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THE THIOLATE ANION AS A NUCLEOPHILE PART XI*. EFFECT OF THE SIZE OF THE NUCLEOPHILE

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SUMMARY

The nucleophilic substitution reactions of some simple fluorobenzenes, $C_6H_{6-x}F_x$ with sodium methanethiolates Na^+SR^-(R=Et, i-Pr, t-Bu) have been studied. Some fully substituted products, $C_6H_{6-x}(SR)_x$, could be obtained in DMF as solvent with R = Et and i-Pr, but not when R = t-Bu. All the new products isolated have been characterized by elemental analysis, and NMR (H-1 and F-19), infrared and mass spectroscopy.

INTRODUCTION

The extent of nucleophilic replacement of fluorine in fluorobenzenes with the thiolate anion depends on the reactant ratio as well as the solvent used [1,2]

$$C_6H_{6-x}F_x + ySR^- \longrightarrow C_6H_{6-x}F_{x-y}(SR)_y + yF^-$$

Complete substitution of the simple fluorobenzenes, $C_6H_{6-x}F_x$, with the methanethiolate anion occurs using N,N-dimethylformamide (DMF) as the solvent [2], but when an ethylene glycol/pyridine mixture (volume ratio 1:2) is used two fluorine atoms, if feasible mutually para, always remain on the aromatic ring [3]. The structure of the products, usually deduced from NMR spectra, indicate that the positions of fluorine replacement depends mainly on the fluorine atoms initially present on the ring, as observed previously with other nucleophiles [4]. One variable that has not been studied specifically is the effect of the bulk of the thiolate anion.

*Part X, see ref. 1

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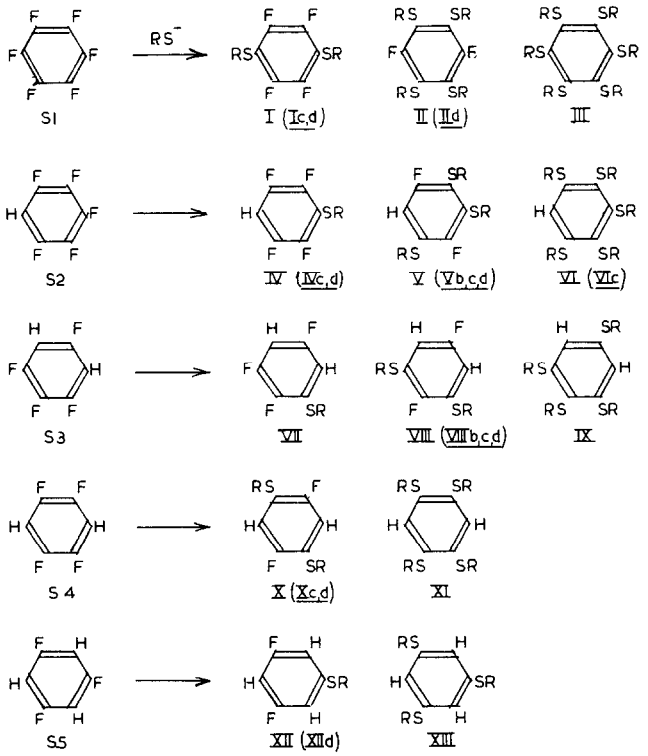
This paper, as an extension of previous work with sodium methanethiolate anion [3], examines the effect of the size of the thiolate anion, $(CH_3)_{3-x}H_xCS^-$ (x = 0,1,2,3) in its reactions with simple fluorobenzenes.

RESULTS AND DISCUSSION

The reactions of various fluorobenzenes with the ethanethiolate, 2-propanethiolate, and 2-methyl-2-propanethiolate anions have been studied. Schematically the reactions can be represented as,



Key: a, R = CH_3; b, R = CH_2CH_3; c, R = $CH(CH_3)_2$; d, R = $C(CH_3)_3$

This paper describes the preparation and characterization of the products underlined on the diagram, namely Ic, Id, IId, IVc, IVd, Vb, Vc, Vd, VIc, VIIIb, VIIIc, VIIId, Xc, Xd, and XIId. Various compounds have been prepared

previously: Ia, Ib, IIa, IIb [5];IIc, IIIb, IIIc, VIc, IXc, XIc, XIIIc [6]; Vb [7]; IIIa, VIa, IXa, XIa, XIIIa [2]; IVa, Va, VIIa, VIIIa, Xa, XIIa [3]. The reaction conditions were analogous to those used previously [2,3]. Only the major products of the reactions were isolated and characterized. It is clear that both the solvent employed and the molar ratio of the reactants is of major importance.

