Mechanisms for Reactions of Halogenated Compounds. Part 1. Activating Effects of Fluorine in Polyfluoropyridines in Reactions with Ammonia

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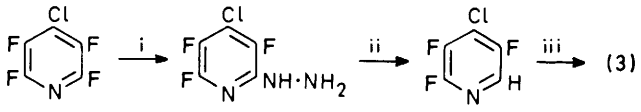
Rate constants have been determined for reactions of various polyfluoropyridines with ammonia in water–dioxan (60 : 40 v/v) at 25 °C. Comparison of these rate constants allows the separate effects of fluorine atoms *ortho*, *meta*, and *para* to the reaction centre to be established. The activating influence decreases in the series *ortho* > *meta* ≫ *para* (31 : 23 : 0.26 relative to a hydrogen atom at the same position). The hitherto puzzling orientation of nucleophilic substitution in polyfluoro-pyridines and -benzenes is, therefore, accounted for by the activating influence of fluoro-substituents being at a maximum. A synthesis of 2,3,4,5-tetrafluoropyridine is described.

THERE has been considerable interest in reactions of polyfluorinated aromatic compounds;[1] the complementary nature of the chemistry of aromatic hydrocarbons and their fluorinated analogues has been stressed. The perfluorinated compounds are very susceptible to nucleophilic attack and pose orientation problems for nucleophilic aromatic substitution which are complementary to the orientation problems in electrophilic aromatic substitution. Much is known about the effect of fluorine on carbanion stabilities in acyclic systems[2] and, previously, the most commonly used rationale[3] of the results of nucleophilic substitution in polyfluorinated aromatic compounds involved, essentially, an extrapolation of these data, but also attributed a dominant role to fluorine *para* to the point of nucleophilic attack.

In the work described here, we set out to determine the separate influences of fluorine at positions *ortho*, *meta*, and *para* to the point of nucleophilic attack in polyfluorinated pyridines.

RESULTS AND DISCUSSION

The compounds investigated in this study are shown in the Table; compounds (1)[4] and (2)[5] have been reported previously, and (4) was obtained by the reaction of copper(II) chloride with 2,3,5,6-tetrafluoro-4-hydrazinopyridine. Compound (3) was obtained from 4-chlorotetrafluoropyridine (4), by the route shown. This



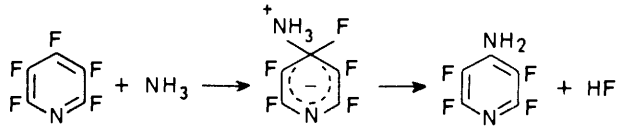
(4)

i, $NH_2{\cdot}NH_2$–H_2O; ii, aq. $CuSO_4$; iii, CsF–$[CH_2]_4SO_2$

procedure is necessary since it is the 4-position in pentafluoropyridine which undergoes attack by nucleophiles.[6,7] Compound (5) was obtained from 2,3,4,6-tetrafluoropyridine, by similar procedures.

Sodium methoxide in methanol was investigated initially for rate measurements, since this system has been used with fluorinated benzenes.[8] However, reactions of this reagent with polyfluoropyridines were generally too fast for convenient rate measurement at normal temperatures, whereas ammonia in dioxan–water (60 : 40 v/v) at 25 °C provided a convenient system. Second-order rate constants were determined by following the disappearance of ammonia, by conventional acid–base titrations.

In interpreting the results given in Table 1 it is assumed that reaction occurs in two stages, with the formation of the intermediate delocalised anion (7) as the rate-limiting stage. This is normally the case for displacement of fluorine from aromatic systems,[9] although it is by no means always so. Nevertheless, rate-limiting addition



(7)

is supported by our present work where attack in (4) occurs with displacement of the 2-fluorine rather than the 4-chlorine atom, even though attack occurs exclusively at the 4-position in (1). A rate-limiting second-stage would be expected to lead to loss of chlorine from (4). Furthermore there was no evidence of base-catalysis in these reactions: when the initial concentration of ammonia was doubled, rate constants were unchanged and the observed instantaneous rate constants were strictly constant throughout each kinetic run (which was usually followed to *ca.* 80% reaction).

Comparing the rate constants for attack at the 4-position in compounds (1) and (2) leads to a measure of the effect of an *ortho*-fluorine atom, relative to the point of attack, in comparison with hydrogen at the same position.

