internat. Edn.*, 1964, **3**, 1.

[25] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3879.

[26] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3217.

i.e. the ratio of the rate coefficients for the catalysed and the uncatalysed step. For 2-fluoro-5-nitropyridine reacting with *N*-methylaniline, $k_3/k_2 = 110$ l mol^{-1} (80°) while for the corresponding reaction of the 3-nitro-compound (70°) k_3/k_2 is *ca.* 55. The corresponding value for the reaction of 1-fluoro-2,4-dinitrobenzene [26] at 67·2° is *ca.* 145. One must beware of comparing the ratios at slightly different temperatures, but it seems clear that the second nitro-group favours the catalysed relative to the uncatalysed reaction rather more than the heterocyclic nitrogen atom. The rate coefficients for the reactions of aniline with 2-chloro-5-nitropyridine and 1-chloro-2,4-dinitrobenzene suggest that an *o*-nitro-group may be somewhat more effective than an *o*-aza-atom in withdrawing electrons from the reaction centre.[11a] An *o*-nitro-group might thus facilitate the loss of the proton from the intermediate but inhibit the removal of the fluoride ion. Thus k_3 is subject to opposing factors, while k_2 will be decreased by the nitro-group relative to the ring nitrogen, since the stability of the intermediate complex is due to the difficulty of heterolysing the C–F bond rather than to difficulty in losing the proton. Thus the observed order of k_3/k_2 values, *o*-NO_2 > *o*-=N–, may be rationalised. The relatively low value of k_3/k_2 for the reaction of 2-fluoro-3-nitropyridine may suggest at first sight that the electron-attracting effect of *o*-NO_2 is less than that of *p*-NO_2 in these systems. However, 2-chloro-3-nitropyridine is considerably more reactive towards amines than 2-chloro-5-nitropyridine (see, for example, Table 4, items 2 and 23; note the difference in temperature). This suggests either that the electron-attracting effect of *o*-NO_2 is greater than that of *p*-NO_2 in these systems, or that some other favourable influence is at work in 2-chloro-3-nitropyridine. It has been suggested that the *o*-NO_2 group may facilitate reaction with primary and secondary amines by a process of internal solvation by hydrogen bonding which assists the removal of the proton.[11a,27] Such an effect operating in the reaction of 2-fluoro-3-nitropyridine might well hinder the acetate-ion catalysed decomposition of the intermediate (reduce k_3) and favour its spontaneous decomposition to products (increase k_2) (I). Thus the relatively low value



(I)

of k_3/k_2 is perhaps understandable. The measurement of k_3/k_2 for 3-cyano-2-fluoro-5-nitropyridine reacting with *N*-methylaniline is complicated by the slight catalytic effect of *N*-methylaniline, but the value for proper comparison with that for 2-fluoro-5-nitropyridine is *ca.* 700 at 20°. This very high value may well be due to the electron-attracting effect of the cyano-group hindering the loss of F^- from the intermediate and thereby reducing k_2 (*cf.* the discussion above for the 5-nitro-group). For the corresponding reaction with *N*-ethylaniline, k_3/k_2 is *ca.* 560. This lower relative sensitivity to acetate-ion catalysis may be due to the $+I$ effect of the ethyl group, or its bulk hindering the removal of the proton, *i.e.* reducing k_3.

The acetate-ion catalysis of the reaction of 3-cyano-2-fluoro-5-nitropyridine with aniline is feeble; *ca.* 0·01M-acetate increases k_2^a by *ca.* 25%, but this is much more than the increase produced by the same concentration of sodium perchlorate. It seems likely that here neither of the extreme conditions $k_{-1} \gg z$ or $k_{-1} \ll z$ pertains so that the general expression (11) for k_2^a must be applied. [It was noted above that the observed mobility order F ≫ Cl for 2-fluoro(or chloro)-3-cyano-5-nitropyridine reacting with aniline is not shown by the other systems we have studied.] Thus the extent of the acetate-ion catalysis is small because [OAc^-] occurs in both numerator and denominator of expression (11) and valid comparison with the other systems is not possible. This interpretation requires that the plot of k_2^a *vs.* [OAc^-] be curvilinear for this system, but we have not yet had an opportunity of testing this prediction.

