Nucleophilic Displacement in Polyhalogenoaromatic Compounds. Part 2.† Kinetics of Halogen Displacement from Bromopolyfluoroaromatic Compounds

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The nucleophilic displacement of fluorine and of bromine from *m*-dibromotetrafluorobenzene and from bromopentafluorobenzene by sodium methoxide in butanone–methanol mixtures at 298 K involves competing second-order processes. The rate of nucleophilic displacement of fluorine is somewhat more sensitive to substituent effects (ρ 6.0) than that of the corresponding displacement of bromine (ρ 4.3 ± 0.6) in butanone–methanol (3 :1 v/v) at 298 K. Debromination is much more affected by changes in the butanone concentration than is defluorination, and the depression of rate which results from lowering the amount of ketone in the solvent is far greater than that predicted on the basis of a simple acid–base equilibrium involving the ketone anion.

NUCLEOPHILIC displacement of halogen by attack upon aromatic carbon is a common feature in the reactions of polyfluoroaromatic compounds,[1] and has a mechanism similar to that of the analogous reactions of polynitrohalogenobenzene derivatives.[2] Bunnett [3] has identified a mechanism by which isomerisation of polybromobenzenes,[4] and further bromination of such compounds,[5] proceeds through nucleophilic displacement reactions by carbanions upon bromine. This process has also been suggested to occur in the reduction of hexa- and pentabromobenzene by alkaline solutions of ketones in methanol.[6] Unlike the corresponding polychloroaromatic compounds, these aryl bromides give reduction products and not methyl ethers.[7] A variety of sources of carbanions each gave similar products with hexabromobenzene, leading Collins and Suschitzky [6] to suggest the sequence shown in equations (1)—(3). This

$$\mathrm{MeCO{\cdot}CH_2Me + MeO^- \rightleftharpoons MeCO{\cdot}\bar{C}HMe + MeOH} \tag{1}$$

$$\mathrm{MeCO{\cdot}\bar{C}HMe + ArBr \longrightarrow MeCO{\cdot}CHBrMe + Ar^-} \tag{2}$$

$$\mathrm{Ar^- + MeOH \rightleftharpoons ArH + MeO^-} \tag{3}$$

loss of bromine from hexabromobenzene occurs more

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† Part 1, R. Bolton and J. P. B. Sandall, preceding paper.

[1] W. A. Sheppard and C. M. Sharts, 'Organic Fluorine Chemistry,' Benjamin, New York, 1969.

[2] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.

[3] J. F. Bunnett, *Accounts Chem. Res.*, 1972, **5**, 139.

[4] C. E. Moyer and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1963, **85**, 1891.

[5] C. E. Moyer and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1971, **93**, 1183.

[6] I. Collins and H. Suschitzky, *J. Chem. Soc.* (*C*), 1969, 2337.

[7] T. van den Linden, *Rec. Trav. chim.*, 1938, **57**, 781.

readily than the displacement of chlorine from hexachlorobenzene under the same conditions.[7]

Recently we have noted[8] that polyfluorobromobenzenes can lose both bromine and fluorine on treatment with sodium methoxide in butanone–methanol. This result was unexpected, first because fluorine is much more easily displaced from aromatic carbon by methoxide ion,[2,9] and also because ketonic solvents accelerate such nucleophilic displacements of fluorine, often markedly.[10]

We now report a kinetic study of the reaction which appears to confirm some aspects of the proposed mechanism.

