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NUCLEOPHILIC DISPLACEMENT IN POLYHALOGENOAROMATIC COMPOUNDS.
PART IV. FLUORIDE ION ATTACK UPON HEXACHLORO-, PENTACHLORO-,
FLUORO-2,3,5,6-TETRACHLORO-, AND NITRO-2,3,5,6-TETRACHLORO-BENZENE

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SUMMARY

Potassium fluoride in boiling sulpholan reacted readily with the title compounds. The course of each reaction was followed by sampling, using gas chromatography and ^{19}F -NMR spectroscopy as complementary and confirmatory analytical methods. Unlike the reactions of hexachlorobenzene and of 2,3,5,6-tetrachloronitrobenzene, displacement in the pentachloro- and fluorotetrachlorobenzene systems is not preparatively useful. Approximate values of the individual rate constants of each stage within each system could be obtained from the reaction study, and are compared with the predictions made from empirical calculation.

INTRODUCTION

Fluoride ion exchange has been a popular preparative method for the synthesis of derivatives of fluorobenzene [1]. Hexachlorobenzene gives many polyfluorochlorobenzenes in this reaction, both in solution [2] and on heating under pressure [3] but the analogous reactions of pentachlorobenzene have been less thoroughly studied. An early report [4] described the products of reaction under high temperature and pressure, and a later patent [5] dealt with a mixture obtained by heating potassium fluoride and pentachlorobenzene together in sulpholan (tetramethylene sulphone). A recent, semi-quantitative study by Dickerson, Finger and Shiley [6] gave some understanding of the reaction mechanism in dimethyl

sulphoxide at 180° for twenty-four hours, but did not allow a detailed analysis of the associated rates. Similarly, the reaction with nitro-2,3,5,6-tetrachlorobenzene has been reported to give only fluoro-2,3,5,6-tetrachlorobenzene [7].

We now report a more detailed study of the pentachlorobenzene - potassium fluoride system in sulpholan, together with a complementary investigation of the corresponding reactions of hexachlorobenzene, 2,3,5,6-tetrachlorofluorobenzene, and of 2,3,5,6-tetrachloronitrobenzene. These results allowed approximate rate constants for the individual processes to be estimated; they also allowed the preparative use of the reactions to be assessed.

RESULTS AND DISCUSSION

Table 1 shows the relative concentrations of polyfluorochlorobenzenes formed from solutions of pentachlorobenzene in sulpholan (initially 1.0M) over one hundred minutes, after which time all the starting material had been consumed. All three isomeric tetrachlorofluorobenzenes were formed in similar amount, but further reaction was mainly confined to the formation of 1,3-difluoro-2,4,5-trichlorobenzene (24-F₂)*, especially earlier on. Further reaction of the mixture gave only 1,3-dichloro-2,4,6-trifluorobenzene (246-F₃)*. At no time does the concentration of any tetrachlorofluoro- or trichlorodifluoro-benzene exceed 0.35M (24-F₂), and the concurrent presence of isomers makes isolation of a pure sample of little preparative value.

In contrast, hexachlorobenzene gives a preponderance of 1,3-difluoro-2,4,5,6-tetrachlorobenzene (Table 2), this undergoing further rapid exchange to give 1,3,5-trifluoro-2,4,6-trichlorobenzene. This product is kinetically more stable than its isomers resulting

(*) The abbreviations, in parenthesis, identify only the orientations of the fluorine substituents with respect to hydrogen in C₆Cl_xF_{5-x}H. Thus, 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrachlorofluorobenzenes are 2-F, 3-F, and 4-F respectively, and 1,2-difluoro-3,4,5- and 1,2-difluoro-3,4,6-trichlorobenzenes are 2,3-F₂ and 3,4-F₂.