For several of the reactions of the fluoro-compounds in Tables 4 and 5, addition of acetic acid in the absence of potassium acetate significantly increases k_2^a. Since there is no corresponding effect for chloro-compounds, the rate-enhancing effect must be exerted through the second step of the mechanism (Scheme 1). Acetic acid may act as an acidic catalyst for the loss of fluoride ion from the intermediate, or as a bifunctional catalyst assisting both the deprotonation and the expulsion of fluoride, but these effects would be difficult to reconcile with the absence of any special effect of acetic acid when equimolar potassium acetate is present. The addition of acetic acid alone to a solution of, say, *N*-methylaniline in ethanol will produce some acetate ion through the equilibria (14) and (15). It is therefore

$$PhNHMe + AcOH \rightleftharpoons Ph\overset{+}{N}H_2Me + OAc^- \quad (14)$$

$$EtOH + AcOH \rightleftharpoons EtOH_2^+ + OAc^- \quad (15)$$

possible that a considerable part of the rate-enhancing effect of acetic acid is due to base catalysis by the acetate ion produced, with acid catalysis of the expulsion of fluoride by $PhNH_2Me^+$ and/or $EtOH_2^+$, as an additional contribution. Such ' indirect ' catalysis by acetic acid would probably not be observed in the presence of equimolar potassium acetate, which would displace the above equilibria to the left. An approximate calculation (accurate values of the relevant equilibrium constants are not available) suggests that [OAc^-] in a solution of acetic acid and *N*-methylaniline in ethanol (both 0·110M) is *ca.* 0·002M (*cf.* ref. 22*c*, p. 420). Acetate ion catalysis would thus lead to $10^5 k_2^a$ *ca.* 2·2 for reaction with 2-fluoro-5-nitropyridine (*cf.* Table 4, items

[27] S. D. Ross and M. Finkelstein, *J. Amer. Chem. Soc.*, 1963, **85**, 2603.

6 and 8), whereas the observed value is 4·73 (Table 4, item 22). This suggests that there is some effect additional to the acetate ion catalysis; and acid catalysis of the expulsion of fluoride by $PhN\overset{+}{H}_2Me$ seems likely. The rate-enhancing effect of acetic acid is much smaller for the reactions of 3-cyano-2-fluoro-5-nitropyridine, in spite of the increased sensitivity to acetate ion catalysis (Table 5). However since the reactions of 3-cyano-2-fluoro-5-nitropyridine were studied at 20°, while those of 2-fluoro-5-nitropyridine were studied at 80°, this comparison will not be discussed further.

The Role of the Amine.—Several points merit attention. There is first the striking occurrence of appreciable base catalysis by the amine in the reaction of 3-cyano-2-fluoro-5-nitropyridine with *N*-methylaniline (Table 5, item 17 and footnote ¶) but not with *N*-ethylaniline (Table 5, item 30 and footnote ¶).

We assume that the absence of amine catalysis in the reaction of 2-fluoro-5-nitropyridine with *N*-methylaniline (Table 4, item 6, and footnotes), by contrast with very marked acetate-ion catalysis, is due to *N*-methylaniline being a much weaker base than acetate ion in ethanolic solution. This is shown by the solvolysis rates for 2-fluoro-5-nitropyridine in the presence of 0·10M-*N*-methylaniline and in the presence or absence of 0·10M-potassium acetate and 0·10M-acetic acid. The solvolysis is due to EtOH and/or ethoxide ion produced through equilibria (9) and (16), and acetolysis by OAc^- will also occur. The addition

$$EtOH + PhNHMe \rightleftharpoons EtO^- + PhN\overset{+}{H}_2Me \quad (16)$$

of 0·10M-potassium acetate increases $10^6k_1^s$ from 0·25 (Table 4, item 6) to *ca.* 167 s^{-1} (item 12). Subsequent addition of 0·10M-acetic acid decreases $10^6k_1^s$ to *ca.* 62 s^{-1} (estimated from items 19 and 20) by almost completely suppressing OEt^- and this corresponds to acetolysis by 0·10M-acetate ion and to ethanolysis by EtOH. Thus the contribution of OEt^- to the solvolysis rate in the presence of 0·10M-*N*-methylaniline and 0·10M-potassium acetate would be *ca.* (167 − 62) = *ca.* 105 s^{-1}. Thus the addition of 0·10M-potassium acetate increases the rate of solvolysis involving OEt^- by a factor of *ca.* 400, indicating that in the above equilibria OAc^- has a far greater ability than PhNHMe to remove a proton from EtOH.

