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Nucleophilic substitution of the nitro group, fluorine and chlorine in aromatic compounds

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Abstract. The published data on the comparative activities of the nitro group, fluorine and chlorine in aromatic nucleophilic substitution reactions are generalised and systematised. The factors influencing the relative activities of these substituents, *viz*., the structure of the substrate, the nature of the nucleophile and reaction conditions, are discussed. The synthetic applications and possible mechanisms of nucleophilic substitution of the nitro group, fluorine and chlorine in aromatic compounds are considered. The bibliography includes 265 references.

I. Introduction

Nucleophilic aromatic substitution is still the field of organic chemistry that is the most intensively developed [1,2] owing to the diversity of reaction mechanisms [1–4] and high synthetic potentials of these reactions.[5–7] Nucleophilic substitution of hydrogen (S_N^H) in arenes is an efficient approach to their functionalisation,[1,2,8,9] but *ipso*-substitution (S_N^{ipso}) of the nucleofugal group in aromatic compounds is of no less importance, since it allows regioselective synthesis of not only *ortho*- and *para*-isomers, but also of their *meta*-derivatives.[1] The present review is mostly concerned with the S_N^{ipso} reactions of arenes under the conditions where the role of a nucleofuge is played by the nitro group or halogens (fluorine and chlorine).[1,10–12] The popularity of these leaving groups is due primarily to the high accessibility of the corresponding derivatives [13–16] and activity of these groups in aromatic nucleophilic substitution reactions.[1,10–12,17]

Some physicochemical characteristics of the Ar–X bonds and the leaving groups X, where X = NO_2, F and Cl, are given in Table 1. The C–F bond is much shorter, more stable and less polarisable than the C–NO_2 and C–Cl bonds. The NO_2 and F groups are characterised by a strong polar effect (*cf*. relatively high values of the constants σ_χ and σ_F), but the steric (E_S) and polarisability (σ_α) effects for the NO_2 group are much stronger than those for fluorine (the minus sign designates an enhancement of the corresponding effect). Chlorine is the most polarisable and the least electronegative among the substituents mentioned. These characteristics of the leaving groups X have a pronounced effect on their relative activities in nucleophilic substitution reactions. The rates and directions of these reactions depend on the structure of the starting arene, the nature of the nucleophile and the experimental conditions. A combination of these factors determines the reaction mechanism.[11,12,17,23] For this reason, an analysis of kinetic data on the comparative activities of a nitro group, fluorine and chlorine bound to an aromatic ring is very important for the correct choice of the most efficient approaches to the synthesis of functionalised arenes.[16]

Nucleophilic substitution of the aromatic nitro group has been reviewed previously [24] with the main emphasis on the synthetic results. The present review is devoted to the analysis and systematisation of the data on comparative activities of the NO_2, F and Cl groups in arenes under the action of various nucleophilic agents published in the past 10–15 years. The main emphasis is laid on reactions of NO_2-, F- or Cl-substituted aromatic compounds with anions as nucleophiles.

Table 1. Characteristics of the Ar–X bonds and groups X in substituted arenes.

Parameter	Group X			Ref.
	NO_2	F	Cl	
Bond length /Å	1.4982	1.305	1.766	15, 18
Bond dissociation energy /kJ mol^{-1}	298.0	525.4	400.0	19
Refraction of the Ar–X bond /cm^3	6.9	1.43	6.62	20
Constants:				
electronegativity (σ_χ)	0.46	0.70	0.16	21
polarisability (σ_α)	−0.26	0.13	−0.43	21
field (σ_F)	0.65	0.44	0.45	21
resonance (σ_R)	0.18	−0.25	−0.17	21
steric (E_S) (see [a])	−0.75	0.49	0.18	22

[a] The constant of the *ortho*-substituent X (E_S = 0 for the CH_3 group) is given.

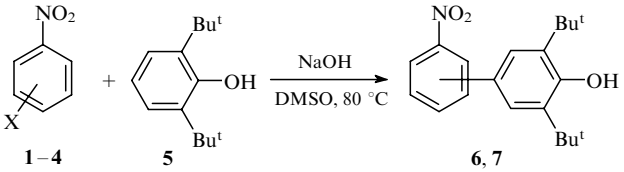
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II. Reactions with carbanions

The methods for the formation of a new carbon–carbon bond in arenes, particularly through aromatic nucleophilic substitution of the nitro group, fluorine and chlorine under the action of carbanions, have been discussed previously.[7,25] We shall dwell only on specific features of carbanions in the reactions from the standpoint of relative activities of the substituents mentioned.

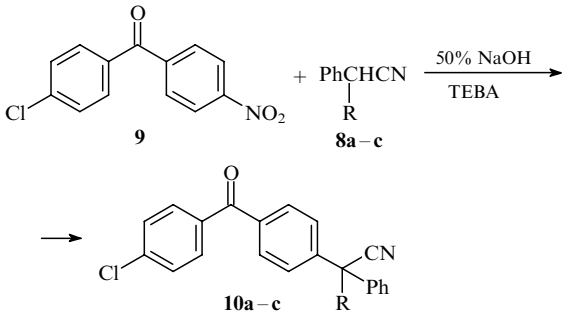
Thus the arylation of 4- and 2-substituted nitrobenzenes **1**–**4** under the action of a 2,6-di-*tert*-butylphenol anion (**5**), which acts as a C- rather than an O-nucleophile due to steric hindrance, yields 4- and 2-nitro-substituted biphenyls **6** and **7** according to the S_NAr mechanism.



Compound	X	Reaction time /h	Product	Yield (%)
1	4-NO_2	3	**6**	77
2	2-NO_2	17	**7**	64
3	2-F	18	**7**	97
4	2-Cl	24	**7**	71

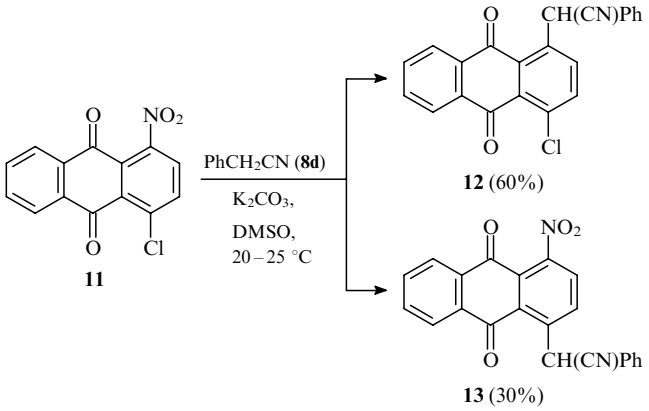
Although the results of this study are purely qualitative,[26] it is nevertheless evident that the activity of fluorine is higher than that of the nitro group or chlorine. Obviously, steric hindrance in the 1,2-disubstituted substrate **2** decreases the activity of the nitro group making it similar to that of chlorine. Therefore, the activity of the nitro group in sterically non-hindered 1,4-dinitrobenzene (**1**) is much higher.[26]

Under conditions of phase-transfer catalysis, carbanions of disubstituted acetonitriles **8a**–**c** attack 4-chloro-4′-nitrobenzophenone (**9**) exclusively with the substitution of the nitro group and the formation of the chloro derivatives **10a**–**c**.[27]



R = Me (**8a**; **10a**, 75%), Pr^n (**8b**; **10b**, 78%), Bn (**8c**; **10c**).

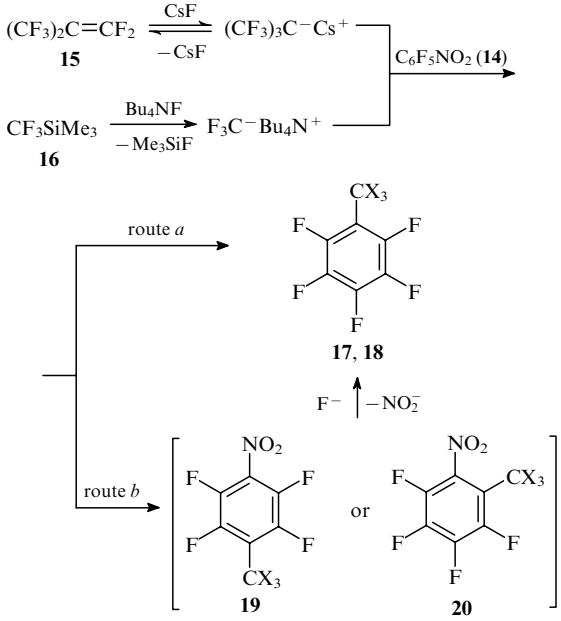
Similarly, a higher activity of the nitro group in comparison with chlorine was observed in the reaction of a tricyclic 1-chloro-4-nitrobenzene analogue **11** with the phenylacetonitrile carbanion **8d** (R = H), the yield of 1-chloro-4-(α-cyanobenzyl)anthraquinone (**12**) being twice as high as that of 1-(α-cyanobenzyl)-4-nitroanthraquinone (**13**).[28]



These results can be explained by the softness of the carbanions **8** which preferentially attack the carbon atom of the $C-NO_2$ group which makes a more significant contribution to LUMO (orbital control) than the carbon atom of the C–Cl group which bears a higher positive charge (charge control).[29]

Reactions of pentafluoronitrobenzene (**14**) with perfluoro-*tert*-butyl and trifluoromethyl anions [these are generated from perfluoroisobutylene (**15**) and trifluoromethyltrimethylsilane (**16**), respectively under the action of the fluoride ion] afford formally the substitution products of the nitro group **17** and **18**.[30–32] However, the mechanism of direct nucleophilic substitution (route *a*) can be argued (Scheme 1).