TABLE 1

Experimental and calculated compositions of mixture formed from
 KF (1.0 mole) - C_6Cl_5H (0.10 mole) - sulpholan (100 ml.) at ca. 245°

Arene	[Arene](M) at				$10^5 k_1$ (sec. ⁻¹) (formation) ^(a)	
	t = 25 min.	50 min.	75 min.	100 min.		
2-F ^(b)	exp.:	0.164	0.176	0.140	0.070	$k^2 = 10^{(c)}$
	calc.:	(0.160)	(0.176)	(0.145)	(0.110)	
3-F	exp.:	0.148	0.159	0.150	0.101	$k^3 = 9$
	calc.:	(0.145)	(0.159)	(0.133)	(0.101)	
4-F	exp.:	0.181	0.207	0.176	0.083	$k^4 = 22$
	calc.:	(0.184)	(0.210)	(0.179)	(0.147)	
23-F ₂	exp.:	0.000	0.022	0.032	0.056	$k^{23} = 1$
	calc.:	(0.008)	(0.026)	(0.042)	(0.054)	
24-F ₂	exp.:	0.033	0.146	0.240	0.347	$k^{24} = 18$
	calc.:	(0.043)	(0.145)	(0.242)	(0.321)	
26-F ₂	exp.:	0.005	0.025	0.042	0.056	$k^{26} = 7$
	calc.:	(0.010)	(0.029)	(0.045)	(0.059)	
34-F ₂	exp.:	0.005	0.043	0.071	0.105	$k^{34} = 11$
	calc.:	(0.000)	(0.039)	(0.080)	(0.108)	
35-F ₂	exp.:	0.005	0.030	0.049	0.093	$k^{35} = 8.5$
	calc.:	(0.013)	(0.033)	(0.052)	(0.066)	
C_6Cl_5H	exp.:	0.455	0.172	0.062	0.00 ^(d)	$a^1 = -59$
	calc.:	(0.413)	(0.170)	(0.070)	(0.029)	
C_6Cl_4HF	exp.:	0.485	0.557	0.439	0.170	
$C_6Cl_3HF_2$	exp.:	0.059	0.250	0.450	0.680	
$C_6Cl_2HF_3$	exp.:	0.002	0.025	0.047	0.150	

(a) Apparent first-order rate constant for formation per equivalent site

(b) Measured from ¹⁹F-NMR signal integrals (c) Superscripts as in text

(d) Measured from g.l.c. trace

in their preferential removal. The ready attack of positions meta to existing fluorine substituents allows this ion exchange to be used in the preparation of both 1,3,5-trifluoro-2,4,6-trichlorobenzene [2, 7] and also 1,3-difluoro-2,4,5,6-tetrachlorobenzene [8].

Nitro-2,3,5,6-tetrachlorobenzene gives only fluoro-2,3,5,6-tetrachlorobenzene, with no evidence of fluorodechlorination under these conditions. In contrast, the chlorine and nitro-substituents are replaced with similar ease by methoxide ion in methanol at 50° [8]. In sulpholan at these temperatures, both potassium nitrite and fluoro-2,3,5,6-tetrachlorobenzene are unstable; the first with respect to the formation of nitric oxide, and the second with respect to further ion-exchange with potassium fluoride. Polyfluorination may be minimized by a short reaction time, and side-reactions involving bases which arise from the decomposition of nitrite ion may be lessened by using a more stable solvent. Thus, we obtained 66% yield of fluoro-2,3,5,6-tetrachlorobenzene from the nitro-analogue (0.15 mole), potassium fluoride (1.5 mole) and sulpholan (75 ml.) on boiling for thirty minutes, whereas 37% yields were obtained in a similar reaction carried out in dimethylformamide [7].

TABLE 2

Molar ratios of fluorine-containing products formed from KF (1.0 mole) - C_6Cl_6 (0.10 mole) - sulpholan (100 ml.) at ca. 250°

Fluoro-arene	Mole% fluoroarene at.					
	t = 10	20	30	40	50	60 min.
Fluoropentachlorobenzene	85.3	45.9	28.5	0	-	-
1,3-Difluoro-2,4,5,6-tetrachlorobenzene	12.1	39.8	41.4	19.1	7.8	0
1,2-Difluoro-3,4,5,6-tetrachlorobenzene	2.6	12.0	22.8	9.4	5.7	0
1,4-Difluoro-2,3,5,6-tetrachlorobenzene	0	0.2	2.5	0	-	-
1,3,5-Trifluoro-2,4,6-trichlorobenzene	0	2.0	5.2	48.0	72.2	100
1,2,3-Trifluoro-4,5,6-trichlorobenzene	0	0	0	14.6	10.8	0
1,2,4-Trifluoro-3,5,6-trichlorobenzene	0	0	1.0	9.0	3.6	0

