Nucleophilic Displacement in Polyhalogenoaromatic Compounds. Part 6.[1] Kinetics of Methoxydefluorination of Polybromofluorobenzenes

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Rates of displacement of fluorine from a number of polybromofluorobenzenes by methanolic sodium methoxide have been measured at 323.2 K. The effects of bromine substituents, whether measured by substituent rate factors or by the two-term process described earlier, fall in a regular sequence of halogen effects, from fluorine to iodine. The poorer agreement between calculated and experimental figures for the heavier halogens must reflect other unconsidered factors perhaps arising from crowding or from mutual interaction of the substituents.

EARLIER work [2,3] has described the effects of fluorine and chlorine substituents upon nucleophilic displacement reactions of halogenobenzenes in terms of a three-parameter, two-term equation which separated a general activating influence of the halogen substituent (I_{Hal}) from an interaction (μ, $m\mu$) † acting only at sites *ortho* and *para* to the halogen substituent and which accounts for the orientation effects seen in both electrophilic and nucleophilic aromatic substitution. Recently, and extending a previous communication,[4] Chambers *et al.*[5] have reported substituent rate factors for fluorine in a similar reaction.

We now report the extension of our work to polybromofluorobenzenes, and an assessment of the relative merits of the two-term equation and of substituent rate factors (s.r.f.s) as measures of substituent effects.

DISCUSSION

Polybromofluorobenzenes.—A summary of the second-order rate constants found for attack upon these substrates by sodium methoxide in methanol at 323.2 K is given in Table 1. The organic products of reaction were polyhalogenoanisoles resulting from methoxydefluorination. In general only one such product predominated ($>95\%$). The attack of bromopentafluorobenzene under these conditions gave the three isomeric bromotetrafluoroanisoles in relative amounts ($o:m:p::12:1:87$) in complete agreement with the reported values.[6] The products of reaction of 2-bromo-1,3,4,5- and of 3-bromo-1,2,4,5-tetrafluorobenzene were obtained by heating these compounds with one mol. equiv. of methanolic sodium methoxide in sealed tubes at 353 K, because of the slowness of the reaction at 323 K. 2-Bromo-1,3,4,5-tetrafluorobenzene gave two products, 2-bromo-1,4,5-trifluoro-3-methoxy- (76%) and 2-bromo-1,3,4-trifluoro-5-methoxy-benzene (24%), in agreement with expectation. 3-Bromo-1,2,4,5-tetrafluorobenzene also gave the two expected products,

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† μ Is the general term associated with orientation and described as α for fluorine, β for chlorine, γ for bromine, and δ for iodine in the text.

[1] Part 5, R. Bolton, S. M. Kazeroonian, and J. P. B. Sandall, *J. Fluorine Chem.*, in the press.

[2] R. Bolton and J. P. B. Sandall, *J.C.S. Perkin II*, 1976, 1541.

[3] R. Bolton, S. M. Kazeroonian, and J. P. B. Sandall, *J. Fluorine Chem.*, 1976, **8**, 471.

[4] 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.

[5] R. D. Chambers, J. S. Waterhouse, and D. L. H. Williams, *J.C.S. Perkin II*, 1977, 585.

[6] J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *Tetrahedron* 1966, **22**, 1183.