The occurrence of appreciable amine catalysis for 3-cyano-2-fluoro-5-nitropyridine reacting with *N*-methylaniline is presumably due to the much greater sensitivity of the reactions of this substrate to base catalysis. The value of the ratio for amine catalysis corresponding to k_3/k_2 (Scheme 1) appears to be *ca.* 5·7 (*cf. ca.* 700 for acetate-ion catalysis), *i.e.* *N*-methylaniline is a weaker catalyst than acetate ion by a factor of *ca.* 120. The absence of amine catalysis in the corresponding reaction of *N*-ethylaniline may be due to various factors, *e.g.* the ability of the amine to abstract the proton from the intermediate complex may well be subject to steric hindrance by the larger alkyl group. Amine catalysis is also absent in the reaction of 3-cyano-2-fluoro-5-nitropyridine with aniline, and this is reasonable since the reaction shows but slight sensitivity to acetate-ion catalysis.

The nucleophilicity order, aniline > *N*-methylaniline > *N*-ethylaniline, for reaction with a given 2-halogen-3-cyano-5-nitropyridine (Table 5) may arise from the operation of various factors. For the chloro-compounds the order reflects that of values of k_1, and is the opposite of what might be expected on the basis of the naïve assumption that nucleophilicity should parallel basicity in water exactly; the pK_a values of the amines (25°) are 4·58, 4·85, and 5·11 respectively.[28] The observed nucleophilicity order may well be due to a primary steric effect H < Me < Et, or to steric inhibition of solvation of the positive charge-centre in the intermediate. A $+I$ polar effect of the alkyl groups reducing the solvation of the intermediate or stabilising the initial amine through solvation may also be envisaged. The same factors would operate to produce the order aniline > *N*-methylaniline in the reaction with 2-chloro-5-nitropyridine (Table 4).

The spread of rate coefficients for the reaction of the amine nucleophiles with the fluoro-compound is somewhat greater. Doubtless the order of k_1 values is moderated by the influence of k_2 and k_{-1}. Since the condition $k_{-1} \gg z$ is effective for the *N*-alkylanilines but not for aniline (see above) no detailed interpretation of the pattern of k_2^a values is possible.

The Side-reactions.—The last section required brief discussion of these, but we now examine them more thoroughly. Tables 4 and 5 give the relevant information; *viz.* values of *Y*, the percentage yield of substituted anilinopyridine (100 − *Y* is the percentage of halogenopyridine substrate diverted to side-reactions), k_1^s, the first order rate coefficient for solvolysis,† and where appropriate, $k_1^s/[KOAc]$.

In a solution of a 2-halogeno-5-nitropyridine and *N*-methylaniline in ethanol at 80° (Table 4), solvolysis is negligible with the chloro-compound (*Y* = 100), but for the fluoro-compound there is slow competitive solvolysis (Table 4, items 6 and 7; *Y* = *ca.* 90, $10^6k_1^s$ = *ca.* 0·3), either by EtOH itself or by ethoxide ion produced through equilibrium (16). Results of experiments with 3-cyano-2-fluoro-5-nitropyridine (below) make it appear likely that in the above system solvolysis is mainly by EtOH rather than by EtO^-. The relative reactivity in solvolysis, F ≫ Cl, is typical of second-order nucleophilic aromatic substitution reactions involving alcohols or alkoxide ions,[7] and may be attributed to the powerful $-I$ effect of F, which facilitates the addition of the reagent to the seat of substitution in the first and rate-determining stage of reaction.

The addition of potassium acetate markedly reduces *Y* and increases k_1^s for 2-halogeno-5-nitropyridines.

† ' Solvolysis ' is used in a general sense to include all paths for removal of halogeno-compound other than amination.

[28] A. Albert and E. P. Serjeant, ' Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

Solvolysis is now appreciable for the chloro-compound (Table 4, item 3) but our detailed results for the fluoro-compound show more clearly what happens (Table 4, items 8—17), *viz.* Y is reduced to a value of *ca.* 12%, essentially independent of the acetate concentration, while k_1^s increases approximately linearly with the acetate concentration, k_1^s/[KOAc] being effectively constant. (The values of k_1^s are not very precise.) The addition of equimolar acetic acid increases Y to *ca.* 25%; the values of k_1^s being considerably decreased, while k_1^s/[KOAc] has a lower, but still approximately constant value (Table 4, items 18—21). Acetic acid by itself has little effect on Y or k_1^s; *cf.* items 6 and 22 in Table 4. The effects of acetic acid for the chloro-compound seem analogous (Table 4, items 1 and 5).

