THE THIOLATE ANION AS A NUCLEOPHILE
PART III*. REACTIONS WITH VARIOUS FLUOROBENZENES

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Summary

The reactions of the fluorobenzenes, C_6F_5H, o-$C_6H_2F_4$, m-$C_6H_2F_4$, p-$C_6H_2F_4$, $1,3,5$-$C_6F_3H_3$, $1,2,4$-$C_6F_3H_3$, o-$C_6F_2H_4$, m-$C_6F_2H_4$, p-$C_6F_2H_4$ and C_6F_5H with thiolate anion nucleophiles RS^- (primarily MeS^-), have been studied in ethylene glycol/pyridine mixtures as a solvent. Multiple replacement of fluorine atoms was observed in the more highly fluorinated compounds, but in all cases two aromatic fluorine atoms were not replaced. Difluorobenzene and fluorobenzene did not react. The product orientations have been deduced from their NMR spectra. The mass spectra of the isomeric products $C_6F_2H_3(SMe)$, $C_6F_3H_2(SMe)$ and $C_6F_2H_2(SMe)_2$ have been examined.

Introduction

In the first paper of this series, the reactions of thiolate anions as nucleophiles with hexafluorobenzene, hexachlorobenzene and decafluorobiphenyl were described [2]. This paper extends the previous work to the reaction of thiolate anions with various fluorobenzenes, $C_6H_{6-x}F_x$, $x = 1$ - 5. The major products were isolated and characterized by elemental analysis and NMR spectra. The mass spectra of various isomeric products have been recorded.

The reaction of thiolates with the various fluorobenzenes has not been studied extensively. The fluorine in fluorobenzene has been replaced by the SBu group, using HMPA/THF as a solvent in the presence of sodamide [3]:

$$C_6H_5F + BuSH \rightarrow C_6H_5SBu + HF$$
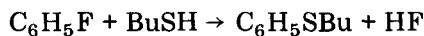
The choice of solvent is important and an ideal mixture for substitution in fluorobenzene was found to be 1HMPA + 3THF at 45°C, the RS^- ion being generated in THF in the presence of sodium metal [4]. The fluorine in 1- and 2-fluoronaphthalenes may be replaced by BuS in refluxing DMSO with butane thiol [5]. In compounds where the fluorine may be activated towards

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* For Part II, see ref. 1.

nucleophilic substitution, such as halonitrobenzenes [6] or 1-fluoro-2-nitro-benzene [7], replacement of fluorine by the thiolate anion has also been observed. Replacement of the fluorine *para* to the hydrogen in pentafluoro-benzene has been observed when various thiolate anions have been used as nucleophiles [8]. Copper(I) thiolates have been used as a source of thiolate anions [9] in many of these studies.

Results and discussion

The reactions described in this paper involve the use of a pyridine/ethyl-ene glycol mixture as the solvent. In the reactions described two fluorine atoms always remain on the aromatic ring, but replacement of the fluorine in fluorobenzene is possible in other solvents. No reactions were observed be-tween MeS$^-$ and *o*-, *m*-, or *p*-C$_6$F$_2$H$_4$ and C$_6$H$_5$F.