TABLE 3

Experimental and calculated compositions of mixtures formed from KF (1.0 mole) - fluoro-2,3,5,6-tetrachlorobenzene (0.10 mole) - sulpholan (100 ml.) at ca. 260°

Arene	t = 15	[Arene](M) at				10 ⁵ k ₁ (sec ⁻¹) (formation)
		30	45	60	75 min	
4-F ^(a)	exp.: 0.589	0.356	0.182	0.101	0.080	-60 ^(b)
	calc.:(0.582)	(0.340)	(0.198)	(0.115)	(0.067)	
24-F ₂	exp.: 0.323	0.480	0.568	0.594	0.640	24.5
	calc.:(0.326)	(0.491)	(0.563)	(0.584)	(0.576)	
34-F ₂	exp.: 0.078	0.109	0.337	0.148	0.107	5
	calc.:(0.069)	(0.110)	(0.134)	(0.147)	(0.155)	
246-F ₃	exp.: 0.010	0.054	0.114	0.148	0.161	10
	calc.:(0.016)	(0.054)	(0.101)	(0.152)	(0.203)	
4-F ^(c)	0.635	0.322	0.069	0.067	0.052	
C ₆ Cl ₃ HF ₂ ^(c)	0.351	0.614	0.807	0.758	0.739	
246-F ₃ ^(c)	0.014	0.064	0.124	0.173	0.194	
C ₆ Cl ₂ H ₂ F ₂ (?) ^(d)	0.00	<0.001	0.001	0.003	0.015	

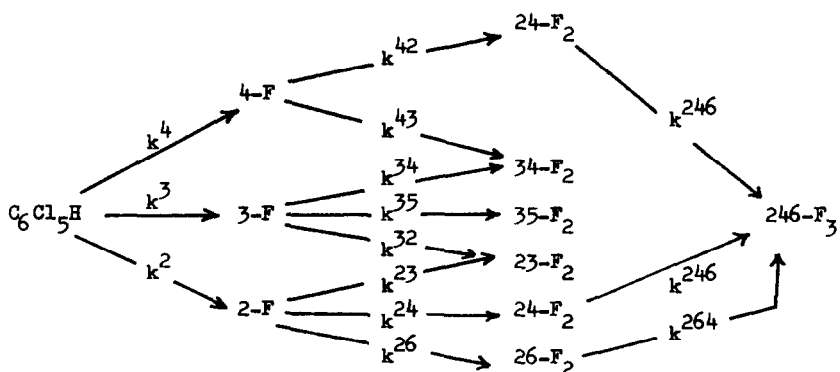
(a) From ¹⁹F-NMR integrals (b) Apparent first-order rate constants

(c) From g.l.c. trace (d) Possible reduction product: see text.

The elucidation of rate constants

The concentration of intermediates in the course of these ion exchange reactions is controlled by the rates of formation and of consumption of the intermediate; these are in turn influenced by the concentrations of precursors and of the intermediate itself, as well as by the associated rate constants. In all the reactions studied here, the amount of potassium fluoride greatly exceeds that of the aryl halide. The reaction can only show kinetic dependence with respect to the aryl halide under such conditions, since all kinetic terms involving [F⁻] are contained in the apparent first-order rate constant. This holds whether all the fluoride ion, or only that in the saturated solution, is kinetically significant.

The consumption of starting materials in each case showed first-order dependence upon the concentration of this reagent. Rough values of the rate constants associated with the further reactions of the initial products could be made (a) when relative yields of the secondary products paralleled (initial) rates of reaction, and (b) when the reacting intermediate maintained a stationary concentration. More accurate values could only be found by a mathematically rigorous method, shown here for the sequential reactions of pentachlorobenzene (cf. [9]). Scheme 1 shows the necessary



Scheme 1: Sequential attack of pentachlorobenzene by fluoride ion.

steps to describe the formation of the observed products.

