Review

Fluoride ion as a nucleophile and a leaving group in aromatic nucleophilic substitution reactions

V. M. Vlasov
Institute of Organic Chemistry, 630090, Novosibirsk (Russian Federation)

(Received January 10, 1992; accepted July 8, 1992)

Abstract

This paper analyzes the behaviour of the fluoride ion as a nucleophile and a leaving group in S_NAr reactions in the gas phase and in solution. Attention is focused on quantitative data relating to fluoride ion reactivity in S_NAr reactions relative to other halide ions and groups. The factors governing the regioselectivity of fluorine atom substitution in S_NAr reactions are discussed, as well as the synthetic consequences of such substitution.

Introduction

The fluoride ion is widely used as a nucleophile and a leaving group in organic nucleophilic reactions, in particular in arene chemistry [1–8]. The electronegativity of the fluorine atom, and hence the substantial negative inductive effect on the one hand and the substantial positive conjugation effect on the other, cause the specific behaviour of the fluoride ion in nucleophilic reactions. The present paper analyzes the peculiarities in the behaviour of the fluoride ion in S_NAr reactions. Emphasis is laid on a quantitative comparison of the behaviour of the fluoride ion in S_NAr reactions in the gas phase and in solution (mainly in DMSO, since sufficient data are only available for reactions in this solvent).

Basicity and nucleophilicity of the fluoride ion in the gas phase and in solution

It is well known that the reactivity of the fluoride ion dramatically decreases in solution relative to the gas phase because of solvation, as demonstrated for S_N2 reactions [9]. In the absence of solvation, the fluoride ion shows the usual reactivity of anions, including halide ions, in S_N2 reactions, which depends on their basicity [10]. For this reason it would be interesting

0022-1139/93/$6.00

to compare the variation in the basicity and nucleophilicity of the fluoride ion and other anions for S_NAr reactions in the gas phase and in solution.

The basicity of the fluoride ion in the gas phase and in solution. Comparison with halide ions and other anions

Table 1 lists the data on the basicity of the fluoride ion and other anions in the gas phase and in solution (DMSO and H_2O). As can be seen, the fluoride ion is one of a number of highly basic nucleophiles whose basicity sharply decreases in aprotic and especially protic media. In the latter case, another reason for the decreased basicity is specific solvation due to the formation of a strong hydrogen bond, i.e. $F^-...H-OH$ [13]. Thus, in the gas phase, the CH_3O^- ion is only *c.* 7 kcal mol^{-1} more basic than the F^- ion, whereas in solution the difference between the basicity of these anions is 19 kcal mol^{-1} (14 pK units) or 16.9 kcal mol^{-1} (12.3 pK units) in DMSO and water, respectively. In the gas phase, the difference in basicity between the F^- ion and other halide ions, and between HS^- and N_3^- ions, is quite large, whereas in solution such differences are considerably diminished. In water, the basicity for the series of ions F^-, HS^- and N_3^- is reversed relative to that in the gas phase.

Figure 1 depicts the ratios between the DMSO and gas-phase basicities of the anions listed in Table 1 and in ref. 14. The straight line for strongly delocalized carbanions (open circles) has a slope equal to unity (expressed in terms of kcal mol^{-1}). This implies compensation of the solvation of neutral CH acids and carbanions. The solvation of charged nucleophiles, however, is much stronger, with the points being located below the line. For the related halide ions (filled circles), the corresponding line intersects that described above at the point for the I^- ion. The substantial deviation for

TABLE 1

Basicity of nucleophiles in the gas phase, DMSO and water

Nucleophile	$-\Delta G_g^0$ (kcal mol^{-1}) [11]	pK(DMSO) [12]	pK(H_2O) [12]
F^-	365.7	15	3.2
Cl^-	328.0	1.8	−8
Br^-	318.2	0.9	−9
I^-	309.3	–	−11
CH_3^-	408.5	56.0	–
NH_2^-	396.1	41.0	35
CH_3O^-	374.0	29.0	15.5
HO^-	384.0	31.2	15.7
HS^-	344.8	12.2	7.0
N_3^-	338.0	7.9	4.7
ONO^-	330.5	7.5	–

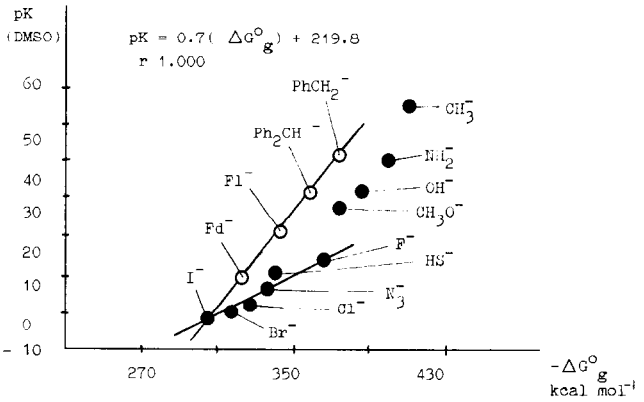


Fig. 1. Acidity ratio of some compounds in the gas phase ($-\Delta G_g^0$) and in DMSO (pK). Fl^- is the fluorenyl anion; Fd^- the fluoradenyl anion.

TABLE 2

Solvation energies of halide ions in DMSO and water [1, 15, 16]

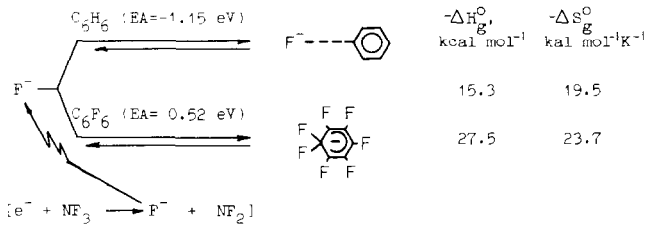
Halide ion	$-\Delta H_{solv}^0$ (kcal mol^{-1})	
	DMSO	H_2O
F^-	102	123
Cl^-	80.3	89
Br^-	76.1	81
I^-	70.0	72

the fluoride ion from the line for strongly delocalized carbanions is possibly due to its greater solvation.

Table 2 lists the solvation energies of halide ions in DMSO and water, from which it is seen that the maximum solvation effect is exhibited by the fluoride ion. As the size of the halide ion increases, the solvation effect decreases and solvents exert a similar influence [15, 16]. Naturally, the solvation effect of the fluoride ion strongly affects its reactivity in solution [16, 17].

The nucleophilicity of the fluoride ion in the gas phase in S_NAr reactions

The fluoride ion reacts readily with benzene in the gas phase to give an ion–dipole complex, whereas with hexafluorobenzene the Meisenheimer σ-complex is formed [18]:



Ab initio calculations have confirmed the geometry of a hydrogen-bonded complex of the fluoride ion with benzene and the σ-complex of the fluoride ion with hexafluorobenzene. In the latter case, the reaction enthalpy increases sharply ($-\Delta H_g^0 = 27.5$ kcal mol^{-1}) [18]. Such a difference may possibly be due to the great difference between the electron affinities (E_A) of benzene and hexafluorobenzene [19].

The reaction between the fluoride ion and pentafluorobenzene derivatives C_6F_5X also leads to the formation of σ-complexes. As the acceptor nature of the substituent X increases, the enthalpy of formation of the σ-complex ($-\Delta H_g^0$) also increases; its variation correlates with the σ_R and σ_F con-

X	$-\Delta H_g^0$ (kcal mol^{-1})	X	$-\Delta H_g^0$ (kcal mol^{-1})
F	27.0	$COCH_3$	37.5
H	29.2	CN	39.3
CF_3	33.6	NO_2	41.1

stants included in the two-parameter equation [16]. It should be noted that when the fluorine atom acts as the substituent X in C_6F_5X it has donating properties, but in solution it behaves as an acceptor substituent [20].

Figure 2 depicts the reaction coordinate of the fluoride ion with C_6F_5X derivatives in the gas phase [16] and in DMSO [20]. The deeper the well for the σ-complex in the gas phase (the $-\Delta H_g^0$ value), the smaller the height of the activation barrier in solution (E_a). The $-\Delta H_g^0$ and E_a values correlate

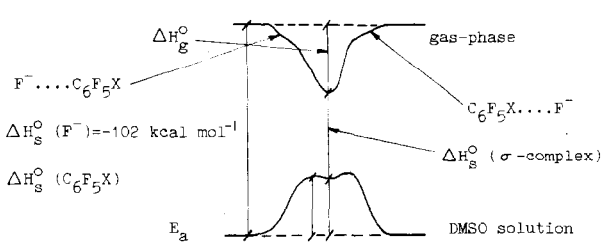


Fig. 2. Reaction coordinates of the fluoride ion with C_6F_5X derivatives in the gas phase and in DMSO solution.