These results may be understood in terms of the equilibrium (9). The addition of acetate ion promotes ethanolysis by EtO^-, but acetolysis also occurs. The addition of equimolar acetic acid displaces the equilibrium (9) to the left so that k_1^s then relates essentially to acetolysis and to a less extent to ethanolysis by EtOH (see later). Thus the second-order rate coefficient for attack of the fluoro-compound by acetate ion is *ca.* 6×10^{-4} l mol^{-1} s^{-1}, and for the corresponding reaction of the chloro-compound 4×10^{-6} l mol^{-1} s^{-1}. The high fluorine/chlorine mobility ratio (*ca.* 160) is typical of second-order nucleophilic aromatic substitution reactions of oxyanion reagents (*cf.* above).[7] The much higher values of k_1^s/[KOAc] in the absence of added acetic acid show that under such conditions the attack by ethoxide ion is a very important side reaction, but the apparent constancy of the ratio for the fluoro-compound must be fortuitous since [EtO^-] will be approximately proportional to [KOAc]$^{\frac{1}{2}}$. Thus the plot of k_1^s *vs.* [KOAc] must really be a gentle curve rather than a straight line, and on careful inspection the results do in fact show signs of this. Possibly a more definite curvature is concealed by a rate-enhancing 'inert' salt effect of the potassium acetate. (Such salt effects in solvolytic reactions are well established.[29])

The general pattern of results for the side-reactions of 2-halogeno-3-cyano-5-nitropyridines (Table 5) is susceptible to the same explanation as for the side-reactions of 2-halogeno-5-nitropyridines. The fluorine/chlorine mobility ratio is very high, both in ethanolysis and acetolysis. The 'side-reactions' of the fluoro-compound are so pronounced in certain cases that the amination reaction of principal interest occurs to the extent of only a few percent, *e.g.* Table 5, items 32—35, Y = *ca.* 3%.

The solvolysis of the chloro-compound promoted by acetate ion is somewhat suppressed by the addition of acetic acid (*e.g.* Table 5, items 3; 4; 14; 15) but for the fluoro-compound the addition of acetic acid scarcely affects the influence of the potassium acetate (items 8; 9; 19, 22; 32, 35). The acetate-promoted side reaction of the fluoro-compound thus appears to be acetolysis rather than ethanolysis by EtO^- produced through the equilibrium (9).

We carried out a few experiments on the solvolysis of the fluoro-compound in the absence of amine (Table 5, items 37—41). The rate of solvolysis is only slightly smaller than in the presence of amine (items 6, 17, and 30) and the addition of acetic acid has little effect on the rate of ethanolysis (a small amount of acetolysis occurs). It seems likely that ethanolysis of this fluoro-compound in the presence of the amine involves the solvent ethanol rather than the minute concentration of EtO^- produced through equilibrium (16).

The Reactions of 2-*Chloro*-3-*cyano- or* 3-*Cyano*-2-*fluoro*-5-*nitropyridine with Aniline,* N-*Methylaniline, or* N-*Ethylaniline in Ethyl Acetate.*—In an attempt to obtain direct evidence for the role of the intermediate complex in the reactions of chloro-compounds, we examined the effect of varying the amine concentration on the second-order rate coefficients for these reactions. We hoped that the stability of the intermediate chloro-complex might be so enhanced by the use of an aprotic solvent considerably less polar than ethanol (*i.e.* k_2 decreased relative to k_{-1} to produce the condition $k_{-1} \gg k_2$) that base catalysis would become observable. (Potassium acetate is insufficiently soluble in ethyl acetate for it to be used as base.) The experiments were arranged to give first-order kinetics, with the amine present in large excess, at least 30-fold, over the substrate. The results are summarised in Table 6.