EXPERIMENTAL

m-Dibromotetrafluorobenzene and bromopentafluorobenzene were commercial samples (I.S.C., Avonmouth), and were pure by g.l.c. and by ^{19}F n.m.r. spectroscopy. Bromopentafluorobenzene gave *p*-bromotetrafluorophenylhydrazine, m.p. 78—79° (lit.,[11] 78—79.5°). Oxidation of this with bromine in aqueous hydrogen bromide (6M) (*cf.* ref. 12) and steam-distillation of the product gave *p*-dibromotetrafluorobenzene, m.p. 77—78° (lit.,[12] 75—77°). The hydrazine also gave 4-bromo-2,3,5,6-tetrafluorobiphenyl, m.p. 105—105.5° (lit.,[13] 104—105°), on oxidation with bleaching powder in benzene,[14] a method used successfully to make 2,3,4,5,6-pentafluorobiphenyl and analogous biaryls.[15] Reduction of *p*-bromotetrafluorophenylhydrazine (66% hydrogen iodide; 2 h)[16] gave only 2,3,5,6-tetrafluoroaniline; bromination[17] gave the required bromotetrafluoroaniline, m.p. 59—60° (lit.,[17] 60—61°). Fractional distillation of the organic product of the reaction of bromopentafluorobenzene and sodium methoxide in methanol[18] gave a mixture containing bromotetrafluoroanisoles (6% *ortho*-, 90% *para*-) and starting material (4%). A crude sample of 4-bromoheptafluorotoluene was obtained from octafluorotoluene *via* 4-hydrazinoheptafluorotoluene, m.p. 77—78° (lit.,[11] 77—79.5°) by a series of reactions analogous to those by which *p*-dibromotetrafluorobenzene was prepared. ^{19}F N.m.r. showed the presence of 4-hydrazinoheptafluorotoluene and 4-hydroxyheptafluorotoluene as impurities; these did not interfere with the debromination process under study.

Solutions of sodium methoxide were made by dissolving sodium metal in methanol (99.95%; <10 p.p.m. water); standard solutions of sulphuric acid and of silver nitrate were used to follow the course of the reaction of the polyhalogenoaromatic compounds with sodium methoxide in butanone–methanol. The aromatic compounds, dissolved in butanone (b.p. 79.5—79.6°; $^{20}_{4}d$ 0.804 8), were brought to thermostat temperature with a quantity of methanol such that, after initiation of the reaction by the addition of a known volume of standard sodium methoxide in methanol, a mixture of butanone and methanol (3 : 1 v/v) resulted.

In this way, the effects of the heat of mixing butanone and methanol could be lessened so that a steady temperature was reached within a minute of initiating the reaction.

Samples were quenched by dilution with water (CO_2-free) and were titrated first with acid (phenolphthalein) and then with silver nitrate (potentiometrically); determinations of fluoride ion by using thorium nitrate and Alizarin Red S were not sufficiently accurate to give good kinetic plots and were therefore avoided where possible.

The products of reaction were identified and the purity of starting materials was demonstrated by ^{19}F n.m.r. spectroscopy (Perkin-Elmer R12B; 56.4 MHz; trichlorofluoromethane as solvent) (see Table 1).

TABLE 1

^{19}F N.m.r. absorptions used for identification of *p*-XC_6F_4Y ($CFCl_3$ solvent and standard; 56.4 MHz; shifts in p.p.m. upfield from $CFCl_3$)

X	Y	*ortho* to X	*ortho* to Y
H	NH_2	142.9	163.6
Br	NH_2	136.7	161.8
Br	OMe	135.6	157.2
Br	Ph	132.5	141.0
Br	CF_3 [a]	131.2	140.0
$NH{\cdot}NH_2$	CF_3 [b]	151.4	141.2
OH	CF_3 [c]	163.2	144.1

[a] CF_3 at 57.1 p.p.m. [b] CF_3 at 56.6 p.p.m. [c] CF_3 at 55.7 p.p.m.

DISCUSSION

Stoicheiometry and Kinetic Form.—The stoicheiometry of the two displacement reactions was most readily found by studying compounds in which only one of the two modes was detectable. Table 2 shows the yields of bromide ion, fluoride ion, and organic compound in the reaction of some derivatives of 3-bromo-1,2,4,5-tetrafluorobenzene (*p*-XC_6F_4Br) with 1 mol. equiv. of sodium methoxide in butanone–methanol (3 : 1 v/v) at 298 K.