Scheme 1

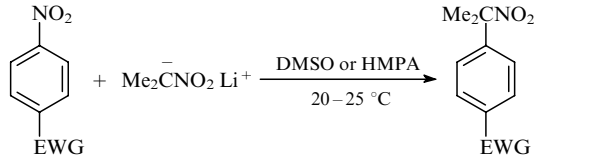


X = CF_3 (**17**, 65.5%), F (**18**, 90%).

Indeed, in the reactions of pentafluoronitrobenzene with nucleophilic reagents (hard N- and O- or soft S-anions) it is the fluorine atom in position 2 or 4 that is usually replaced whereas the nitro group remains unaffected.[33,34] It is therefore more likely that this reaction occurs according to the route *b* where the additionally activated nitro group in the intermediate compounds **19** and **20** is replaced by the fluorine ion resulting in perfluoro-*tert*-butylbenzene (**17**) or perfluorotoluene (**18**).[30,35] Supporting evidence in favour of this route can be derived from the yields of

compounds **17** and **18**: the yield of a direct substitution product according to the route *a* is smaller for the more nucleophilic perfluorobutyl anion. Moreover, the more electron-withdrawing CF_3 group in the intermediates **19** and **20** significantly facilitates the substitution of F for the NO_2 group.

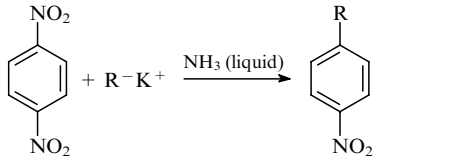
The nitro group in compounds **1**, **21**–**24,** which is activated by an electron-withdrawing substituent, is readily replaced even by weakly basic nitroalkane anions in aprotic polar solvents to give compounds **25**–**29.**[36–38]



1, **21**–**24** **25**–**29** (60%–82%)

EWG = NO_2 (**1**, **25**), CN (**21**, **26**), SO_2Ph (**22**, **27**), CO_2Me (**23**, **28**), COPh (**24**, **29**).

The bulky tetrabutylammonium cation can be used as a counterion for accelerating these reactions and promoting better separation of the ion pairs.[39,40] A similar effect is observed when the reactions of compound **1** with stabilised carbanions of different basicities are carried out in liquid ammonia;[41] this reaction gives nitroarenes **30a**–**e**.

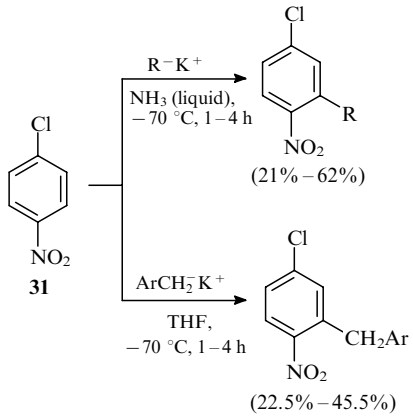


1 **30a**–**e** (40%–97%)

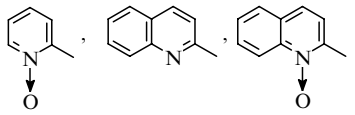
R = CH_2COMe (**a**), CH(Me)COEt (**b**), CH_2CO_2Et (**c**), CH_2CN (**d**), CH(Ph)CN (**e**).

As a rule, the reactions of carbanions with substitution of the nitro group, fluorine and chlorine in arenes proceed according to the S_NAr mechanism with formation of a σ-complex in the limiting step. This is corroborated by the results of kinetic studies of reactions of 9-substituted fluorenyl anions with *para*-halonitrobenzenes in DMSO, the activities of the leaving groups changing in the following order: F > Cl > Br ≈ I; the ratio of the reaction rate constants (k^F/k^{Cl}) is 3.5–8.0 (see Ref. 42). Free ions or solvent-separated ion pairs are more reactive than contact ion pairs (for reactions in THF).[43]

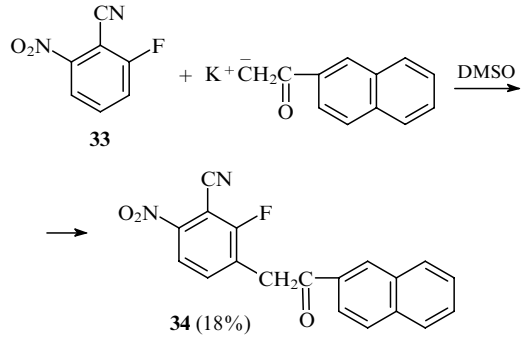
The formation of stable anionic σ-complexes at unsubstituted positions of the aromatic ring is a distinguishing feature of reactions of some carbanions with substituted halogeno- and nitroarenes; their further conversions yield S_N^H products as a result of oxidation or vicarious nucleophilic substitution with retention of the nucleofugal groups.[9,25,44] This route is realised not only for low-active substrates, such as nitro-[45] and 1,3-dinitrobenzenes,[26] 1-nitro-[46,47] and 1,8-dinitronaphthalenes[48] and 9-nitroanthracene,[49] but also for substrates with highly reactive nitro groups and halogens, *e.g.*, 1,3,5-trinitrobenzene,[50] 4-nitrophthalonitrile,[51] 4-chloro- (**31**) and 4-fluoronitrobenzenes (**32**), 1,4-dinitrobenzene (**1**), halo-2,4-dinitrobenzenes[25,44,52,53] and 3,6-dichloropyridazine as well as 2-chloro-3- and -5-nitropyridines.[54] The direction of the substitution of the leaving group or hydrogen in arenes under the action of carbanions depends not only on the structure of the substrate but also on the nature of the nucleophile and the reaction conditions. Thus compound **31**, in contrast to the 1,4-dinitro derivative **1**,[41] reacts with some stabilised carbanions in liquid ammonia or THF with substitution of hydrogen rather than halogen. In this case, the starting nitro compound seems to serve as an oxidant of the corresponding σ-complex.[55,56]



R = CH_2COMe, CH(Me)COPh, CH_2CN, $CH_2CO_2Bu^t$;

Ar = 

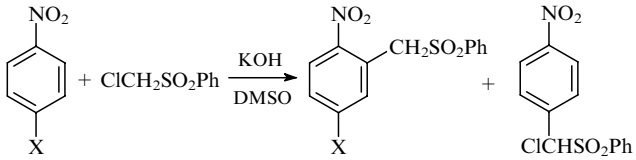
Similarly, the main reaction product of 2-acetylnaphthalene anion with 2-fluoro-6-nitrobenzonitrile (**33**) in DMSO retains all the functional groups in the benzene ring, *viz*., 2-fluoro-3-(2-naphthoylmethyl)-6-nitrobenzonitrile (**34**).[57]



The activated nitro group is unaffected under these conditions, which may be ascribed to the steric effect.

Under conditions of vicarious nucleophilic substitution (VNS), the substrates **1** and **32** containing reactive NO_2 and F groups react with chloromethylphenyl sulfone according to both VNS and S_NAr mechanisms. At the same time, 4-nitrochlorobenzene **31** reacts exclusively according to the vicarious route (Scheme 2).[44,52]

Scheme 2



1, **31**, **32** **35**–**37** **38**

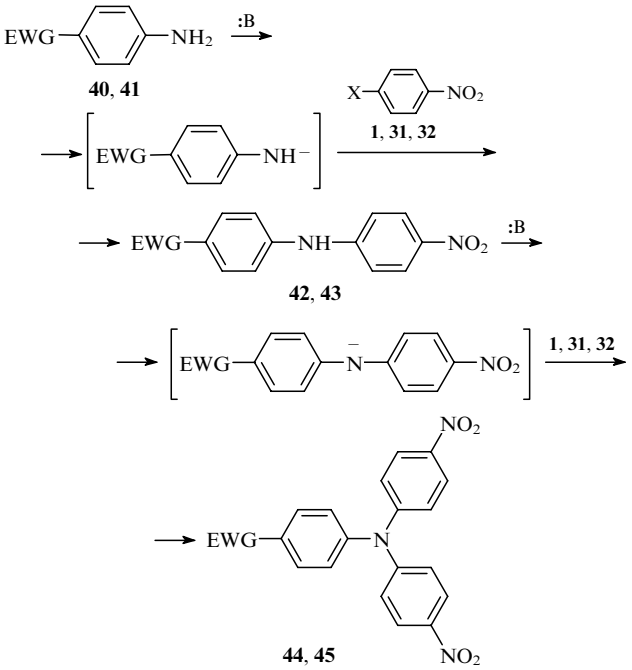
Compound	X	Product [yield (%)]	
		VNS	S_NAr
1	NO_2	**35** (13)	**38** (6)
32	F	**36** (18)	**38** (27)
31	Cl	**37** (69)	–

In those cases where VNS is to be employed for the preparation of products with preservation of nucleofuges in the aromatic ring, it is desirable that the starting arene contains neither activated nitro group nor fluorine.