TABLE 3

Rate constants for the gas-phase S_N2 reactions of methyl chloride and methyl bromide with various nucleophiles [10]

Methyl halide	Rate constants 10^{10} k_2 [cm^3 (molecule s)$^{-1}$]				
	Nucleophile ($-\Delta G_g^0$ (kcal mol^{-1}))				
	HO^- (384.0)	CH_3O^- (374.0)	F^- (365.7)	HS^- (344.8)	Cl^- (328.0)
CH_3Cl	20	13	13	0.12	0.001
CH_3Br	22	17	20	3.2	0.27

TABLE 4

Influence of stepwise solvation on the kinetics of the S_N2 reactions of solvated halide ions with CH_3Br [9]

$Y^- \cdot S_n$	Rate constant 10^9 k_2 [cm^3 (molecule s)$^{-1}$] at different values of n			
	0	1	2	3
F^- $(CH_3OH)_n$	1.2	0.16	$\leqslant$0.0005	
Cl^- $(CH_3OH)_n$	0.0017	$\leqslant$0.0004	$\leqslant$0.0004	$\leqslant$0.0004

TABLE 5

Rate constants for the reaction of 1,2,4-trinitrobenzene (k_1) and for *p*-fluoronitrobenzene (k_2) with different nucleophiles in DMSO

Nucleophile	pK(DMSO) [12]	k_1 [l (molecule s)$^{-1}$] (at 25 °C)[a]	10^3 k_2 [l (molecule s)$^{-1}$] (at 100 °C)
F^-	15	16 [21]	18.6 [20]
NO_2^-	–	6.8 [22]	1.29 [22]
ONO^-	7.5	8 [21]	0.32 [22]
Cl^-	1.8	0.05 [21]	–
I^-	–	0.001 [21]	–

[a]Leading to the production of 2,4-dinitrophenoxide as a result of the subsequent increase in the rate of reaction of the substitution product with the ONO^- ion formed.

dinitrofluorobenzene, the more reactive ion is the ONO^- ion [22], whereas in reaction with *p*-fluoronitrobenzene, the nucleophilicity of the F^- ion is much higher (Table 5). The latter situation is associated with the changed rate-limiting step for the S_NAr reaction involving the ONO^- ion [22].

The more basic, hard F^- ion is closer in its reactivity to the less basic hard N_3^- ion, although still being slightly less reactive than the latter (Table 6) [22]. The activation parameters for the S_NAr reactions of these localized ions are also quite similar but differ strongly from the same parameters for

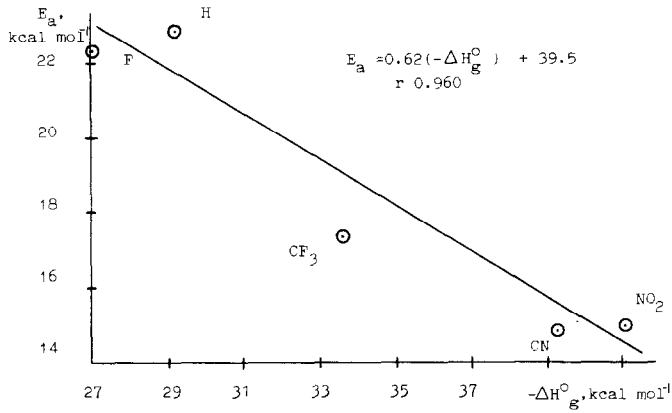


Fig. 3. Correlation between the activation energy (E_a) for the reaction of sodium methoxide with C_6F_5X derivatives in methanol and the affinity of the F^- ion towards C_6F_5X derivatives in the gas phase ($-\Delta H_g^0$). The E_a data have been taken from ref. 8 while the $-\Delta H_g^0$ data are taken from ref. 16.

with each other (Fig. 3), the activation energy E_a of the reaction decreasing with increasing fluoride ion affinity towards the substrate in the gas phase ($-\Delta H_g^0$) [16]. It is important to note that the E_a values listed include those for the CH_3O^- ion which has similar properties to the F^- ion, rather than for the F^- ion itself. This suggests the possibility of using the fluoride-ion affinities of arenes in the gas phase for predicting the reactivities of other ions in solution in S_NAr reactions.

The nucleophilicity of halide ions in S_NAr and S_N2 reactions in the gas phase and in solution. Comparison with other anions

Unfortunately, no comparative reactivities for halide ions in gas-phase S_NAr reactions are found in the literature. For this reason, we shall restrict ourselves to an analysis of the gas-phase reactivities of halide ions and other anions in S_N2 reactions.

The data in Table 3 show that the rate of S_N2 reactions with different anions decreases with their basicities (or with the increased acidities of the conjugated acids), with the F^- ion exhibiting no remarkable reactivity in comparison with other anions. The peculiar reactivity of the F^- ion arises from its solvation in proton-donating media. Thus, as seen from Tables 3 and 4, in the gas phase the F^- ion is much more reactive than the Cl^- ion, whereas in solution even in the presence of only two methanol molecules per halide ion there is no difference in the reactivities of these ions (Table 4).

The nucleophilicities of halide ions in S_NAr reactions in dipolar aprotic media vary in the following order: $F^- \gg Cl^- > Br^- > I^-$ [21, 22]. Indeed, the nucleophilicity of the F^- ion may be higher than that for the NO_2^- ion (Table 5). The relative nucleophilicities of F^- and ONO^- ions of different basicities, however, depend on the substrate; thus, in reaction with 2,4-

TABLE 6

Rate constant for the reaction of *p*-fluoronitrobenzene with different nucleophiles in DMSO at 25 °C and the activation parameters for these reactions

Nucleophile	p*K*(DMSO) [12]	k_2 [l (molecule s)$^{-1}$]	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (e.u.)
N_3^-	7.9	5.68×10^{-4} [24]	21.1[a]	−12.5[a]
F^-	15.0	2.35×10^{-4} [20]	20.0	−10.0
9-PhFl$^-$	17.9	4.88×10^{-2} [23]	10.0	−31.0
PhO$^-$	18.0	5.2×10^{-1} [25]	–	–

[a]Data corresponding to reaction in MeOH at 0 °C [26].

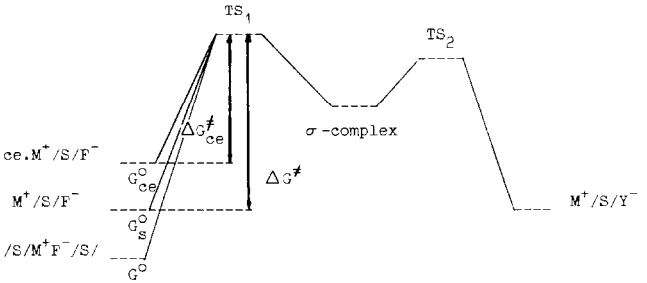


Fig. 4. The S_NAr reaction coordinate between an aromatic substrate ArY and the F^- ion salt M^+F^- in a solvent. ΔG^0 is the free energy associated with solvation of M^+F^-; ΔG_s^0 is the free energy of solvation of the ion pair M^+F^-; and ΔG_{ce}^0 is the free energy of solvation associated with complexation with crown ether.

the delocalized anions listed (Table 6). In protic and aprotic dipolar media, solvent molecules are significantly bound with small-size localized anions. As a result, the activation entropy for the F^- and N_3^- ions increases in comparison with that for the delocalized 9-PhFl$^-$ anion [23].