TABLE 6

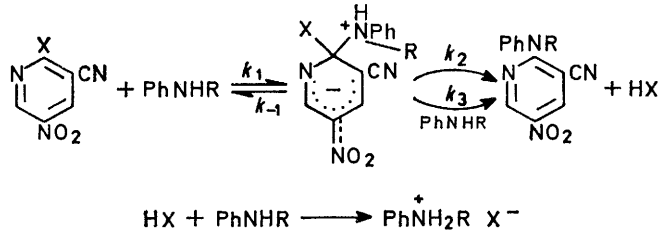
Kinetics of the reactions of 2-halogeno-3-cyano-5-nitropyridines with aniline (20·0°), *N*-methylaniline (60·0°), or *N*-ethylaniline (60·0° or 80·0°) (PhNHR) in ethyl acetate. Effect of amine concentration on the second-order rate coefficient

No.	R	Halogen	Initial [PhNHR] (M)	$10^4 k_2^a$ * (l mol^{-1} s^{-1})	Temp. (°C)
1	H	Cl	0·1007	2·84	20
2	H	Cl	0·2006	2·85	20
3	H	Cl	0·3006	2·87	20
4	H	F	0·1018	18·1	20
5	H	F	0·1507	27·0	20
6	H	F	0·2014	35·9	20
7	H	F	0·2514	44·9	20
8	H	F	0·3002	54·1	20
9	Me	Cl	0·1003	10·2	60
10	Me	Cl	0·2016	10·3	60
11	Me	F	0·0998	0·787	60
12	Me	F	0·1495	1·11	60
13	Me	F	0·2004	1·44	60
14	Me	F	0·2509	1·76	60
15	Me	F	0·3010	2·07	60
16	Et	Cl	0·1015	3·30	60
17	Et	Cl	0·1995	3·34	60
18	Et	Cl	0·2982	3·25	60
19	Et	F	0·2991	0·136	80
20	Et	F	0·4505	0·198	80
21	Et	F	0·5996	0·258	80
22	Et	F	0·7480	0·318	80
23	Et	F	0·8983	0·379	80

* Initial concentration of halogenopyridine 6—30 $\times 10^{-4}$M. Values of k_2^a were reproducible at ±2%. For the chloro-compounds titrimetric and spectrophotometric methods of following the reactions gave identical results.

[29] A. Streitwieser, 'Solvolytic Displacement Reactions,' McGraw-Hill, New York, 1962.

The rate coefficients for the reactions of the chloro-compound remain effectively constant as the amine concentration is varied two- or three-fold. For the reactions of the fluoro-compound they increase markedly and linearly as the amine concentration is increased, and indeed the reaction with aniline is effectively third order, *i.e.* second order in amine. This contrasts markedly with the reaction in ethanol in which only that involving *N*-methylaniline shows slight signs of catalysis by the amine. Thus the change to the less polar solvent has rendered base catalysis more readily detectable, but it has still not become detectable for the chloro-compounds. These observations are best interpreted in terms of the catalysis of the decomposition of the intermediate by the amine (Scheme 6). The



SCHEME 6

lack of any concentration dependence for the chloro-compound suggests that only a relatively small proportion of the effect for the fluoro-compound is due to the medium (see later discussion for reactions of 1-fluoro-2,4-dinitrobenzene).

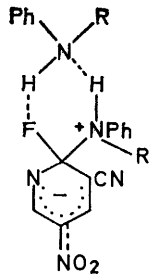
The second-order rate coefficient for the overall reaction is given by equation (17). For the chloro-compound it appears that even in an aprotic solvent

$$k_2^a = k_1(k_2 + k_3[\mathrm{PhNHR}])/(k_{-1} + k_2 + k_3[\mathrm{PhNHR}]) \quad (17)$$

of low polarity $k_{-1} \ll (k_2 + k_3[\mathrm{PhNHR}])$, so that $k_2^a = k_1$ and there is no amine catalysis. For the fluoro-compound it appears that $k_{-1} \gg (k_2 + k_3[\mathrm{PhNHR}])$, so that equation (17) is simplified to (18),

$$k_2^a = k_1k_2/k_{-1} + k_1k_3[\mathrm{PhNHR}]/k_{-1} \quad (18)$$

and the second-order rate coefficient is a linear function of the amine concentration. It seems likely that the amine acts as a bifunctional catalyst, assisting both



(III)

the removal of the fluoride ion and the proton, *i.e.* as in (II). Values of k_3/k_2 obtained by a procedure analogous to that used for acetate ion catalysis of the reactions in ethanol (see p. 1795) are $>10^3$ for aniline, 42 for *N*-methylaniline, and 26 for *N*-ethylaniline, *i.e.* catalysis becomes weaker as the amine becomes a stronger base in water. This is consistent with the importance of the ability of the catalyst to assist the removal of the fluoride ion from (II), but the magnitude of the structural effect, particularly as between aniline and the two *N*-alkylanilines, suggests that a primary steric effect interferes with the catalytic function of the amine, whatever this may consist of in detail. It must also be remembered that aniline has the advantage of two hydrogen atoms for assisting the removal of the fluoride ion.