The hydrogen in the aromatic ring determines the position of the initial substitution, fluorine atoms *para* or *ortho* to the hydrogen being replaced, with the *para* being replaced preferentially. When one fluorine atom has been replaced by an SR group the position of further substitution is deter-mined by the *ortho/para*-directing effects of both the SR group and the hy-drogen. The results of these experiments are summarized in the list of formu-lae given below. The structures of the products can be deduced from the above reasoning and are consistent with the observed NMR data. It is note-worthy that when the dielectric constant of the solvent is lower than about 30 D, replacement of the fluorine *ortho* to the nitro group in pentafluoroni-trobenzene is also observed in addition to *para* substitution [10].
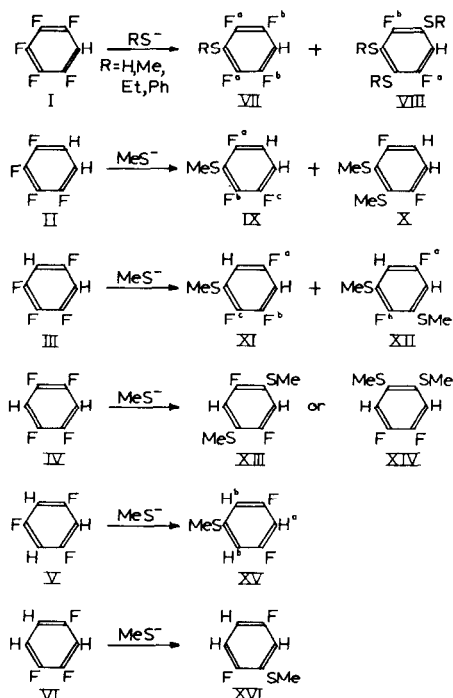
Three different atoms or groups may be examined by NMR spectroscopy in the products, *viz.* the aromatic hydrogen, the aromatic fluorine and the hydrogen in the RS (usually MeS) group. The aromatic hydrogens can be coupled to other aromatic hydrogen atoms or to the aromatic fluorine. These spectra are usually relatively simple, and as the position of the hydrogen in the aromatic nucleus does not change during the reaction, the spectrum can be interpreted. The side-chain aliphatic methylene protons can be coupled to the *ortho*-fluorine atoms in compounds such as C_6F_5SMe where the proton spectrum is observed as a triplet [11]. In a symmetrical structure such as $1,4$-$C_6(SMe)_4F_2$, the methyl protons are observed as a triplet due to averaged coupling to *ortho*- and *meta*-fluorine atoms [1]. Coupling of the methyl protons *ortho* to the fluorine is observed in compounds such as (XVII) where a doublet is formed, but the methyl protons *meta* to the fluorine are not coupled. Similarly, in compounds such as (XVIII) and XIX), the methyl proton occurs as a singlet, and this also occurs in the proton spectrum of the methoxy analog of (XVIII) [13].

XVII   XVIII   IXX
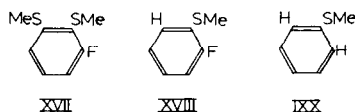
The fluorine spectra were complex in most cases due to multiple couplings, but when a first-order spectrum could be sufficiently well resolved, coupling to other aromatic fluorine atoms, aromatic hydrogen and sometimes SR groups was observed and the coupling constants could be compared with other values quoted in the literature. Self-consistent values of the H−F coupling constants may be deduced from the fluorine and proton spectra. Details of the NMR spectra together with literature values are shown in Table 1.

Compounds of type (VII) would be expected to possess an aromatic hydrogen spectrum exhibiting a triplet of triplets due to coupling to two *ortho* and two *meta* fluorines as is, in fact, observed. Two different fluorine atoms can be detected, and when R = Me the methyl protons appear as a triplet due to coupling to the two *ortho*-fluorine atoms. In previous work on the substitution of (I) using the thiolate anion as a nucleophile, only products of the type (VII) were isolated. Multiple substitution of fluorine, which would lead to derivatives similar to (VIII), was not observed [8], although multiple substitution of hexafluorobenzene to form p-$C_6F_2(SR)_4$ has been reported [2].

The aromatic proton in (VIII) appears as a quartet in the NMR spectrum due to coupling to one *ortho* and one *meta* fluorine. Two different fluorine atoms are observed in the ^{19}F NMR spectrum. Coupling is observed to the *para* fluorine, the aromatic hydrogen and the SR group (when R = Me or Et). When R = Me, three different proton signals are observed, and these may be separated using shift reagent into a singlet (SMe, *ortho* to hydrogen) and two doublets (SMe, *meta* and *para* to hydrogen) due to coupling to *ortho* fluorine.