The pseudo first-order rate constants are distinguished by superscripts which, reading from left to right, indicate the order in which fluorine substituents are introduced into pentachlorobenzene ($H = 1$). Thus, the formation of 1,3-difluoro-2,4,5-trichlorobenzene ($24-F_2$) is controlled by two rate constants: k^{24} is associated with attack upon 2,3,4,5-tetrachlorofluorobenzene (2-F), and k^{42} with attack upon the 2,3,5,6-isomer (4-F). When a^1 is the rate constant for consumption of the starting material (pentachlorobenzene),

$$[C_6Cl_5H]_t = [C_6Cl_5H]_{t=0} \cdot e^{-a^1 t}.$$

The formation of 2,3,4,5-tetrachlorofluorobenzene (2-F) is governed by the rate constant of formation, k^2 , and the sum of the rate constants associated with its destruction, a^2 . This destruction forms $23-F_2$, $24-F_2$, and $26-F_2$, so that

$$a^2 = k^{23} + k^{24} + k^{26}.$$

The instantaneous concentration of 2-F reflects these conflicting effects:

$$[2-F]_t = [C_6Cl_5H]_{t=0} \cdot \frac{k^2}{a^1 - a^2} \left[e^{-a^2 t} - e^{-a^1 t} \right]$$

Analogous terms may be written for the formation of 3-F and 4-F, although allowance must be made for the presence of equivalent sites before comparing the derived rate constants.

The subsequent reaction to form 1,2-difluoro-3,4,5-trichlorobenzene (23-F₂) involves contributions from two terms, the first reflecting the formation of 23-F₂ from 2-F and the second reflecting the route from 3-F.

$$[23-F_2]_t = [C_6Cl_5H]_{t=0} \left\{ k^{23} \cdot k^2 \left[\frac{1}{a^1 \cdot a^2} - \frac{e^{-a^1 t}}{a^1(a^2 - a^1)} - \frac{e^{-a^2 t}}{a^2(a^1 - a^2)} \right] + k^{32} \cdot k^3 \left[\frac{1}{a^1 \cdot a^3} - \frac{e^{-a^1 t}}{a^1(a^3 - a^1)} - \frac{e^{-a^3 t}}{a^3(a^1 - a^3)} \right] \right\}$$

Again, analogous functions can be derived for the other four difluorotrichlorobenzenes.

From this treatment, rate constants for each stage were found which were mutually consistent within each system and which reproduced the rise and fall in concentration of each intermediate. While the results in Tables 1 and 3 were obtained at different temperatures, the relative values of rate constants for the same stages in each system, although independently derived, agreed.

Relative reactivities of aryl halides

The simple additivity calculus already described [8] has been successfully applied to the prediction of shifts in the ¹⁹F-NMR spectra of many polychloropolyfluorobenzenes, and to the estimation of the rate constants for methoxydefluorination of these substrates in methanol at 50°. Table 4 shows the comparison between the rate constants calculated by this method and the values given by the detailed mathematical treatment of the sequential reactions of pentachlorobenzene.

TABLE 4

Comparison of calculated and derived rate constants in the fluorodechlorination of pentachlorobenzene at ca. 245°

Free energy parameter	$10^5 k$ (sec. ⁻¹) (derived)	$10^5 k$ (sec. ⁻¹) (calculated)
2β	24	$k^4 = 22$; $k^{24} = 18$
(m + 1)β	15	$k^2 = 10$; $k^{42} = 9$; $k^{26} = ?$
(m + 2)β	8.5 (standard)	$k^3 = 9$; $k^{35} = 8.5$
α + β	10	$k^{34} = 11$
α + mβ	6	$k^{32} = 6$
α + (m + 1)β	3.5	$k^{43} = 1.5$; $k^{23} = 1$

(*) Calculated rate constants are those given in Table 1; derived values are those found using the empirical parameters $m = 1.85$, $\alpha = -1.50$ Kcal.mole⁻¹, and $\beta = -0.60$ Kcal.mole⁻¹

The calculated rate constants are in fair agreement with those derived by use of the empirical equations [8]. The yields of some of the intermediates, from which the rate constants were calculated, were often small; this gave rise to disproportionate errors in the rate constants. These errors are compounded when there is more than one route to or from a particular compound in the sequence; in some cases, such as those involving the formation of derivatives of ortho-difluorobenzene, considerable variation of the rate constants could be made without marked alteration in the derived product ratio. In view of this, further refinement of the empirical equations, such as by the consideration of inductive contributions of the halogen substituents, is unwarranted.