When allowance is made for the amine catalysis of the reaction of the fluoro-compound, the F/Cl mobility ratios are low, $\ll 10^{-1}$ in all cases, and thus much lower than observed in the corresponding reactions in ethanol as solvent. This means that the k_1 order, F $\gg$ Cl, is greatly moderated by the participation of the second (k_2) step with the fluoro-compound, so that the order shown by the observed k_2^a values corresponds more to the k_2 order, F $\ll$ Cl.

The value of $10^4k_2^a$ for the reaction of aniline with 2-chloro-3-cyano-5-nitropyridine at 60° is *ca.* 26. (Arrhenius parameters are in Part XI.) The three amines thus show the same order of nucleophilicity in ethyl acetate as they do in ethanol (see p. 1797) *viz.* aniline > *N*-methylaniline > *N*-ethylaniline, and this is susceptible to similar explanations.

An attempted investigation of the effect on the reactions of 2-chloro-3-cyano-5-nitropyridine of the addition of triethylamine (*i.e.* a much stronger base than the aromatic amines) in ethyl acetate yielded complex results whose interpretation is uncertain.[22c]

Base Catalysis of the Reactions of 1-*Fluoro*-2,4-*dinitrobenzene with Aniline or* N-*Methylaniline in Various Solvents at* 30°.—The failure of the reactions of aniline with aromatic [21] or heterocyclic activated fluoro-compounds in ethanol to show base catalysis prompted an examination of this aspect of the reactions of 1-fluoro-2,4-dinitrobenzene with aniline in various solvents. In ethanol $k_2 \gg k_{-1}$ (*cf.* Scheme 1), and base catalysis is not observed but we hoped by varying the solvent to produce the condition $k_{-1} \gg z$, or at least $k_{-1} \approx k_2$, so that base catalysis might become detectable. In an oversimplified way one may argue that decreasing the 'polarity' of the solvent should diminish k_2 (release of ions into solution retarded) and increase k_{-1} (reversion to neutral reactants facilitated). Suhr [30] has shown that the effectiveness of piperidine as a catalyst in the reactions of *p*-fluoronitrobenzene with piperidine increases with decreasing polarity of the solvent. In the present work methanol and ethanol were selected as highly polar alcohols, benzyl alcohol as a somewhat less polar alcohol (as judged by dielectric constant), and ethyl acetate and especially toluene

[30] H. Suhr, *Ber. Bunsengesellschaft Phys. Chem.*, 1963, **67**, 893.

as aprotic solvents of low polarity. The results are in Table 7.

For the reactions of aniline in the three alcohols studied (items 1—28) only small increases in k_2^a were to be regarded as an effect of an 'inert' salt. When ethyl acetate or toluene is used as solvent, much more striking results are obtained (items 29—51), although it is not possible to investigate the influence of potassium

TABLE 7

Kinetics of the reactions of 1-fluoro-2,4-dinitrobenzene (0·0005000M) with aniline or *N*-methylaniline in various solvents at 30·0°, with or without added bases

