The Relative Nucleophilicities of Fluoride and Aryloxy Ions towards Acyl and Nitroaryl Groups

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Fluoride ion as potassium fluoride–18-crown-6 reacted with p-nitrophenyl sulphonates exclusively at the sulphonyl group with phenoxide displacement. The 2,4-dinitrophenyl sulphonates showed, in addition, minor attack at aryl group with sulphonate displacement. The aryloxy anions generated reacted further with aryl sulphonate to generate the diaryl ether. This distinction between the nucleophilicities of fluoride and aryloxy anions was shown to apply also to carboxy and phosphoryl centres.

As a part of a programme of radiopharmaceutical and metabolic tracer syntheses, we required a route to aryl fluorides which involved the introduction of the fluorine atom *via* the F^- anion. Because of its common occurrence in the compounds of interest, the replacement of a phenolic hydroxy-group was considered as a possible approach. The conversion of phenols to aryl fluorides has only been achieved by vapour phase pyrolysis of aryl fluoroformates [1] and fluorosulphites [2] at 600—800 °C. Fluoride ion, recently [3] in the form of potassium fluoride–

18-crown-6 ('naked fluoride') has been used to displace only other halide ions in suitably activated substrates. As a simple system in which to test the displacement of oxyanions, we have examined the reaction of fluoride ion with a series of nitroaryl sulphonates, and analogous species, since sulphonate can be an order of magnitude more reactive than chloride in such reactions.[4]

The aryl sulphonates (1)—(5) were treated with an excess of anhydrous potassium fluoride in acetonitrile,

[1] K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, 1965, **30**, 3170, 4104; 1966, **31**, 559.
[2] R. Cramer and D. D. Coffman, *J. Org. Chem.*, 1961, **26**, 4164.
[3] C. L. Liotta and H. P. Harris, *J. Amer. Chem. Soc.*, 1974, **96** 2250.
[4] J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385.

benzene, diglyme, or hexamethylphosphoric triamide (HMPA) usually in the presence of 0.4 equivalents of 18-crown-6 [5] at 80—135 °C (see Table). Under these
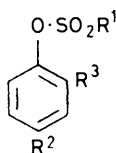

(1) R^1 = p-tolyl, R^2 = NO_2, R^3 = H
(2) R^1 = CF_3, R^2 = R^3 = H
(3) R^1 = CF_3, R^2 = NO_2, R^3 = H
(4) R^1 = p- bromophenyl, R^2 = NO_2, R^3 = H
(5) R^1 = CF_3, R^2 = R^3 = NO_2
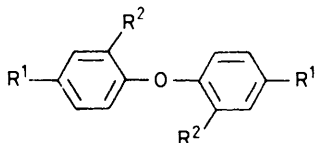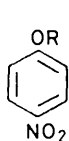
(6) R = $COCF_3$
(7) R = $PO(OPh)_2$
(8) R^1 = NO_2, R^2 = H
(9) R^1 = R^2 = NO_2

conditions, p-nitrophenyl toluene-p-sulphonate (1) and phenyl trifluoromethanesulphonate (2) gave no reaction,

The analogous reaction with 2,4-dinitrophenyl trifluoromethanesulphonate (5), however, did give up to 21% of the aryl fluoride, but again fluoride attack at the sulphonyl centre was the predominant reaction. Although the rates of reaction varied with solvent, being notably faster in HMPA, the course of the reaction was not significantly changed with solvent variation.
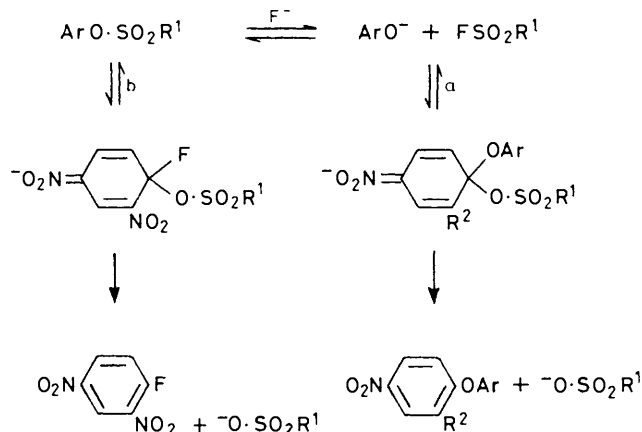
SCHEME