In conclusion it may be mentioned that reactions of structurally different carbanions with arenes most often result in the substitution of the most active nucleofuges NO_2 and F according to the S_NAr mechanism. The substitution of chlorine in arenes under the action of the same C-anions according to the S_N^{ipso} mechanism proceeds at a much slower rate and shows a tendency for hydrogen substitution (the S_N^H mechanism).

III. Reactions with N- and P-anions

Like carbanions, N- and P-anions naturally manifest certain specificity with respect to the substitution of the nitro group, fluorine and chlorine in arenes. The differences in the activity, *i.e.*, the ratios of the rate constants of the substitution reactions † of fluorine and chlorine in arenes under the action of N-anions **39a**,**b**, are usually of about two orders of magnitude (Table 2) [42] and the activity of fluorine in these reactions is similar to that of the nitro group.[58] Presumably, steric hindrance in the N-anion should decrease the activity of the bulky nitro group in arenes and make it similar to the activity of chlorine. Thus the reactions of N-anions of 4-cyanoaniline (**40**) or 4-nitroaniline (**41**) with 4-substituted nitrobenzenes **1**, **31** and **32** afford di- (**42**, **43**) and triarylamines (**44**, **45**); their ratios depend on the nature of the leaving group X (Table 3).[58–60]

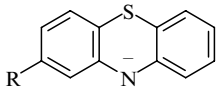


EWG = CN (**40**, **42**, **44**), NO_2 (**41**, **43**, **45**);
:B is base; X = NO_2 (**1**), Cl (**31**), F (**32**).

Under the action of the N-anions of anilines **40** and **41**, the relative activities of the leaving groups X in compounds **1**, **31** and **32** decrease in the following order: F ⩾ NO_2 > Cl.[59] However, the activities of the same substituents under the action of the N-anions of diarylamines **42** and **43** decrease in the following order: F ≫ NO_2 ≈ Cl.[58] The sharp (in comparison with the activity of fluorine in the latter reaction) decrease in the activity of the nitro group, which is similar to that of chlorine, seems to be due to its steric (but not polar) effect [58] (see Table 1).

† This parameter is always indicated for identical conditions.

Table 2. Basicities of N-anions (pK_B)

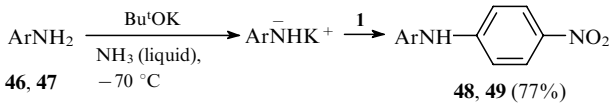


39a,**b**

and the rate constants for the halogen substitution reactions in compounds **31** and **32** (DMSO, 25 °C; the counterion is K^+).[42]

Anion	R	pK_B	Compound	X	k_2 /litre mol^{-1} s^{-1}	$k_{rel} = k_2^F/k_2^{Cl}$
39a	H	22.72	**31**	Cl	9.95×10^{-3}	94.5
			32	F	0.941	
39b	Cl	20.79	**31**	Cl	4.35×10^{-4}	214
			32	F	9.31×10^{-2}	

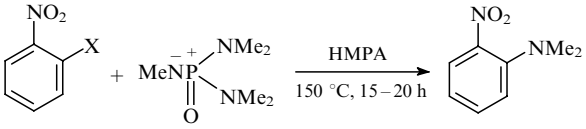
Obviously, it is for this reason that the reactions of the N-anions generated from aniline (**46**) and 2-aminopyridine (**47**) with 1,4-dinitrobenzene (**1**) give exclusively diarylamines **48** and **49** in high yields.[41]



46, **47**

Ar = Ph (**46**, **48**), 2-Py (**47**, **49**).

Reactions of the dimethylamide anion (from HMFTA) with *ortho*-substituted nitrobenzenes corroborate the fact that in the absence of steric hindrance in the N-anion the activity of the nitro group is high and comparable to that of fluorine.[61] In this case, the activities of the NO_2, F and Cl groups were determined from the degree of conversion of the starting compounds **2**–**4** after 5 h (GLC and NMR).



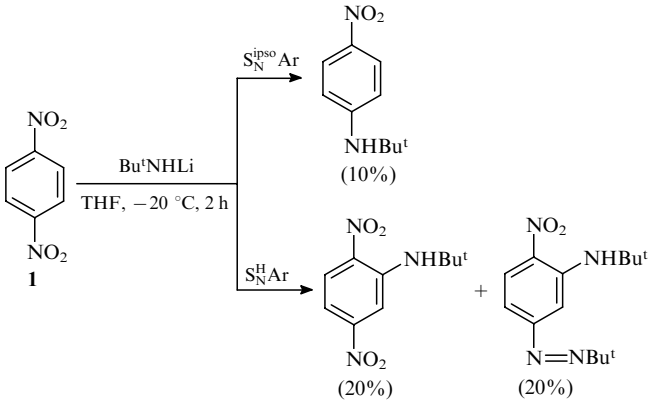
2–**4**

Compound	X	Conversion of compounds **2**–**4** (%)	
		GLC	NMR
2	NO_2	93	86
3	F	84	83
4	Cl	41	40

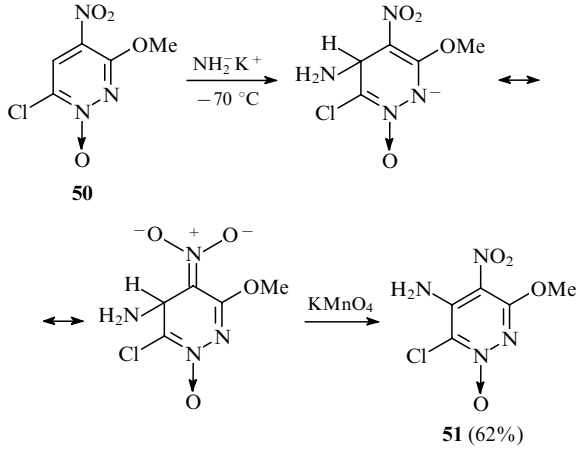
Steric hindrance in the N-anion changes the direction of the reaction, which sharply decreases the yields of the substitution products of the nitro group. Thus the substitution of the nitro group in the reaction of lithium *tert*-butylamide with 1,4-dinitrobenzene (**1**) proceeds with a rather small yield (10%), while the substitution of the hydrogen atom occurs to a larger extent. In this case, the nitrite ion generated in the $S_N^{ipso}Ar$ reaction [62] behaves as an oxidant of the corresponding σ-complex in the substitution of the hydrogen atom.[62] This occurs in parallel with partial reduction of the nitro compound formed by the hydride ion liberated in the reaction and condensation with *tert*-butylamine.

Table 3. Ratios of the yields of di-(**42**, **43**) and triarylamines (**44**, **45**) in the reaction of 4-substituted anilines **40** and **41** with nitrobenzenes **1**, **31** and **32**.[58–60]

Nitroarene	X	Aniline	:B	Solvent	Temperature /°C	Time /h	Reaction products [yield (%)]	
							diarylamine	triarylamine
1	NO_2	**40**	K_2CO_3	DMSO	120–130	5	**42** (50)	**44** (3)
32	F	**40**	K_2CO_3	DMSO	120–130	5.5	**42** (5)	**44** (64)
31	Cl	**41**	K_2CO_3	DMSO	145–150	5	**43** (71)	**45** (1–2)
31	Cl	**41**	NaH	DMF	100	2	**43** (38)	–

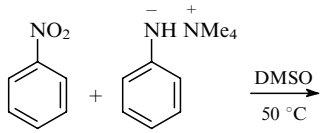


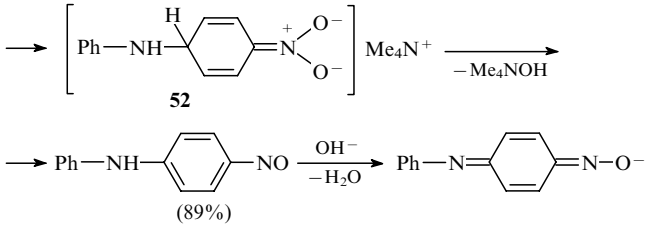
Substitution reactions of hydrogen in (het)arenes, which occur with retention of the halogens and/or the nitro group in the ring, are very typical of N-anions. They involve the intermediate formation of a σ^H-complex which can react with an external oxidant to give a substituted (het)arene.[2,63] Thus the reaction of 6-chloro-3-methoxy-4-nitropyridazine *N*-oxide (**50**) with potassium amide yields a σ-complex at the unsubstituted position 5 of the ring; this complex is further oxidised to the aromatic amine **51**.[64]



