Mechanisms for Reactions of Halogenated Compounds. Part 2.[1] Orienting Effects of Chlorine Substituents in Nucleophilic Aromatic Substitution

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Rate constants and product analyses are provided for reactions of various chloropolyfluoropyridines with ammonia in dioxan–water (60 : 40 v/v) at 25 °C. Comparison of these rate constants with the values for appropriate polyfluoropyridines allows the separate effects of chlorine atoms *ortho*, *meta*, and *para* to the reaction centre to be established. The activating influence of chlorine decreases in the series *ortho* > *meta* > *para* (86 : 24 : 6.9 relative to hydrogen atom at the same position). The rate constant ratios $k_{Cl} : k_F$ for chlorine or fluorine at the same position are : *ortho ca.* 3 : 1, *meta ca.* 1 : 1, and *para ca.* 2.6 : 1. These ratios have been measured for a number of different substitutions and are remarkably constant. The results help to explain the orientation and reactivity of nucleophilic substitution in polyhalogenoaromatic compounds.

THERE has been considerable interest in nucleophilic substitution reactions in polyfluoro-[2] and polychloro-[3] aromatic compounds, but hitherto discussion of the orienting influence of the halogens in these systems has been incomplete. In Part 1,[1] we described experiments which separated the activating effects of fluorine atoms situated *ortho*, *meta*, and *para* to the reaction centre, and this enabled a satisfactory description of the orienting influence of these halogen atoms in benzene and in pyridine systems to be developed. In this paper we describe a similar approach for separating the effects of chlorine atoms *ortho*, *meta*, and *para* to the reaction centre, relative to hydrogen at the same position.

The compounds studied are shown in Tables 1 and 2. The synthesis of compounds (1) and (3),[4] (2) and (4),[5,6] (5), and (7) [1] has been described previously; 2-chlorotetrafluoropyridine (6), 3,4-dichloro- (8) and 2,6-dichloro- (12) trifluoropyridines, and 3,4,5-trichlorodifluoropyridine (9) have been synthesised by known procedures. Ammonia in dioxan–water (60 : 40 v/v) has been used previously [1] for reactions with fluoropyridines because this system leads to rates which are convenient to measure at normal temperatures; the same procedures were used in this work.

A comparison of the rate constants in Table 1 for attack at the 4-position in compounds (1) and (2) and compounds (3) and (4) allows the effect of a chlorine atom *ortho* to the reaction centre to be established, in comparison with hydrogen. Similar comparison for compounds (5) and (6) leads to an assessment of the effect of chlorine *meta* to the point of attack, and comparison of the rate constants for attack at the 6-positions in compounds (7) and (8) indicates the effect of a chlorine atom *para* to the point of attack.

Attack at the 4-position:

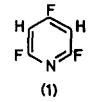
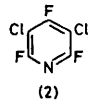
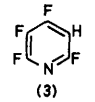
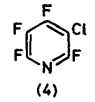
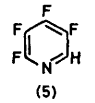
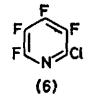
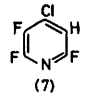
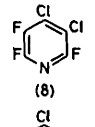
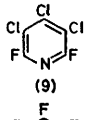
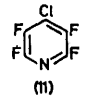
$$k(4)/k(3) = k(\mathrm{Cl})/k(\mathrm{H})\ \textit{ortho}$$
$$= 86 \text{ per } \textit{ortho}\text{-chlorine atom}$$
$$k(2)/k(1) = k(\mathrm{Cl})/k(\mathrm{H})\ \textit{ortho}$$
$$= \sqrt{6.79 \times 10^3},\ \textit{i.e.}\ 82 \text{ per } \textit{ortho}\text{-chlorine atom}$$
$$k(6)/k(5) = k(\mathrm{Cl})/k(\mathrm{H})\ \textit{meta}$$
$$= 24 \text{ per } \textit{meta}\text{-chlorine atom}$$

Attack at the 6-position:

$$k(8)/k(7) = k(\mathrm{Cl})/k(\mathrm{H})\ \textit{para}$$
$$= 6.9 \text{ per } \textit{para}\text{-chlorine atom}$$

[1] Part 1, R. D. Chambers, J. S. Waterhouse, and D. L. H. Williams, *J.C.S. Perkin II*, 1977, 585.
[2] R. D. Chambers, 'Fluorine in Organic Chemistry,' Wiley–Interscience, New York, 1973, ch. 9 and references therein.
[3] 'Polychloroaromatic Compounds,' ed. H. Suschitzky, Plenum, London, 1974, and references therein.
[4] R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5045.
[5] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3573.
[6] R. E. Banks, R. N. Haszeldine, J. V. Latham, and I. M. Young, *J. Chem. Soc.*, 1965, 594.