A reasonable explanation of these results is expressed in the Scheme. In the p-nitroaryl series attack by the hard fluoride ion is solely at the hard sulphonyl centre.[7]

Fluoride displacements with KF–18-crown-6 [a]

					Yield %			
Run	Substrate	Solvent	Temp. (°C)	Time (h)	Starting material	Ether	Phenol	Fluoride
1	1	b	80—155 °	48	98			
2	2	b	80—155	48	(100) [c]			
3	3	MeCN	82	16	20	65	12	
4	3	C_6H_6	80	16	20	65	12	
5	3	$DIGO_2$	140	16	20	65	12	
6	3	HMPA	155	3	0	97		
7 [d]	3		200	4	73	4		
8	4	MeCN	82	48	2	2	32	
9	5	C_6H_6	80	1		27	57	15
10 [f]	5	C_6H_6	80	0.5		33	51	10
11	5	HMPA	80	0.5		17	59	21
12	6	MeCN	82	48	50	27	10	
13	7	MeCN	82	48	52	12	28	

[a] 2.5 equiv. KF + 0.4 equiv. 18-crown-6 routinely used. [b] The range of solvents given in column three were all tried. [c] Sole detectable product—not isolated. [d] No crown ether was used in this run. [e] The mixture of substrate and ether was not separable. [f] CsF replaced KF in this run.

even on prolonged heating. However, the more reactive p-nitrophenyl p-bromobenzene- and trifluoro-methane-sulphonates, (4) and (5) respectively, in acetonitrile solution gave di-p-nitrophenyl ether (8) together with p-nitrophenol and unchanged sulphonate (see Table). In the case of the p-bromobenzenesulphonate (4), p-bromobenzenesulphonyl fluoride (16%) was also isolated. The use of caesium fluoride [run (10)] did not significantly alter the yields.[6] Under all the conditions used, no aryl fluoride was produced.

The aryloxy anion so liberated can attack the p-nitroaryl sulphonate at the softer aryl centre and form the diaryl ether (route a). This proposal is consistent with the conclusions from extensive studies of nucleophilic aromatic substitution [8] which would rule out the likelihood of a dominant F^- attack at the aryl centre. It seems probable that the extent of such attack in the 4-nitro-series is insignificant, since no 4-fluoronitro-benzene was detected in any run, unlike the 2,4-dinitro-analogue in which F^- attack at the aryl centre was

[5] R. N. Greene, *Tetrahedron Letters*, 1972, 1793.
[6] *Cf.* N. N. Vorozhtsov and G. G. Yakobson, *Zhur Obshch. Khim.*, 1961, **31**, 3705.

[7] R. G. Pearson, *J. Amer. Chem. Soc.*, 1963, **85**, 3533.
[8] See J. Miller, 'Aromatic Nucleophilic Substitution ', Elsevier Publishing Company, Amsterdam, 1968.

observed and the product survived the reaction conditions.

Conversely, aryloxy anion attack at the sulphonyl centre could be rapid, though undetectable in this system. In order to check this, 4-nitrophenyl triflate (trifluoromethanesulphonate) was treated with 2-nitrophenoxide ion. The only product detectable (by t.l.c. analysis against authentic specimens) during the course of the reaction was 2-nitrophenyl-4-nitrophenyl ether. No significant amount of 2-nitrophenyl triflate was present, so that in this mono nitro- series, aryloxy anion attack must be predominantly at the aryl centre.

This phenomenon shows a clear distinction between the nucleophilicity of fluoride ion and the oxyanion towards these electrophilic centres. Only in the highly electron-deficient dinitroaryl system does fluoride ion attack at carbon (route b) compete with attack at sulphonyl group.

It was of interest to determine if this distinction applied only to sulphonyl groups. Consequently, the analogous reaction with p-nitrophenyl trifluoroacetate (6) and diphenyl phosphate (7) were studied. In each case [runs (12) and (13)] the products were the ether (8) and p-nitrophenol. Again, fluoride ion exhibited a nucleophilicity distinct from the oxyanions and the phenomena appears to be general for attack at very hard centres. The use of fluoride ion for the removal of sulphonate protecting groups is under investigation.