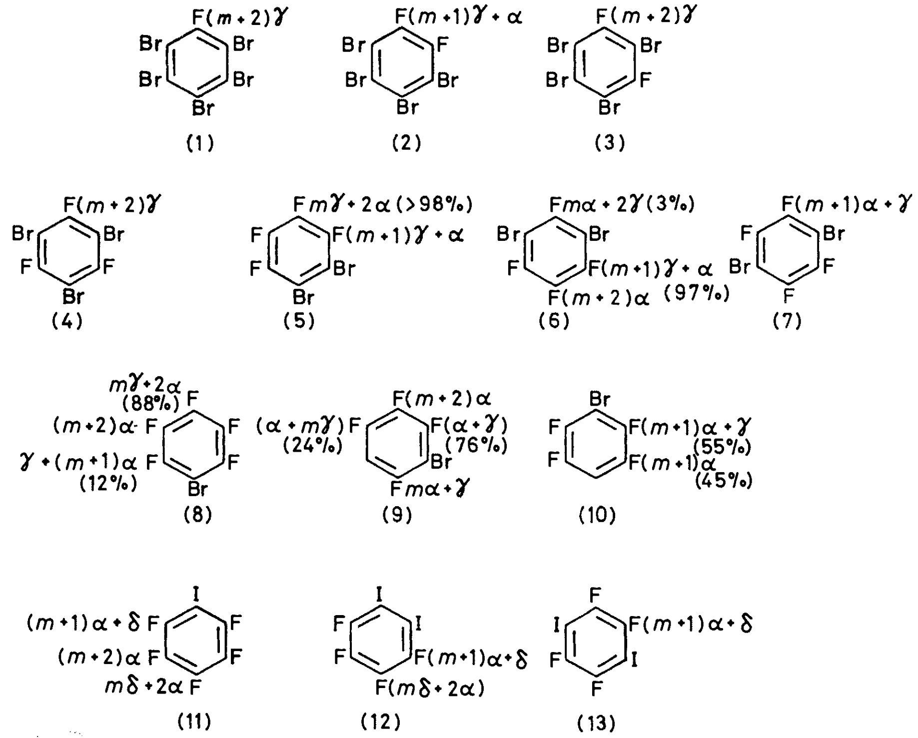
TABLE 1

Second-order rate constants for methoxide ion attack upon polyhalogenofluorobenzenes (MeOH; 323.2 K)

Substrate	10^4k_2(obs.)/ l mol^{-1} s^{-1}	10^4k_2(calc.)/ l mol^{-1} s^{-1}
Pentabromofluorobenzene (1)	8.0 ± 0.4	13
1,2,3,4-Tetrabromo-5,6-difluorobenzene (2)	26.2 ± 0.9	17
1,2,3,5-Tetrabromo-4,6-difluorobenzene (3)	37.1 ± 0.6	47
1,3,5-Tribromo-2,4,6-trifluorobenzene (4)	107 ± 2	125
1,2-Dibromo-3,4,5,6-tetrafluorobenzene (5)	31 ± 1	22
1,3-Dibromo-2,4,5,6-tetrafluorobenzene (6)	68 ± 2	58
1,4-Dibromo-2,3,5,6-tetrafluorobenzene (7)	2.6 ± 0.2	2.6
Bromopentafluorobenzene (8)	22.3 ± 1.8	18.1
2-Bromo-1,3,4,5-tetrafluorobenzene (9)	3.4 ± 0.2	2.2
3-Bromo-1,2,4,5-tetrafluorobenzene (10)	0.08 ± 0.01	0.077
Pentafluoroiodobenzene (11)	48 ±3	46
1,2,3,4-Tetrafluoro-5,6-di-iodobenzene (12)	11.4 ± 0.3	10.7
1,2,4,5-Tetrafluoro-3,6-di-iodobenzene (13)	0.35 ± 0.01	0.35

* Calculated rate constants used parameters in Table 2.

3-bromo-2,4,5-trifluoroanisole (45%) and 3-bromo-1,4,5-trifluoro-2-methoxybenzene (55%), but in relative yields which are contrary to predictions based upon s.r.f.s or on semi-empirical grounds.[2,7] As identification of all these products was made from a study of the ^{19}F n.m.r. spectra of the components, an authentic sample of 3-bromo-1,4,5-trifluoro-2-methoxybenzene was prepared.



Calculated deactivation parameters and experimentally found isomer distributions for methoxydefluorination

1,2,4,5-Tetrafluorobenzene gave 2,4,5-trifluorophenol[8] on heating with potassium hydroxide in dimethyl sulphoxide; bromination of this phenol gave 3-bromo-1,4,5-trifluoro-2-hydroxybenzene as a low melting solid which, on methylation (Me_2SO_4–NaOH) provides a material showing identical ^{1}H and ^{19}F n.m.r. spectra to those assigned to 3-bromo-1,4,5-trifluoro-2-methoxybenzene.

The unexpected order of attack of the sites in 3-bromo-1,2,4,5-tetrafluorobenzene is not consistent with arguments based on classical electronic and steric effects, but might have arisen from the different reaction conditions used. The orientation of attack otherwise agrees with that predicted by each [2,4,7] of the reported methods; the values of the parameters found using our approach [2] are shown in the Figure, with the experimental isomer distributions determined by ^{19}F n.m.r. spectroscopy. Since these are parameters measuring deactivation, and since the numerical values of the terms α, β, γ, and δ decrease in that order, the carbon atom with the smallest contribution is the one most susceptible to nucleophilic attack within each molecule. Consideration of the I terms in the free energy equation is needed before differences in reaction rate may be found between molecules. Thus, (1), (3), and (4) in the Figure show the same degree of deactivation; their differences in reaction rate follow from the replacement of bromine by fluorine in the *meta*-position, which does not affect the

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[7] J. Burdon, *Tetrahedron*, 1965, **21**, 3373.