[1] See *e.g.* R. D. Chambers, 'Fluorine in Organic Chemistry,' Wiley–Interscience, New York, 1973, and references therein.
[2] Ref. 1, ch. 4 and references therein.
[3] J. Burdon, *Tetrahedron*, 1965, **21**, 3373.
[4] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3573.
[5] R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5045.
[6] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3736, 5634.
[7] R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 576.
[8] J. Burdon, W. B. Hollyhead, C. R. Patrick, and K. V. Wilson, *J. Chem. Soc.*, 1965, 6375.
[9] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968, pp. 19—22.

In a similar way, comparing (1) and (3) leads to evaluation of a *meta*-effect, and comparing attack at the 6-

TABLE 1

Rate constants for attack by ammonia in dioxan–water (60 : 40 v/v) at 25 °C

Substrate	Position of attack	k/l mol^{-1} s^{-1}	k_{rel} [w.r.t. (1)]
 (1)	4-	(6.80 ± 0.03) × 10^{-4}	1
 (2)	4-	(2.22 ± 0.1 [c]) × 10^{-5}	3.26 × 10^{-2}
	6-	(5.87 ± 0.3 [c]) × 10^{-6}	8.63 × 10^{-3}
 (3)	4-	(2.93 ± 0.03) × 10^{-5}	4.31 × 10^{-2}
 (4)	6- [a]	(1.55 ± 0.01) × 10^{-6}	2.28 × 10^{-3}
 (5)	6-	(5.92 ± 0.02) × 10^{-6}	8.70 × 10^{-3}
 (6)	4- [b]	*ca.* 0.7 [c] × 10^{-6}	*ca.* 10^{-3}
	6- [b]	*ca.* 0.2 [c] × 10^{-6}	*ca.* 3 × 10^{-4}

[a] Observed rate constant divided by 2. [b] Approximate k value, owing to the slowness of the reaction. [c] Separate k values calculated from n.m.r. and g.l.c. integrations.

position in compounds (4) and (5) leads to estimation of a *para*-effect, as follows:

For attack at the 4-position:

$$k_{(1)}/k_{(2)} = k_F/k_H \text{ (ortho)} = 31$$

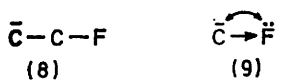
and

$$k_{(1)}/k_{(3)} = k_F/k_H \text{ (meta)} = 23$$

For attack at the 6-position:

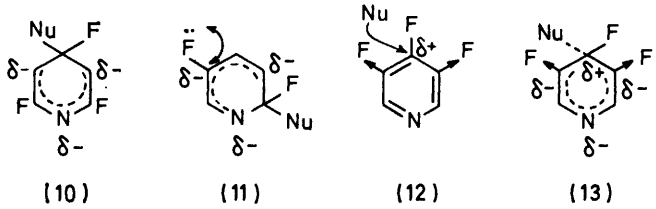
$$k_{(4)}/k_{(5)} = k_F/k_H \text{ (para)} = 0.26$$

It is now well established [2] that a fluorine atom in the situation (8) is strongly carbanion-stabilising, whereas in the situation (9), electron-withdrawal is strongly



(8) (9)

offset by electron-pair repulsion and the resultant effect can be that fluorine is slightly destabilising, with respect to hydrogen at the same position.[2,10,11] Therefore, for a transition-state like (10), we would expect fluorine atoms at the 2- and 6-positions, *i.e.* *meta* to the point of attack, to be activating. We can also understand the fact that a *para*-fluorine atom is slightly deactivating,[3] *i.e.* as in (11),

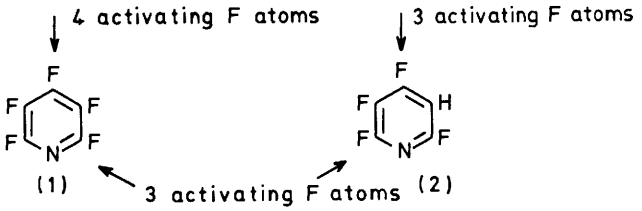


(10) (11) (12) (13)

but then we might also anticipate that the effect of fluorine would be the same at the *ortho*-position. This is clearly *not* the case, since *ortho*-fluorine is more activating than *meta*-. Therefore, there must be some non-conjugative effect arising from fluorine at the *ortho*-position. In a preliminary communication [12] we described this as an initial-state effect, making the carbon atom under attack more electron-deficient (12). However, the basis of this effect probably lies in the hard/soft acid/base theory,[13] *i.e.* the carbon atom under attack is made 'harder', therefore facilitating attack by a relatively 'hard' nucleophile, ammonia, and this could be described as a transition-state effect (13).