Further work on the substituent effects in fluorodechlorination of polychloro-arenes is in progress to determine the application of these empirical equations and their limitations.

EXPERIMENTAL

Sulpholan (BDH) was commercial material, solid at room temperature, which was used without further purification. Potassium fluoride was

commercial anhydrous material, dried at 120° for two hours. The organic starting materials were commercial products (hexa- and pentachlorobenzene, and 2,3,5,6-tetrachloronitrobenzene) which were recrystallised from ethanol, or obtained by literature methods [7] (2,3,5,6-tetrachlorofluorobenzene). In all cases, the m.p. were in good agreement with literature values.

Stirred mixtures of potassium fluoride (1.0 mole), sulpholan (100 ml.), and the organic polychloro-arene (0.10 mole) were brought to reflux temperature, when small amounts of water were removed by distillation until the still-head temperature exceeded 180°. Stirring was continued as samples were taken from the boiling reaction mixture. These were quenched in water, and the organic products were extracted with fluorotrichloromethane and were characterised by ¹⁹F-NMR spectro-

TABLE 5

¹⁹F-NMR shifts and coupling constants of some polychloropolyfluorobenzenes (shifts, in p.p.m., upfield of fluorotrichloromethane).

<u>Arene</u>	<u>δ(exp)</u>	<u>δ(calc.)</u>	<u>Coupling constant</u> ^(*)
2,3,4,5-Tetrachlorofluorobenzene	109.5	111.2	F-H, 9.6
2,3,4,6-Tetrachlorofluorobenzene	110.0	109.0	F-H, 7.2
2,3,5,6-Tetrachlorofluorobenzene	103.7	109.6	F-H, 2.4
1,2-Difluoro-3,4,5-trichlorobenzene	F ₁ :133.9 F ₂ :132.2	135.7 133.5	F ₁ -F ₂ , 21.6; F ₂ -H ₆ , 7.8 F ₁ -H ₆ , 10.0;
1,3-Difluoro-2,4,5-trichlorobenzene	F ₁ :113.0 F ₃ :106.7	111.2 109.6	F-F, 2.0; F ₁ -H, 8.4 F ₃ -H, 2.0.
1,5-Difluoro-2,3,4-trichlorobenzene	107.8	111.2	F-H, 9.6.
1,2-Difluoro-3,4,6-trichlorobenzene	F ₁ :135.5 F ₂ :128.8	133.5 134.0	F-F, 19.0; F ₁ -H, 7.0 F ₂ -H, 2.0.
2,4-Difluoro-1,3,5-trichlorobenzene	112.6	109.0	F-H, 7.2.
2,4,6-Trifluoro-1,3-dichlorobenzene	F ₂ :110.4 F ₄ :111.8	109.6 111.2	F ₂ -H, not resolved ^(**) F ₄ -H, 7.2; F-F, 2.0
(2,3-Difluoro-1,4-dichlorobenzene) ^(***)	142.0	-	F-F, 18.0; F-H, 6.0.

(*) Hz. (**) Reported [10] F₂ = 110.3 p.p.m., F₄ = 111.9 p.p.m.

(***) Structure suggested by quartet in NMR spectrum, and a retention time on g.l.c. only slightly greater than those of polyfluoro-1,3-dichlorobenzenes

scopy (Perkin-Elmer R12B, 56.4 MHz) and by gas-chromatography (Pye 104). The polyfluoro-arenes were identified using the simple method based upon the additivity calculus [8], and the structures were confirmed by consideration of the F-F and F-H coupling constants. Table 5 lists the chemical shifts and coupling constants obtained.

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