[8] G. C. Finger, M. J. Gortatowski, R. H. Shiley, and R. H. White, *J. Amer. Chem. Soc.*, 1959, **81**, 94.

terms associated with sites *ortho* and *para* to the displaced fluorine. These distinctions are clearly shown in the corresponding relationships (1)—(3).

$$\Delta\Delta G(\mathrm{C_6Br_5F}) = \Delta\Delta G(\mathrm{C_6F_6}) - 5I_{\mathrm{F}} + 5I_{\mathrm{Br}} + (\gamma - \alpha)(m + 2) \quad (1)$$

$$\Delta\Delta G(m\text{-}\mathrm{C_6Br_4F_2}) = \Delta\Delta G(\mathrm{C_6F_6}) - 4I_{\mathrm{F}} + 4I_{\mathrm{Br}} + (\gamma - \alpha)(m + 2) \quad (2)$$

$$\Delta\Delta G(sym\text{-}\mathrm{C_6Br_3F_3}) = \Delta\Delta G(\mathrm{C_6F_6}) - 3I_{\mathrm{F}} + 3I_{\mathrm{Br}} + (\gamma - \alpha)(m + 2) \quad (3)$$

The values of the parameters, and of the corresponding s.r.f.s, for the four halogens are given in Table 2; the terms for iodine have been found using the rates of methoxydefluorination found for the three polyfluoroiodobenzenes listed in Table 1. No evidence was found of protiodehalogenation in any of the compounds studied, although in the absence of a source of carbanions this is not expected.[9]

TABLE 2

Substituent rate factors and other parameters for methoxydefluorination of polyhalogenofluorobenzenes ($\mathrm{MeO^-}$ in MeOH; 323.2 K)

Halogen	S.r.f. *ortho*	 *meta*	 *para*	μ/kcal mol^{-1}	I/kcal mol^{-1}	m
Fluorine	42	180	0.75	-0.95	3.34	3.8
Chlorine	83	123	26	-0.25	3.09	4.0
Bromine	65	100	18	-0.29	2.97	3.8
Iodine	29	31	26	-0.03	2.20	3.8

The earlier figures for fluorine and chlorine have been amended. Although s.r.f.s and the corresponding terms I and μ are internally self-consistent to within very small limits for fluorine and chlorine, the inclusion of heavier halogen substituents causes a definite range of results, best reflected by the worsening of the agreement between calculated and experimental rate constants (Table 1). The separation of any effect into two opposing contributions inevitably increases the limits of error of each term, especially when the magnitudes of the two components are very different. This situation is true for all the halogen substituents excepting fluorine. Steric effects, which may cause buckling of individual molecules, or induced dipolar interactions such as have already been found in electric dipole moment studies,[10] may also contribute to this breakdown of additivity.

Comparison of the Two Methods of Treatment.—The two modes of describing the substituent effect, s.r.f.s and the two-term function,[2] reflect two complementary attitudes. Substituent rate factors describe the individual contributions of substituents to the reaction rate, without any recourse to classical concepts of electronic effects, and are expressed by a single, experimentally derived, constant. Equations such as the Hammett linear free energy relationship bring these constants into line by dissecting the substituent's influence into one term reflecting the intrinsic properties of the substituent and another denoting the sensitivity of the reaction to electronic effects; however, no understanding of the source of these electronic effects, apart from the observation of activation or deactivation by the substituent, can be deduced from these terms alone, although they may be interpreted in terms of classical theories. Thus, Table 2 shows that the relative efficiencies of *meta*-halogeno-substituents falls in the order F > Cl > Br > I, the order of the inductive effects, and that *ortho*- and *para*-halogens show less activation than the *meta*-substituents in aromatic nucleophilic substitution. The *relative* deactivation also lies in the order F > Cl, Br > I which is again consistent with a classical mesomeric effect.

