Mechanisms for Reactions of Halogenated Compounds. Part 6.[1] Investigations into the Activating Effect of *ortho*-Fluorine in Nucleophilic Aromatic Substitution

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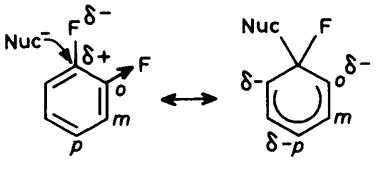
Separate activating effects for *ortho*- and *meta*-fluorine, on nucleophilic aromatic substitution, are determined for pyrimidine and pyridine systems. Comparisons confirm the importance of ion–dipole interactions for activation by *ortho*-fluorine. The effects of *ortho*-fluorine on anionic σ-complexes are also discussed.

In earlier parts of this series, we have developed an empirical approach to accounting for the orientation of substitution and reactivity orders in reactions of nucleophiles with highly fluorinated aromatic systems. Broadly, we have established that fluorine atoms that are substituents at positions *ortho*- and *meta*- to the site of attack are significantly activating, whereas *para*-fluorine is slightly deactivating with respect to hydrogen atoms at the same positions. The effects of *meta*- and *para*-fluorine have been rationalised on the basis of known effects of fluorine on adjacent (**1**) or attached (**2**) carbanionic sites,[2] applied to the corresponding Meisenheimer complexes (**4**).

(**1**) (strongly activating)

(**2**) (Inductive electron withdrawal offset by electron-pair repulsions)

It is evident, however, that on the basis of this model we would expect *ortho*- and *para*-fluorine to have similar effects on reactivity, which is clearly not so. The greater reactivity of carbon–fluorine, over carbon–chlorine in aromatic systems is generally accounted for by taking into consideration the contribution to reactivity of ion–dipole effects, *i.e.* structure (**3**). Furthermore, we have argued that *ortho*-fluorine will accentuate the effect and that this is the basis of *ortho*-activation by fluorine.[3] If this is valid, however, then with increasing reactivity of the system, the effect of *ortho*-fluorine should become more important relative to the effect of *meta*-fluorine; this follows from the Hammond postulate[4] whereby the transition state (**4**), as represented by structure (**3**)/(**4**), occurs earlier along the reaction path, *i.e.* becomes more like structure (**3**).



(**3**) (**4**)

We describe here experiments to determine the relative activating influences of *ortho*- and *meta*-fluorine in the pyrimidine system and compare these with effects determined in the less reactive pyridine and benzene systems. We have also compared the relative effects of nucleophiles of differing reactivity, *i.e.*, ammonia in aqueous dioxane and sodium methoxide in methanol. The results of these new measurements are shown in Table 1 and the relative activating influence for pyrimidine and pyridine systems were derived as shown in Table 2. These values are then compared in Table 3 with analogous effects derived from the benzene system.

Table 1. Rate constants for the reactions of (a) ammonia in dioxane–water (3:2 v/v) and (b) sodium methoxide in methanol with polyfluoropyrimidines and with polyfluoropyridines at 25.0 °C

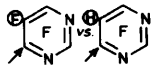
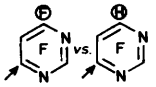
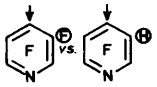
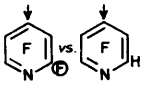
Compound	Position of substitution	Rate constant, k_{II}/l mol^{-1} s^{-1} (a) Attack by ammonia	(b) Attack by MeO^-
	4-[a]	1.35 ± 0.01[b]	(3.90 ± 0.02) × 10^3
	2-[c]	(1.89 ± 0.04) × 10^{-1}	(1.48 ± 0.03) × 10^2
	4-[a,c]	(0.33 ± 0.04) × 10^{-1}	(1.34 ± 0.03) × 10^2
	6-	(4.49 ± 0.02) × 10^{-1}	(1.61 ± 0.02) × 10^3
	4-	(6.80 ± 0.03) × 10^{-4}	(1.42 + 0.01) × 10^1
	4-[c]	(2.22 ± 0.1) × 10^{-5}[d]	(5.94 ± 0.04) × 10^{-1}
	6-[c]	(5.87 ± 0.3) × 10^{-6}[d]	(0.30 ± 0.06) × 10^{-1}
	4-	(2.93 ± 0.03) × 10^{-5}[d]	(9.34 ± 0.03) × 10^{-1}

[a] Observed rate constant divided by 2 (statistical factor). [b] Rate constant from ref. 16. [c] Separate k_{II} values calculated from n.m.r. and g.l.c. integrations. [d] Rate constants from ref. 17.