The nucleophilicity of the fluoride ion in solution in S_NAr reactions and its increase

Aromatic nucleophilic substitution reactions of the ion–dipole type proceeding in aprotic dipolar solvents are characterized by their high energy barrier ($\Delta G^{\neq} = 22 \pm 8$ kcal mol^{-1} [20, 23, 27]); these include reactions involving the F^- ion (Table 6). Hence, the increased nucleophilicity of the F^- ion in S_NAr reactions is associated firstly with its decreased solvation. Figure 4 illustrates the S_NAr reaction coordinate for solution reactions involving the F^- ion. The magnitude of the activation barrier value $\Delta G^{\neq}$ for the reaction may be decreased by separating the tight ion pair M^+F^-. This may be accomplished through complexation of the M^+ cation with a suitable agent, for example a crown ether. Such complexation is known to be most efficient for cations bound with hard anions possessing a small ionic radius and a small degree of polarization [28]. The energy gain for the F^- ion arising from complexation of the counterion with crown ether is 4–9

TABLE 7

Interaction of chloroaromatic compounds $ArCl_n$ with caesium fluoride in the presence of 18-crown-6 [30][a]

$ArCl_n$/crown ether (in mol)								
	τ[b]	r[c]	τ[b]	r[c]	τ[b]	r[c]	τ[b]	r[c]
1:0.182	2020	11	1940	11	2.6	6.2	2.3	5.2
1:0	22700		22060		16		12	

[a]Mole ratio $ArCl_n/CsF = 1:1$; CH_3CN, 80 °C.
[b]Time τ (min) required for preparation of the monofluoroaromatic compound in 30% yield.
[c]Ratio of the time τ for reaction in the absence of crown ether to the time τ for reaction in the presence of crown ether.

kcal mol^{-1} for different solvents and complexing agents [29]. If this value is compared with the energy barrier $\Delta G^{\neq}$, the increase may only amount to 20%. Hence, the main contribution to the energy barrier is still made by desolvation of the F^- ion in the transition state (TS_1). Desolvation of the F^- ion in TS_1 should be somewhat smaller for a more reactive substrate because of the earlier bonding between them. This latter fact may be the reason for the slightly smaller effect of crown ether on the reactivity of the F^- ion with a more reactive substrate in S_NAr reactions involving 2,4-dinitrochlorobenzene and pentachloropyridine as compared to *o*- and *p*-nitrochlorobenzenes (Table 7) [30].

The fluoride ion as a leaving group in S_NAr reactions

As a leaving group in aromatic nucleophilic substitution, the fluoride ion has long been used as an identification measure of the reaction mechanism. Due to the strong polarization of the $C_{Ar}^{\delta+}-F^{\delta-}$ bond, the F > Cl > Br > I order of the leaving group effects indicates the addition–elimination mechanism of S_NAr reactions with a limiting stage involving σ-complex formation [31]. In some cases, however, the limiting stage can change, with C–F bond cleavage determining the rate of the process as a whole [22]. This sharply decreases the mobility of fluorine as a leaving group because of the very high C–F bond energy. The resulting synthetic consequences of such substitution are very interesting, and it is thus of interest to discuss fluorine substitution in S_NAr reactions both in solution and in the gas phase.

Fluorine substitution in fluoroaryls by different nucleophiles in the gas phase

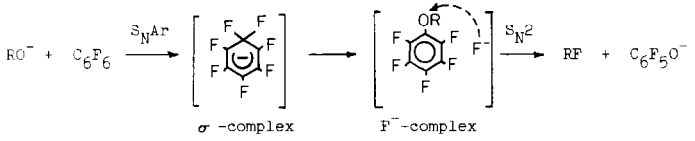
In the gas phase, S_NAr reactions involving fluorine substitution proceed very rapidly. Thus the reactions of alkoxides with fluorobenzene and hexa-

fluorobenzene proceed at similar rates, despite great differences in the reactivity of the substrates [32].

$$CH_3O^- + PhF \xrightarrow{\text{gas phase}} PhOCH_3 + F^- \qquad k_{icr} = 2.4 \times 10^{10}\ mol^{-1}\ s^{-1}$$

$$RO^- + C_6F_6 \xrightarrow{\text{gas phase}} RF + C_6F_5O^- \qquad k_{icr} = 9 \times 10^{11}\ mol^{-1}\ s^{-1}$$

The latter reaction occurs via an S_NAr mechanism, whereby the fluoride ion forms a long-living ion–molecule complex which undergoes an S_N2 reaction to form the very stable pentafluorophenoxide ion [32, 33]:



A similar mechanism involving the formation of an ion–molecule complex by the F^- ion has also been suggested for the reactions of polyfluorinated olefins with alkoxides [34].

The ability of pentafluoroanisole to react via S_N2 and S_NAr mechanisms is dependent on the nature of the nucleophile Y^-:

$$Y^- + C_6F_5OCH_3 \quad (Y^- = NH_2^-,\ RO^-,\ RS^-) \xrightarrow{S_N2} C_6F_5O^- + CH_3YH$$

$$\xrightarrow{\text{ipso}} C_6F_5Y^- + CH_3OH$$

$$\xrightarrow{S_NAr} CH_3OC_6F_4Y^- + HF$$

Soft nucleophiles (RS^-) react predominantly via the S_N2 route, whereas hard ones (NH_2^-, RO^-) involve the S_NAr mechanism. Attack at the ipso position is not very significant and takes place only for hard nucleophiles. The difference between O and S nucleophiles depends mainly on the polarity of the $C_{Ar}^{\delta+}-F^{\delta-}$ bond, with S nucleophiles being less capable of substituting the hard F^- ion [35].

Most experimental work on S_NAr substitution of fluorine, including a quantitative description of the leaving ability of fluorine relative to other groups, has been performed in solution.

Quantitative description of the leaving ability of fluorine in S_NAr reactions in solution under the action of charged nucleophiles

A considerable advance has been recently achieved in studies of S_NAr reactions with charged nucleophiles in DMSO, including their quantitative description in terms of the extended Brønsted equation [36]:

$$S_NAr:\ Nu^- + Ar-Y \xrightarrow{k} Ar-Nu + Y^-$$

$$\log k = \beta_{Nuc} pK + \text{const.}$$

It is important to note that specific features of substituent substitution are exhibited only under certain conditions, i.e. when the nucleophilicity is studied over a wide range of nucleophile basicity and substrate electrophilicity,

employing a constant nucleophile donor atom, the same solvent and constant steric factors [36].

Table 8 lists the data obtained for S_NAr substitution in *p*-nitrohalobenzenes under the action of charged nucleophiles. Although the leaving group (F^- or Cl^-) is changed, the reactivity order remains the same, i.e. $S^- \gg C^- > O^- > N^-$. However, the range of rate constants observed for the F^- ion as a leaving group is much smaller, particularly in the case of soft S^- and C^- nucleophiles. For the harder O^- and N^- anions, the rate constant ratio k_F/k_{Cl} is significantly greater than for the soft S^- and C^- anions because of the greater degree of C–F bond polarization in fluoronitroarenes. This is supported by the similar values for the rate constant ratios k_{Br}/k_{Cl} for all nucleophiles which may be attributed to the virtually constant polarization of the C–Hal bond [23].

The slope of the log *k* versus p*K* line arising from the Brønsted equation and corresponding to β_{Nuc} increases in going from S^- to N^- anions when the chloride ion is the leaving group, whereas for the fluoride ion the opposite effect is observed. The value of β_{Nuc} increases for the same nucleophile donor atom in going from fluorine to chlorine (Table 8). Such data indicate an electrostatic term contribution to the β_{Nuc} value.

Figure 5 depicts the Brønsted plots obtained for the reactions of various aryl- and diaryl-substituted N anions with aryl fluorides in DMSO. The anion basicity range is *c.* 16 p*K* units while the reactivity range extends over approximately five orders of magnitude of rate constant. The fact that the β_{Nuc} values vary for the same substrate (for example, *p*-fluoronitrobenzene) as the basicity of the nucleophile is varied, while the donor atom is kept constant as well as the solvation and steric factors, indicates the influence of the changed transition state structure on the reaction coordinate. However, if the variation in the β_{Nuc} value is only correlated with ion–dipole interaction [39] (complex I in the scheme below), such a statement is not quite true for the situation is much more complex than that depicted. All that can be

TABLE 8

Relative leaving group abilities and β_{Nuc} coefficients arising from the Brønsted equation in the reaction of 4-halonitrobenzenes, 4-Hal$C_6H_4NO_2$ (Hal = Cl, F), with different nucleophiles, Nu^-, in DMSO at 25 °C [23]

Nu^-	k_{rel}		k_F/k_{Cl}	k_{Br}/k_{Cl}	β_{Nuc}	
	Cl	F			Cl	F
ArS^-	10^9	10^6	8.0	2.5	0.52	–
Ar_3C^-	10^5	10^3	3.5–5.3	2.4	0.65	0.58
ArO^-	10^2	10^2	260	1.7	–	0.52[a]
Ar_2N^-[b]	1	1	96	1.0	0.70	0.51
ArNH	–	0.14[a]	–	–	–	0.28[a]

[a]According to ref. 37.
[b]Phenothiazinide anions.