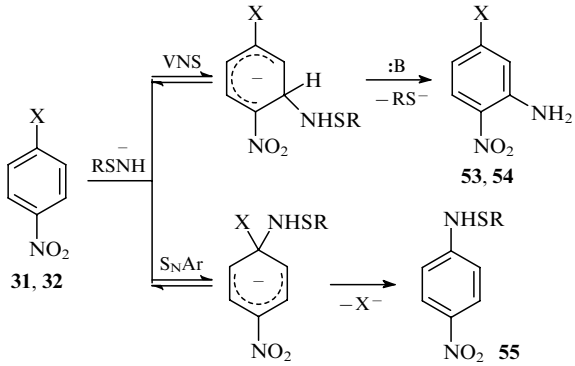
Other examples of nucleophilic hydrogen substitution with retention of the nitro group and the chlorine atom in the azine ring have been described.[2,63]

Intramolecular oxidation of a σ-complex is also possible. Thus the oxidation of the σ-complex **52** by the nitro-group oxygen is the main direction in the reaction of the anilide ion with nitrobenzene.[65]





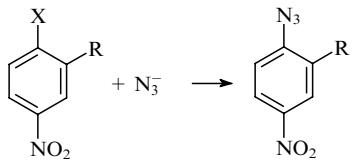
The conversion of the σ-complex can also proceed according to the vicarious substitution route. In this case, the N-nucleophile should contain a good leaving group, *e.g.*, a triazole,[66] an acetyl,[67] an ammonium[68] or a sulfide group.[69] However, in contrast to chlorine, the substitution of fluorine in arenes follows the S_NAr mechanism rather than VNS. The formation of compounds **53**–**55** is an example.[69]



R = 2,4,6-$Cl_3C_6H_2$.

Compound	X	Products [yield (%)]
31	Cl	**53** (60), **55** (0)
32	F	**54** (7), **55** (66)

The relative activities of the nitro group, fluorine and chlorine in reactions of arenes with the azide ion change in the following order: $NO_2 \geqslant F \gg Cl$ (see Ref. 11, p. 165; Refs 70 and 71). This dependence was established for the substitution of the 4-nitrobenzene derivatives **1**, **31**, **32** and **56**–**59** (Table 4):



R = H: X = NO_2 (**1**), Cl (**31**), F (**32**), I (**56**);
R = NO_2: X = F (**57**), Cl (**58**), I (**59**).

The nitro group activated by the electron-withdrawing substituents in the arene is readily replaced by a small-size azide ion in *N*-methyl-3,5-dinitrophthalimide,[72] 3-nitrothioxanthone deriva-

Table 4. Rate constants for the reactions of 1-X-4-nitrobenzenes (**1**, **31**, **32**, **56**) and 1-X-2,4-dinitrobenzenes (**57** – **59**) with the azide ion.[11, 70, 71]

Compound	R	X	Solvent	Temperature /°C	$10^4 k_2$ /litre mol^{-1} s^{-1}	$k_{rel} = k_2^X/k_2^I$
1	H	NO_2	MeOH	100	5.31	78.7 [a]
32	H	F	MeOH	100	2.32	68.8
			PhCl	80	649	54.1
31	H	Cl	PhCl	80	9.5	0.79
56	H	I	MeOH	100	0.0338	1
			PhCl	80	12	1
57	NO_2	F	MeOH (25%)	25	400	432
58	NO_2	Cl	MeOH (25%)	25	0.79	0.85
59	NO_2	I	MeOH (25%)	25	0.925	1

[a] With allowance for the statistical factor.

tives,[73] 2,5-dinitro-4-trifluoromethyl- and 5-chloro-2-nitrobenzonitriles[74] and 2-chloro-1-nitroanthraquinone.[75] In the case of 1-chloro-2-nitro- and 2-chloro-3-nitroanthraquinones containing a less active nitro group, it is only chlorine that is substituted.[76]

Some ambident ions (NO_2^-, SCN^-) react as N-anions in S_NAr reactions. The activities of the substituted groups in 1-X-4-nitrobenzenes **1**, **31** and **32** in their reactions with the nitrite ion decrease in the following order: F > Cl ≈ NO_2,‡ while those in 1-X-2,4-dinitrobenzenes **57**, **58** and **60** change as follows: NO_2 > Cl > F (Table 5).[77, 78] The reason for the change in the activities of substituents is that the limiting step of the reaction of low-reactive substrates with the nitrite ion is the formation of the σ-complex, in the reaction with highly reactive substrates it is its decomposition.[78] Thus, it is reasonable to use chlorine as a leaving group (especially in the case of highly reactive arenes) for the introduction of the nitro group into arenes according to the S_NAr mechanism, This has recently been demonstrated for the synthesis of 1,2,4-trinitrobenzene (**60**) from 2,4-dinitrochlorobenzene (**58**) and KNO_2 under the conditions of phase-transfer catalysis (yield 71%).[79] Substitution of the nitro group for fluorine is especially efficient in the case of low-reactive arenes, *e.g.*, penta- or hexafluorobenzenes.[80]

Table 5. Rate constants for the reactions of 1-X-4-nitrobenzenes **1**, **31** and **32** and 1-X-2,4-dinitrobenzenes **57**, **58** and **60** with the nitrite ion (DMSO).[77, 78]

Compound	X	Temperature /°C	$10^2 k_2$ /litre mol^{-1} s^{-1}	$k_{rel} = k_2^X/k_2^{Cl}$
1	NO_2	100	158	0.89
32	F	100	1290	7.25
31	Cl	100	178	1
60	NO_2	25	680	17
57	F	25	3.2	0.08
58	Cl	25	40	1

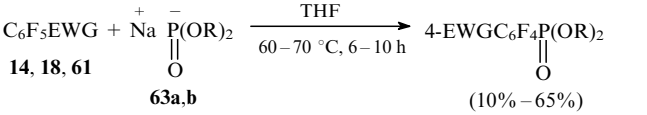
In the case of the thiocyanate ion, the activities of the leaving groups in the S_NAr reaction with 2,4-dinitrobenzenes **57**, **58** and **60** change in the following order: F ≈ NO_2 > Cl (Table 6).[81] The formation of the σ-complex is the limiting step of this reaction.

P-Anions react with nitro- and haloarenes to form preferably hydrogen substitution products rather than functional-group substitution products. Hydrogen substitution is observed not only for activated arenes, *e.g.*, trinitrobenzene[82] and 1-chloro-4-nitronaphthalene,[83] but also for less reactive substrates, such as 1-amino- and 1-methoxy-4-nitronaphthalenes[84] and 1-nitronaphthalene.[85] However, $S_N^{ipso}Ar$-substitution of fluorine and chlorine in activated polyhaloarenes **14**, **18**, **61** and **62** under the action of the dialkyl phosphite ions **63** is also possible in moderate yields.[86, 87] These reactions are usually carried out in weakly polar aprotic solvents (*e.g.*, ethers, hydrocarbons).

‡ The substitution of the nitrite ion for the nitro group is an example of a degenerate reaction.

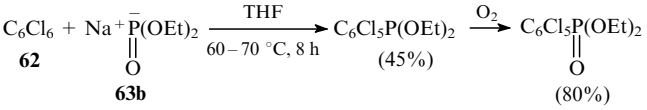
Table 6. Rate constants for the reactions of 1-X-2,4-dinitrobenzenes **57**, **58**, **60** with the thiocyanate ion SCN^- (DMSO, 75.2 °C).[81]

Compound	X	$10^3 k_2$ /litre mol^{-1} s^{-1}	$k_{rel} = k_2^X/k_2^{Cl}$
60	NO_2	1	50
57	F	1	50
58	Cl	0.0199	1



14, **18**, **61** — **63a**,**b**

EWG = NO_2 (**14**), CF_3 (**18**), CN (**61**); R = Me (**63a**), Et (**63b**).



62 — **63b**

Thus the N-anions of amines and the P-anions of dialkyl phosphites replace hydrogen in reactions with arenes, which is mainly due to steric factors. Compact inorganic azide, nitrite and thiocyanate ions readily replace the nitro group, fluorine and chlorine in activated arenes according to the S_NAr mechanism; in the case of the nitrite ion, the electrophilicity of the substrate determines the limiting step of the process.

IV. Reactions with O- and S-anions

The majority of papers devoted to nucleophilic substitution of the nitro group, fluorine and chlorine in arenes deal with their reactions with O- and S-anions. Many such reactions have been reviewed previously,[1, 7, 10 – 12, 20, 24] but a series of important kinetic studies in this area has appeared only in the past 10 – 15 years. The main differences in the relative activities of aromatic substituents under the action of hard O- or soft S-anions are determined by the different nature of the nucleophiles.[20, 88] S-Anions are much more reactive in both S_N2[89] and S_NAr reactions[20, 42] carried out in solutions than O-anions with similar basicities. This is due to the smaller solvation of S-anions in comparison with O-anions;[90, 91] therefore, the reactivities of S- and O-anions of equal basicities in the gas-phase S_N2-reactions differ only insignificantly.[92, 93] Consequently, the enhanced reactivity of S-anions in solution is not their intrinsic property (*cf.* Ref. 89).