TABLE 1

Summary of NMR spectral data (CCl$_4$ solution)

Compound	Chemical shifts			Coupling constants/Hz						
	^{1}H(Ar)/τ	^{1}H(R)/τ	^{19}F/ppm*	$J(H-F_o)$	$J(H-F_m)$	$J(H-F_p)$	$J(Me-F_o)$	$J(F-F_o)$	$J(F-F_m)$	$J(F-F_p)$
(VI);(R = Me)	3.020 TT	7.460 T	—	9.57	7.35	—	0.95	—	—	—
(VII);(R = Ph)	3.077 TT	2.783 M	133.06(a) M	9.65	7.32	—	—	21.4	1.8‡	10.5
			138.11(b) M							
(VIII);(R = Me)	3.189 Q	7.359 D	110.00(a) M	9.50	6.35	—	1.39(a)	—	—	15.24
		7.417 D	109.08(b) M				2.05(b)			
		7.480 S								
(VIII);(R = Et)	3.092 Q	7.042 M	108.46(a) Q†	9.00	6.25	—	—	—	—	14.5
		8.703 Q	105.24(b) Q†							
(VIII);(R = Ph)	3.439 Q	2.867 D	104.45(a) Q	8.45	6.25	—	—	—	—	14.8
		2.64 D	102.55(b) Q							
(IX)	3.152 M	7.542 T	110.43(a) M	9.1	5.7	—	<0.8	—	6.9	13.8
			127.69(b) M	—	5.6	2.0	0.9	21.6	7.05	—
			140.38(c) M	9.3	5.43	—	0.89	21.99	—	13.98
(X)	3.106 T	7.531 T	126.9 T	—	—	—	—	—	—	—
(XI)	3.311 M	7.534 S	115.57(a) M	8.38	—	—	—	—	3.24	13.42
			142.01(b) M	8.46	—	1.90	—	21.06	3.16	13.40
			133.77(c) M	—	5.56	—	—	21.20	—	—
(XII)	3.328 Q	7.565 S	118.27(a) M	8.38	5.46	—	—	—	—	14.33
			117.01(b) M	8.26	5.43	—	—	—	—	14.33
(XIV)	3.103 T	7.575 S	117.34 T	—	—	—	—	—	—	—
(XV)	3.510(a) TT	7.521 S	109.91 TQ	8.7(a)	7.67	1.92	2.2(H–H$_m$)	—	1.05	—
	3.357(b) M			6.6(b)						
(XVI)	3.167 M	7.535 S	118.97 M	—	—	—	—	—	—	—
Lit. range [12]				{6.2 {10.1	{6.2 {8.3	{2.1 {2.3	—	{20.2 {20.8	{0.0 {7.0	{0.0 {15.0

S = singlet; T = triplet; D = doublet; Q = quartet; M = multiplet.

* Using CFCl$_3$ as internal standard.

† Sweep width 1000 Hz.

‡ Two distinct signals which could not be resolved.

When R = Et, the proton spectrum appears as a quartet due to the Me group and a quartet due to the CH_2 group, the latter being further split by coupling to fluorine. This spectrum cannot be resolved completely for at least two different Et groups should be observable.

The NMR spectra of (IX) and (X) are complex, but a detailed analysis of the second-order spectra of (X) is consistent with this structure (this will be published in co-operation with Prof. Dr. G. Hägele). If (IX) acts as an intermediate in the formation of (X), the only possible structure for (IX) is as shown. In the ^1H NMR spectrum, the methyl protons of (IX) are split into a triplet, and in the ^{19}F NMR spectrum there are three different fluorine atoms, the aromatic proton spectrum being complex due to the multiple couplings expected. The monosubstituted products of (II) with MeO^-, NH_2NH_2, or H (from $LiAlH_4$) are also consistent with structures similar to (IX) [13], the methyl protons in the ^1H NMR spectrum being again split into a triplet. No disubstituted product is formed in the reaction of (II) with MeO^-.

When (III) is converted into (XI), replacement of the fluorine atoms *ortho* to both hydrogens, or *ortho* and *para* to the hydrogen atoms would be expected, with the latter alternative being preferred. The NMR spectra are consistent with this structure for (XI), there being three different fluorines in the ^{19}F spectrum (all other possibilities would have two different fluorine atoms in the ratio 2:1). In the ^1H NMR spectrum, the methyl proton is observed as a singlet and the aromatic proton spectrum is complex due to multiple couplings. In a similar manner, monosubstitution of (III) with MeO^- afforded the analog of (XI); no disubstituted product was observed [13].

Compound (XII) has a symmetrical structure. In the ^1H NMR spectrum, the aromatic protons give rise to a quartet due to coupling to *ortho*- and *meta*-fluorine atoms. In the ^{19}F spectrum, two slightly different fluorine atoms are observed, the F–F coupling constant being consistent with *para* fluorines. The methyl protons appear as a singlet.