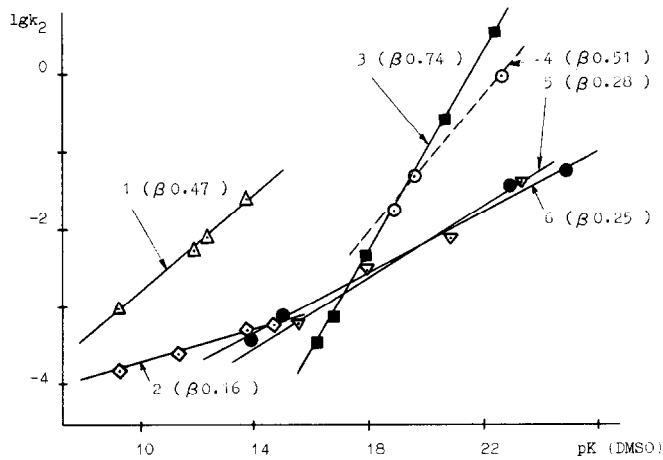
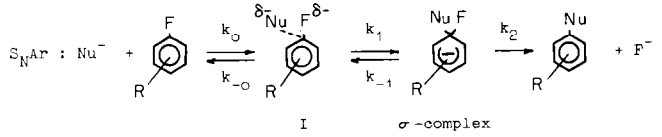


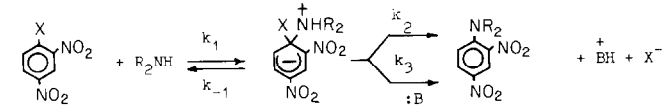
Fig. 5. Brønsted plots for S_NAr reactions of aryl- and diaryl-substituted N anions with aryl fluorides in DMSO at 25 °C: 1, reaction of ArN̄Ar′ with pentafluoropyridine [37]; 2, reaction of ArN̄Ar′ with hexafluorobenzene [37]; 3, reaction of ArN̄H with hexafluorobenzene [38]; 4, reaction of phenothiazinide anions with *p*-fluoronitrobenzene [23]; 5, reaction of ArN̄H with *p*-fluoronitrobenzene [37]; and 6, reaction of ArN̄Ar′ with *p*-fluoronitrobenzene [37].

said is that the transition state structure is certainly related to the β_{Nuc} value.



Nucleophilic substitution of fluorine in fluoroaryls by amines

The fluoride ion behaves in an interesting manner as a leaving group in S_NAr reactions with uncharged nucleophiles. Reactions with amines are known to proceed catalytically with a limiting second stage [40–44]:



X = F,Cl II

The mechanism of the catalytic conversion of the internal salt II may be written as follows [43]:

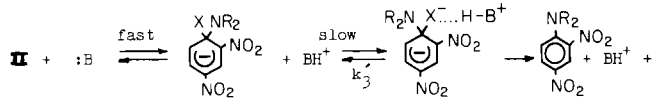


TABLE 9

Rate constants for the reaction of 2,4-dinitrohalobenzenes, 1-X-2,4-$(NO_2)_2C_6H_3$, with aromatic amines, 4-$CH_3OC_6H_4NHR$, in benzene at 30 °C [43]

X	10^5 k_{obs} [l (mol s)$^{-1}$]	
	R=H	R=Me
Cl	0.31[a]	0.42
F	22.1[a]	0.26[a]

[a]Catalysis by reagent employed.

For primary amines, the reaction is much faster when the leaving group is the fluoride ion due to formation of the hydrogen bond $F^- \ldots H-B^+$ in complex III (see Table 9). Such acceleration is, however, eliminated in the reaction with secondary amines because of the stability of complex IV when $R = CH_3$.

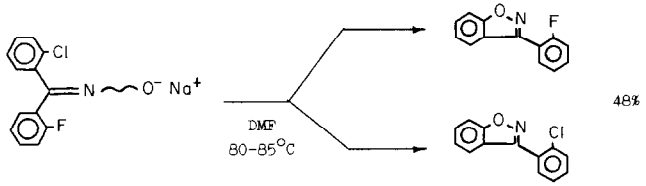
IV R=H, CH_3

Hence, the ability of the fluorine atom to form a strong hydrogen bond with amines largely determines the rate-limiting stage of the reaction, i.e. fluoride ion elimination.

Regioselectivity of nucleophilic substitution of fluorine in fluoroaryls

The problem of regioselectivity is important from the viewpoint of both mechanistic studies and synthetic consequences. Thus, it is of interest to analyze the influence of different factors on the regioselectivity of fluorine substitution in these reactions. These factors may be the following: (a) steric orientation of the nucleophile; (b) coordination between the substrate and the nucleophile; (c) relative magnitude of entropy and enthalpy control; (d) nature of the nucleophile; and (e) nature of the substrate. The latter two factors could lead to a change in the limiting stage of the reaction and hence affect the synthetic consequences of substitution.

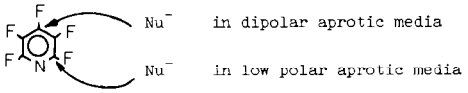
The scheme below indicates that intramolecular substitution in the sodium salt of benzophenone oximate occurs to a greater extent with the chlorine rather than the fluorine atom [45]:



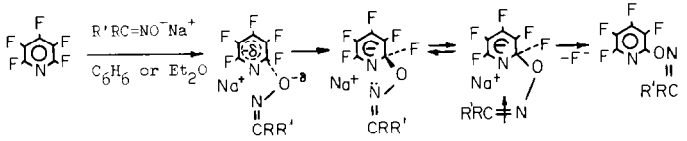
(E- and Z-isomer mixture)

This is a striking result at first sight, since fluorine is known to be more mobile in S_NAr reactions than chlorine [31]. If higher selectivity is to be achieved in this reaction, steric orientation of the nucleophile is important. Thus, if only one isomer is involved in the reaction, e.g. the *Z*-oximate, then the 1,2-benzisoxazole with only chlorine atom substituted results in 89% yield [45].

The regioselectivity of fluorine substitution may be affected by coordination of the substrate with a nucleophile. Thus, in the reaction of pentafluoropyridine with sodium oximates in aprotic media of low polarity only products arising from fluorine substitution in the 2-position are observed, whereas only the 4-position is substituted in dipolar aprotic media.



The route whereby substitution occurs in media of low polarity may involve coordination of the nucleophile with a substrate in the transition state with participation of the metal cation [46]:



Destruction of such coordination by adding a crown ether to the low polarity medium leads to substitution in the 4-position [46].

Thus, the creation of conditions which allow substituent coordination in the substrate by the nucleophile provides a powerful method for isomer ratio control in S_NAr reactions. As a rule, the *o*-isomers of pentafluorobenzene derivatives C_6F_5X ($X=NO_2$, SO_2CH_3, $COOCH_3$, COOH, C=O) are formed in media of low polarity due to formation of a cyclic transition state (chelate formation), but in polar media, where formation of such a transition state is hindered, the fluorine atom in the position *para* to the substituent is predominantly substituted [47–49]. A similar medium effect occurs for S_NAr reactions involving 1,2,3,4-tetrafluoroanthraquinone, where coordination of the nucleophile with the carbonyl group leads only to the α-derivative in media of low polarity whereas the β-derivative is formed in highly polar media [50].

However, chelate formation is not the only method for controlling the regioselectivity of S_NAr substitutions. Recently, it has been shown that varying

the medium can lead to changes in the entropy to enthalpy control in S_NAr reactions [51, 52]. Thus, the *ortho/para* ratio in S_NAr substitution reactions of halogens in alcohols is generally entropy-controlled [53, 54]. A comparison of fluorine and chlorine substitution in halonitrobenzenes shows that fluorine atoms in monohalonitrobenzenes are preferably substituted due to the smaller steric requirements of the *o*-fluorine atom (Table 10) [54]. However, in dihalobenzenes the situation is reversed, since entropy control for reactions in alcohols favours *o*-substitution because of steric hindrance towards solvation in the transition state (Table 10) [54]. At low temperatures in liquid ammonia, entropy control of the reactions of fluoronitrobenzenes with alkoxides changes to enthalpy control (see activation parameters listed in Table 10), leading to sharply enhanced *o*-substitution. Thus, the *ortho/para* ratio for the substitution products in the reaction of 2,4-difluoronitrobenzenes with alkoxides in liquid ammonia can be increased over the range 3–8 depending on the nature of the alkoxide and alkali metal: the greater the extent of radical branching in the alkoxide and the larger the size of the alkali metal atom, the greater the *ortho/para* ratio [50].