Unfortunately, there are still no literature data on the quantitative aspects of nucleofugicities of leaving groups in arenes in the gas phase (with the exception of fluorine).[94, 95] Therefore, comparative activities of the aromatic nitro group, fluorine and chlorine with respect to the O- and S-anions are discussed exclusively for reactions carried out in solutions.

The data on the relative activities of the nitro group, fluorine and chlorine in structurally different arenes in their reactions with O- and S-anions are given in Table 7. The table contains both the kinetic characteristics and the most interesting synthetic results which altogether provide more detailed information about the dependence of the nucleofugicities of these groups on various factors.

First of all, it is worth comparing the activity series of the nitro group, fluorine and chlorine for those cases where substitution occurs according to the S_NAr mechanism with σ-complex for-

Table 7. Activities of the leaving groups X = NO_2, F and Cl in the reactions of ArX with O- and S-anions.

Ar	Entry	Nucleophile	Reaction conditions		Rate constant k_2^{Cl} /litre mol^{-1} s^{-1}	Relative activity $k_{rel} = k_2^X/k_2^{Cl}$ at X		Yield (%) [a] for X			Ref.
			solvent	temperature /°C		NO_2	F	NO_2	F	Cl	
4-$NO_2C_6H_4$	1	MeONa	MeOH	25	3.78×10^{-7}	224 [b]	473	–	–	–	96, 97
	2	MeONa	MeOH	50	8.46×10^{-6}	183 [b]	312	–	–	–	70, 98, 99
	3	MeONa	MeOH	50	8.46×10^{-6}	378 [b]	–	–	–	–	100, 101
	4	EtONa	EtOH	50	2.38×10^{-5}	500 [b]	360	–	–	–	100, 101
	5	Pr^{i}OK	Pr^{i}OH	75	1.2×10^{-5} (see [c])	–	250	–	–	–	102
	6	PhONa	DMSO	25	2.0×10^{-3}	–	260	–	–	–	103, 104
	7	PhONa	DMSO	90	–	–	–	77	–	–	105
	8	2,6-Br_2-4-MeC_6H_2ONa	DMSO	90	–	–	–	65	8	–	105
	9	1-$C_{10}H_7ONa$	DMSO	90	–	–	–	89	–	–	105
	10	MeSNa	Pr^{i}OH	40	1.09×10^{-3} (see [c])	–	–	–	–	100 (1.5)	106
	11	MeSNa	Pr^{i}OH	25	–	–	–	–	100	–	106
	12	Pr^{i}SNa	Pr^{i}OH	40	2.41×10^{-4} (see [c])	–	–	–	–	96	106
	13	PhSNa	MeOH	25	2.1×10^{-5}	–	10	–	–	–	20
	14	PhSNa	MeOH	50	3.2×10^{-4}	556 [b]	7.2	–	–	–	107, 108
	15	PhSNa	Pr^{i}OH	40	1.59×10^{-4} (see [c])	–	–	–	–	96	106
	16	$NaNO_2$	DMSO	100	0.89×10^{-4}	1.11	3.55	–	–	–	77, 78
	17	PhCH = NONa	DMSO	30	–	–	–	78	79	–	109
2-$NO_2C_6H_4$	18	MeONa	MeOH	50	2.52×10^{-6}	252 [b]	718	–	–	–	110, 111, 112
	19	CF_3CH_2ONa	HMPA	150	–	–	–	98 (2)	93 (2)	95 (2)	113
	20	Pr^{i}OK	Pr^{i}OH	75	8.1×10^{-5} (see [c])	–	395	–	92	98	102
	21	MeSNa	Pr^{i}OH	40	0.778×10^{-3} (see [c])	–	–	–	–	95	106
	22	Pr^{i}SNa	Pr^{i}OH	40	0.231×10^{-3} (see [c])	–	–	–	–	95	106
	23	PhSNa	Pr^{i}OH	40	0.098×10^{-3}	–	–	–	–	95	106
3-$NO_2C_6H_4$	24	MeONa	MeOH	49.55	1.59×10^{-7} (see [d])	–	–	–	–	–	114, 115
	25	MeONa	HMPA	25	–	–	–	83	–	–	36
	26	CF_3CH_2ONa	HMPA	25	–	–	–	93	78	–	116
	27	PhONa	DMSO	80	–	–	–	18	–	–	26
	28	PhOK	DMF	135	–	1.5 [e]	1	98	60	–	117
	29	3-$NO_2C_6H_4OK$	DMF	135	–	1.9 [e]	1	55	34	–	117
	30	PhSK	DMF	90	–	1.3 [e]	1	98	97	–	117
	31	PhSNa	HMPA	25	–	–	–	88	–	–	36
	32	Pr^{i}SNa	HMPA	25	–	–	–	86	–	–	118
4-CNC_6H_4	33	MeONa	DMF	25	–	–	–	92	–	–	119
	34	CF_3CH_2ONa	HMPA	25	–	–	–	95 (1.5)	58 [f]	64 [g]	116
	35	PhCH = NONa	DMSO	25	–	–	–	94	–	–	109
	36	PhONa	DMSO	50	3.39×10^{-2} (see [h])	–	–	93	–	–	120
	37	PhONa	DMSO	100	64.3×10^{-2} (see [h])	–	–	–	–	–	121
3-CNC_6H_4	38	CF_3CH_2ONa	HMPA	50	–	–	–	84	–	57 [g]	116
	39	PhONa	DMSO	100	1.2×10^{-2} (see [h])	–	–	–	–	–	121
4-$CF_3SO_2C_6H_4$	40	MeONa	MeOH	50	1.6×10^{-4}	690	160	–	–	–	122
	41	PhSNa	MeOH	50	1.03×10^{-4}	1300	8.6	–	–	–	123

Table 7 (continued).

Ar	Entry	Nucleophile	Reaction conditions		Rate constant k_2^{Cl} /litre mol^{-1} s^{-1}	Relative activity $k_{rel} = k_2^X/k_2^{Cl}$ at X		Yield (%) [a] for X			Ref.
			solvent	temperature /°C		NO_2	F	NO_2	F	Cl	
$C_6H_5COC_6H_4$	42	MeONa	DMSO	20	–	–	–	100	–	–	124
4-$NO_2C_6H_4COC_6H_4$	43	MeONa	DMSO	20	–	–	–	100	–	–	124
2,4-$(NO_2)_2C_6H_3$	44	MeONa	MeOH	25	2.9×10^{-2}	531	610 (562) [i]	–	–	–	20, 125 126
	45	PhSNa	MeOH	0	3.89	100	26.5 (33) [i]	–	–	–	107 127
	46	PhSNa	MeOH	25	21.0	1857	37	–	–	–	20
	47	2,4-$(NO_2)_2C_6H_3SK$	MeOH	30	3.63×10^{-2}	1585	17.8	–	–	–	81
	48	$NaNO_2$	DMSO	25	0.6	13.3	0.23	–	–	–	77, 78
	49	KSCN	DMF	75.2	1×10^{-2}	199.5	0.25	–	–	–	81
	50	$C_{16}H_{33}P^+Bu_3NCS^-$	PhCl	60	2.3×10^{-3}	–	1.4	–	–	–	71
4-NO_2-2-CNC_6H_3	51	MeONa	MeOH	25	24.2 [g]	–	–	–	–	–	126
2-NO_2-5-ClC_6H_3	52	MeONa	MeOH	25	7.28×10^{-3} (see [h])	–	–	–	–	–	10, 128
3-Cl-2-CNC_6H_3	53	MeONa	DMF – H_2O	25	–	–	–	67	–	–	74
	54	MeSK	DMF – H_2O	25	–	–	–	83	–	–	74
3-Cl-6-CNC_6H_3	55	$KSCH_2COOMe$	DMF – H_2O	0	–	–	–	84	–	–	129
	56	Na_2S	DMF – H_2O	0	–	–	–	66	–	–	130
2-SO_2CF_3-5-ClC_6H_3	57	MeONa	MeOH	65	–	–	–	61	–	–	131
	58	PhONa	MeOH	65	–	–	–	49	–	–	132
4-SO_2CF_3-3-ClC_6H_3	59	MeONa	MeOH	65	–	–	–	96.3	–	–	129
3-NO_2-4-$SO_2CF_3C_6H_3$	60	MeONa	MeOH	25	–	–	–	70	–	–	129
	61	PhONa	MeOH	25	–	–	–	32	–	–	130
	62	PhSNa	MeOH	25	–	–	–	(see [j])	–	–	130
3,5-$(NO_2)_2C_6H_3$	63	MeONa	MeOH	25	2.57×10^{-4} (see [d])	–	–	–	–	–	97
	64	MeONa	MeOH	40	4.1×10^{-4} (see [h])	–	–	–	–	–	133
	65	MeONa	MeOH	49.55	4.19×10^{-3} (see [d])	–	–	–	–	–	114
	66	MeONa	MeOH	100	4.06×10^{-1} (see [d])	–	–	–	–	–	115
	67	MeOK	MeOH	65	–	–	–	65 (0.3)	–	–	134
	68	MeONa	MeOH	65	–	–	–	–	–	(see [k])	135
	69	Na_2CO_3	EtOH (60%)	25	1.02×10^{-3} (see [d])	–	–	–	–	–	97
3-NO_2-5-$SO_2CF_3C_6H_3$	70	MeONa	MeOH	65	–	–	–	62 (1.5)	–	–	134
	71	PhSNa	MeOH	25	–	–	–	35	–	–	134
3-NO_2-5-CNC_6H_3	72	MeOK	MeOH	25	–	–	–	90	–	–	136
3-NO_2-5-$CF_3C_6H_3$	73	MeOK	MeOH	65	–	–	–	89 (0.3)	–	–	137
	74	MeONa	MeOH	100	3.23×10^{-2} (see [d])	–	–	–	–	–	115
	75	3-NO_2-5-$CF_3C_6H_3OK$	DMF	80	–	0.59 [e]	1	–	–	–	138
3,5-$(SO_2CF_3)_2C_6H_3$	76	MeONa	MeOH	25	–	–	–	31.4 (20)	92.5 (1)	0 (2)	139
	77	MeONa	MeOH	50	–	–	–	58.5 (2)	–	10.8 (2)	139
	78	PhSNa	MeOH	25	–	–	–	77 (1.5)	58.6 (2)	16.2 (2)	139
3,5-$(CF_3)_2C_6H_3$	79	MeONa	MeOH	100	1.17×10^{-3} (see [d])	–	–	–	–	–	115
	80	PhSNa	HMPA	25	–	–	–	92	–	–	36