The order of activating influence of substituent fluorine atoms, relative to the point of nucleophilic attack, *ortho* > *meta* ≫ *para*, leads to a simple explanation of the controlling influence by fluoro-substituents of the orientation of nucleophilic substitution in pentafluoropyridine. Activation of the system by ring nitrogen is substantial, and there is some discrimination, by nitrogen, between the 2- and 4-positions. This is clear from the fact that 4-chloropyridine is more reactive than 2-chloropyridine towards attack by methoxide ion [14] and in (6) (Table 1) k_{4-}/k_{6-} is *ca.* 4.

The orientation of substitution in polyfluorinated pyridines is therefore governed by the effect of both the nitrogen atom and the fluoro-substituents. Thus nucleophilic substitution in pentafluoropyridine gives monosubstitution exclusively at the 4-position, where the



SCHEME 1

number of activating *ortho*- and *meta*-fluorine atoms is at a maximum (Scheme 1). An explanation for the attack

[10] A. Streitweiser and F. Mares, *J. Amer. Chem. Soc.*, 1968, **90**, 2444.
[11] L. A. Kaplan and H. B. Pickard, *Chem. Comm.*, 1969, 1500.
[12] R. D. Chambers, W. K. R. Musgrave, J. S. Waterhouse, D. L. H. Williams, J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J.C.S. Chem. Comm.*, 1974, 239.
[13] R. G. Pearson, *Chem. in Britain*, 1967, **3**, 103; *J. Chem. Educ.*, 1968, **34**, 581, 643.
[14] M. Liveris and J. Miller, *J. Chem. Soc.*, 1963, 3486.

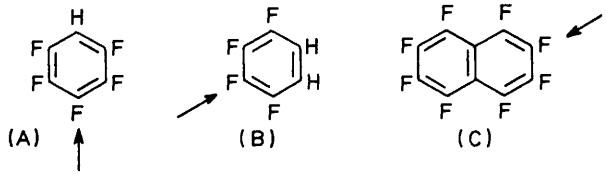
in 2,3,4,6-tetrafluoropyridine (2) at both the 4- and 6-positions also becomes clear. In contrast to pentafluoropyridine, attack at each of the 4- and 6-positions is associated with the same number of activating fluorine atoms.

We have recently [12] reconsidered the rate constants observed for reactions of sodium methoxide in methanol with hexa-, penta-, and tetra-fluorobenzenes and concluded that, in this system, the relative activating influence of fluorine atoms is *meta* > *ortho* ≫ *para*. The following comparison thus arises:

Fluoropyridines (NH_3) *ortho* (119): *meta* (88): *para* (1)

Benzenes (MeO^-) *meta* (167): *ortho* (56): *para* (1)

It is not surprising that the *ortho*/*meta* order differs for these two widely different systems, but the important point is that both series show a large activation by *ortho*-fluorine, whereas the *para*-fluorine atom has an effect little different from a hydrogen atom. Therefore, we may also conclude that the orientations of substitution in various polyfluorobenzenes, like the arrowed examples (A)—(C),[15-17] are governed by the necessity to maximise



the number of activating fluorine atoms. An earlier theory [3] laid stress on a controlling influence of *para*-fluorine, whereas it is now clear that this is, indeed, the least influential position. Miller,[18] however, anticipated the present results by extrapolation from σ^- values, although no value was available for a fluorine atom in the *ortho*-position.

In this paper, we have been discussing gross features which affect nucleophilic aromatic substitution; these effects are certainly modified by more subtle factors like solvation and steric effects in some systems.

EXPERIMENTAL

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

Materials.—Pentafluoropyridine [4] and 2,3,4,6-tetrafluoropyridine [5] were prepared by procedures described previously.

4-Chlorotetrafluoropyridine (with D. Lomas). 2,3,5,6-Tetrafluoro-4-hydrazinopyridine [6] (16 g) was added slowly to a stirred solution of copper(II) chloride (80.4 g) in conc. hydrochloric acid (550 ml). The mixture was stirred at room temperature for 2 h and then heated under reflux for 30 min, after which evolution of nitrogen had ceased. The aqueous distillate was extracted with ether and the ether layer dried ($MgSO_4$) and evaporated to give crude *4-chlorotetrafluoropyridine* (12 g, 66%). A sample purified by preparative scale g.l.c. (didecyl phthalate; 140 °C) had b.p. 122—123° (Found: C, 32.8; Cl, 19.1; F, 40.6. C_5ClF_4N requires C, 32.4; Cl, 19.1; F, 41.0%).