Hence, control of the ratio of the rates of substitution at different positions in the aromatic ring provides new synthetic possibilities. Thus, for 2,3,4- and 2,4,6-trifluoronitrobenzenes as listed in Table 10, an increase in the

TABLE 10

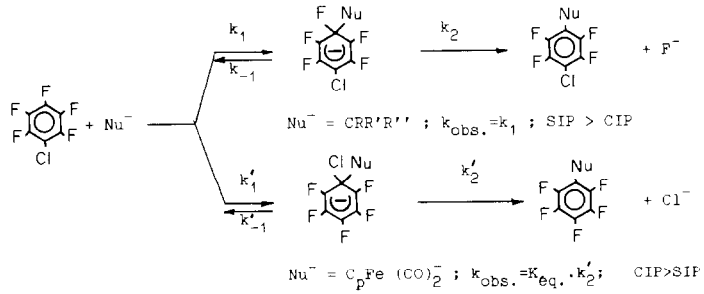
Reactions of *o*- and *p*-chloronitrobenzenes and -fluoronitrobenzenes, 2,4-dichloro- and 2,4-difluoro-, 2,3,4- and 2,4,6-trifluoropentafluoronitrobenzenes with sodium methoxide in MeOH (25 °C) or liquid NH_3 (−70 °C)

Compound	Solvent	k_{ortho}/k_{para}	Difference in activation parameters		Ref.
			$E_a^{ortho} - E_a^{para}$ (kcal mol^{-1})	$\Delta S^{\neq}_{ortho} - \Delta S^{\neq}_{para}$ [cal (mol K)$^{-1}$]	
2-$ClC_6H_4NO_2$	MeOH	0.27[a]	2.1	3.2	54
4-$ClC_6H_4NO_2$					
2,4-$Cl_2C_6H_3NO_2$	MeOH	1.98[a]	–	–	54
2-$FC_6H_4NO_2$	MeOH	0.7	−0.5	−2.3	54, 55
4-$FC_6H_4NO_2$	liq. NH_3	2.85 1.60[b]	−1.6	−6.0	51
2,4-$F_2C_6H_3NO_2$	MeOH	1.22 1.35	– –	– –	54 55
	liq. NH_3	2.6 (3.3[c]) 1.85[b]	−0.8	−2.4	52
2,3,4-$F_3C_6H_2NO_2$	MeOH	1.7	–	–	55
2,4,6-$F_3C_6H_2NO_2$	MeOH	0.9	–	–	55
$C_6F_5NO_2$	MeOH	0.043	–	–	55

[a]At 90 °C and 85 °C.
[b]At −33 °C.
[c]In the reaction with potassium methoxide.

yield of *o*-substitution products may be expected on passing from methanol to liquid ammonia as a solvent. For pentafluoronitrobenzene, no such change in regioselectivity may be expected, since the electronic effect of two fluorines *ortho* to position 4 determine that the most probable attack of the charged nucleophile occurs exactly in this position [55]. In the latter case, orientation of the nucleophilic attack into the position *ortho* to the nitro group may be regulated via the cyclic transition state by performing the reaction in a medium of low polarity [47, 48].

The regioselectivity of fluorine substitution in S_NAr reactions can depend on the nature of the nucleophile and, as a consequence, on the reaction mechanism. Thus, in the reaction of pentafluorochlorobenzene with carbanions, the limiting stage is formation of a σ-complex with rapid loss of the fluoride ion, whereas in the reaction with iron carbonylate, the limiting stage corresponds to chloride ion elimination [56]:



For this reason, carbonylate contact ion pairs (CIP) are more reactive than solvent-separated ion pairs (SIP). For carbanions, however, the reactivity order of the ion pairs is reversed, i.e. SIP > CIP [56].

The limiting stage also changes in the reaction of the ambident nitrite ion with 2,4-dinitrofluorobenzene in aprotic dipolar solvents; in this case, the rate-limiting stage of the reaction is σ-complex decomposition. As a result, the order of X group mobility in the reaction of 1-X-2,4-dinitrobenzene with nitrite ion is $NO_2 \gg Cl > I > F$ (Table 11). However, in the reaction of the nitrite ion with *p*-X-nitrobenzenes, the leaving group mobility varies over a narrow range in the order $F > NO_2 \simeq Cl \simeq I$, indicating σ-complex formation as the limiting stage (Table 11) [22].

Thus, in the S_NAr reactions of the nitrite ion involving σ-complex formation as the limiting stage and the fluoride ion as the leaving group, predominant formation of nitro products may be anticipated. Hence, in reactions involving slightly activated substrates, i.e. penta- and hexa-fluorobenzenes with the nitrite ion, nitro derivatives are formed. In contrast, with highly activated substrates such as C_6F_5X ($X = NO_2$, CN, COOEt), reaction leads to O-substitution products [57]. These results are in full agreement with those obtained for the changed limiting stage involved in the S_NAr reaction with the nitrite ion [22].

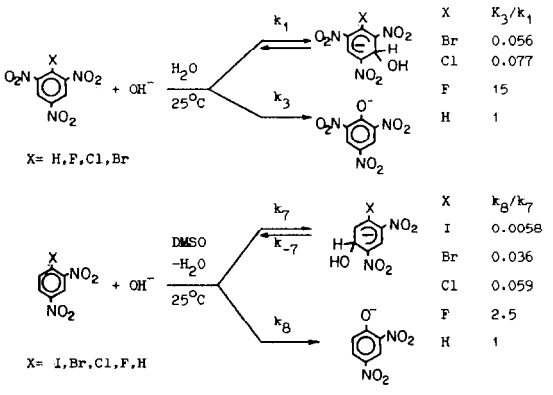
TABLE 11

The rate constants for the reaction of 1-X-2,4-dinitrofluorobenzene and 1-X-nitrobenzene with the ambident nitrite ion in DMSO [21, 22]

Nucleophile	Leaving group	k_2 [l (mol s)$^{-1}$] for 1-X-2,4-$(NO_2)_2C_6H_3$ at 25 °C	10^4 k_2 [l (mol s)$^{-1}$] for 1-X-4-$NO_2C_6H_4$ at 100 °C
ONO^-	NO_2	8	1.0
	F	0.14	3.16
	Cl	0.6	0.89
	I	0.27	0.63
NO_2^-	NO_2	6.8	1.58
	F	0.032	12.9
	Cl	0.4	1.78
	I	0.27	5.0

It has been shown recently that in the reaction of halonitrobenzenes with potassium isopropoxide in isopropanol, the reaction route depends on the type of halogen involved and its position in the benzene ring [58]. Thus, for 2- and 4-fluoronitrobenzenes, the reaction corresponds only to the S_NAr type, being independent of cation–anion interactions in solution. For other 2-, 3- and 4-halonitrobenzenes (Hal = Cl, Br, I) and *m*-fluoronitrobenzene, the radical-ion mechanism is predominant with intermediate formation of a radical anion of the substrate which is subsequently transformed either into nitrobenzene via dehalogenation or to the azoxy or anilino derivatives via nitro-group reduction. The nature of the nucleophile does not change the S_NAr mechanism for the reaction of 2- and 4-fluoronitrobenzenes, whereas for other leaving halides any change in the reaction mechanism depends largely on the nature of the nucleophile [58].