The reaction of (IV) with the methane thiolate anion gives rise to two product orientations, *i.e.* (XIII) or (XIV). These cannot be distinguished from a simple interpretation of the NMR spectra, but a detailed analysis supports structure (XIV) (this will be published in co-operation with Prof. Dr. G. Hägele). Reaction of (IV) with MeO^- leads to the formation of only a monosubstituted product, with only one structure being possible [13]. No monosubstituted product was isolated from the reaction of (IV) with MeS^-.

There is only one possible structure for (XV) and this is confirmed by the NMR spectra. The SMe protons appear as a singlet in the ^1H NMR spectrum, the aromatic protons being resolved into a triplet of triplets at 220 MHz due to H^a and into a multiplet due to H^b. The ^{19}F NMR spectrum appears as a triplet of quartets which is the spectrum expected from two equivalent fluorine atoms coupled twice to *ortho* hydrogen, once to *meta* fluorine and to *para* hydrogen, but not to the SMe group.

The spectrum of (XVI) is complex, but a consideration of the directing effects of the aromatic hydrogen atoms suggests that the structure indicated

is the most possible. This is confirmed from an analysis of the 220 MHz ^{1}H NMR spectrum, where the aromatic protons are observed as a multiplet and the methyl protons as a singlet. The fluorine spectrum is a complex multiplet. (This will be published in greater detail later in co-operation with Prof. Dr. G. Hägele).

The groups of compounds (IX), (XI); (X), (XII) and (XIV); (XV) and (XVI) are isomeric. Their mass spectra are interesting theoretically as they should show the effect of the positions of the various groups H, SMe and F in the aromatic nucleus on the observed fragmentation patterns. The primary ion mass spectra and ion kinetic energy spectra have been recorded.

All the mass spectra show that the initial mode of fragmentation from the molecular ion involves fracture of the Me–S or Ar–S bonds. There is no evidence for the initial loss of H or F from the molecular ion although loss of fluorine from the molecular ion is one of the initial fragmentation modes of compounds of the type C_6F_5SX, such as C_6F_5SMe [14]. In addition, in the latter case the loss of three hydrogens from the molecular ion is also observed.

Other features of the mass spectra include the formation of many doubly-charged ions mainly containing sulfur, thus indicating the formation of relatively stable ions. Rearrangements must occur in reactions such as:

$$C_6F_3H_2(SMe)^{\ddagger} \xrightarrow{*} C_7H_4F_3^+ + SH\cdot$$
$$C_6F_3H_2(SMe)^{\ddagger} \xrightarrow{*} C_6H_3F_3^{\ddagger} + SCH_2$$
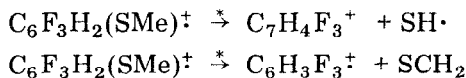
All the above isomeric series exhibit virtually identical ion kinetic energy s ·ctra, although the relative peak intensities may vary slightly; this indicates tł. ιt the fragmentation modes are effectively the same in each group. At m/e values < 100, the primary ion spectra for each group are effectively the same.
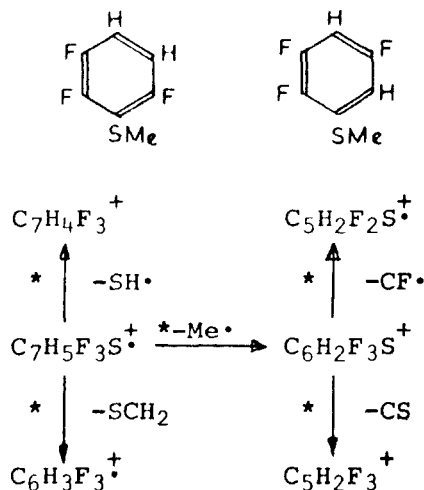

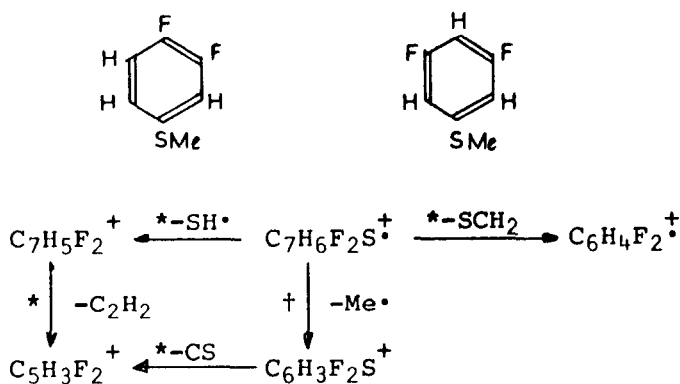Fig. 1. Initial fragmentation modes of $C_6H_2F_3(SMe)$.