EXPERIMENTAL

Unless otherwise stated i.r. spectra were recorded for solutions in chloroform and u.v. spectra were determined for ethanolic solutions. M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. Acetonitrile was dried with calcium hydride and distilled. Benzene was dried with sodium hydride and distilled. Digol was fractionally distilled (b.p. 89 °C/0.43 mmHg) prior to use, only the middle fraction being collected. Hexamethylphosphoric triamide (HMPA) was dried over activated Linde 3A molecular sieve, distilled at reduced pressure under nitrogen and over molecular sieve, and stored over freshly activated molecular sieve. Potassium and caesium fluorides were dried by heating in a nickel crucible to just below fusion point with constant stirring, and allowed to cool in a desiccator *in vacuo*.

Reactions of p-*Nitrophenyl Toluene-*p-*sulphonate and Phenyl Trifluoromethanesulphonate with Potassium Fluoride.* —Neither p-nitrophenyl toluene-p-sulphonate (1) nor phenyl trifluoromethanesulphonate (2) reacted with potassium fluoride in refluxing solvent. The solvents used were acetonitrile, benzene, diglyme, and HMPA (at 155 °C).

Reaction of p-*Nitrophenyl Trifluoromethanesulphonate with Potassium Fluoride.*—(i) *In acetonitrile, benzene, or digol.* A mixture of 18-crown-6 (0.165 g, 0.4 equiv., 0.59 mmol) and dry potassium fluoride (2.5 equiv.) in dry solvent (7.0 ml) was stirred at room temperature for 30 min under dry, oxygen-free nitrogen. p-Nitrophenyl trifluoromethanesulphonate (3) (0.4 g, 1.48 mmol) was added and the mixture was refluxed overnight with vigorous stirring.

T.l.c. of the reaction mixture showed some unchanged starting material and a new u.v.-active product, slightly more polar than the former. Refluxing for longer periods of time did not appear to alter the relative amounts of both compounds. The reaction mixture was diluted with chloroform (25 ml) and washed with brine (2 × 10 ml). The organic layer was dried and concentrated *in vacuo* to give a crystalline residue (0.342 g). This was purified by p.l.c. [SiO$_2$ gel, eluant benzene–chloroform (95 : 5)]. The main product was identified as di-4-nitrophenyl ether (8) (0.128 g, 65%), m.p. 142—143 °C (lit.,[9] m.p. 142—143 °C), $v_{max.}$(CHCl$_3$) 1 617, 1 607, 1 582, 1 489, 1 349, 1 161, and 1 115 cm^{-1}; δ(CDCl$_3$) 7.75 (ABq, 8 H, Ar); m/e 260 (M^+), 230, 179, and 167. Unchanged starting material (0.078 g, 20%) and p-nitrophenol (0.025 g, 12% yield) were also isolated from the reaction mixture.

(ii) *In HMPA.* The reaction was carried out as above but with dry HMPA as the solvent. After 3 h at 150—155 °C all the substrate was converted into di-4-nitrophenyl ether (8) which was isolated in 97% yield.

(iii) *In the absence of solvent.* p-Nitrophenyl trifluoromethanesulphonate (3) (0.2 g, 0.74 mmol) was heated at 200 °C with dry potassium fluoride (2.5 equiv.) under an atmosphere of dry oxygen-free nitrogen. After 4 h, toluene (10 ml) was added and the solids were filtered off. The filtrate was concentrated at reduced pressure to give a pale yellow oil (0.152 g), which was purified by p.l.c. [SiO$_2$ gel, eluant benzene–chloroform (95 : 5)]. Two compounds were isolated: unchanged starting material (0.146 g, 73%) and di-4-nitrophenyl ether (8) (7 mg, 3.6%), identical with an authentic sample.