Regioselectivity in S_NAr reactions depends strongly on the steric effects caused by the presence of a substituent in the substrate. In this respect, the fluorine atom is advantageous due to its small size. At the same time, the high electronegativity of the fluorine atom strongly polarizes the C–F bond in a substrate. The scheme below provides data regarding the reactions of di- and tri-nitrohalobenzenes with the hydroxide ion [59]:



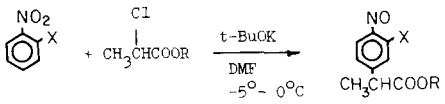
X	K_3/K_1
Br	0.056
Cl	0.077
F	15
H	1

X	k_8/k_7
I	0.0058
Br	0.036
Cl	0.059
F	2.5
H	1

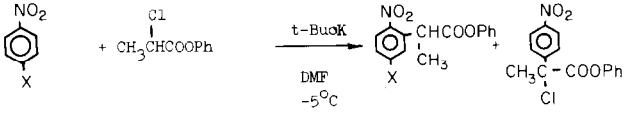
Attack at an unsubstituted position in the benzene ring is known to be faster than at a substituted position, as seen from the rate constant ratios k_3/k_1 and k_8/k_7 [59, 60]. The specific feature of the fluorine effect is that the rate ratio is only reversed when the fluoride ion is the leaving group. When substantial steric hindrance occurs in a substrate, the rate ratio increases in favour of fluorine substitution (e.g. reaction of picryl fluoride with hydroxide ion). This arises from the considerable polarization of the C—F bond in the substrate and the small size of the fluorine atom, which is not typical of other halides.

These features of the fluorine atom are also exhibited in S_NAr reactions involving 3,5-bis(trifluoromethylsulphonyl-X-benzenes) with nucleophiles where the mobility of the X group changes in the presence of sodium methoxide in the order $F > NO_2 > Cl > SO_2CF_3$ [61]. The low mobility of the SO_2CF_3 group may be mainly associated with the preferential attack of the nucleophile on the unsubstituted position in the benzene ring, since for the *p*-X-substituted derivatives of phenyltrifluoromethylsulphone the order of X group mobility is $SO_2CF_3 > NO_2 > F > Cl$ [62].

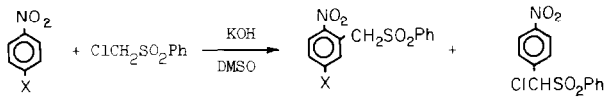
Another example of the specific properties of fluorine is provided by nucleophilic substitution reactions which proceed via a vicarious mechanism (VNS). The scheme below shows the reactions of carbanions with *o*- and *p*-nitrosubstituted benzenes [63–66]:



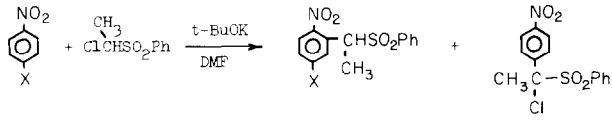
X	Yield (%) [63]
H	80
Cl	68–83
F	55–65



X	Yield (%) [64] VNS	S_NAr
Cl	45	–
F	33	10

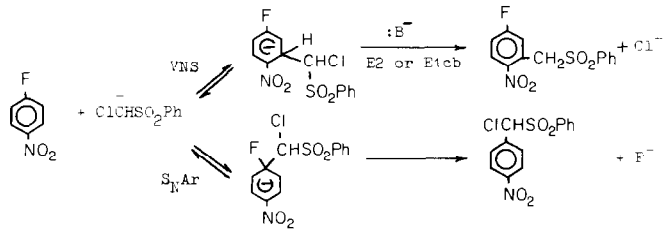


X	Yield (%) [65] VNS	S_NAr
Cl	69	–
Br	61	–
I	74	–
F	18	27
NO_2	13	6



X	Yield (%) [65] VNS	S_NAr
Cl	82	–
F	50	14

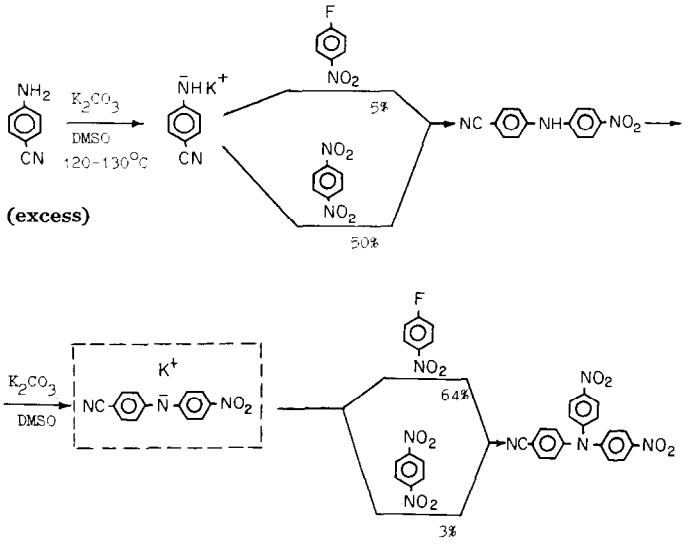
In all cases employing the fluoride ion as a leaving group, the proportion of the vicarious mechanism decreases and that of the S_NAr mechanism increases. The difference between the vicarious and the S_NAr mechanisms lies in the fact that the σ-complex involved in the vicarious route undergoes further transformation via an $E2$ or $E1cb$ mechanism [67]:



With a fluorine-containing substrate, σ-complex formation via the S_NAr route is favoured. Recently, the specific behaviour of 2-fluoronitrobenzene in the reaction with chloromethylphenylsulphone has also been attributed to the increased reactivity of *o*- and *p*-fluoronitrobenzenes associated with the S_NAr mechanism rather than the vicarious mechanism [68]. However, under certain conditions, a product may be obtained from *p*-fluoronitrobenzene only via the vicarious route [64]. Thus, to obtain a substitution product in which the

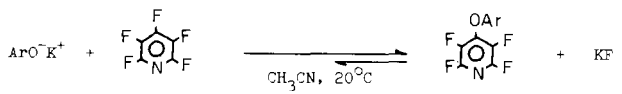
aromatic ring substituent is preserved, vicarious substitution should preferably be performed for substrates in which fluorine atoms are not present.

An interesting example of the strong steric effect of the nitro group relative to that of the fluorine atom in the S_NAr reaction has been described [69]:



Due to large C—F and C—NO_2 bond polarizations, fluorine and the NO_2 group are quite mobile in S_NAr reactions [22] and hence the difference in the reactivity between these groups is mainly associated with the greater steric effect of the NO_2 group. Indeed, the 4-cyano-4′-nitrodiphenylamine N anion (shown in the dotted box in the scheme above) is quite sensitive to the steric effect of a nitro group in the substrate, so that the yield of triarylamine is only as high as 3% in this case with the major product being 4-cyano-4′-nitrodiphenylamine in 50% yield. The reverse occurs with *p*-fluoronitrobenzene; in this case the major reaction product is triarylamine (64% yield) with diarylamine being formed in <5% yield [69].

An interesting steric effect of the pentafluorophenoxy group has been found for the S_NAr reactions of potassium aryl oxides with pentafluoropyridine in CH_3CN or DMSO [70]:



On comparing the logarithms of the rate constants with the aryl oxide basicities via the Brønsted equation, it has been shown that the behaviour of the pentafluorophenoxy anion deviates from the normal straight line as a result of the increased contribution of the reverse reaction, since the

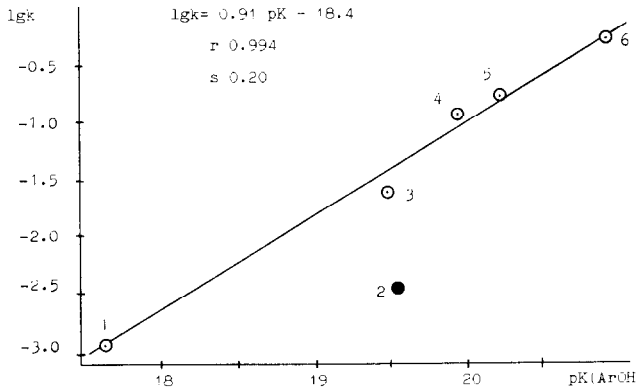
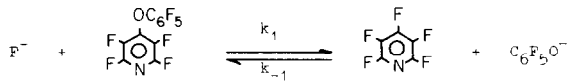


