Mechanisms for Reactions of Halogenated Compounds. Part 3.[1] Variation in Activating Influence of Halogen Substituents in Nucleophilic Aromatic Substitution

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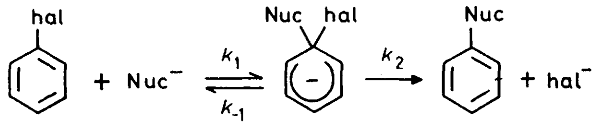
Rate constants are reported for reactions of polyhalogeno-pyridines and -benzenes with sodium methoxide in methanol. Relative activating effects of individual fluorine and chlorine atoms at positions *ortho*, *meta*, and *para* to the reaction site are determined and compared with orders determined from reactions involving ammonia in aqueous dioxan. The results are remarkably similar. Additional support is provided for earlier explanations of the activating effects of *ortho*-fluorine and -chlorine. Activation parameters, determined for reactions of polyhalogenopyridines with ammonia in aqueous dioxan, clearly demonstrate that differences in reactivity along the series arise mainly from changes in activation energy.

In Parts 1 and 2, we established the separate activating effects of fluorine and of chlorine as substituents in nucleophilic aromatic substitution. We have presented evidence earlier[2] for the normal two-stage addition–elimination mechanism, with the first stage being effectively rate limiting. For reactions of polyhalogeno-pyridines with ammonia, in aqueous dioxan, the activating order of both fluorine[2] and chlorine[1] as substituents is *ortho* > *meta* ≫ *para*, with respect to the point of nucleophilic attack on the ring. The activation by *ortho*-substituents is more difficult to explain than the effect of *meta*-substituents. Therefore, in this paper, we probe the importance of this *ortho*-effect with change in nucleophile and substrate as a test of the generality of our earlier findings and, more importantly, of our explanation of this *ortho*-effect.



Ammonia in aqueous dioxan was used for the previous study because this system gave rate constants for reactions with highly halogenated pyridines, that are convenient to measure. In contrast, sodium methoxide in methanol presented difficulties but we have now been able to measure rate constants of acceptable accuracy for reactions of highly halogenated pyridines with this system, at −7.60 °C.

Table 1

Rate constants for reactions of halogeno-pyridines with sodium methoxide in methanol at −7.60 °C

Pyridine	Position of attack	k/l mol^{-1} s^{-1}
F_5 (1)	4	1.90
2,3,4,6-F_4 (2)	4	2.42×10^{-2} [a]
	2	0.03×10^{-2} [a]
2,3,4,5-F_4 (3)	4	6.42×10^{-2}
2,3,5,6-F_4 (4)	2, 6	3.47×10^{-5} [b]
4-Cl-2,3,5,6-F_4 (5)	2, 6	2.09×10^{-3} [b]
4-Cl-2,3,6-F_3 (6)	2	6.37×10^{-3}
2,4,6-F_3 (7)	4	6.28×10^{-4}
	2, 6	5×10^{-5} [b]

[a] Separate k values calculated from n.m.r. and g.l.c. integrations. [b] Corrected for statistical factor.

The kinetic results for reaction of a variety of fluorinated pyridines with methoxide ion in methanol are shown in Table 1. A comparison of the rate constants, for attack at the 4-position, for different pairs of compounds allows the activating influence of fluorine atoms *ortho* and *meta* to the reaction centre to be deduced. Similarly, comparison of the rate constants for attack at the 2-position in compounds (5) and (6) allows the effect of a *para*-fluorine to be deduced.

Attack at the 4-position:

$$k(1)/k(2) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{ortho} = 79$$

$$k(1)/k(3) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{meta} = 30$$

Attack at the 2-position:

$$k(5)/k(6) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{para} = 0.33$$

Therefore, we are now able to summarise and compare values obtained from reactions involving ammonia with corresponding values involving sodium methoxide.

F-Pyridine derivatives:

ortho *meta* *para*
(NH_3; aqueous dioxan; 25 °C)
31 : 23 : 0.26 (relative to H)
(119 : 88 : 1) (relative to the *para*-position)
(MeO^-; MeOH; −7.60 °C)
79 : 30 : 0.33 (relative to H)
(239 : 91 : 1) (relative to the *para*-position)

These values are quite remarkably close, considering the difference of nucleophile, solvent, and reaction temperature.

Reactions of several polyfluorobenzene derivatives with sodium methoxide in methanol have been studied previously;[3] we have determined rate constants for compounds (8)—(12) at 58.00 °C and the values, contained in Table 2, do not differ to any significant degree with the values determined earlier. However, the activating influence of fluorine atoms at different positions in the benzene system may be deduced from these values by appropriate comparisons with the statistically corrected value for hexafluorobenzene.