The first clear point that emerges is a marked reduction in the effect of *meta*-fluorine, relative to hydrogen, as the reactivity of the system increases. In contrast, this is not mirrored by corresponding changes in the effect of *ortho*-fluorine, the net result being that the ratio of effects *ortho*-F:*meta*-F increases with reactivity, as would be required by the model described above. Therefore, in considering activation by *ortho*-fluorine, we must include 'initial state' effects.

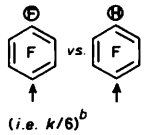
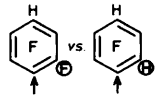
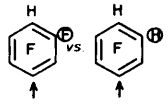
Although these results clearly demonstrate an activation

Table 2. Activating influences of fluorine in the pyrimidine and pyridine ring systems

Comparison[a]	Effect determined	k_F/k_H (Ammonia)	k_F/k_H (Methoxide)
	*ortho*-F / *ortho*-H	41	29
	*meta*-F / *meta*-H	3.0	2.4
	*ortho*-F / *ortho*-H	31	24
	*meta*-F / *meta*-H	23	15

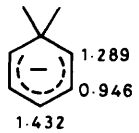
[a] Position of substitution arrowed.

Table 3. Activating influences of fluorine in benzene systems

Comparison[a]	Effect determined	k_F/k_H(MeO$^-$–MeOH, 58 °C)
 (*i.e.* *k*/6)[b]	*para*-F / *para*-H	0.43
	*ortho*-F / *ortho*-H	57
	*meta*-F / *meta*-H	106

[a] Position of substitution arrowed. [b] Statistically corrected.

by *ortho*-fluorine that is not related to an effect on charge delocalization into the ring in the transition state (**4**), nevertheless, from the work[5,6] of Crampton and that of others[7] on the rates of formation of Meisenheimer complexes, it has been concluded that *ortho*-fluorine, relative to hydrogen, stabilises anionic σ-complexes whereas *para*-fluorine is slightly destabilising. The same conclusions may be drawn from work on the rates of de-tritiation of toluene derivatives[8] and, more remarkably, calculations[9,10] indicate the same effect. What does not emerge from discussion of these calculated results, however, is a qualitative description of how *ortho*-fluorine can stabilise anionic σ-complexes whereas *para*-fluorine destabilises. An obvious explanation would be, simply, that charge density in the transition state is greatest at *para*-positions, but then this would require similar developing charge density at *ortho*- and *meta*-positions in order to account for the observed similar effects of fluorine at these sites. In fact, calculations reveal a slight preference for charge density at the *para*-position[11] (**5**) but a major difference in charge density at *ortho*- in comparison with *meta*-positions. This seems to be quite incompatible with explanations based on differences in charge density between

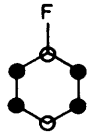


(**5**)

ortho- and *para*-positions. The only factor which does distinguish *ortho*- from the *para*-position in transition state (**4**) is the effect of *ortho*-fluorine on the 'ipso' site. Calculations reveal that total charge (as opposed to π-charge density) is greatest at the 'ipso' site and it has been argued[12] that the effect of *ortho*-fluorine on the position would be substantial. This could be regarded as a qualitative description of what calculations and experiment have shown.

Therefore, we conclude that the observed activating influence of *ortho*-fluorine is a composite of the 'initial state' effect (*i.e.* ion–dipole interaction) described earlier in this paper and a clearly established ability of *ortho*-fluorine to stabilise ionic σ-complexes.