TABLE 1
Rate constants for reactions with ammonia in (60 : 40 v/v) dioxan–water at 25 °C

Compound	Position of attack	k / l mol^{-1} s^{-1}
 (1)	4-[1,a] 6-[1,a]	*ca.* 0.7 [b] × 10^{-6} *ca.* 0.2 [b] × 10^{-6}
 (2)	4-	(4.75 ± 0.04) × 10^{-3}
 (3)	4-[1] 6-[1]	(2.22 ± 0.1 [b]) × 10^{-5} (5.87 ± 0.3 [b]) × 10^{-6}
 (4)	4-	(1.92 ± 0.02) × 10^{-3}
 (5)	4-[1]	(2.93 ± 0.03) × 10^{-5}
 (6)	4-	(7.12 ± 0.04) × 10^{-4}
 (7)	6-[1]	(5.92 ± 0.02) × 10^{-6}
 (8)	2- 6-	(4.87 ± 0.2 [b]) × 10^{-6} (4.10 ± 0.2 [b]) × 10^{-5}
 (9)	2-	(1.30 ± 0.01) × 10^{-4}
 (10)	4-[1]	(6.80 ± 0.03) × 10^{-4}
 (11)	2-[1]	(1.55 ± 0.01) × 10^{-6}
 (12)	4-	(6.47 ± 0.04) × 10^{-4}

[a] Approximate value, owing to the slowness of the reaction. [b] Separate k values calculated from n.m.r. and g.l.c. integrations. All k values have been corrected for statistical factors where appropriate.

Therefore the order of the activating influence of chlorine, relative to the position of nucleophilic attack is:

Cl *ortho* *meta* *para*
86 : 24 : 6.9 (relative to hydrogen
(12.5 : 3.5 : 1) (relative to the *para*-position)

[7] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

For comparison, values for fluorine in the pyridine system which have been determined previously [1] are:

F *ortho* *meta* *para*
31 : 23 : 0.26 (relative to hydrogen)
(119 : 88 : 1) (relative to the *para*-position)

The most striking aspect of the chlorine series is the much closer similarity of the effects at *meta*- and *para*-positions, as compared with the values for fluorine. Values for relative activation by fluorine and chlorine at different positions may be obtained directly, from the following comparisons:

Attack at the 4-position:

$k(2)/k(10) = k(\mathrm{Cl})/k(\mathrm{F})$ *ortho*
= 7.0, *i.e.* 2.6 per *ortho*-chlorine atom

$k(4)/k(10) = k(\mathrm{Cl})/k(\mathrm{F})$ *ortho*
= 2.8 per *ortho*-chlorine atom

$k(6)/k(10) = k(\mathrm{Cl})/k(\mathrm{F})$ *meta*
= 1.05 per *meta*-chlorine atom

$k(12)/k(6) = k(\mathrm{Cl})/k(\mathrm{F})$ *meta*
= 0.91 per *meta*-chlorine atom

$k(12)/k(10) = k(\mathrm{Cl})/k(\mathrm{F})$ *meta*
= 0.95, *i.e.* 0.98 per *meta*-chlorine atom

Attack at the 6- (or 2-) position:

$k(8)$ (6-)$/k(11) = k(\mathrm{Cl})/k(\mathrm{F})$ *para*
= 26.5 per *para*-chlorine atom

$k(9)/k(8)$ (2-) $= k(\mathrm{Cl})/k(\mathrm{F})$ *para*
= 26.7 per *para*-chlorine atom

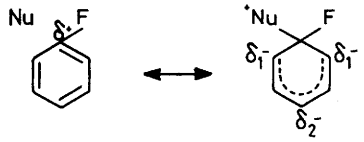
$k(9)/k(8)$ (6-) $= k(\mathrm{Cl})/k(\mathrm{F})$ *ortho*
= 3.2 per *ortho*-chlorine atom

$k(8)$ (2-)$/k(11) = k(\mathrm{Cl})/k(\mathrm{F})$ *ortho*
= 3.1 per *ortho*-chlorine atom