The fully substituted methylthio compounds, IIIa, VIa, IXa, XIa and XIIIa were readily prepared in DMF using an excess of the methanethiolate anion [2]. The ethylthio compound $C_6(SEt)_6$ (IIIb) could not be prepared analogously [2], however it and the i-propyl analog, $C_6(SPr^i)_6$ (IIIc) were prepared in HMPA (hexamethylphosphoramide) at 20° and 0° respectively [6]. Other fully substituted i-propyl compounds, VIc, IXc, XIc and XIIIc were also prepared in HMPA [6]. When DMF, rather than HMPA, was used as solvent in the present study it was possible to isolate VIc, but not VIIIc or IXc. Steric crowding cannot be a major factor with the reactions of 2-propanethiolate if $HC_6(SCHMe_2)_5$ (VIc) could be prepared in DMF.

Using a 6:1 ratio of 2-methyl-2-propanethiolate anion: substrate in DMF it was not possible to prepare the t-butyl analogs IIId, VId, IXd, XId, XIIId and the compounds IId, Vd, VIIId, Xd and XIId were obtained. In these reactions the bulk of the thiolate anion does appear to be one of the factors determining the extent of the replacement of the fluorine.

When an excess of the thiolate anion nucleophile is used in HMPA dealkylation can occur [2,6].

$$C_6F_6 \xrightarrow[\text{HMPA}]{\text{excess } MeS^-} (MeS)_5C_6SH$$

This reaction has been used to prepare polymercaptobenzenes [7]. Similar reactions have not, as yet, been observed in DMF.

The yields are, in some cases, relatively low. This may well be due to the difficulties encountered in the purification procedures.

The NMR spectra of the products isolated have been examined and are reported in Table 1. The isomeric configuration can usually be deduced from the aromatic hydrogen-aromatic hydrogen, aromatic hydrogen- fluorine and fluorine-fluorine coupling constants, as observed in the aromatic proton region of the proton spectrum and the fluorine spectrum. The spectra of the methylthio compounds Ia - XIIIa have been analysed in considerable detail [8,9] and, by comparison, the coupling constants and structures can be readily assigned. In the spectra of the methyl derivatives, such as

TABLE 1

Summary of NMR Spectra

Compound		Chemical shifts/p.p.m.	Coupling constants/Hz
Ic	Me	1.25D	J(H-H) 6.8
	CH	3.50SE	J(H-H) 6.8
	F	133.3S	
Id	Me	1.37S ($CDCl_3$)	
IId	Me	1.40S	
($CDCl_3$)	F	80.1S	
IVc	Me	1.25D	J(H-H) 6.5
	CH	3.40SE	J(H-H) 6.5
	ArH	6.93TT	J(H-F_o) 9.6, J(H-Fm) 7.2
	F	132.8DDD	J(F-Hm) 7.7, J(F-Fp) 14.4, J(F-Fo) 23.5
	F	138.1DDD	J(F-Ho) 10.5, J(F-Fp) 14.6, J(F-Fo) 23.4
IVd	Me	1.36S	
	ArH	7.00TT	J(H-Fo) 9.6, J(H-Fm) 7.2
	F	129.6DDD	J(F-Hm) 7.5, J(F-Fp) 13.5, J(F-Fo) 21.0
		138.0DDD	J(F-Ho) 9.0, J(F-Fp) 12.6, J(F-Fo) 23.5
Vb	Me	1.26M	
	CH_2	2.86M	
	ArH	6.83DD	J(F-Fo) 9.0, J(H-Fm) 6.2
	F	106.0DD	J(F-Hm) 7.5, J(F-Fp) 16.0
	F	108.3DD	J(F-Ho) 9.1, J(F-Fp) 15.5
Vc	Me	1.248D	J(H-H) 6.6
(C_6F_6)	Me	1.257D	J(H-H) 6.6
	Me	1.320D	J(H-H) 6.6
	CH	3.483SE (2)*	J(H-H) 6.6
	CH	3.627SE (1)*	J(H-H) 6.6
	ArH	7.013DD	J(H-Fo) 8.64, J(H-Fm) 6.04
($CDCl_3$)	F	90.84DD	J(F-Hm) 6.2, J(F-Fp) 15.6
	F	95.75DD	J(F-Ho) 8.5, J(F-Fp) 16.5
Vd	Me	1.30S	
	ArH	7.26DD	J(F-Fo) 7.6, J(H-Fm) 6.4
	F	88.6DD	J(F-Hm) 6.1, J(F-Fp) 16.6
	F	99.7DD	J(F-Ho) 7.6, J(F-Fp) 15.6
VIc	Me	1.26D	J(H-H) 6.6
	CH	3.40SE	J(H-H) 6.8
	ArH	6.60S	