Fig. 2. Initial fragmentation modes of $C_6H_3F_2$ (SMe). † Confirmed from I.K.E. data.
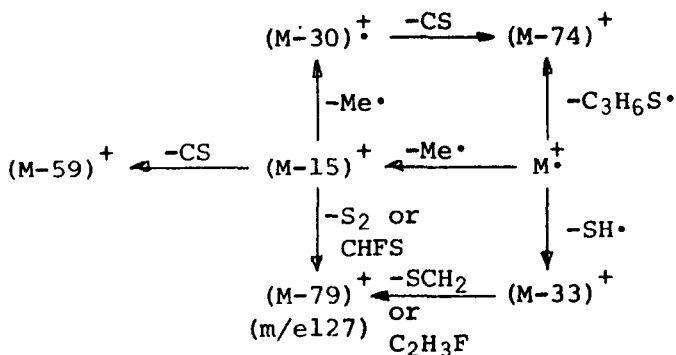

Fig. 3. Initial fragmentation modes of $C_6H_2F_2(SMe)_2$.

Details of the initial fragmentation modes deduced from metastable peaks, together with ion kinetic energy spectra in some cases, are shown in Figures 1 - 3. In the spectra of the series $C_6H_2F_2(SMe)_2$, the initial fragmentation modes observed correspond to fracture of the C–S and Ar–S bonds of both the SMe groups. In some cases a specific fragmentation cannot be associated with a metastable transition as accurate mass measurements show that two combinations are possible for a specific m/e value. Of particular interest are the following ions, the existence of both alternatives being demonstrated by accurate mass measurements: m/e 127, corresponding to $C_7H_5F_2^+$ or $C_6H_4FS^+$; m/e 144, corresponding to $C_6H_2F_2S^{\ddagger}$ or $C_5HFS_2^{\ddagger}$; and m/e 147, corresponding to $C_6H_5F_2S^+$ or $C_5H_4FS_2^{\ddagger}$.

The infrared spectra of all the products (VII)–(XVI) are consistent with their structures although such spectra were of little value in confirming the product orientations as they were relatively complex.

TABLE 2

Chemical analyses and physical properties of new compounds

Compound[a]	M.p/°C or b.p./°C/mmHg	n_D^b	Calculated (%)			Found (%)		
			C	H	S	C	H	S
(VIII);(R = Me)	73 - 74	—	42.83	3.99	38.12	42.93	3.93	38.16
(VIII);(R = Et)	122 - 124/0.15	1.5939(20)	48.95	5.47	32.67	49.01	5.41	32.62
(VIII);(R = Ph)	92 - 93	—	65.73	3.67	21.93	65.62	3.62	21.82
(IX)	24 - 25/0.15	1.5068(25)	47.19	2.83	17.99	47.19	2.83	17.94
(X)	55 - 57/0.15	1.5821(24)	46.58	3.91	31.09	46.72	3.87	30.29
(XI)	86 - 88/22	1.5135(25)	47.19	2.83	17.99	47.32	2.87	17.91
(XII)	74 - 75	—	46.58	3.91	31.09	46.64	3.90	30.98
(XIV)	122 - 123	—	46.58	3.91	31.09	46.20	3.90	31.18
(XV)	83 - 85/22	1.5324(20)	52.49	3.78	20.02	52.58	3.78	19.98
(XVI)	84 - 86/22	1.5325(30.5)	52.49	3.78	20.02	52.49	3.87	20.07

[a]All colorless liquids or white solids.
[b]Temperature (in °C) in brackets.