An attractive alternative explanation of the foregoing results could be based on a Frontier-Orbital approach.[13] Obviously, the contribution arising from ion–dipole interaction is embodied in this approach but also the similar effect of *ortho*- and *meta*-fluorine would follow from an assumption that the LUMOs involved had essentially the form (**6**).



(**6**)

Some discussion on this approach has occurred in the literature and it has been argued[14] that structure (**6**) would be the LUMO for polyfluorobenzenes. Other workers[15] have criticised this approach but, in doing so, ignored the importance of ion–dipole interactions arising from the initial state. Also, both groups[14,15] ignored in their discussion the experimentally derived effects of fluorine, especially the role of *ortho*-fluorine as discussed here.

Experimental

^{19}F N.m.r. spectra were recorded on a Bruker HK 90 instrument; chemical shifts are quoted in p.p.m. relative to internal $CFCl_3$ (upfield positive).

Materials.—Tetrafluoro-,[18] 5*H*-trifluoro-,[19] 4*H*-trifluoro-,[20] pentafluoro-,[21] 3*H*-tetrafluoro,[22] and 2*H*-tetrafluoropyrimidine[17] were prepared by known methods.

Product Identifications.—Reactions of the above systems with ammonia and with sodium methoxide have been studied extensively[19,23] with the exception of 4*H*-trifluoropyrimidine. Where applicable, product isomer analysis was carried out by ^{19}F n.m.r. spectroscopy and by gas density balance g.l.c. Products were usually isolated by the same general procedures.

(a) *Reactions of ammonia in dioxane–water* (3:2 v/v) *with* 4H-*trifluoropyrimidine.* 4*H*-Trifluoropyrimidine (0.1 g, 0.75 mmol), dioxane (0.3 ml), and aqueous ammonia (0.25 ml, 0.75 mmol) were shaken in an n.m.r. tube and left for 1 h at 25 °C. The resulting white precipitate was dissolved in a minimum amount of [$^2H_6$]acetone. The ^{19}F n.m.r. spectrum of the product

showed only one component, identified as 6-amino-2,5-difluoropyrimidine; δ_F 52.6 (d, 2-F) and 160.3 (d, 5-F); $J_{2F,5F}$ 25.6 Hz.

(b) *Reaction of sodium methoxide in methanol with* 4H-*trifluoropyrimidine*. Sodium methoxide in methanol (*ca.* 0.75M solution) was added dropwise to a solution of 4*H*-trifluoropyrimidine (0.1 g, 0.75 mmol) in methanol (1 ml) in an n.m.r. tube at 25 °C. The ^{19}F n.m.r. spectrum of the product (after *ca.* 50% reaction) showed two fluorine atoms in the methoxylated adduct, identified as 2,5-difluoro-6-methoxypyrimidine; ^{19}F δ_F 49.6 (d, 2-F) and 159.3 (d, 5-F); $J_{2F,5F}$ 27 Hz.

Rate Measurements.—All kinetic measurements were carried out at 25.0 °C.

(a) *Reactions of polyfluoropyrimidines with ammonia and polyfluoropyridines with sodium methoxide*. These runs were determined spectrophotometrically, in a large (known) excess of nucleophile, by following the appearance of product with time at a fixed wavelength. First-order rate constants (k_1) were then calculated from the following equation,

$$k_1 t = \ln\left[\frac{O.D._\infty - O.D._0}{O.D._\infty - O.D._t}\right]$$

where $O.D._\infty$ = optical density at infinity, $O.D._0$ = optical density at the time zero, and $O.D._t$ = optical density at time t. Dividing k_1 by the known nucleophile concentration (assumed constant throughout) gave the second-order rate constant k_{II}.

(b) *Reactions of polyfluoropyrimidines with sodium methoxide*. These reactions were extremely rapid and were followed spectrophotometrically using the stopped-flow technique. This technique has been described.[24] The absorbance of the solution at a given wavelength was displayed as a voltage (V) on an oscilloscope; first-order rate constants were calculated from a slope of a plot of $\ln(V_\infty - V_t)$ against time, where V_∞ and V_t were the voltages corresponding to the optical densities at time ∞ and time t, respectively.

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