TABLE 2

Product yields from reaction of NaOMe in MeCOEt–MeOH with *p*-XC_6F_4Br at 298 K (mol % per mole base consumed)

X	Br^-(%)	F^-(%)	Organic product
Br	98	0	*p*-HC_6F_4Br
H	97	1	*p*-$H_2C_6F_4$
F [a]	87	13	C_6F_5H, *p*-$BrC_6H_4{\cdot}OMe$
OMe	96	1	*p*H-$C_6F_4{\cdot}OMe$
NH_2	*ca.* 95	0	*p*-$HC_6F_4{\cdot}NH_2$
Ph	97	1	*p*-HC_6F_4Ph

[a] Relative yields depend upon the initial concentrations of reagents.

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[8] R. Bolton and J. P. B. Sandall, *J. Fluorine Chem.*, 1976, **7**, 540.

[9] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

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[17] G. G. Yakobson, G. G. Furin, L. S. Kobrina, and N. N. Vorozhtsov, *Zhur. obshchei Khim.*, 1967, **37**(6), 1289.

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The relative yields reported in Table 2 suggest the main reaction to be (4). Fluorine displacement is appreciable

$$(\mathrm{RH}) + \mathrm{MeO}^- + \mathrm{ArBr} = \mathrm{ArH} + \mathrm{Br}^- (+ \mathrm{ROMe}) \quad (4)$$

only in the reactions of bromopentafluorobenzene and of *m*-dibromotetrafluorobenzene.

The reactions of all the bromopolyfluoroaromatic compounds with solutions of sodium methoxide in butanone–methanol (3 : 1 v/v; 298 K) followed the kinetic form (5). The kinetic plot was linear over the

$$-\mathrm{d}[\mathrm{OMe}^-]/\mathrm{d}t = k_2[\mathrm{ArBr}][\mathrm{OMe}^-] \quad (5)$$

first 50—70% of reaction, but often showed a later curvature. The derived rate constants agreed to within ±3% for each substrate over a range of initial concentrations of each reagent. Where more than one mode of displacement occurred concurrently, the reproducibility of rate constants was no better than ±7% over a similar range of initial concentrations of reagents. This error probably reflected the cumulative errors associated with the titrations, especially the difficulties associated with the accurate estimation of small amounts of fluoride ion and the measurement of concentrations of strong alkali in the presence of fluoride ion. Reactions in which only fluoride ion was displaced, such as those of hexa- and penta-fluorobenzene, or in which bromine was displaced predominantly, gave second-order rate constants reproducible to within ±3%, and which agreed to within ±2% through each individual kinetic study. Bromine displacement was also followed argentimetrically; when it was the only mode of reaction, the expected relationship [equation (6)] was found to hold.

$$-\mathrm{d}[\mathrm{OMe}^-]/\mathrm{d}t = \mathrm{d}[\mathrm{Br}^-]/\mathrm{d}t = k_2[\mathrm{ArBr}][\mathrm{OMe}^-] \quad (6)$$

Substituent Effects in the Debromination Reaction.—The second-order rate constants associated with the debromination of a number of substituted 3-bromo-1,2,4,5-tetrafluorobenzene derivatives (p-$\mathrm{XC_6F_4Br}$) in butanone–methanol (3 : 1 v/v; 298 K) are shown in Table 3, together with the Hammett substituent constants of the substituents X. The derived linear free energy plot gives $\rho = 4.3 \pm 0.6$; other parameters (*e.g.* σ^-) gave no better fit, nor was there a correlation with the free energy of displacement of fluorine in $\mathrm{C_6F_5X}$ by methoxide ion in methanol at 323 K.[2] The substituent effect is consistent with a nucleophilic attack upon an atom attached to the aromatic system but not well able to conjugate with it in the transition state: it is suggested that the poor correlation with σ arises from a relatively small contribution from the mesomeric effect of the substituent. The base-catalysed debromination may, therefore, involve anionic attack at exocyclic bromine, but the kinetic studies give no hint of the identity of the anion.