2,3,4,5-Tetrafluoropyridine (3). 4-Chlorotetrafluoropyridine (51.5 g), hydrazine hydrate (27.8 g), and ethanol (500 ml) were stirred together at room temperature for 3 h. The solution was then poured into water (1.5 l). The orange precipitate was extracted with ether and the extract washed with water, dried, and evaporated leaving the hydrazino-derivative (50 g). This was stirred with water (100 ml) and copper(II) sulphate solution (200 g in a saturated solution) was added dropwise with stirring. The mixture was steam-distilled; the reduction product (31 g) was collected and dissolved in tetramethylene sulphone (180 ml). Caesium fluoride (60 g) was added and the mixture stirred at 100° for 5 h. The reaction was monitored by analytical g.l.c. After *ca.* 50% conversion, the volatile material was removed by vacuum transfer, traces of sulphone were removed by washing with water, and the product was separated by preparative g.l.c. The *2,3,4,5-tetrafluoropyridine* was pure by g.l.c. (Found: C, 39.5; N, 9.4; F, 49.9%; M^+, 151. C_5HF_4N requires C, 39.7; N, 9.3; F, 50.3%; *M*, 151). ^{19}F δ (pure liquid) 90.3 (2-F) and 150.7, 155.8, and 164.5 p.p.m. (3-, 4-, and 5-F).

4-Chloro-2,3,6-trifluoropyridine (5). 2,3,4,6-Tetrafluoropyridine (16.6 g, 0.11 mol) was added dropwise to a stirred solution of hydrazine hydrate (9 g) in methanol (30 ml) and the mixture was stirred overnight at room temperature. It was then poured into water (150 ml) and ether (150 ml) was added, to dissolve the solid. The aqueous layer was further extracted with ether (5 × 30 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under vacuum, leaving a yellow solid (13.5 g). This hydrazino-derivative, without further treatment, was added slowly to a stirred solution of copper(II) chloride (80.4 g, 0.60 mol) in conc. hydrochloric acid (550 ml). The mixture was stirred at room temperature for 2 h, and then heated under reflux. When evolution of nitrogen had ceased the mixture was distilled. The organic layer of the distillate, a yellow oil, was separated, washed several times with water, and dried ($MgSO_4$). G.l.c. showed the presence of two isomers, and n.m.r. spectroscopy indicated that the minor component was 2-chloro-3,4,6-trifluoropyridine. A sample of the major component was isolated pure by preparative-scale g.l.c. (tricresyl phosphate; 140 °C) and shown to be *4-chloro-2,3,6-trifluoropyridine* (5), b.p. 128° (Found: C, 35.9; N, 8.5%; M^+, 167. C_5HClF_3N requires C, 35.9; N, 8.4%; M^+, 167); ^{19}F δ 72.1br (6-F), 85.1br (2-F), and 149 p.p.m. (3-F) ($J_{3F,6F}$ 24 Hz; $J_{3F,2F}$ 20 Hz).

Product Identification.—Products were all isolated by the same general procedure. After the kinetic runs were complete, the remaining mixture was poured into an excess of water (100 ml) and extracted with ether (2 × 20 ml). The ether fraction was washed several times with water and dried ($MgSO_4$); distillation left a solid product. Before further purification, the products were analysed by g.l.c. and n.m.r. in order to determine the number and relative amounts of any isomers formed. 4-Aminotetrafluoropyridine was characterised by comparison of the i.r. spectrum with that of an authentic specimen.[6]

(a) *From 2,3,4,6-tetrafluoropyridine* (2). Integration of the ^{19}F n.m.r. spectrum of the crude solid product showed it

[15] J. C. Tatlow, *Endeavour*, 1963, **22**, 89, and references therein.

[16] J. Burdon and W. B. Hollyhead, *J. Chem. Soc.*, 1965, 6326.

[17] B. Gething, C. R. Patrick, and J. C. Tatlow, *J. Chem. Soc.*, 1963, 186.

[18] Ref. 9, p. 126.

to consist of two compounds. The major component (79%) was 4-amino-2,3,6-trifluoropyridine, ^{19}F δ (Me_2CO) 76.4 (dd, 6-F), 95.0 (dd, 2-F), and 173.7 p.p.m. (td, 3-F) ($J_{2F,6F}$ 13 Hz; $J_{6F,3F} = J_{3F,2F} = 20$ Hz). The minor component was 2-amino-3,4,6-trifluoropyridine, ^{19}F δ (Me_2CO), 70.9 (dd, 6-F), 124.6 (td, 4-F), and 172.6 p.p.m. (ddd, 3-F) ($J_{6F,3F}$, 24 Hz; $J_{6F,4F} = J_{4F,3F} = 18$ Hz). The mixture of isomers, after sublimation (80 °C; 0.01 mmHg) was analysed (Found: C, 40.3; N, 18.9. $C_5H_3F_3N_2$ requires C, 40.5; N, 18.9%).