Reaction of p-*Nitrophenyl* p-*Bromobenzenesulphonate with Potassium Fluoride.*—18-Crown-6 (0.118 g, 0.4 equiv., 0.446 mmol) and dry potassium fluoride (2.5 equiv.) in dry acetonitrile (7.0 ml) were stirred for 30 min at room temperature under dry oxygen-free nitrogen. p-Nitrophenyl p-bromobenzene sulphonate, (4) (0.4 g, 1.117 mmol), was added and the mixture refluxed for 48 h with vigorous stirring. After work-up, carried out as previously described, a colourless oil (0.358 g) was obtained. The crude product was purified by p.l.c. (SiO$_2$ gel, eluant chloroform) and three bands were separated. The more polar material (0.05 g, 32% yield) was p-nitrophenol, identified by comparison with an authentic sample. The material with intermediate R_F (0.257) was a mixture of unchanged starting material and di-4-nitrophenyl ether (8); it was impossible to separate the two compounds due to their very similar R_F values, but a mass spectrum showed that the ether was present. Thus, while a mass spectrum of an authentic sample of di-4-nitrophenyl ether shows peaks at m/e 260 (M^+), 230, 179, and 167, none of these peaks are present in the spectrum of p-nitrophenyl p-bromobenzenesulphonate. The mass spectrum of the mixture obtained in the present reaction, after p.l.c., presented peaks at m/e 260, 230, 179, and 167, plus the peaks characteristic of the starting material, at m/e 359 (M^+), 357, 221, 219, 157, and 155.

The less-polar product isolated upon p.l.c. was identified as p-bromobenzenesulphonyl fluoride (0.042 g, 15.7% yield), m.p. (from light petroleum) 61—62 °C, $v_{max.}$(CHCl$_3$) 1 712, 1 578, 1 465, 1 392, and 1 090 cm^{-1}; $\lambda_{max.}$(EtOH) 237 (ε 15 000), and 268.5 nm (1 147) [lit.,[10] 240 (ε 13 100) and

[9] C. P. Smyth and W. S. Walls, *J. Amer. Chem. Soc.*, 1932, **54**, 3230.

[10] Yu. I. Naumov and V. I. Minkin, *Russ. J. Phys. Chem.*, 1966, **40**, 1370.

270 nm (ε 900)]; δ(CDCl$_3$) 7.60—8.10 (m, 4 H, Ar); m/e 240 (M^+), 238, 173, 171, 157, 155, 145, and 143 (Found: C, 30.05; H, 1.7; S, 13.7. C$_6$H$_4$BrFO$_2$S requires C, 30.15; H, 1.69; S, 13.41%).

Reaction of 2,4-Dinitrophenyl Trifluoromethanesulphonate with Potassium or Caesium Fluoride.—(i) *In benzene.* 18-Crown-6 (0.067 g, 0.4 equiv., 0.235 mmol) and dry potassium fluoride (2.5 equiv.) in dry benzene (4.0 ml) were stirred for 30 min under dry oxygen-free nitrogen. 2,4-Dinitrophenyl trifluoromethanesulphonate (5) (0.2 g, 0.633 mmol) was added and the mixture refluxed for 1 h with vigorous stirring. T.l.c. after this period of time showed that there was no starting material left and that two more polar u.v.-active products had formed; some of the corresponding phenol was also detected. The reaction mixture was diluted with dichloromethane (30 ml) and extracted with 5% aqueous sodium hydrogen carbonate (3 × 12 ml). The aqueous layer was then acidified with orthophosphoric acid, saturated with sodium chloride, and extracted with ether (5 × 20 ml). The ether solution was washed with water, dried, and concentrated *in vacuo* to give a pale yellow crystalline solid. This was recrystallised from cold ether to give 2,4-dinitrophenol (0.066 g, 57% yield), m.p. 113—113.5 °C (lit.,[11] m.p. 113 °C), identical with an authentic sample.

The dichloromethane solution was washed with water (2 × 15 ml), dried, and concentrated *in vacuo* to give a pale yellow film (0.1 g) and t.l.c. showed it was a mixture of two compounds. These were separated by p.l.c. (SiO$_2$ gel, eluant dichloromethane). The more-polar product was identified as di-(2,4-dinitrophenyl) ether (9) (0.029 g, 27% yield), m.p. 196—197 °C (lit.,[12] m.p. 194—195 °C), $\nu_{max.}$(Nujol) 1 599, 1 539, 1 351, and 1 273 cm^{-1}; δ([²H$_6$]-Me$_2$CO) 7.10—8.60 (ABX system, 6 H, Ar); m/e 350 (M^+), 273, 230, 184, and 167. The less-polar product was identified as 1-fluoro-2,4-dinitrobenzene (0.018 g, 15% yield), $\nu_{max.}$(CHCl$_3$) 1 617, 1 538, 1 347, 1 269, 1 128, 1 069, 916, and 840 cm^{-1}; δ(CDCl$_3$) 7.40—9.40 (ABX system, 3 H, Ar) and was identical with reported data for this compound.[13]