The two-term, three-parameter function [2] divides the s.r.f. into two contributions; the first is constant at all positions of the ring, and is equivalent to the s.r.f. at the *meta*-position, while the second reflects the differential effects found at the *ortho*- and *para*-positions. These functions are inter-related by the expressions (4)—(6)

$$RT\ln(k_{\mathrm{o}}/k_{\mathrm{H}}) = RT\ln(\text{s.r.f.}_{ortho}) = 2.3RT\sigma_{ortho}\rho = I_{\mathrm{Hal}} + \mu(ortho\text{-X}) \quad (4)$$

$$RT\ln(k_{\mathrm{m}}/k_{\mathrm{H}}) = RT\ln(\text{s.r.f.}_{meta}) = 2.3RT\sigma_{meta}\rho = I_{\mathrm{Hal}}(meta\text{-X}) \quad (5)$$

$$RT\ln(k_{\mathrm{p}}/k_{\mathrm{H}}) = RT\ln(\text{s.r.f.}_{para}) = 2.3RT\sigma_{para}\rho = I_{\mathrm{Hal}} + m\mu(para\text{-X}) \quad (6)$$

where k_x is the rate constant in the presence of the substituent at the x-site of the aromatic system, k_{H} the rate constant when hydrogen replaces the group at that position, ρ the Hammett reaction constant for the process under study, σ_x the substituent constant for the designated group and position, and R and T have their usual significance. This particular inter-relation allows I_{Hal} and σ_{meta} to have the same sign, minimising further confusion. The division of s.r.f.s into a general ubiquitous effect and a specific contribution reflecting orientation effects (the I and μ terms respectively) is a convenient way to observe the working of two conflicting effects in nucleophilic and electrophilic substitutions, but it is evident that the numerical values of these I and μ terms need not reflect the absolute values of the classical inductive and mesomeric contributions.

Both methods of understanding substituent effects show greater errors when applied to groups more polarisable than fluorine, and this error is seen in the prediction of rate constants and of n.m.r. shifts, and is common to each interpretation because both rely upon the additivity of effect. The main advantage of the newer system is that by separating s.r.f.s into two terms, attention is drawn to the part of the substituent effect (μ, $m\mu$) which is responsible for determining orientation of attack.

Other Substituents.—The iodine substituent effect has been defined in three cases. The associated error is therefore high, but the value of the I_{Hal} term falls below that of any of the other halogens, and the small value of μ reflects the very small influence which iodine

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[9] R. Bolton and J. P. B. Sandall, *J.C.S. Perkin II*, 1976, 1545.

[10] R. Bolton and J. P. B. Sandall, in preparation.

has upon the orientation of attack. This is confirmed by the ratio of *para* : *ortho* attack found in both pentafluoroiodobenzene and pentafluorobenzene, both of which show nucleophilic attack at the carbon atom *para* to the non-fluorine substituent to *ca.* 95%.[6]

The earlier reports of rates of methoxide ion attack upon pentafluorobenzene derivatives[11] allow s.r.f.s to be derived for the methoxy-group (s.r.f.$_o$ 0.660; s.r.f.$_m$ 5.5; s.r.f.$_p$ 0.08), for the *p*-methyl substituent (0.15), and for the *ortho*- (2.3×10^7) and *para*- (0.95×10^7) nitro-substituents. All these effects are consistent in direction and magnitude with general chemical observations. The high s.r.f. found for the *ortho*-nitro-group relies upon a small extent of attack at this site: relative rates of attack at sites *ortho* and *para* to a nitro-group in such systems may vary complexly according to the nature of both the nucleophile[12] and the solvent[12,13] where localised interactions may overshadow basic electronic effects.

TABLE 3

^{19} N.m.r. chemical shifts used for analysis (p.p.m. upfield of $CFCl_3$)

Compound	δ
(1)	80.3
(2)	118.0
(3)	88.4
(4)	95.4
(5)	125.0 (3-F); 154.3 (4-F)
(6)	102.3 (2-F); 125.1 (4-F); 159.4 (5-F)
(8)	132.7 (2-F); 160.9 (3-F); 154.9 (4-F)
(9)	109.7 (1-F); 125.5 (3-F); 163.2 4-(F)
	133.2 (5-F)
(10)	137.9 (1-F); 133.4 (2-F)
o-Bromotetrafluoroanisole	132.1 (3-F); 161.4 (4-F); 161.1 (5-F)
	156.0 (6-F)
p-Bromotetrafluoroanisole	156.7 (2-F); 135.2 (3-F)
2,3-Dibromotrifluoroanisole	125.8 (4-F); 156.2 (5-F); 149.2 (6-F)
2,4-Dibromotrifluoroanisole	128.3 (5-F); 156.0 (6-F)
2,6-Dibromotrifluoroanisole	125.4 (3-F)
3,4-Dibromotrifluoroanisole	119.5 (2-F); 126.9 (5-F); 150.1 (6-F)
2-Bromo-1,4,5-trifluoro-3-methoxybenzene	109.0 (1-F); 158.2 (4-F); 135.2 (5-F)
4-Bromo-2,3,5-trifluoroanisole	161.8 (2-F); 129.5 (3-F); 111.5 (5-F)
3-Bromo-2,4,5-trifluoroanisole	130.9 (2-F); 140.0 (4- and 5-F)
3-Bromo-1,4,5-trifluoro-2-methoxybenzene *	130.9 (1-F); 132.7 (4-F); 139.1 (5-F)

* $J_{4,5}$ 22.6; $J_{1,4}$ 11.2; $J_{1,5}$ 0.5; $J_{1\text{-F},H}$ 11.3; $J_{5\text{-F}\,H}$ 9.8; $J_{4\text{-F},H}$ 7.3; $J_{OMe,1\text{-F}}$ 1.2 Hz.