The very similarity of these ratios of rate constants, deduced in a variety of ways, *e.g.* from 2- and 4-substitution and from a variety of chlorofluoropyridines, is remarkable, and shows (i) that steric effects are relatively insignificant with this ammonia–solvent system, otherwise the *ortho*-ratio determined from 4-attack, where there are two adjacent halogenated positions, would be markedly different from the ratio by 2- or 6-attack; and (ii) that the effects of the halogens are simply additive, otherwise the values would not be in such close agreement. Indeed, these results from polyhalogenated compounds agree with the conclusions of Bunnett and Zahler [7] about the relative reactivities of 1,2-, 1,3-, and 1,4-dichloro- and -chlorofluoro-benzenes. The dichloro-compounds showed the order of reactivity *meta* > *ortho* > *para*, whereas the chlorofluoro-compounds showed *ortho* > *meta* > *para*, but the *ortho*-activation is difficult to account for. That $k(\mathrm{Cl})/k(\mathrm{H})$ values (referred to as substituent rate factors by Miller [8]) for activation of nucleophilic aromatic substitution by

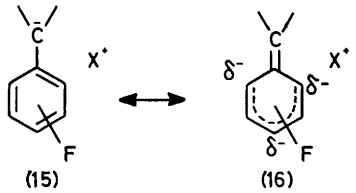
chloro-substituents are higher at the *meta*- than at the *para*-position is well known.[8,9]

The influence of a chlorine atom *meta* or *para* to the reaction centre in nucleophilic aromatic substitution may be understood on the basis of the approximate model (14) for the transition state. Chlorine attached



(13) (14)

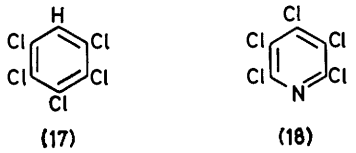
directly to a carbanion centre ($\bar{C}$–Cl) is stabilising when the carbanion is derived from a saturated carbon atom,[10] but the fact that a *para*-chlorine atom is only *ca.* 7 times more activating than a hydrogen atom at the same position means that electron-pair repulsion ($\bar{C}$l–$\bar{C}$) offsets the normal carbanion stabilisation, although the effect is clearly less important for chlorine than for fluorine. This effect would not be significant at the *meta*-position; consequently, chlorine is considerably more activating relative to hydrogen at this position. Furthermore, chlorine and fluorine have a clearly similar effect at the *meta*-position. While this is not surprising there is, nevertheless, no effective comparison available between the stabilising influence of these two halogens on carbanions such as $\bar{C}$–C–X (X = Cl or F), where the carbanion is derived from a saturated system, because of the ready elimination of chlorine, although it has been established that chlorine and fluorine have a similar acidifying influence on an adjacent hydrogen atom in an aromatic system, *i.e.* –$\bar{C}$=C–X.[11-13] The activation by *ortho*-chlorine is, however, more difficult to describe, but an explanation for the corresponding *ortho*-activation by fluorine has been given previously:[1] essentially we argued that the Wheland intermediate, which is often regarded as an appropriate model for the transition state in nucleophilic aromatic substitution, is inadequate for these systems. Very significant contributions from initial states must be taken into account, as reflected by (13) ⟷ (14). In this model of the transition state, the nature of the bond being formed with the nucleophile would depend partly on the electrophilic nature of the carbon atom being attacked, which *ortho*-chlorine or -fluorine atoms would obviously enhance. Arguments based solely on a transition state like (14) would lead to halogens at *ortho*-positions having a similar effect to that of the same halogen at the *para*-position, which is patently not the case. The greater *ortho*-activation by chlorine than by fluorine is, however, consistent with the contribution from (13) where a greater destabilising electron-pair repulsion would operate for fluorine.[14-16] A useful comparison may be made with work by Streitwieser and Koch [17] on base-induced detritiation of *ortho*-, *meta*-, and *para*-$T_3C{\cdot}C_6H_4F$. The relative k values observed are H, 1; *ortho*-F 12; *meta*-F 22; *para*-F 0.73. In this system the transition state must be like (15) ⟷ (16), and it is understandable that *ortho*-fluorine would



(15) (16)

have a pronounced stabilising effect on charge centred on the side-chain [*cf.* (15)], which would be offset by a resultant and destabilising effect on charge delocalised into the ring [*cf.* (16)]. However, only the latter destabilising effect would be significant for a *para*-fluorine atom.