Table 7 (continued).

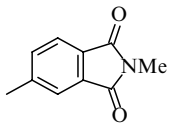
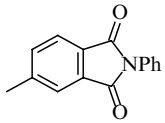
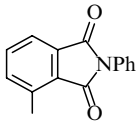
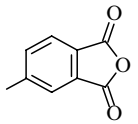
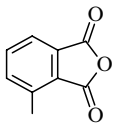
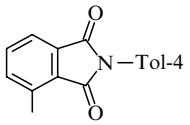
Ar	Entry	Nucleophile	Reaction conditions		Rate constant k_2^{Cl} /litre mol^{-1} s^{-1}	Relative activity $k_{rel} = k_2^X/k_2^{Cl}$ at X		Yield (%)[a] for X			Ref.
			solvent	temperature /°C		NO_2	F	NO_2	F	Cl	
	81	PhONa	DMSO	25	–	37[1]	4	–	–	–	140
	82	4-MeC_6F_4SNa	DMSO	25	–	250[1]	8	–	–	–	141
	83	PhONa	DMSO	25	–	130[1]	20	–	–	–	140
	84	4-MeC_6H_4SNa	DMSO	25	–	93.8[1]	4.8	–	–	–	141
	85	PhONa	DMSO	25	–	520[1]	65	–	–	–	140
	86	4-MeC_6H_4SNa	DMSO	25	–	2667[1]	31.7	–	–	–	141
	87	4-MeC_6H_4SNa	DMF	25	–	66.7[1]	6.7	–	–	–	142
	88	4-MeC_6H_4SNa	DMF	25	–	1400[1]	20	–	–	–	142
	89	4-MeC_6H_4ONa	THF	0	–	–	–	77	–	–	72
	90	PhSNa	DMSO	25	–	–	–	95	–	–	72

Table 7 (continued).

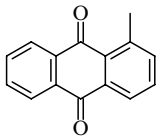
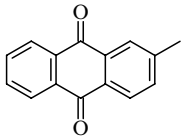
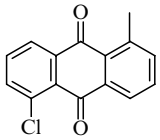
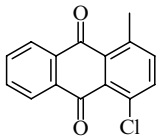
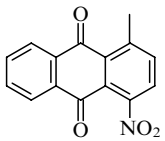
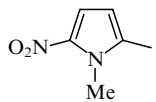
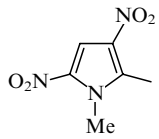
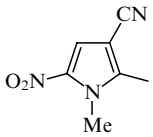
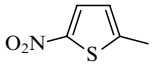
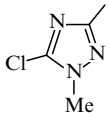
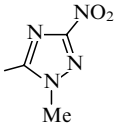
Ar	Entry	Nucleophile	Reaction conditions		Rate constant k_2^{Cl} /litre mol^{-1} s^{-1}	Relative activity $k_{rel} = k_2^X/k_2^{Cl}$ at X		Yield (%) [a] for X			Ref.
			solvent	temperature /°C		NO_2	F	NO_2	F	Cl	
	91	MeONa	MeOH	50	3.2×10^{-6}	214	535	–	–	–	143
	92	MeONa	MeOH	50	2.53×10^{-6}	713	783	–	–	–	143
	93	PhSNa	EtOH	80	–	–	–	90	–	–	144
	94	PhSNa	DMSO	20–25	–	–	–	80	–	–	29
	95	4-$NO_2C_6H_4ONa$	DMSO	60–70	–	–	–	–	–	90	29
	96	4-$NO_2C_6H_4ONa$	DMSO	65	–	–	–	–	77	–	145
	97	MeONa	MeOH	25	1.22×10^{-4}	11.1	–	–	–	–	96
	98	MeONa	MeOH	25	20.7 [h]	–	–	–	–	–	126

Table 7 (continued).

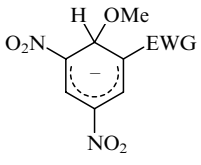
Ar	Entry	Nucleophile	Reaction conditions		Rate constant k_2^{Cl} /litre mol^{-1} s^{-1}	Relative activity $k_{rel} = k_2^X/k_2^{Cl}$ at X		Yield (%) [a] for X			Ref.
			solvent	temperature /°C		NO_2	F	NO_2	F	Cl	
	99	MeONa	MeOH	25	6.3 [g]	–	–	–	–	–	126
	100	PhSNa	MeOH	20	1.26×10^{-1}	1032	80	–	–	–	146
	101	MeONa	MeOH	25	0.42×10^{-4} (see [h])	–	–	–	–	–	147
	102	MeONa	MeOH	25	1.24×10^{-2}	–	–	–	–	–	147

[a] In parentheses, the reaction time /h. [b] With allowance for the statistical factor. [c] The pseudo-first order constant /s^{-1}. [d] k_2^F. [e] The activity relative to fluorine, determined from competitive reactions. [f] At 50 °C. [g] At 150 °C. [h] $k_2^{NO_2}$. [i] The value for fluorine calculated relative to chlorine. [j] Substitution of the SO_2CF_3 group (yield 95%). [k] Substitution of the nitro group (yield 10%). [l] Determined from competitive reactions.

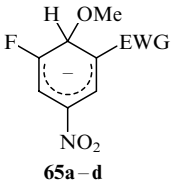
mation in the limiting step. For O-anions, the activities of the leaving groups decrease in the following order: F > NO_2 > Cl (Table 7, entries 1–3, 16, 18, 44, 75–77, 91, 92, 97), whereas those for S-anions change as follows: NO_2 > F > Cl (entries 14, 30, 47, 78, 82, 84, 86–88, 93, 94, 100). The activity series of the leaving groups NO_2, F and Cl present no peculiarities for various derivatives of 2- and 4-nitrobenzenes, 2,4- and 3,5-dinitrobenzenes, 3,5-bis(trifluoromethylsulfonyl)benzenes, 1- and 2-anthraquinones, 1-methyl-5-nitropyrroles and 5-nitrothiophenes and are attributable to different polarisabilities of O- and S-anions.[20] At the same time, in the case of 3-nitrobenzene, 3- and 4-cyanobenzene, 4-trifluoromethylsulfonylbenzene and 3- and 4-phthalimide derivatives (entries 26, 28–30, 34, 38, 40, 41, 81–86), the activity series of the leaving groups are the same for both O- and S-anions: NO_2 > F > Cl. However, for some compounds of this group the differences in the relative activities of the nitro group and fluorine for S-anions are more significant: $NO_2 \gg F$.[123, 141, 142]

It is known that in some compounds of the benzene series the electron-withdrawing substituents favour the replacement of the leaving group by the O- and S-anions in the order: *ortho* ⩾ *para* > *meta* (entries 5 and 20, 12 and 22, 15 and 23, 34 and 38). The degree of activation depends not only on the electronic properties of the substituent in the *ortho*- or *para*-positions relative to the leaving group (entries 2 and 40, 14 and 41, 6 and 36, 97–99), but also on the steric effect of the *ortho*-substituent. Thus steric hindrance due to the *ortho*-nitrile group is smaller than that of the *ortho*-nitro group in 2-substituted 1,4-dinitrobenzenes. Therefore, substitution of the methoxy group for the nitro group occurs faster in nitrile derivatives (entries 44 and 51). The activating effects of electron-withdrawing substituents in the *meta*-position of the benzene ring are strong enough for the substitution of the nitro group, fluorine and chlorine by both O- and S-anions (entries 25, 26, 28–32, 38, 39). In the case of simultaneous activation of the nitro group and chlorine by electron-withdrawing substituents in the *ortho*- and/or *para*-position(s) of the benzene ring, the activity of the nitro group exceeds markedly that of chlorine for both O- and S-anions (entries 52–59).