Benzene system:

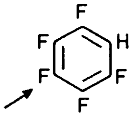
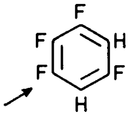
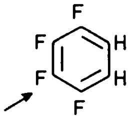
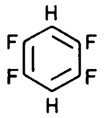
$$k(9)/k(10) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{ortho} = 57$$

$$k(9)/k(11) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{meta} = 106$$

$$k(8)/k(9) = k(\mathrm{F})/k(\mathrm{H}) \quad \textit{para} = 0.43$$

TABLE 2

Rate constants for reactions of polyfluorobenzenes with sodium methoxide in methanol at 58.00 °C

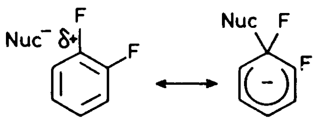
Compound	k/l mol^{-1} s^{-1}
C_6F_6 (8)	$1.29 \times 10^{-4\,a}$
 (9)	3.02×10^{-4}
 (10)	$5.28 \times 10^{-6\,a}$
 (11)	$2.85 \times 10^{-6\,a}$
 (12)	$2.57 \times 10^{-8\,a}$

[a] Corrected for statistical factor. Position of substitution indicated by an arrow.

Therefore, we are able to compare the activating influence of fluorine, as a substituent, in the benzene and the pyridine systems, for reactions involving methoxide.

F	*ortho*	*meta*	*para*
Benzenes	57	: 106	: 0.43 (relative to H)
	(133	: 246	: 1) (relative to the *para*-position)
Pyridines	(239	: 91	: 1) (relative to the *para*-position)

The most important feature of this comparison is that, indeed, fluorine which is *ortho* or *meta* to the reaction centre is very substantially more activating than *para*-fluorine, in both systems. It is interesting, however, that the relative importance of activating *ortho*- and *meta*-fluorine atoms depends on the system; in the more reactive pyridine derivatives, *ortho*-fluorine is more activating than *meta*-fluorine, whereas this is reversed in the benzene system. This is significant because it adds substance to an explanation of the *ortho*-activating effect that we have advanced previously.



(13a) (13b)

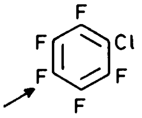
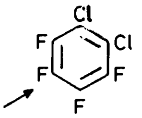
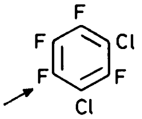
It was suggested that, in the transition state for substitution represented by (13), fluorine atoms *ortho* to the site of attack by the nucleophile, enhance the electrophilic nature of the carbon atom under attack [(13a)]. On this basis, a more reactive system should lead to an earlier transition state (Hammond postulate[4]), which means a greater contribution from (13a) to the structure of the transition-state. In turn, this implies a greater importance of *ortho*-, relative to *meta*-activation, which has been observed.

We have commented previously on the surprising additivity of fluorine substituents in the pyridine system and this is no less so in benzene derivatives. A rate constant for (12) may be calculated from the observed value for hexafluorobenzene, allowing for the replacement of one fluorine atom *ortho* and one fluorine atom *meta* to the reaction site, *i.e.* $1.29 \times 10^{-4}/57 \times 106 = 2.1 \times 10^{-8}$ l mol^{-1} s^{-1} (*cf.* observed value of 2.57×10^{-8} l mol^{-1} s^{-1}).

Rate constants for the reaction of various chlorofluorobenzenes with sodium methoxide in methanol at −7.6 °C are given in Table 3, from which the relative activating influences of chlorine *vs.* fluorine at different positions may be derived:

TABLE 3

Rate constants for reactions of chlorofluorobenzenes with sodium methoxide in methanol at −7.6 °C

Compound	k/l mol^{-1} s^{-1}
C_6F_6 (8)	$8.94 \times 10^{-8\,a}$
 (14)	3.12×10^{-6}
 (15)	$2.14 \times 10^{-6\,a}$
 (16)	$1.00 \times 10^{-5\,a}$

[a] Corrected for statistical factor. Position of substitution indicated by an arrow.

$$k(16)/k(14) = k(\mathrm{Cl})/k(\mathrm{F}) \quad ortho = 3.2$$

$$k(15)/k(14) = k(\mathrm{Cl})/k(\mathrm{F}) \quad meta = 0.69$$

$$k(14)/k(8) = k(\mathrm{Cl})/k(\mathrm{F}) \quad para = 35$$

A comparable set of factors has been obtained from reactions of ammonia in aqueous dioxan,[1] *i.e.* *ortho* *ca.* 3, *meta ca.* 1, *para* 27. The main point to conclude, therefore, is that the *order* of activating influence is not, apparently, very dependent on nucleophile or solvent and, indeed, the factors are quite surprisingly similar for these quite different systems.