There are some observations concerning the orientation of nucleophilic substitution in polychloroaromatic compounds which can be rationalised on the basis of the effects established here. Monosubstitution in pentachlorobenzene occurs preferentially *para* to the hydrogen atom,[18] and reaction of pentachloropyridine with different nucleophiles leads to preferential, but not exclusive, 4-substitution.[19-21] Attack *para* to hydrogen in (17) obviously leads to the maximum activating



(17) (18)

influence by the chlorine atoms, *i.e.* two *meta* and two *ortho* to the point of nucleophilic attack and, in an analogous way, attack at the 4-position in pentachloropyridine (18) maximises the activating influence of the chlorine atoms. However, from the foregoing results, this orienting influence of chlorine atoms in pentachloropyridine is markedly less than that of the fluorine atoms in pentafluoropyridine. Multiplying the activating influences of the appropriate halogens leads to calculated ratios of rate constants for 4- to 2-attack in

[8] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.
[9] W. Greizerstein, R. A. Bonelli, and J. A. Brieux, *J. Amer. Chem. Soc.*, 1962, **84**, 1026.
[10] J. Hine, ' Physical Organic Chemistry,' McGraw-Hill, New York, 1962, p. 487, and references therein.
[11] J. Hine and P. B. Langford, *J. Org. Chem.*, 1962, **27**, 4149.
[12] C. E. Hall, R. Piccolini, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1955, **77**, 4540.
[13] J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A. Carlsmith, *J. Amer. Chem. Soc.*, 1956, **78**, 601.
[14] D. T. Clark, J. N. Murrell, and J. M. Tedder, *J. Chem. Soc.*, 1963, 1250.
[15] A. Streitwieser and F. Mares, *J. Amer. Chem. Soc.*, 1968, **90**, 2444.
[16] J. Burdon, *Tetrahedron*, 1965, **21**, 3373.
[17] A. Streitwieser and H. F. Koch, *J. Amer. Chem. Soc.*, 1964, **86**, 404.
[18] A. F. Holleman, *Rec. Trav. chim.*, 1920, **39**, 736.
[19] A. Roedig and K. Grohe, *Chem. Ber.*, 1965, **98**, 923.
[20] W. T. Flowers, R. Haszeldine, and S. A. Majid, *Tetrahedron Letters*, 1967, 2503.
[21] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 1537, 2844.

pentafluoropyridine of 238.5 : 1 and in pentachloropyridine of 22.3 : 1. Consistent with this model is the fact that in all nucleophilic substitutions reported so far on pentafluoropyridine, monosubstitution takes place exclusively at the 4-position, whereas with pentachloropyridine the ratio of 4- to 2-attack varies with the steric requirements of the nucleophile.[22]

The much more important role of steric effects with systems containing chlorine is illustrated by the rate constants in Table 2. These data were determined for the reaction of diethylamine in dioxan, at 25 °C.

TABLE 2

Rate constants for reactions with diethylamine in dioxan at 25 °C

Compound	Position of attack	k / l mol^{-1} s^{-1}
 (10)	4-	$(5.08 \pm 0.02) \times 10^{-3}$
	4- [a]	$(1.23 \pm 0.02) \times 10^{-2}$
 (4)	4-	$(9.68 \pm 0.60$ [b]$) \times 10^{-4}$
	6-	$(1.73 \pm 0.10$ [b]$) \times 10^{-3}$
 (11)	2-	$(7.43 \pm 0.06) \times 10^{-5}$
 (2)	2-	$(1.15 \pm 0.01) \times 10^{-3}$
 (8)	6-	$(1.95 \pm 0.02) \times 10^{-3}$
 (12)	4-	$(2.98 \pm 0.02) \times 10^{-3}$
 (9)	2-	$(7.27 \pm 0.03) \times 10^{-4}$

[a] In nitrobenzene. [b] As Table 1.

