The Mechanism of the Nucleophilic Substitution Reactions of Polyfluoroarenes

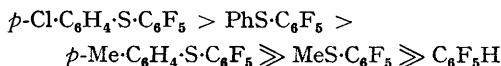By J. M. BIRCHALL, M. GREEN, R. N. HASZELDINE, and A. D. PITTS

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ALTHOUGH the preparative aspects of the nucleophilic replacement reactions of polyfluoroarenes have been extensively explored, until recently[1] there have been no systematic mechanistic studies of these interesting reactions. The reactions of hexafluorobenzene with nucleophiles normally give monosubstituted products, although thiophenoxide ion has been reported to yield the 1,4-disubstituted product.[2] Disubstitution was attributed[2] to an unidentified activating effect at the *para*-position of the C_6F_5 ring in pentafluorophenyl phenyl sulphide. Similar activation by the bivalent sulphur atom has been observed during the displacement of chloride from 4-chloro-3-nitrothioanisole by methoxide ion.[3]

We now report a kinetic study of the reactions of the compounds C_6F_5H, $C_6F_5 \cdot SMe$, and $p\text{-}X \cdot C_6H_4 \cdot S \cdot C_6F_5$ (where X = H, Cl, or Me) with various nucleophiles in ethanol; in every case attack by the nucleophile was detected only at the *para*-position, and the kinetic results are tabulated.

It is evident that the SMe group exerts a powerful activating effect towards attack on the ring by both ethoxide and thiophenoxide. Of particular interest is the reactivity sequence

$$p\text{-}Cl \cdot C_6H_4 \cdot S \cdot C_6F_5 > PhS \cdot C_6F_5 >$$
$$p\text{-}Me \cdot C_6H_4 \cdot S \cdot C_6F_5 \gg MeS \cdot C_6F_5 \gg C_6F_5H$$

observed for the reactions with thiophenoxide. The rate constants for the reactions of the compounds $p\text{-}X \cdot C_6H_4 \cdot S \cdot C_6F_5$, correlated by the Hammett equation, give a value for ρ of $+2 \cdot 1$. The differences in reaction rate are considerable for substituents which are so well removed from the reaction site.

This suggests that, at least in the case of the thioethers, an S_N2-type displacement is not operating and that, as in many nucleophilic aromatic substitution reactions,[4] an intermediate of some stability is formed by addition of the nucleophile to the aromatic ring. The general activating effect of a thiophenoxide substituent towards nucleophilic attack on the ring can be ascribed to the stabilisation of the negative charge in the intermediate by the use of the vacant d-orbitals of the sulphur atom.[5] A $-I$-effect for X in $p\text{-}X \cdot C_6H_4 \cdot S \cdot C_6F_5$ would thus assist in the stabilisation of the intermediate (*e.g.*, X = Cl) relative to the intermediate where X = H, and a $+I$-effect (*e.g.*, X = Me) would tend to destabilise the intermediate:
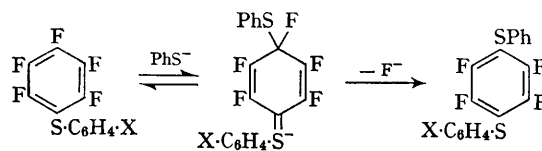
Further information concerning the mechanisms of the reactions of the compounds C_6F_5Z (Z = H, SMe, SPh) with nucleophiles was obtained by a kinetic study using *para*-substituted thiophenoxides ($p\text{-}Y \cdot C_6H_4 \cdot S^-$) in ethanol under conditions (50—70°) which gave exclusively the product $p\text{-}Y \cdot C_6H_4 \cdot S \cdot C_6F_4 \cdot Z\text{-}p$. A plot of reaction rate versus temperature for the series Z = H or SMe, Y = H, Br, or Bu^t, generated a set of non-converging curves, showing[6] that if the series of reactions is isokinetic, the isokinetic temperature must be considerably greater than 70°; the rate data may thus be interpreted in terms of a specific reaction mechanism.

Of a number of free-energy correlations examined, one of particular interest in relation to the establishment of mechanism involves the log k_2 values for the reaction of $C_6F_5 \cdot SPh$ with the series of thiophenoxides $p\text{-}Y \cdot C_6H_4 \cdot S^-$ (Y = H, Br, Cl, F, Me, MeO) versus the corresponding log k_2 values for the reaction of C_6F_5H or $C_6F_5 \cdot SMe$ with the same thiophenoxides. These plots generated straight lines with a slope of unity,[7] *i.e.*, the reactions have identical ρ-values. This

TABLE

Rates of reactions of C_6F_5Z with nucleophiles in ethanol at 61°

Z	Nucleophile	k_2 (l.mol.$^{-1}$ sec.$^{-1}$ × 10^4)
H	EtO$^-$	7·00
SMe	EtO$^-$	125
H	PhS$^-$	1·22
SMe	PhS$^-$	80·8
SPh	PhS$^-$	1530
S·C$_6$H$_4$·Cl-*p* . .	PhS$^-$	7250
S·C$_6$H$_4$·Me-*p* . .	PhS$^-$	930

suggests that the compounds C_6F_5H, $C_6F_5 \cdot SMe$, and $C_6F_5 \cdot SPh$ react with thiophenoxides by a similar mechanism. Hence, pentafluorobenzene probably also reacts by the addition–elimination mechanism, and it follows that most other nucleophilic reactions of polyfluorinated aromatic compounds are likely to be of this type.

The relative reactivities of the nucleophiles ethoxide and thiophenoxide towards different electrophilic centres have been related to transition-state structure.[8] In typical S_N2 reactions log $[k_{PhS^-}/k_{EtO^-}] > 1$, whereas in reactions involving a high degree of bond formation in the transition state log $[k_{PhS^-}/k_{EtO^-}] < 2$. Thus, the greater reactivity of ethoxide compared with thiophenoxide towards C_6F_5H and $C_6F_5 \cdot SMe$ implies a degree of bond formation which is consistent with the suggestion that an intermediate complex is involved.

[1] J. Burdon, W. B. Hollyhead, and C. R. Patrick, *J. Chem. Soc.*, 1964, 4663; J. Burdon, W. B. Hollyhead, C. R. Patrick, and K. V. Wilson, *ibid.*, 1965, 6375; K. C. Ho and J. Miller, *Austral. J. Chem.*, 1966, **19**, 423.

[2] P. Robson, T. A. Smith, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1963, 3692; J. Burdon, V. A. Damodaran, and J. C. Tatlow, *ibid.*, 1964, 763.

[3] N. J. Daly, G. Kruger, and J. Miller, *Austral. J. Chem.*, 1958, **11**, 290.

[4] See, for example, J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3879, and references cited therein.

[5] F. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, 1956, **78**, 854.

[6] J. F. Bunnett, "Technique of Organic Chemistry" (ed. A. Weissberger), Interscience, New York, Vol. 8 (2nd Edn., 1961), part I, 210.

[7] J. R. Knowles, R. O. C. Norman, and J. H. Prosser, *Proc. Chem. Soc.*, 1961, 341; J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.

[8] R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry", Academic Press, 1965, 104.