TABLE 3

Reaction stoichiometry and products

Fluoroaromatic compound (mmol)	Thiolate anion (mmol)	Major product	Purification[b]	Yield[a] (%)
(I)(30)	MeS⁻(30)	(VII);(R = Me)	D	70
(I)(10)	MeS⁻(50)	(VIII);(R = Me)	R(MeOH) :S	56
(I)(10)	MeS⁻(100)	(VIII);(R = Me)	R(MeOH) :S	84
(I)(20)	HS⁻(20)	(VII);(R = H)	D	37
(I)(20)	HS⁻(100)	(VII);(R = H) and tar	D	18
(I)(10)	EtS⁻(50)	(VIII);(R = Et)	D	61
(I)(20)	PhS⁻(20)	(VII);(R = Ph) and Ph₂S₂	D	61
(I)(10)	PhS⁻(50)	(VIII);(R = Ph) and Ph₂S₂	S	58
(II)(20)	MeS⁻(100)	(X)	D	74
(II)(20)	MeS⁻(20)	(IX) and	D	45
		(X)	D	17
(III)(20)	MeS⁻(100)	(XI) and	D	14
		(XII)	R(MeOH)	58
(III)(20)	MeS⁻(20)	(XI)	D	71
(IV)(20)	MeS⁻(100)	(XIV)	R(MeOH)	76
(IV)(20)	MeS⁻(20)	(XIV)	R(MeOH)	78
(IV)(20)	MeS⁻(50)	(XIV)	R(MeOH)	31
(V)(20)	MeS⁻(20)	(XV)	D	63
(V)(10)	MeS⁻(100)	(XV)	D	63
(VI)(20)	MeS⁻(20)	(XVI)	D	65
(VI)(10)	MeS⁻(100)	(XVI)	D	81

[a] Based on fluoroaromatic.
[b] D = distillation; R = recrystallization (solvent); S = sublimation.

Experimental

All the fluorobenzenes used were available commercially. Microanalyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, West Germany. The analytical data and some physical properties of the new compounds prepared are shown in Table 2. Infrared spectra were recorded on a Perkin–Elmer 457 spectrophotometer as mulls with Nujol or hexachlorobutadiene, or as KBr discs. Mass spectra were recorded on a DuPont/CEC Model 21-110B mass spectrometer, by direct introduction with sample temperature within the range $-90°C$ to $+87°C$. In cases of ambiguity, ion identification was confirmed by high-resolution measurements ($R \simeq 1500$) based on spectra recorded photographically. Ion kinetic energy data were obtained as described previously [15]. NMR spectra were recorded in CCl_4 solution using TMS or $FCCl_3$ as internal standards on a Varian HA 56/60, A60, HA100, or HR220 instrument.

The procedure followed in the preparative work has been described previously [1]. Various details of the reaction stoichiometry and method of purification are shown in Table 3. Known products isolated were identified by various physical properties: p-$MeSC_6F_4H$, b.p. 64 - 65 °C/5.0 mmHg (lit. value [8]: 169 - 174 °C/760 mmHg); p-HSC_6F_4H, b.p. 48 - 50 °C/22 mmHg, n_D^{22} 1.4831 (lit. value [8]: b.p. 147 °C/760 mmHg, n_D^{22} 1.4827); p-PhS-C_6F_4H, b.p. 62 - 64 °C/0.4 mmHg, n_D^{26} 1.5565 (lit. value [8]: b.p. 265 °C/760 mmHg, n_D^{22} 1.5541); Ph_2S_2, m. p. 61 - 62 °C (lit. value [16]: 61 - 62 °C). No replacement of fluorine with methane thiolate anion was observed in reactions with o-$C_6F_2H_4$, m-$C_6F_2H_4$, p-$C_6F_2H_4$ and C_6H_5F at molar ratios of thiolate: fluoroaromatic of 1:1 and 5:1, and the starting fluoroaromatic was recovered in high yield.

Acknowledgements

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Note added in proof

The detailed interpretation of the NMR spectra of the $C_6H_2F_2(SMe)_2$ isomers will appear in Org. Magn. Resonance, (G. Hägele, J. Richter, and M. Peach), and confirm the structures (XIV) and (X). A detailed analysis of the NMR spectrum of (IX) has been submitted to Z. Naturforsch. B, (G. Hägele, J. Richter and M. Peach).