Monosubstitution by ammonia occurs in both pentafluoropyridine and 3-chlorotetrafluoropyridine (4), exclusively at the 4-position (see Table 1), whereas the reaction of diethylamine with (4) gives monosubstitution at both the 4- and the 6-positions. The 3-chlorine atom obviously deactivates the 4-position, because the rate constant for attack at the 4-position in (4) is less than for attack at the 4-position in pentafluoropyridine (10). This is in marked contrast to the reactions with ammonia, where 3-chlorotetrafluoropyridine (4) is activated in comparison with (10). Crowding at the 4-position is increased by the further introduction of chlorine, as shown by attack by diethylamine occurring only at the 6-position in 3,5-dichlorotrifluoropyridine (2), whereas ammonia reacts at the 4-position in (2). Indeed, it is likely that there is even steric retardation by the 3- and 5-fluorine atoms in pentafluoropyridine, in reactions with diethylamine: the difference in reactivity between pentafluoropyridine (10) and 4-chlorotetrafluoropyridine (11) [Table 1, $k(10)/k(11) = 440$] is much greater with ammonia than with diethylamine [Table 2, $k(10)/k(11) = 68$].

An increase of 2.5 occurs in the rate constant for reaction of diethylamine with pentafluoropyridine on changing the solvent from dioxan (ε 2.2) to nitrobenzene (ε 34.8). This is a surprisingly small increase for a reaction in which charge separation increases substantially in the transition state. However, a doubling of the rate constant was observed for the same solvent change for the reaction of 1-chloro-2,4-dinitrobenzene with *p*-toluidine.[23] It has been proposed that dioxan has the greater ability to stabilise the transition state by hydrogen bonding, but it is also possible that the steric requirements of the reagent vary substantially with the solvent, to offset the effects of dielectric constant.

EXPERIMENTAL

^{19}F N.m.r. spectra were recorded with a Varian A56/60D spectrometer; chemical shifts are quoted with reference to external $CFCl_3$ (upfield positive).

Materials.—3,5-Dichlorotrifluoro- (2), 3-chlorotetrafluoro- (4),[5,6] 2,3,4,5-tetrafluoro- (5),[1] and 4-chloro-2,3,6-trifluoropyridine (7) [1] were prepared by procedures described previously.

3,4-*Dichlorotrifluoropyridine* (8). 3-Chloro-4-hydrazinotrifluoropyridine [24] was purified by recrystallisation (methanol) and sublimation under vacuum. This material (10 g) was added to a solution of copper(II) chloride (45 g) in concentrated hydrochloric acid (300 ml). The mixture was heated under vacuum until evolution of nitrogen ceased (several hours), and then distilled. Sodium hydrogen carbonate was added carefully to neutralise the distillate, which was then extracted with ether (2 × 20 ml); the extracts were dried, and the ether removed by distillation. Analytical-scale g.l.c. showed the residue (8.2 g, 80%) to be essentially one compound; preparative-scale g.l.c. gave 3,4-*dichlorotrifluoropyridine*, b.p. 156° (Found: C, 29.5; N, 6.7%; *M*, 201. $C_5Cl_2F_3N$ requires C, 29.7; N, 6.9%; *M*, 201), ^{19}F δ 72.2 (2-F), 85.5 (6-F), and 142.5 p.p.m. (5-F); $J_{2F,6F}$ 13, $J_{2F,5F}$ 26, $J_{5F,6F}$ 20 Hz.

3,4,5-*Trichlorodifluoropyridine* (9). Sodium nitrite (6 g) was added to a stirred solution of 4-amino-3,5-dichlorodifluoropyridine (7.3 g) in aqueous hydrogen fluoride (80% w/w; 50 ml) at −25 °C, over 30 min. With the temperature maintained between −25 and −30 °C, a solution of copper(I) chloride in concentrated hydrochloric acid [made by addition of hydrated copper(II) chloride (30 g) and hydrated sodium sulphite (45.6 g) to concentrated hydrochloric acid (60 ml)] was added dropwise over 30 min. When the solution had attained room temperature, the mixture was diluted with water (750 ml), neutralised by

[22] Ref. 3, p. 238.

[23] L. A. Suchkova and S. M. Shein, *Reakts. spos. org. Soedinenii*, 1969, **6**, 586 (*Chem. Abs.*, 1970, **72**, 2787).

[24] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 5634.

careful addition of sodium hydrogen carbonate, and extracted with ether (2 × 50 ml). The combined ethereal solutions were washed with water and dried; removal of the ether by distillation gave a colourless liquid (6.8 g). G.l.c. showed two major products, which were separated on a preparative scale, giving 3,5-dichlorotrifluoropyridine (16% of the mixture) and 3,4,5-*trichlorodifluoropyridine* (5 g, 64%), b.p. 189° (Found: C, 27.2; N, 6.2%; *M*, 217. $C_5Cl_3F_2N$ requires C, 27.4; N, 6.4%; *M*, 217), ^{19}F δ 68.6 p.p.m. (2- and 6-F).