EXPERIMENTAL

Polybromofluorobenzenes were generally obtained by the aluminium catalysed bromination of the corresponding fluorobenzene.[14] In this way pentabromofluorobenzene, m.p. 197—199° (lit.,[15] 196°), 1,2,3,4-tetrabromo-5,6-difluorobenzene, m.p. 124—125° (lit.,[14] 124—125°), 1,2,3,5-tetrabromo-4,6-difluorobenzene, m.p. 86.5—87° (lit.,[16] 86°), and 1,3,5-tribromo-2,4,6-trifluorobenzene, m.p. 94—95° (lit.,[17] 94.5—95°), were prepared. The parent polyfluorobenzenes, and other polybromopolyfluorobenzenes and *o*- and *p*-di-iodotetrafluorobenzenes, were commercial samples (Bristol Organics); their physical properties were in good agreement with reported values and they were pure by ^{19}F n.m.r. spectroscopy and by g.l.c. We are indebted to Dr. G. Fuller and the Imperial Smelting Corporation, Avonmouth, for gifts of bromo- and iodo-pentafluorobenzene and of *m*-dibromotetrafluorobenzene.

Solutions of sodium methoxide in purified methanol were prepared and standardised by reported methods which were also used to follow the course of each displacement reaction.[2] Each reaction showed good second-order kinetics, often past three half-lives; in no case was bromide ion found among the displacement products.

The organic products were generally identified by ^{19}F n.m.r. spectroscopy (Perkin-Elmer R12B; shifts in p.p.m. upfield of trichlorofluoromethane solvent), the chemical shifts used for analysis being reported in Table 3. Each absorption showed the expected splitting pattern as well as the anticipated chemical shift.[2] The products of methoxy-defluorination of 3-bromo-1,2,4,5-tetrafluorobenzene were also identified by ^{1}H n.m.r. with the methoxy-protons of each component clearly resolved at δ 3.90 and 3.98.

3-Bromo-1,4,5-trifluoro-2-methoxybenzene.— 1,2,4,5-Tetrafluorobenzene (3.8 g) and potassium hydroxide (4 g; excess) were heated in dimethyl sulphoxide (15 ml) under reflux and with stirring for 4 h. The brown mixture was cooled and the inorganic material was dissolved in water (50 ml) before steam distillation removed the non-acidic organic compounds. Similar steam distillation of the acidified aqueous residue gave 2,4,5-trifluorophenol (1.6 g) as an oil after ether extraction and concentration of the dried ($MgSO_4$) ether extract; the m.p. appears to be sensitive to small amounts of water as in the parent phenol. Bromination of 2,4,5-trifluorophenol in acetic acid using an equal weight of bromine gave, upon evaporation of the ether

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[11] J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 6375; K. C. Ho and J. Miller, *Austral. J. Chem.*, 1966, **19**, 423.

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[13] J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051; T. O. Bamkole, J. Hirst, and E. I. Udoessian, *J.C.S. Perkin II*, 1973, 110.

[14] G. G. Yakobson, L. S. Kobrina, and N. N. Vorozhtsov, jun., *Zhur. obshchei Khim.*, 1965, **35**, 137.

[15] I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc.* (*C*), 1971, 167.

[16] N. N. Vorozhtsov, jun., G. G. Yakobson, and N. I. Krizhechkovskaya, *Zhur. obshchei Khim.*, 1961, **31**, 1674.

[17] G. Fuller, *J. Chem. Soc.*, 1965, 6264.

extract of the steam volatile material, a solid of low m.p. which was dissolved in aqueous sodium hydroxide (2M; excess) and treated with dimethyl sulphate (1.0 ml). Steam distillation from the alkaline reaction mixture gave 3-bromo-1,4,5-trifluoro-2-methoxybenzene as a colourless oil, identified by its ^{19}F n.m.r. spectrum (Table 3), and mass spectrum, *m/e* 240 and 242 (1 : 1).

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