Substitution in the case of activation by electron-withdrawing substituents in the *meta*-position of the benzene ring has a number of specific features. Thus substitution of the nitro group under the action of methoxide occurs more easily in the case of activation by *meta*-CN or -CF_3 substituents than by *meta*-NO_2- or -SO_2CF_3 groups in 5-derivatives of 1,3-dinitrobenzenes (entries 67, 70, 72, 73). The situation is different if the leaving group is fluorine. The activation by a *meta*-NO_2 substituent is more efficient than that by the *meta*-CF_3 group in the same reaction (entries 66 and 74). The reason for the reversal of the substituent effects is the formation of more stable σ-complexes at the unsubstituted positions of the benzene ring **64a–d** (especially for EWG = NO_2 and SO_2CF_3) in comparison with the σ-complexes **65a–d** (see Ref. 148; pp. 173, 276 and 292).



64a–d

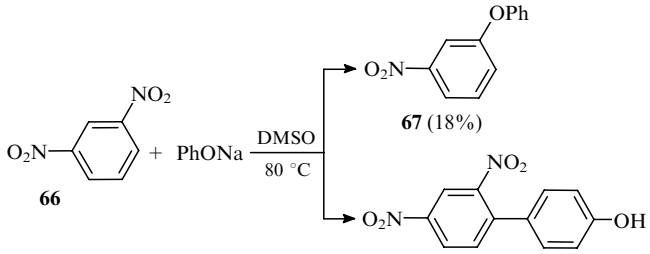


65a–d

EWG = NO_2 (**a**), SO_2CF_3 (**b**), CN (**c**), CF_3 (**d**).

The σ-complexes **65a–d** are significantly less stable; therefore, the activation occurs in an ordinary way in accordance with the Hammett constant, which reflects the effect of the electron-withdrawing *meta*-substituent (EWG) on the reaction centre (σ_M). The greater ease of substitution of the thiolate anion for the nitro group in 1-nitro-3,5-bis(trifluoromethyl)benzene in comparison with 1,3-dinitro-5-trifluoromethylsulfonylbenzene in the same reaction (entries 71 and 80) and the greater activity of fluorine in 3-nitro-5-trifluoromethylfluorobenzene in comparison with 3,5-bis(trifluoromethyl)fluorobenzene in the reaction with sodium methoxide (entries 74 and 79) can be explained in a similar way.

The lower activity of chlorine in comparison with the nitro group is also observed in the case of their simultaneous activation by an electron-withdrawing *meta*-substituent. Thus only the nitro group is substituted in 3,5-dinitrochlorobenzene under the action of methoxide (entry 68). Moreover, the nitro group in 1,3-dinitrobenzene (**66**) can be substituted under the action of the phenolate ion resulting in 3-nitrodiphenyl ether (**67**). The phenolate ion, being an ambident anion, also acts as a C-nucleophile and attacks the non-substituted position of the benzene ring to yield 2,4-dinitro-4′-hydroxybiphenyl (**68**) (entry 27).[26] In the latter case, the starting dinitrobenzene **66** acts as an oxidant of the intermediate σ-complex.[26]



66

68 (17%)

There are some other examples of the dependence of the direction of the substitution reaction on the nature of the nucleophile. Thus the reactions with O-anions result in the substitution of the nitro group in 2,4- (entries 60 and 61) and 3,5-dinitro-1-trifluoromethylsulfonylbenzene (entry 70), whereas reactions with S-anions result predominantly in the substitution of the trifluoromethylsulfonyl group in these compounds (entries 62, 71). The orientation of the substitution reactions in 1-chloro-4-nitroanthraquinone and 1-chloro-5-nitroanthraquinone also depends on the nature of the nucleophile: chlorine is predominantly substituted by O-anions, whereas the nitro group is substituted by S-anions (entries 93–95). Similarly, in 4-chloro-3,5-difluoronitrobenzene fluorine is substituted under the action of sodium methoxide, whereas chlorine is substituted under the action of the benzenethiolate anion.[149] The change in the reaction route on going from hard O-anions to soft easily polarisable S-anions seems to be caused by a transition from charge control to orbital control.[29, 149, 150] However, fluorine is more easily replaced in 1-fluoro-4-nitroanthraquinone irrespective of the nature of the nucleophile, which is consistent with charge control of the reaction.[29, 145]

The ease of substitution of the nitro group, fluorine and chlorine is also determined by the structure of the substrate. Thus the activities of these substituents in reactions with both O- and S-anions are much higher for 3-substituted phthalic acid derivatives than for 4-substituted derivatives (entries 83–88). This is corroborated by the selective substitution of the 3-nitro group in 3,5-dinitro-*N*-arylphthalimide under the action of both O- and S-anions (entries 89 and 90). The activities of the nitro group and fluorine in 2-substituted anthraquinone are somewhat higher than in the 1-isomer, whereas those of chlorine are virtually identical in these compounds (entries 91 and 92). It was found also that the nitro group in 5-chloro-1-methyl-3-nitro-1,2,4-triazole is almost 300 times less active than chlorine in a reaction with methoxide (entries 101 and 102). These data corroborate the fact that different activities of substituents with respect to the same nucleophile are determined by different electronic and steric effects in the substrate.

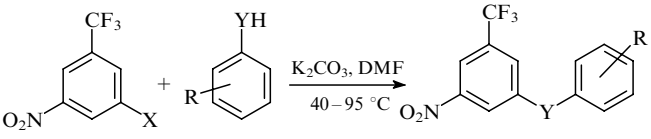
The data on the activities of the nitro group, fluorine and chlorine in the above-described reactions with O- and S-anions are

related to the S_NAr mechanism with the σ-complex formation as a limiting step. If the limiting step is the decomposition of the σ-complex, the activities of the leaving groups in reactions with O- and S-anions will be as follows: $NO_2 > Cl > F$ (entries 48 and 49). This series corresponds to the increase in the dissociation energy of the Ar–X bond on going from X = NO_2 to X = F (see Table 1).

In some substitution reactions by aryloxide anions, the nitro group manifests higher activity (entries 7–9) than fluorine and chlorine (entries 6 and 8). However, the addition of a radical trap to a reaction mixture containing 1,4-dinitrobenzene (**1**) and the 2,6-dibromo-4-cresolate anion inhibits completely the substitution of the nitro group. Presumably, the substitution of the nitro group in compound **1** occurs predominantly according to the electron transfer mechanism.[105]

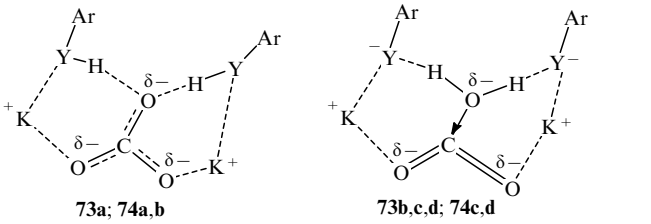
It is known that the energies of bimolecular S_NAr reactions depend on the nature of the leaving group and the nucleophile,[1] whereas the reactivities in these processes are under enthalpy control.[11] Entropy control itself is effective in fast bimolecular reactions occurring in solution involving radicals ($k_2 = 10^6–10^8$ litre mol^{-1} s^{-1} from −85 to −10 °C),[151] carbenes ($k_2 = 10^4–10^9$ litre mol^{-1} s^{-1} at 25 °C)[152] or carbocations ($k_2 = 10^{-1}–10^8$ litre mol^{-1} s^{-1} from −70 to −30 °C)[153] where the contribution of enthalpy is either very small or constant as a result of which the transition state is shifted to earlier position on the reaction coordinate.[152, 153]

Recently, it has been found that the selectivity of substitution of the nitro group and fluorine in S_NAr reactions is connected with entropy control,[154, 155] although bimolecular S_NAr reactions occur at a relatively slow rate ($k_2 = 10^{-4}–10^{-1}$ litre mol^{-1} s^{-1} at 25 °C in DMSO or DMF).[156] However, the relative activities of the nitro group and fluorine in the competitive reactions between nitrobenzotrifluorides **69** and **70**, phenols **71** and arenethiols **72** in the presence of K_2CO_3 in DMF (40–95 °C) are controlled by the entropy of the activation, since $T\Delta S^{\neq} > \Delta\Delta H^{\neq}$ in all cases (Table 8).[154, 155] It was shown[157] that compounds **71** and **72** yield complexes **73** and **74** of the type (2 ArYH)·K_2CO_3 in the reaction with K_2CO_3 in DMF. The structures of these complexes depend on the nature of the substituent in the benzene ring.



69, **70** **71a–d**, **72a–d**

X = NO_2 (**69**), F (**70**).