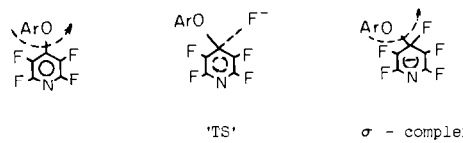
Fig. 6. Brønsted plot for the reaction of potassium aryl oxides ArO^-K^+ with pentafluoropyridine in CH_3CN at 20 °C. Point numbers correspond to Ar = β-$C_{10}F_7$ (1); C_6F_5 (2); α-$C_{10}F_7$ (3); 3-Cl-4-$NO_2C_6H_3$ (4); 4-$CH_3C_6F_4$ (5); and 4-$NO_2C_6H_4$ (6).

fluoride ion eliminated reacts with 4-pentafluorophenoxy-2,3,5,6-tetrafluoropyridine 30-times as rapidly (Fig. 6) [70]:



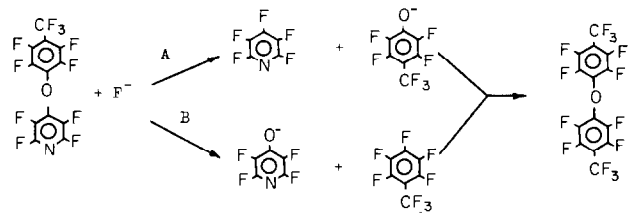
$k_1^{20°C} = 5.45$ l (mol s)$^{-1}$; $k_{-1}^{20\ °C} = 0.18$ l (mol s)$^{-1}$; $k_1/k_{-1} = 30$

The reason for this behaviour lies in the fact that free rotation of the C_6F_5O group is hindered not only in the diaryl ether but also in the σ-complex.



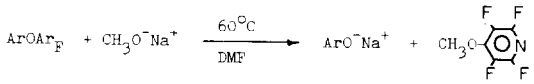
Hence the transition state becomes the more favourable energetically in the attack of the F^- ion on 4-pentafluorophenoxy-2,3,5,6-tetrafluoropyridine. In contrast, rotation is hindered only in the diaryl ethers but not in the σ-complex for pentafluoronaphthoxy substituents.

Ready removal of the pentafluorophenoxy group may also be of synthetic value. Thus, in perfluoro-*p*-tolylpyridyl ether, both groups are easily substituted by the fluoride ion:



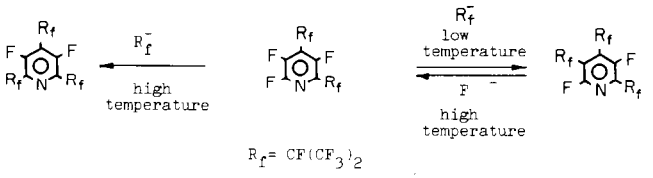
As a result, both the perfluorotolyloxy anion (route A) and octafluorotoluene (route B) give perfluoroditolyl ether as the final reaction product [70].

Ready removal of the phenoxy group is also observed in the reaction of diaryl ethers with sodium methoxide in DMF [71]:



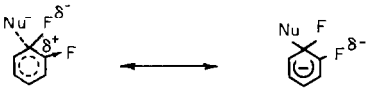
However, if $Ar_F = C_6F_5$, the reaction is extremely sluggish [71].

An interesting effect of the kinetic and thermodynamic control of substitution regioselectivity has been found in the S_NAr reaction of pentafluoropyridine with the perfluoroisopropyl anion [72]. Thus, in 2,4-bis(perfluoroisopropylpyridine) two reaction routes are possible; at low temperature (kinetic control) the 2,4,5-trisubstituted product is formed, whilst at high temperature (thermodynamic control) the product is the 2,4,6-isomer [72]:

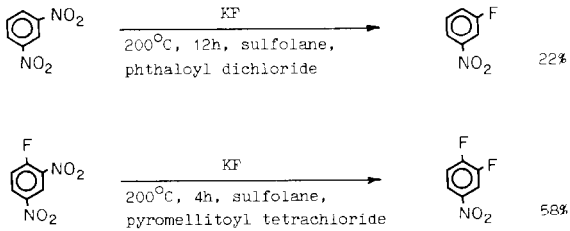


Similar effects have also been observed in the perfluoroalkylation of other perfluoroazines [73].

The problems of regioselectivity of S_NAr reactions in polyfluoroaromatic compounds have recently been reviewed [8]. It is only appropriate to mention the most general conclusions of this discussion here. Essentially, the promoting effect of fluorine atoms in the reactions of polyfluorobenzenes with nucleophilic agents in solution varies in the series *meta-* > *ortho-* > *para*-fluorine, whereas in similar processes with polyfluoro-pyridines and -pyrimidines, the greatest accelerating effect is produced by *ortho*-fluorines [74, 75]. The importance of ion–dipole interaction effects in the activation of the S_NAr reaction by *ortho*-fluorines should be emphasized, leading to the early formation of the transition state and to σ-complex stabilization by *ortho*-fluorine atoms [75]:



Hence, the accelerating effect of *ortho*-fluorines and the minor steric effect of these atoms are quite important in fluoro-organic synthesis. For this reason, it is interesting to compare the results of the following reactions [76]:



Obviously, the *ortho*-fluorine effect increases the yield of 3,4-difluoronitrobenzene appreciably. The yields of *m*-fluoronitrobenzene and 3,4-difluoronitrobenzene also increase considerably with reaction time [76, 77].

Conclusion

This paper analyzes the specific features of the reactivity of the fluoride ion as a nucleophile and as a leaving group in S_NAr reactions. The nucleophilicity of the fluoride ion in solution may be considerably increased by creating the necessary conditions for its desolvation. Investigation of the reactivity of the fluoride ion as a leaving group shows the importance of taking the reaction mechanism for the synthesis of the required compound into account.

References

1 W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*, W. A. Benjamin Inc., New York, 1969.
2 R. D. Chambers, *Fluorine in Organic Chemistry*, Wiley-Interscience, New York, 1973.
3 G. G. Yakobson (ed.), *Reaktsionnaya sposobnost poliftoraromaticheskih soedinenii*, Nauka, Novosibirsk, 1983.
4 L. M. Yagupolsky, *Aromaticheskie i geterotsiklicheskie soedinenia s ftorsoderzhashchimi zamestitelyami*, Naukova Dumka, Kiev, 1988.
5 G. G. Yakobson and V. V. Bardin, *Ftorid-ion v organicheskoi khimii*, Nauka, Novosibirsk, 1986.
6 J. H. Clark, *Chem. Rev.*, *80* (1980) 429; G. G. Yakobson and N. E. Akhmetova, *Synthesis*, (1983) 169.
7 A. Haas and M. Lieb, *Chimia*, *39* (1985) 134.
8 P. P. Rodionov and G. G. Furin, *J. Fluorine Chem.*, *47* (1990) 361.
9 D. K. Bohme and A. B. Raksit, *Can. J. Chem.*, *63* (1985) 3007.
10 C. N. DePuy, S. Gronert, A. Mullin and V. M. Bierbaum, *J. Am. Chem. Soc.*, *112* (1990) 8650.
11 S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, *J. Phys. Chem. Ref. Data*, *17* (1988) Suppl. 1.
12 F. G. Bordwell, *Acc. Chem. Res.*, *21* (1988) 456.
13 J. Emsley, D. J. Jones, J. M. Miller, R. E. Overill and R. A. Waddilove, *J. Am. Chem. Soc.*, *103* (1981) 24.
14 V. M. Vlasov and T. A. Oskina, *Org. React. (USSR)*, *26* (1989) 16.
15 T. F. Magnera, G. Caldwell, J. Sunner, S. Ikuta and P. Kebarle, *J. Am. Chem. Soc.*, *106* (1984) 6140.