2,6-*Dichlorotrifluoropyridine* (12) (with G. Thorpe). Replacement of fluorine in heterocyclic systems by chlorine, using acid-induced processes, has been described previously.[25] Pentafluoropyridine (5 g) and hydrogen chloride were heated together for 9 days in a sealed nickel tube. The resulting complex was hydrolysed cautiously and then extracted with ether (2 × 20 ml). The combined extracts were washed and dried; removal of the ether left a solid, which on sublimation, gave 2,4,6-trichlorodifluoropyridine (4.6 g), identified by comparison (i.r. spectrum) with an authentic sample.[26]

A mixture of 2,4,6-trichlorodifluoropyridine (4.3 g) and dry caesium fluoride (7 g) in dry tetramethylene sulphone (20 ml) was stirred at room temperature under dry nitrogen for 9 days. Volatile material was removed by vacuum distillation (80 °C; 0.01 mmHg) giving a liquid product (3.8 g). G.l.c. showed the mixture to contain mainly two products, which were separated by fractional distillation, giving (i) 2,6-*dichlorotrifluoropyridine* (12), b.p. 156—157° (Found: C, 30.0; N, 7.3%; *M*, 201. $C_5Cl_2F_3N$ requires C, 29.7; N, 6.9%; *M*, 201), ^{19}Fδ 138.5 (3- and 5-F) and 140.5 p.p.m. (4-F), $J_{3F,4F}$ 17 Hz; and (ii) 2-*chlorotetrafluoropyridine* (6), b.p. 119—120° (Found: C, 32.5; N, 7.6%; *M*, 185. C_5ClF_4N requires C, 32.4; N, 7.6%; *M*, 185), ^{19}Fδ 84.4 (6-F), 137.0 (4-F), 140.1 (3-F), and 159.3 p.p.m. (5-F), $J_{5F,6F}$ 23, $J_{4F,6F}$ 16, $J_{3F,6F}$ 26, $J_{4F,5F}$ 16, $J_{3F,5F}$ 4, and $J_{3F,4F}$ 18 Hz.

2-*Chlorotetrafluoropyridine* (6). 4-Bromotetrafluoropyridine (25 g) was added dropwise to a stirred solution of hydrazine hydrate (23.6 g) in ethanol (200 ml) at room temperature. After a further 30 min, the mixture was poured into water (500 ml) and the mixture was extracted with ether. Then the ethereal solution was separated, dried ($MgSO_4$), and evaporated under vacuum, giving 4-bromo-2-hydrazinotrifluoropyridine (23.7 g), which was used without further purification. The hydrazino-derivative (18.9 g) was added in portions to a stirred solution of copper(II) chloride (70 g) in concentrated hydrochloric acid (650 ml), and the resulting mixture was heated under reflux for 2 h. Then the mixture was steam-distilled; a colourless oil (12.5 g) settled from the first portion (50 ml) of distillate, which was identified as 2-chlorotetrafluoropyridine (6) by comparison of spectra. The residue consisted of crude (6) (10 g), contaminated with 2,4-dibromotrifluoropyridine, which was not fully characterised.

Rate Measurements.—The rate constants for reaction with ammonia in dioxan–water were determined as previously described.[1] For the reactions with diethylamine in pure dioxan, samples were withdrawn, quenched in distilled water (100 ml), and titrated against standard acid. The

$$k = [1/(a - b)t] \ln b(a - x)/a(b - x) \qquad (1)$$

rate constants were evaluated from equation (1). A typical run is given in Table 3 for the reaction of diethylamine

Table 3

t/s	0	490	1 020	1 500	2 400	3 300
Titre (ml)	13.55	13.08	12.63	12.30	11.70	11.22
10^3k/l mol^{-1} s^{-1}		2.98	2.98	2.88	2.93	2.93
t/s	4 212	5 430	6 660	7 800	∞	
Titre (ml)	10.81	10.35	10.02	9.72	8.55	
10^3k/l mol^{-1} s^{-1}	2.95	2.97	2.93	3.00		

(0.0680M) with 2,6-dichlorotrifluoropyridine (0.0125M).

In contrast to the ammonia reactions in 60 : 40 dioxan–water there was no evidence of protonation of diethylamine in pure dioxan, so that only 1 mol of base was used up per mol of the substrate.

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