*Intensity Ratio

Table 1 (cont.)

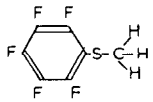
Compound	Chemical shifts/p.p.m.	Coupling constants/Hz
VIIIb	Me 1.33T	J(H-H) 7.2
	CH_2 2.86Q	J(H-H) 7.2
	ArH 6.70DD	J(H-FO) 8.3, J(H-Fm) 5.4
	F 113.8DT	J(F-Hm) 5.4, J(F-Fp) 16.0
	F 117.3DT	J(F-Ho) 8.2, J(F-Fp) 14.6
VIIIc	Me 1.36D	J(H-H) 6.5
	CH 3.36SE	J(H-H) 6.5
	ArH 6.83DD	J(H-FO) 7.9, J(H-Fm) 5.1
	F 110.5DT	J(F-Hm) 5.2, J(F-Fp) 15.5
	F 118.9DT	J(F-Ho) 8.1, J(F-Fp) 16.0
VIIId	Me 1.33S	
	ArH 7.16DD	J(H-Fo) 7.2, J(H-Fm) 5.2
	F 99.7DT	J(F-Hm) 5.0, J(F-Fp) 16.4
	F 118.6DT	J(F-Ho) 7.3, J(F-Fp) 16.9
IXb	Me 1.33M	
	CH_2 2.80M	
	ArH 6.63S	
Xc	Me 1.36D	J(H-H) 6.5
	CH 3.36SE	J(H-H) 6.5
	ArH 6.83DD	J(H-F) 7.4
	F 114.0T	J(H-F) 7.3
Xd	Me 1.30S	
	ArH 7.16T	J(H-F) 6.9
	F 110.0T	J(H-F) 7.0
XIId	Me 1.26S	
	ArH 6.95M	

Notes: (1) Solvents H - all CS_2 with TMS as internal standard
F CS_2 - C_6F_6 int. std. corrected to $CFCl_3$
or $CDCl_3$ with $CFCl_3$ where shown

(2) Abbreviations

S = singlet
D = doublet
T = triplet
Q = quartet
SE = septet
M = multiplet

$C_6F_5SCH_3$ [10] and IIa [11], it was observed that the methyl protons are coupled to the ortho fluorines with a coupling constant of approximately 1 Hz. This has been attributed to a through space effect. No analogous coulpings were observed in the spectra of the ethylthio and i-propylthio (or t-butyl) analogs. This may be due to the methyl group(s), which have replaced the hydrogen, preventing free rotation about the C-S bonds, and



the system becoming more rigid. This could also reduce the coupling constant to less than about 0.5 Hz, when the coupling could not be resolved.

The mass spectra of the products have been examined. These all confirm the molecular weights of the products. Metastable peaks show the stepwise loss of the respective alkene groups, for example in $C_6F_2(SC_4H_9)_4$ (IId) C_4H_8 units are progressively displaced.

$$C_{22}H_{36}F_2S_4]^{\ddagger} \xrightarrow{*} C_{18}H_{28}F_2S_4]^{\ddagger} + C_4H_8$$
$$C_{18}H_{28}F_2S_4]^{\ddagger} \xrightarrow{*} C_{14}H_{20}F_2S_4]^{\ddagger} + C_4H_8$$
$$C_{14}H_{20}F_2S_4]^{\ddagger} \xrightarrow{*} C_{10}H_{12}F_2S_4]^{\ddagger} + C_4H_8$$
$$C_{10}H_{12}F_2S_4]^{\ddagger} \xrightarrow{*} C_6H_4F_2S_4]^{\ddagger} + C_4H_8$$

The spectra all show a peak corresponding to the alkyl group, i.e. at m/z 29 ($C_2H_5^+$), m/z 43 ($C_3H_7^+$) and m/z 57 ($C_4H_9^+$) in the ethylthio, i-propylthio and t-butylthio compounds respectively. In some instances, particularly the compounds containing the t-butyl group, the alkyl group peak may be the base peak.