(b) *From* 2,3,4,5-*tetrafluoropyridine* (3). ^{19}F N.m.r. analysis of the crude solid product showed that it contained one compound only, ^{19}F δ (Me_2CO), 99.3 (2-F), 156.7, and 168.7 p.p.m. (3- and 5-F), which was consistent with 4-*amino*-2,3,5-*trifluoropyridine*. It was analysed after sublimation (Found: C, 40.3; N, 19.5. $C_5H_3F_3N_2$ requires C, 40.5; N, 18.9%).

(c) *From* 4-*chlorotetrafluoropyridine* (4). The product contained only one component which, on sublimation under vacuum, gave 2-*amino*-4-*chlorotrifluoropyridine*, m.p. 117—117.5° (Found: C, 33.1. $C_5H_2ClF_3N_2$ requires C, 32.9%).

(d) *From* 4-*chloro*-2,3,6-*trifluoropyridine* (5). The product contained one component, 2-*amino*-4-*chloro*-3,6-*difluoropyridine*, m.p. 103° [Found: C, 37.2%; M^+ (^{35}Cl) 164. $C_5H_3ClFN_3$ requires C, 36.6%; *M*, 164]; ^{19}F δ 150.7 (3-F) and 74.6 p.p.m. (6-F) ($J_{6F,3F}$ 24 Hz).

(e) *From* 2,4,6-*trifluoropyridine* (6). The major product (isomeric ratio 66 : 34) from the kinetic run was identified by comparing its i.r. spectrum with that of authentic material, prepared and characterised in the following way. A mixture of 2,4,6-trifluoropyridine [5] (1.0 g, 7.5 mmol), aqueous ammonia (30 ml; s.g 0.88), dioxan (30 ml), and water (20 ml) in a sealed Carius tube was heated at 80 °C for 3 weeks. The mixture was then poured into water (100 ml) and extracted with ether (2 × 20 ml); the extracts were dried ($MgSO_4$) and distilled to leave a solid (0.85 g, 87%). Recrystallisation (cyclohexane) gave 4-*amino*-2,6-*difluoropyridine*, m.p. 124—125° (Found: C, 46.4; N, 20.9%; M^+, 130. $C_5H_4F_2N_2$ requires C, 46.2; 21.5%; *M*, 130); ^{19}F δ 68.7 p.p.m.

Kinetics.—Rate measurements were carried out at 25 °C in 60 : 40 (v/v) dioxan–water. Samples were withdrawn at suitable intervals and quenched in a large excess of water, and the unchanged base was titrated against standard hydrochloric acid. The infinity value agreed well with that calculated from the weight of material used. Generally reactions were followed for at least two half-lives, and each run was carried out in duplicate. Second-order rate constants were calculated from equation (i), where *a* and *b*

$$k = \ln[b(a - 2x)/a(b - x)]/(a - 2b)t \qquad \text{(i)}$$

are the initial concentrations of ammonia and substrate respectively, since ammonia becomes protonated by the acid liberated in the reaction. The standard error of the mean in any individual run was ±1% and the duplicate runs agreed to within ±1%. A typical run is given in Table 2 for the reaction of ammonia (7.34×10^{-2}M) with

TABLE 2

Time (s)	0	606	1 200	2 100	3 385	4 500	6 027
Titre (ml)	14.62	13.85	13.18	12.36	11.36	10.70	9.90
10^3k/l mol^{-1} s^{-1}		1.95	1.96	1.92	1.93	1.90	1.92
Time (s)	7 860	10 260	14 040	17 340	23 880	∞	
Titre (ml)	9.20	8.49	7.61	7.10	6.40	5.10	
10^3k/l mol^{-1} s^{-1}	1.88	1.87	1.90	1.88	1.90		

Mean $10^3k = 1.92 \pm 0.02$ l mol^{-1} s^{-1}.

3-chlorotetrafluoropyridine (2.39×10^{-2}M). Where more than one product was formed, the individual rate constants were calculated from the total rate constant and the yields of the isomeric products, as analysed both by n.m.r. and by gas-density balance g.l.c.

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