From the studies described in this paper, we may derive the following conclusions concerning the effects of halogens as substituents in nucleophilic aromatic substitution. (a) Fluorine substituents that are *ortho* and *meta* to the position of nucleophilic attack are strongly activating whereas a *para*-fluorine is slightly deactivating with respect to hydrogen at the same position. This situation has now been demonstrated with a neutral and a negatively charged nucleophile and for both benzene and pyridine systems. Therefore, it seems reasonable to accept the explanations of orientation of nucleophilic aromatic substitution, advanced previously,[2] to be on a sound general basis. (b) The relative activating influence of *ortho*- relative to *meta*-halogen will vary slightly, and will increase with the reactivity of the substrate. (c) The activating influence of chlorine is in the order *ortho* > *meta* > *para* for both the pyridine and benzene series.

These findings put on a sound basis a body of qualitative observations, referred to earlier,[5] but it remains to demonstrate that these activating influences that we have described do, indeed, originate in changes in *energy* of activation. Activation parameters for reaction of five halogenopyridines with ammonia in aqueous dioxan are recorded in Table 4. Rate constants were determined at four temperatures: 288, 298, 308, and 318 K. The given errors in the activation energies E_a and the entropies of activation $\Delta S^\ddagger$ are those computed by least-squares analysis. It is quite clear that the reduced reactivity of the two tetrafluoropyridines (2) and (3) (compared with pentafluoropyridine) arises mostly from the increase in the activation energy; similarly the enhanced reactivities of 3-chlorotetrafluoropyridine (17) and 3,5-dichlorotrifluoropyridine (18) are due to quite large reductions in the activation energies, with relatively little change in the $\Delta S^\ddagger$ term along the series. The sign and magnitude of the $\Delta S^\ddagger$ values are as expected for a bimolecular substitution reaction of this type, and there is no evidence of any trend along the series studied.

TABLE 4

Activation parameters for reactions with ammonia in aqueous dioxan

Pyridine	E_a/kJ mol^{-1}	$\Delta S^\ddagger$/J K^{-1} mol^{-1} [a]
(1)	52.3 ± 0.1	−157 ± 2
(2)	67.1 ± 5	−98 ± 18
(3)	67.8 ± 2	−112 ± 9
5-Cl-2,3,4,6-F_4 (17)	47.6 ± 2	−145 ± 8
3,5-Cl_2-2,4,6-F_3 (18)	38.8 ± 2	−167 ± 10

[a] The $\Delta S^\ddagger$ values refer to 298 K.

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.—Polyhalogenopyridines used are known compounds and were obtained by methods developed in these laboratories.[1,2,6] Polyhalogenobenzenes were obtained from I.S.C. Chemicals Ltd. and Bristol Organics Ltd.

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 and then extracted with ether. The ether fraction was washed several times with water, dried ($MgSO_4$), and then distillation of the ether left the product residue. Before further purification, products were analysed by g.l.c. and n.m.r. to determine the number and relative amounts of any isomers formed. Pentafluoroanisole was identified by comparison of the n.m.r. spectrum with that of an authentic specimen.[7]

(a) *From chloropentafluorobenzene.* Unlike earlier workers,[8] who detected two isomers in a reaction carried out at a higher temperature, in a reaction conducted at −7.6 °C only 4-chlorotetrafluoroanisole was observed (Found: C, 39.2; H, 1.5%; M^+, 214. Calc. for $C_7H_3ClF_4O$: C, 39.15; H, 1.4%; M^+, 214); δ_F 138.8 (3,5-F_2) and 156.2 p.p.m. (2,6-F_2).

(b) *From 1,2-dichlorotetrafluorobenzene.* The isolated product, 3,4-dichlorotrifluoroanisole [8] (Found: C, 36.5; H, 1.4. Calc. for $C_7H_3Cl_2F_3O$: C, 36.35; H, 1.3%) had δ_F 131.9 (2-F), 138.8 (5-F), and 152.2 p.p.m. (6-F).

(c) *From 1,3-dichlorotetrafluorobenzene.* The isolated product was 2,4-dichlorotrifluoroanisole (Found: C, 36.4; H, 1.4%); δ_F 119.3 (3-F), 137.4 (5-F), and 156.7 p.p.m. (6-F).

Rate Measurements.—For the reaction with sodium methoxide in methanol equal concentrations of the substrate and methoxide were used and the second-order rate constant determined from the plot of $1/(a - x)$ *versus* time. Portions were withdrawn at appropriate intervals, quenched by dilution, and titrated with standard acid. A sealed-tube technique was used for the reaction at 58 °C. Good linear plots were obtained generally over a least two half-lives of the reaction and the rate constants were reproducible within ±3%.

Activation parameters were obtained from rate measurements with the ammonia–aqueous dioxan system, at the four temperatures: 15, 25, 35, and 45 °C. The rate constants were obtained as has been described earlier.[2]

[9/1337 *Received*, 21*st August*, 1979]

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[6] See *e.g.* R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5045, and earlier parts of the series.

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