The spectra of the various isomers, namely VIIIc and Xc, and VIIId and Xd, were very similar. The mass spectra could not therefore be used to distinguish between the various isomers prepared. This result is consistent with earlier studies on methylthio containing fluoroanilines [12] and some aromatic thioethers containing the pentafluorophenyl group [13].

The infrared spectra of all the compounds showed the presence of the requisite functional groups.

TABLE 2

Physical properties and chemical analyses

Compound	m.p./°C b.p./°C/Torr	Calculated (%)			Found (%)		
		C	H	S	C	H	S
Ic	49-50	48.3	4.69	21.5	48.1	4.64	21.6
Id	155-6	51.5	5.56	--	51.1	5.56	--
IId	205-6	65.7	7.72	--	56.8	8.02	--
IVc	151/760	48.2	3.60	--	48.7	3.74	--
IVd	23-4	50.4	4.23	--	50.6	4.32	--
Vb	d	49.0	5.44	32.6	49.3	5.44	32.5
Vc	170/760	53.6	6.54	28.6	53.4	6.51	28.9
Vd	37-8	57.1	7.41	25.4	56.1	7.50	25.5
VIc	75/575	56.2	8.03	35.7	56.2	8.38	35.4
VIIIb	d	51.3	5.18	--	51.5	5.88	--
VIIIc	37-8	54.9	6.15	--	55.0	6.08	--
VIIId	34-5	57.9	6.89	--	57.6	6.98	--
IXb	41-2	52.8	6.92	40.3	52.8	7.02	40.7
Xc	32-3	54.9	6.15	--	55.1	5.87	--
Xd	99-100	57.9	6.89	22.1	57.8	6.79	21.6
XIId	125/760	59.4	5.94	15.8	59.5	7.08	16.1

d = liquid decomposing before boiling

EXPERIMENTAL

All reagents were available commercially. Microanalyses were performed by Canadian Microanalytical Services, Vancouver. The analytical data and physical properties of the new compounds are shown in Table 2.

Mass spectra (70eV) were recorded on a DuPont/C.E.C Model 21-491 mass spectrometer using direct introduction techniques. NMR spectra were recorded on a Varian HA-100 (H-1), Varian EM 360L (H-1 and F-19) or Varian T-60 (H-1). The infrared spectra were recorded on a Perkin Elmer 457 spectrophotometer as this films or KBr discs.

The nucleophilic substitution reactions were performed as described previously for the ethylene gylcol/pyridine solvent system or the DMF solvent system [3,2], and details of the reactions are shown in Table 3.

TABLE 3

Reaction Stoichiometry and Products

Starting Compound	Product	Reactant Ratio RS^-:Substrate	Time (h)	Solvent*	Yield (%)	Purification
S1	Ic	2:1	1	EG/P	17	3
		4:1	1	EG/P	16	3
S1	Id	1:1	0.5	EG/P	16	3
		2:1	0.5	EG/P	25	3
S1	IId	6:1	0.25	DMF	10	3
S2	IVc	1:1	0.5	EG/P	56	2
S2	IVd	1:1	1	EG/P	50	2,4
S2	Vb	3:1	14	EG/P	82	2
S2	Vc	2:1	1	EG/P	14	1
		4:1	1	EG/P	46	1
S2	Vd	6:1	0.25	DMF	39	2
S2	VIc	6:1	1	DMF	16	1
S3	VIIIb	1:1	1	EG/P	7	2
S3	VIIIc	1:1	2	EG/P	41	2,3
		2:1	2	EG/P	41	2,3
S3	VIIId	6:1	12	DMF	73	4
S3	IXc	4:1	12	DMF	73	3
S4	Xc	2:1	1	EG/P	25	2,3
	Xd	2.1	16	EG/P	7	3
		6:1	0.5	DMF	58	3
S5	XIId	4:1	12	DMF	73	3

Purification

1 = Kugelrohr vacuum distillation

2 = Column chromatography

3 = Recrystallization from EtOH

4 = Vacuum sublimation

* EG/P = Ethylene glycol/pyridine, volume ratio 1:2

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