No.	Solvent	Initial [Amine](M) *	Base	[Base](M)	*Y* †	$10^3k_2^a$ ($l\,mol^{-1}\,s^{-1}$) ‡	Notes §
1	MeOH	0·500				11·00	[$PhNH_2$,HCl] 0·001M
2	MeOH	0·100				9·00	[$PhNH_2$,HCl] 0·001M
3	MeOH	0·0100				8·70	[$PhNH_2$,HCl] 0·001M
4	MeOH	0·00500				8·32	[$PhNH_2$,HCl] 0·001M
5	MeOH	0·100	KOAc	0·100	95·3	13·4	
6	MeOH	0·100	KOAc	0·200	92·5	18·5	
7	MeOH	0·100	KOAc	0·200	94·5	16·5	[AcOH] 0·200M
8	MeOH	0·100	$NaClO_4$	0·100	93·6	11·3	
9	MeOH	0·100	Py	0·100		11·0	
10	MeOH	0·100	Py	0·200		11·4	
11	EtOH	0·500				12·70	[$PhNH_2$,HCl] 0·001M
12	EtOH	0·100				9·09	[$PhNH_2$,HCl] 0·001M
13	EtOH	0·0100				7·89	[$PhNH_2$,HCl] 0·001M
14	EtOH	0·00500				8·02	[$PhNH_2$,HCl] 0·001M
15	EtOH	0·100	KOAc	0·100	93·7	15·9	
16	EtOH	0·100	KOAc	0·200	92·5	21·7	
17	EtOH	0·100	KOAc	0·100	14·4	16·0	[AcOH] 0·100M
18	EtOH	0·100	$NaClO_4$	0·100	94·8	10·6	
19	$PhCH_2OH$	0·500				2·64	[$PhNH_2$,HCl] 0·001M
20	$PhCH_2OH$	0·200				2·20	[$PhNH_2$,HCl] 0·001M
21	$PhCH_2OH$	0·100				2·04	[$PhNH_2$,HCl] 0·001M
22	$PhCH_2OH$	0·0500				2·02	[$PhNH_2$,HCl] 0·001M
23	$PhCH_2OH$	0·0100				2·03	[$PhNH_2$,HCl] 0·001M
24	$PhCH_2OH$	0·100	KOAc	0·0500	98·4	2·75	
25	$PhCH_2OH$	0·100	KOAc	0·0800	98·2	2·78	
26	$PhCH_2OH$	0·100	KOAc	0·100	98·0	3·35	
27	$PhCH_2OH$	0·100	Py	0·100		2·42	
28	$PhCH_2OH$	0·100	Py	0·200		2·75	
29	EtOAc	0·500				0·362	
30	EtOAc	0·400				0·278	
31	EtOAc	0·300				0·221	
32	EtOAc	0·200				0·141	
33	EtOAc	0·100				0·085	
34	EtOAc	0·100	Py	0·0225		0·214	
35	EtOAc	0·100	Py	0·049		0·285	
36	EtOAc	0·100	Py	0·066		0·390	
37	EtOAc	0·100	Py	0·101		0·480	
38	EtOAc	0·100	Py	0·152		0·755	
39	EtOAc	0·100	Py	0·212		0·988	
40	EtOAc	0·100	Et_3N	0·107		0·171	
41	EtOAc	0·100	Et_3N	0·200		0·239	
42	EtOAc	0·100	Et_3N	0·400		0·381	
43	PhMe	0·800				0·0401	
44	PhMe	0·500				0·0118	
45	PhMe	0·100				0·00125	
46	PhMe	0·100	Py	0·101		0·0767	
47	PhMe	0·100	Py	0·151		0·125	
48	PhMe	0·100	Py	0·203		0·191	
49	PhMe	0·100	Py	0·399		0·576	
50	PhMe	0·100	Et_3N	0·200		0·0580	
51	PhMe	0·100	Et_3N	0·400		0·141	
52	EtOAc	0·200				0·0002	Amine = PhNHMe, 60°
53	EtOAc	0·200	Py	0·200		0·0327	Amine = PhNHMe, 60°
54	EtOAc	0·200	Py	0·400		0·0802	Amine = PhNHMe, 60°

* Amine is $PhNH_2$ unless otherwise stated. † Percentage of substituted diphenylamine: it has the value 100 unless otherwise stated. ‡ Values of k_2^a are reproducible to better than ±2%. § Aniline hydrochloride was added to reduce complications due to MeO^-, EtO^-, or $PhCH_2O^-$.

produced by very large increases in [aniline] (up to 500-fold) and the addition of pyridine had little effect. Such changes as are observed are undoubtedly more properly regarded as medium effects than as base catalysis. Similarly the effect of potassium acetate is comparable with that of sodium perchlorate and is acetate. Aniline, pyridine, and triethylamine all produce substantial increases in k_2^a. However, medium effects will be more noticeable because of the non-polar nature of the solvent, and the question is how much of the rate enhancement is due to base catalysis and how much to a medium effect.