16 G. W. Dillow and P. Kebarle, *J. Am. Chem. Soc., 110* (1988) 4977.
17 D. Landini, A. Maia and A. Rampoldi, *J. Org. Chem., 54* (1989) 328.
18 K. Hiraoka, S. Mizuse and S. Yamabe, *J. Chem. Phys., 86* (1987) 4102.
19 S. Chowdhury, G. Nicol and P. Kebarle, *Chem. Phys. Lett., 127* (1986) 130.
20 F. Cacace, M. Speranza, A. P. Wolf and R. R. Macgregor, *J. Fluorine Chem., 21* (1982) 145.
21 T. J. Broxton, D. M. Muir and A. J. Parker, *J. Org. Chem., 40* (1975) 2037.
22 T. J. Broxton, D. M. Muir and A. J. Parker, *J. Org. Chem., 40* (1975) 3230.
23 F. G. Bordwell and D. L. Hughes, *J. Am. Chem. Soc., 108* (1986) 5991.
24 J. Miller and A. J. Parker, *J. Am. Chem. Soc., 83* (1961) 117.
25 G. Bartoli, F. Ciminale and P. E. Todesco, *J. Org. Chem., 40* (1975) 872.
26 K. C. Ho, J. Miller and K. W. Wong, *J. Chem. Soc. B,* (1966) 311.
27 F. M. Kindall, J. Miller and K. W. Wong, *J. Chem. Soc B,* (1971) 1521; P. H. Gore, S. D. Hammond and D. F. C. Morris, *J. Chem. Soc., Perkin Trans. 2,* (1973) 1883; V. V. Sinev and G. V. Plokhikh, *Zh. Org. Chim., 21* (1985) 2155.
28 N. G. Lukiyanenko, A. V. Bogatsky and T. I. Kirichenko, *Zh. Vses. Khim. Ova., 30* (1985) 571; M. Hiraoka, *Crown Compounds. Their Characteristics and Applications,* Kodansha, Tokyo, 1982.
29 R. M. Izatt, J. S. Bradshow, S. A. Nielsen, J. D. Lamb and J. J. Christensen, *Chem. Rev., 85* (1985) 271.
30 V. V. Aksenov, V. M. Vlasov, I. M. Moryakina, P. P. Rodionov, V. P. Fadeeva, V. S. Chertok and G. G. Yakobson, *J. Fluorine Chem., 28* (1985) 73.
31 J. F. Bunnett, *Q. Rev. Chem. Soc., 12* (1958) 1.
32 J. M. Riveros, S. M. Jose and K. Takashima, *Adv. Phys. Org. Chem., 21* (1985) 197.
33 N. M. M. Nibbering, *Adv. Phys. Org. Chem., 24* (1988) 3.
34 M. D. Brickhouse and R. R. Squires, *J. Phys. Org. Chem., 2* (1989) 389.
35 S. Ingemann, N. M. M. Nibbering, S. A. Sullivan and C. H. DePuy, *J. Am. Chem. Soc., 104* (1982) 6520.
36 F. G. Bordwell, T. A. Cripe and D. L. Hughes, in J. M. Harris and S. P. McManus (eds.), *Nucleophilicity, Adv. Chem. Ser. No. 215,* Am. Chem. Soc., Washington, DC, 1987, p. 137.
37 V. M. Vlasov and I. A. Os'kina, *Abstr. All-Union Conf. Mechanisms of Nucleophilic Substitution and Addition Reactions,* Donetsk, 1991, p. 53.
38 I. A. Os'kina and V. M. Vlasov, *Izv. Sib. Otd. Akad, Nauk SSSR, Ser. Khim. Nauk,* (1984) 102.
39 F. G. Bordwell and D. L. Hughes, *J. Am. Chem. Soc., 108* (1986) 7300.
40 N. S. Nudelman, *J. Phys. Org. Chem., 2* (1989) 1.
41 R. V. Vizgert, S. G. Sheiko, T. P. Kulisheva and L. E. Sukharevskaya, *Zh. Org. Khim., 25* (1989) 1164.
42 N. S. Nudelman and J. M. Montsserrat, *J. Chem. Soc., Perkin Trans. 2,* (1990) 1073.
43 E. T. Akinyela, I. Onyido and J. Hirst, *J. Chem. Soc., Perkin Trans. 2,* (1988) 1859; G. N. Onuoha, I. Onyido and J. Hirst, *J. Chem. Soc., Perkin Trans. 2,* (1988) 971.
44 L. R. Caswell and M. E. Goldsmith, *J. Org. Chem., 54* (1989) 5101.
45 G. M. Shutske, L. L. Setescak, R. C. Allen, L. Davis, R. C. Effland, K. Ranbom, J. M. Kitzen, J. C. Wilker and W. J. Novick Jr., *J. Med. Chem., 25* (1982) 36; M. Shutske, *J. Org. Chem., 49* (1984) 180.
46 R. E. Banks, W. Jondi and A. E. Tipping, *J. Chem. Soc., Chem. Commun.,* (1988) 1268.
47 J. Burdon, D. Fisher, D. King and J. Tatlow, *Chem. Commun.,* (1965) 65.
48 L. S. Kobrina, G. G. Furin and G. G. Yakobson, *Zh. Org. Khim., 6* (1970) 512.
49 T. N. Gerasimova, T. V. Fomenko and E. P. Fokin, *Zh. Org. Khim., 13* (1977) 1562; T. N. Gerasimova, T. V. Fomenko and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk,* (1975) 100.
50 E. P. Fokin and V. A. Loskutov, *Zh. Obshch. Khim., 38* (1968) 1884.
51 T. A. Kizner and V. D. Shteingarts, *Zh. Org. Khim., 20* (1984) 1089.
52 T. A. Kizner and V. D. Shteingarts, *Zh. Org. Khim., 21* (1985) 2376.

53 C. W. L. Bevan, A. J. Foley, J. Hirst and W. O. Uwamu, *J. Chem. Soc. B*, (1970) 794.
54 T. O. Bamkole, J. Hirst and E. J. Udoessien, *J. Chem. Soc., Perkin Trans. 2*, (1973) 110.
55 R. Bolton and J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2*, (1978) 141.
56 G. A. Artamkina, A. Yu. Milchenko, I. P. Beletskaya and O. A. Reutov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1988) 2826.
57 A. O. Miller and G. G. Furin, *Zh. Org. Khim.*, *25* (1989) 355.
58 V. Arca, C. Paradisi and G. Scorrano, *J. Org. Chem.*, *55* (1990) 3617.
59 M. R. Crampton, A. B. Davis, C. Greenhalgh and J. A. Stevens, *J. Chem. Soc., Perkin Trans. 2*, (1989) 675.
60 M. R. Crampton and C. Greenhalgh, *J. Chem. Soc., Perkin Trans. 2*, (1986) 187, 873.
61 V. N. Boiko, G. M. Shchupak, R. K. Orlova and L. M. Yagupolsky, *Zh. Org. Khim.*, *21* (1985) 1477.
62 S. M. Shein and K. V. Solodova, *Zh. Org. Khim.*, *6* (1970) 1465.
63 J. P. Stahly, B. C. Stahly and K. C. Lilje, *J. Org. Chem.*, *49* (1984) 578.
64 B. Mudryk and M. Makosza, *Synthesis*, (1988) 1007.
65 M. Makosza, J. Golinski and J. Baran, *J. Org. Chem.*, *49* (1984) 1488.
66 B. Mudryk and M. Makosza, *Tetrahedron*, *44* (1988) 209.
67 M. Makosza, in H. Nozaki (ed.), *Current Trends in Organic Synthesis*, Pergamon, Oxford, 1983, p. 401; M. Makosza and J. Winiarski, *Acc. Chem. Res.*, *20* (1987) 282.
68 M. Galvagni, F. Kelleher, C. Paradisi and G. Scorrano, *J. Org. Chem.*, *55* (1990) 4454.
69 J. H. Gorrin, *J. Chem. Soc., Chem. Commun.*, (1985) 238; J. H. Corvin, *J. Chem. Soc., Perkin Trans. 1*, (1988) 1331.
70 V. V. Aksenov, V. M. Vlasov and P. P. Rodionov, *Abstr. All-Union Conf. Aromatic Nucleophilic Substitution*, Novosibirsk, 1989, p. 97.
71 M. Jarman and R. McCague, *J. Chem. Soc., Chem. Commun.*, (1984) 125.
72 R. D. Chambers, R. P. Corbally and W. K. R. Musgrave, *J. Chem. Soc., Perkin Trans. 1*, (1972) 1281.
73 R. D. Chambers, R. P. Corbally, W. K. R. Musgrave, J. A. Jackson and R. S. Matthews, *J. Chem. Soc., Perkin Trans. 1*, (1972) 1286.
74 R. D. Chambers, D. Close and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, (1980) 778.
75 R. D. Chambers, M. J. Seabury, D. L. H. Williams and N. Hughes, *J. Chem. Soc., Perkin Trans. 1*, (1988) 255.
76 F. Effenberger and W. Streicher, *Chem. Ber.*, *124* (1991) 157.
77 M. Maggini, M. Passudetti, G. Gonzales-Trueba, M. Prato, U. Quintily and G. Scorrano, *J. Org. Chem.*, *56* (1991) 6406.