TABLE 3

Second-order rate coefficients (k_{Br}) for debromination of p-$\mathrm{XC_6F_4Br}$ by NaOMe in MeCOEt–MeOH (3 : 1 v/v) at 298 K

X	$10^2k_{\mathrm{Br}}/\mathrm{l\ mol^{-1}\ s^{-1}}$	$\sigma_{p\text{-}\mathrm{X}}$
H	0.100 ± 0.006	0
F	4.5 ± 0.02	0.062
Br	10.2 ± 0.4	0.232
OMe	0.075 ± 0.003	−0.268
$\mathrm{CF_3}$	*ca.* 60 ± 5	0.551
Ph	0.087 ± 0.003	0.009
$\mathrm{NH_2}$	0.021 ± 0.001	−0.66

Nucleophilic Displacement of Fluorine.—The attack by base upon polyfluoroaromatic compounds has been shown to involve second-order kinetics in a number of solvents, including methanol.[2,9] On passing from methanol to butanone–methanol mixtures, the rate of a ‘ classical ’ two-stage nucleophilic displacement reaction would be expected to increase considerably; Parker[19] has shown acetone to be a much ‘ faster ’ solvent than methanol for such processes. The rates of reaction of hexafluorobenzene, pentafluorobenzene, and 1,3,5-trichloro-2,4,6-trifluorobenzene with sodium methoxide in methanol at 323 K, and in butanone–methanol (3 : 1 v/v) at 298 K, show that the solvent and temperature changes together affect the rate constant, for each compound, by a factor of between four and six. The effects of the two different reaction conditions upon each of these three compounds may be expressed by equation (7), where

$$\log_{10}k_2(\mathrm{MeOH};\ 323\ \mathrm{K}) = 0.92 \log_{10}k_2(\mathrm{MeOH\text{–}MeCOEt};\ 298\ \mathrm{K}) - 0.86 \quad (7)$$

the second-order rate constants obtained for fluorine displacement in each set of conditions are appropriately indicated.

The reaction of bromopentafluorobenzene and that of *m*-dibromotetrafluorobenzene with sodium methoxide in butanone–methanol were complicated by the simultaneous ejection of fluorine and bromine. Fluoride ion was associated with the formation of *p*-bromotetrafluoroanisole from bromopentafluorobenzene, and of 2,4-dibromo-3,5,6-trifluoroanisole from *m*-dibromotetrafluorobenzene; bromide ion similarly paralleled the formation of pentafluorobenzene (from $\mathrm{C_6F_5Br}$) and of 2-bromo-1,3,4,5-tetrafluorobenzene (from m-$\mathrm{C_6Br_2F_4}$). Although these two second-order processes could be formally separated by measuring the yields of fluoride and of bromide ions concomitantly produced, the reproducibility was often poor when direct measurement of the fluoride ion concentration was used to measure the relative extents of the two processes. It was simpler to treat these competing reactions as irreversible, so that the relative extents of the two could be gauged by the yield of bromide ion produced in comparison with the total base consumed. Since methoxide ion is partly consumed to form butanone anion in such solutions, the concentration of base found by titration is proportional to, but not identical with, the equilibrium concentration

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[19] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.

TABLE 4

Second-order rate coefficients for dehalogenation of some polyhalogeno-aromatic compounds by NaOMe in MeCOEt–MeOH at 298 K

Substrate	Solvent (% MeCOEt)	$[ArX]_0/\text{M}$	$[NaOMe]_0/\text{M}$	10^2k_F	10^2k_{Br}
C_6F_6	75	0.083 1	0.035 7	0.19 ± 0.01	
C_6F_5H	75	0.106 9	0.035 7	0.035 ± 0.002	
sym-$C_6Cl_3F_3$	75	0.022 5	0.035 7	12.4 ± 0.5	
C_6F_5Br	75	0.021 0	0.009 1	1.1 [a]	4.5 [b]
	75	0.022 6	0.017 4	1.3	5.2
	75	0.025 1	0.034 6	1.3	5.2
	75	0.035 4	0.034 6	1.2	4.9
	75	0.028 9	0.060 6	1.1	4.5
	75	0.025 1	0.060 6	1.2	4.9
	75	0.034 3	0.061 2	1.4	4.4
	60	0.036 9	0.060 6	0.44	0.48
	80	0.021 9	0.034 7		11.8
m-$C_6F_4Br_2$*	75	0.017 9	0.017 4	5.8 [c]	6.6
	75	0.050 1	0.017 4	5.8	6.6
	75	0.034 9	0.030 6	5.8	6.7
	75	0.021 1	0.034 7	5.4	6.2
	75	0.034 8	0.034 7	5.9	6.7
	75	0.032 7	0.061 2	5.7	6.5
	60	0.036 7	0.061 2	1.8	0.72
	0	0.043 3	0.034 7	0.66 [d]	