Reactions with aniline in ethyl acetate. Plots of k_2^a against base concentration are linear with all three bases (Figure 2) and the order of effectiveness is pyridine $\gg$ triethylamine $>$ aniline. Becker *et al.*[31] have suggested for a related system that the superposition of a medium effect on base catalysis may lead to a curvilinear relationship between second-order rate coefficients and base concentration, with the rate coefficient proportional to [base]^n, n being >1. In the present case the substantial linear effect, of magnitude highly specific to the base, seems most simply interpreted as base catalysis of the second step of the two-step mechanism. The effectiveness as catalysts does not reflect basicities in water in a simple way; the pK_a values of the conjugate acids lie in the order triethylamine $\gg$ pyridine $>$ aniline. Presumably the catalytic behaviour of triethylamine is greatly reduced by steric hindrance due to the three ethyl groups (*cf.* the opposed nucleophilicity and basicity orders for aniline and *N*-alkylanilines referred to on p. 1797).

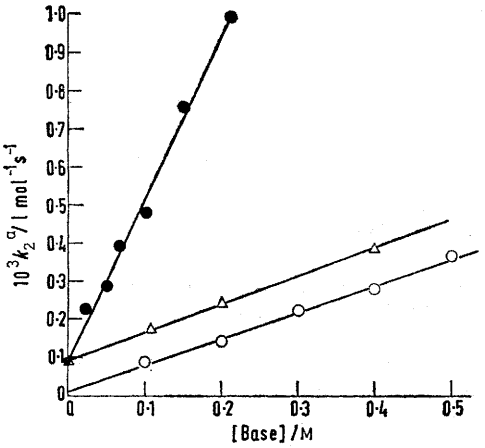


FIGURE 2 The effect of added base on k_2^a for the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in ethyl acetate at 30·0°. Data in Table 7, items 29—42: ○ aniline; ● pyridine; △ triethylamine

Reaction with aniline in toluene. The increase in k_2^a produced by the addition of each base is considerably greater than in ethyl acetate and k_2^a varies in a curvilinear way with [base] (Figure 3). The effect is highly specific, and again the order of effectiveness is pyridine $\gg$ triethylamine $>$ aniline. It seems likely that medium

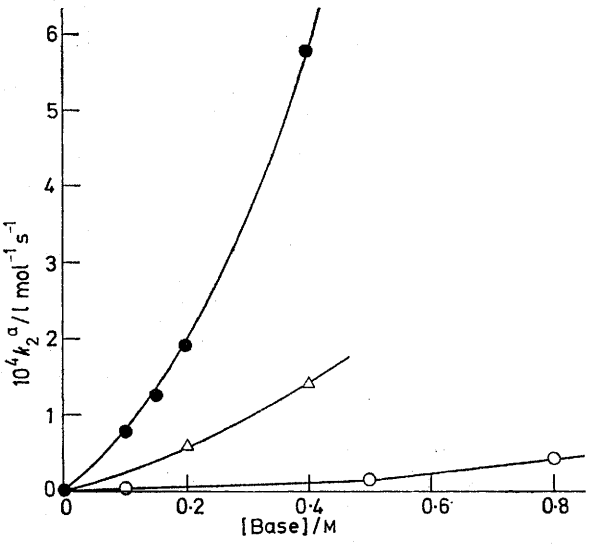


FIGURE 3 The effect of added base on k_2^a for the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in toluene at 30·0°. Data in Table 7, items 43—51; ○ aniline; ● pyridine; △ triethylamine

effects are superimposed on base catalysis (*cf.* above). Self-association of aniline is a possible complication.[32]

Reaction with N*-methylaniline in ethyl acetate.* Items 52—54 in Table 7 show that this reaction is very susceptible to catalysis by pyridine. The addition of 0·2M-pyridine enhances k_2^a 150-fold (*cf.* 11-fold in the corresponding reaction of aniline). Thus in ethyl acetate as in ethanol the reactions of *N*-methylaniline with 1-fluoro-2,4-dinitrobenzene are much more susceptible than those of aniline to base catalysis.

We thank the S.R.C. for maintenance awards (D. M. B., J. S. P., and D. J. W.). This paper was partly written while one of us (N. B. C.) was R. J. Reynolds Visiting Professor at Duke University, N. Carolina. We thank Mr. F. Brown for g.l.c. analyses.

[4/1072 *Received*, 29*th May*, 1974]

[31] G. Becker, C. F. Bernasconi, and H. Zollinger, *Helv. Chim. Acta*, 1967, **50**, 10.

[32] M. M. Davis, 'Acid–Base Behavior in Aprotic Organic Solvents,' NBS Monograph 105, U.S. Department of Commerce, Washington, 1968, p. 21.