When caesium fluoride was used, the reaction was over within 30 min. 2,4-Dinitrophenol (51%) was isolated, together with di-(2,4-dinitrophenyl) ether (33%) and 1-fluoro-2,4-dinitrobenzene (10%).

(ii) *In HMPA.* When HMPA was used as the solvent, with potassium fluoride, the reaction was complete within 30 min and 1-fluoro-2,4-dinitrobenzene (21%) was isolated

together with 2,4-dinitrophenol (57%) and di-(2,4-dinitrophenyl) ether (17%).

Reaction of p-*Nitrophenyl Trifluoroacetate with Potassium Fluoride.*—18-Crown-6 (0.09 g, 0.4 equiv., 0.34 mmol) and dry potassium fluoride (2.5 equiv.) in dry acetonitrile (4.0 ml) were stirred for 30 min at room temperature under dry oxygen-free nitrogen. p-Nitrophenyl trifluoroacetate (6) (0.2 g, 0.815 mmol) was added and the mixture was refluxed for 48 h with vigorous stirring. The reaction mixture was worked up as previously described and the crude product (0.167 g) was purified by p.l.c. with chloroform as the solvent. The following products were isolated: unchanged starting material (0.1 g, 50%), di-4-nitrophenyl ether (8) (6 mg, 27% yield), and p-nitrophenol (0.0113 g, 10%).

Reaction of p-*Nitrophenyl Diphenyl Phosphate with Potassium Fluoride.*—18-Crown-6 (0.085 g, 0.4 equiv., 0.323 mmol) and dry potassium fluoride (2.5 equiv.) in dry acetonitrile (5.0 ml) were stirred for 30 min at room temperature under dry, oxygen-free nitrogen. p-Nitrophenyl diphenyl phosphate (7) (0.3 g, 0.809 mmol) was added and the mixture was refluxed for 48 h with vigorous stirring. T.l.c. showed mainly unchanged starting material, plus a less-polar u.v.-active compound and some phenol. The reaction mixture was worked up as before and the crude product purified by p.l.c. [SiO$_2$ gel, eluant chloroform–benzene (98 : 2)]. Starting material was recovered in 52% yield (0.157 g) together with p-nitrophenol (0.032 g, 28%) and di-4-nitrophenyl ether (8) (0.0123 g, 12%).

Reaction of p-*Nitrophenyl Triflate with Sodium* o-*Nitrophenoxide.*—p-Nitrophenyl triflate (0.2811 g, 1.037 mmol) in dry dimethylsulphoxide (5.0 ml) was treated with sodium o-nitrophenoxide (0.167 g, 1 equiv.). Triethylamine (0.145 ml, 1.0474 mmol) was added and the mixture heated at 80 °C under dry N$_2$. After 4 h, t.l.c. (silica–CHCl$_3$) showed that no starting material was left. The mixture was worked up by dilution with benzene (25 ml), extraction with 8% aqueous phosphoric acid (2 × 10 ml), H$_2$O (2 × 10 ml), dried (Na$_2$SO$_4$), and concentrated *in vacuo* to give a pale yellow oil (0.287 g). This was purified by silica column chromatography with elution with 10% benzene in chloroform. The main product, m.p. 100—102 °C (0.218 g, 81.2%) was identified as 2-nitrophenyl 4-nitrophenyl ether by comparison with an authentic sample.[14]

[11] M. Brandstatter, *Monatsch.*, 1947, **77**, 7.
[12] E. E. Turner and D. L. Fox, *J. Chem. Soc.*, 1930, 1115.
[13] G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, 1956, **78**, 6034.
[14] N. Ishikawa, *Nippon Kagaku Zasshi*, 1967, **88**, 479 (*Chem. Abs.*, 1968, **68**, 59208f).