[a] Using F^-/Br^- product ratio of 0.35 ± 0.05; precision ±5%. [b] Using solvent mixture + base after 24 h at 298 K [c] Using F^-/Br^- product ratio of 0.88 ± 0.07; precision ±5%. [d] At 323 K; precision ±6%.

* Organic product is 2-bromo-1,3,4,5-tetrafluorobenzene + 2,4-dibromo-3,5,6-trifluoroanisole; ^{19}F n.m.r. absorptions for the former agreed with those reported (K. Jones and E. F. Mooney, *Ann. Reports NMR Spectroscopy*, 1971, **4**, 427), excepting the 4-F (δ −163.6 p.p.m.). The following absorptions were found for 2,4-dibromotrifluoroanisole: 3-F (δ −103. 2 p.p.m.), 5-F (δ −128.7 p.p.m.), and 6-F (δ −155.4 p.p.m.).

of methoxide ($K = [OMe^-][MeCOEt]/[MeCO\cdot\bar{C}HMe][MeOH]$) [equations (8) and (9)] and $k_{Br}/k_2 = [Br^-\text{ formed}]/[\text{Base consumed}]$ at any time.

$$\begin{aligned} -d[\text{Base}]/dt &= d[F^-]/dt + d[Br^-]/dt \\ &= (k_F + k_{Br})[ArBr][\text{Base}] \\ &= k_2[ArBr][\text{Base}]; \qquad (8) \end{aligned}$$

where

$$k_F = k_F'\,.\,\{K[MeOH]/[MeCOEt]\}/\{1 + K[MeOH]/[MeCOEt]\} \qquad (9)$$

In this way, the individual rate constants k_2 and k_{Br} could be found, from which k_F could be calculated. The values of k_F so obtained agreed well with those found by direct measurement, but were less liable to scatter.

The derived second-order rate constants were generally consistent throughout each kinetic study until 70% reaction; although occasionally no change in k_{Br} could be found even at 95% reaction, the kinetic plot usually showed a slight downward trend after two half-lives. If this is significant, it may reflect the presence of another acid–base system [ArH in equation (3)] or some minor reversibility of the debromination step. As we were unable to detect isomeric bromobutanones or their anticipated decomposition products, this second point could not be tested.

The second-order rate constants for fluorine displacement in butanone–methanol (3 : 1 v/v) which were found in this way (Table 4) agree well with those calculated by applying equation (7) to the values found for the analogous displacement in methanol, in which no debromination was observed. It seems likely, therefore, that the mechanism of this defluorination process is the expected, two-stage process associated with nucleophilic displacement from activated positions of an aromatic system.

Nucleophilic Displacement of Bromine.—Substituent effects suggest (Table 3) that bromine is lost in an attack by a nucleophile upon $\overset{\delta-}{Ar}-\overset{\delta+}{Br}$. Under the experimental conditions, the most probable reagent seems to be the butanone anion [equation (1)]. When K, the equilibrium constant linking the concentrations of butanone anion and methoxide ion [equation (9)], is large, the equilibrium concentration of butanone anion is proportional to [MeOH]/[MeCOEt]. When K is small, the equilibrium concentration of butanone anion is nearly that of added base. Changing the solvent composition (Table 4) affects nucleophilic displacement of both fluorine and bromine in the same direction; however, debromination is much more sensitive. While this is consistent with a difference in the solvent effect upon the two reactions, it is also consistent with $K \gg 1$, in keeping with the value ($K = 1\,000$) derived from the estimated acidity constants of methanol and butanone.[20]

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