73a; **74a**,**b** **73b**,**c**,**d**; **74c**,**d**

Compound	Y	R	Compound	Y	R
71a, **73a**	O	H	**72a**, **74a**	S	H
71b, **73b**	O	4-Cl	**72b**, **74b**	S	4-MeO
71c, **73c**	O	3-NO_2	**72c**, **74c**	S	3-CF_3
71d, **73d**	O	4-CN	**72d**, **74d**	S	4-NO_2

As the changes in the entropy $\Delta\Delta S^{\neq}$ are positive, the reactions of the fluoro derivative **70** with complexes **73** and **74** are more organised in comparison with analogous reactions of the dinitro-substituted compound **69**. Therefore, the S_NAr-substitution of the nitro group in compound **69** is characterised by an earlier transition state on the reaction coordinate than the substitution of fluorine in compound **70**.[154, 155]

Table 8. Relative activities of the nitro group and fluorine and the activation parameters for the competitive reactions of compounds **69** and **70** with phenols **71a–d** and arenethiols **72a–d** in the presence of K_2CO_3 (DMF, 70 °C).[154, 155]

Compound	$k_{rel} = k^{NO_2}/k^F$	$\Delta\Delta H^{\neq}$ (see [a]) /kJ mol^{-1}	$T\Delta\Delta S^{\neq}$ (see [b]) /kJ mol^{-1}
71a	1.11	18.1	18.2
71b	1.20	21.8	22.0
71c	1.38	27.6	28.7
71d	1.58	80.3	82.8
72a	10.1	69.1	72.3
72b	6.73	60.6	63.2
72c	32.8	94.1	98.6
72d	116.2	124.8	130.9

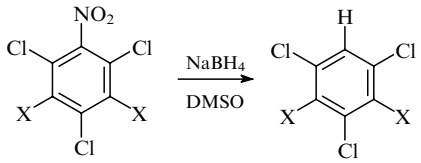
[a] $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{NO_2} - \Delta H^{\neq}_{F}$, [b] $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{NO_2} - \Delta S^{\neq}_{F}$.

Summing up the results of the discussion of the reactivities of O- and S-anions, special mention should be made of the following items. First of all, it is obvious that the reactions of O- and S-anions are very sensitive to the nature of both the substrate and the leaving group in the arene. Soft S-anions usually react with those centres in the arene which carry highly polarisable leaving groups owing to the orbital control of the reaction. The reactions of hard O-anions are characterised by charge control. As a result, the activity series of the leaving groups changes from $NO_2 > F > Cl$ (RS^-) to $F > NO_2 \geqslant Cl$ (RO^-) within the framework of the same reaction mechanism. It should be stressed that the selectivity of substitution of the nitro group and halogens under the action of O- and S-anions may depend on the transition from enthalpy to the entropy control as the nature of the nucleophile is changed.

V. Reactions with hydride and halide ions

S_NAr substitution of the nitro group and halogens in arenes under the action of hydride and halide ions has been described in a number of reviews.[7, 148, 158] Here, it seems expedient to emphasise only some peculiarities of activities of aromatic substituents with respect to these nucleophiles.

The activity of the nitro group is somewhat higher than that of chlorine in the reaction of *para*-substituted nitrobenzenes with the hydride ion in DMSO,[159] which is also characteristic of other hard anions, *e.g.*, N- and O-anions (see Sections III and IV). However, the nucleofugicity of the nitro group in arenes is increased drastically if it becomes non-coplanar with the aromatic ring under the influence of steric factors. Thus only the nitro group is replaced by hydrogen in the reaction of pentachloronitrobenzene (**75**) or 1,3,5-trichloro-2,4,6-trinitrobenzene (**76**) with sodium borohydride.[160, 161]

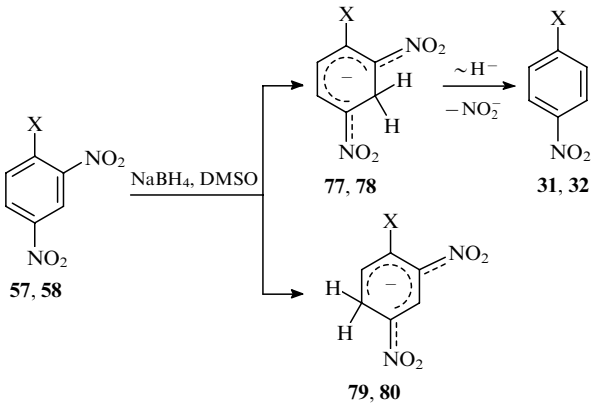


75, **76**

X = Cl (**75**), NO_2 (**76**).

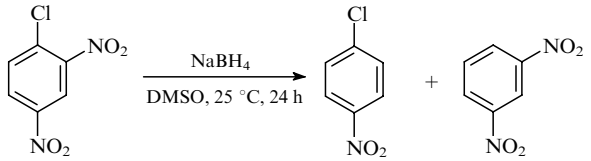
The enhanced activity of the aromatic nitro group (in comparison with fluorine and chlorine) with respect to the hydride ion may be due to a predominant attack on the unsubstituted position of the aromatic ring. Thus the reaction of compounds **57** and **58** with sodium borohydride in DMSO occurs *via* the anionic σ^H-complexes **77–80**. It is noteworthy that the conversion of the

σ-complexes **77** and **78** into halonitrobenzenes **31** and **32** proceeds as the intramolecular substitution of the hydride ion for the nitro group.[159]



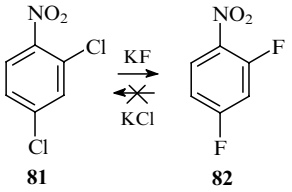
X = F (**32**, **57**, **77**, **79**), Cl (**31**, **58**, **78**, **80**).

Owing to such a vicinal attack, the yield of the substitution product of the nitro group (compound **31**) in the case of the chloro derivative **58** markedly exceeds the yield of the substitution product of chlorine (compound **66**),[159] which is formed upon a significant increase in the reaction time.

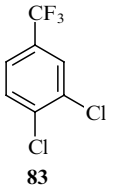


Recently, it has been shown that reactions of nitroarenes with the hydride ion ($NaBH_4$) strongly depend on the spatial structures of the substituents adjacent to the reaction centre.[162, 163] Moreover, one should not rule out the possibility that the predominant substitution of the nitro group in comparison with halogens in the reactions of halonitroarenes with the borohydride anion is due to the steric features of the nucleophile.

Substitution of chlorine and the nitro group in arenes under the action of the fluoride ion is a main route to the introduction of fluorine into the aromatic ring;[14, 15, 164] this approach has a considerable preparative significance.[165–169] The nucleophilicity of the halide ions in S_NAr reactions occurring in dipolar aprotic solvents changes in the following order: $F \gg Cl > Br > I$.[77, 78, 170] Thus the rate of the substitution of the fluoride ion (DMSO, 25 °C) for the nitro group in compound **60** exceeds 320-fold the rate of an analogous reaction with the chloride ion.[77] The halogen exchange in 2,4-dichloro- (**81**) and 2,4-difluoronitrobenzenes (**82**) under the action of KF and KCl, respectively (DMF, 125 °C) is yet another example of a higher nucleophilicity of the fluoride ion.[171]



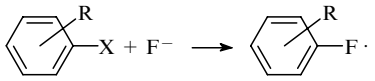
If the substitution of chlorine for fluorine in compound **82** does not take place, compound **81** reacts with KF to give product **82** in a quantitative yield; the rate constant of this pseudo-first order reaction (k_1) is 3.43×10^{-4} s^{-1} (125 °C).[171] This value is similar to the value of the rate constant ($k_1 = 1.1 \times 10^{-4}$ s^{-1}) for the substitution of fluorine for chlorine in 3,4-dichlorobenzotrifluoride (**83**)



under the action of KF (sulfolane, 180 °C) in the presence of Ph_4PCl.[172] However, the nucleophilicity of the chloride ion in the substitution of the nitro group in compound **76** (LiCl in acetone) is high enough [$k_2 = 0.525$ litre mol^{-1} s^{-1} (25 °C)].[173] The high substitution rate and the low activation energy of the latter reaction are due to alleviation of steric strain on going from the starting compound to the intermediate σ-complex.[173]

Relative activities of the nitro group, fluorine and chlorine in various disubstituted arenes with respect to the fluoride ion are listed in Table 9. The activity series of these substituents in the

Table 9. Activities of the leaving groups X in reactions of compounds ArX with the fluoride ion.



R	Entry	Reagent	Reaction conditions	Temperature /°C	Time /h	k_2^{Cl} /litre mol^{-1} s^{-1} [$k_{rel} = k_2^X/k_2^{Cl}$]	Yield (%) at X		Ref.
							NO_2	Cl (F)	
4-NO_2	1	RbF	DMSO	150	0.5	[500(NO_2), 1(Cl), 50(F)][a]	–	–	35
	2	RbF	DMSO	110	0.5	–	87	–	35, 174
	3	RbF	DMSO	165	0.25	–	–	35–50	175
	4	CsF	DMSO	80	0.3	1.0×10^{-4} (see [b])	50	–	176
	5	RbF	DMSO	25	–	0.92×10^{-4} (see [c])	–	–	177
	6	KF	DMSO	190	14	–	–	72	178
2-NO_2	7	RbF	DMSO	150	0.5	[1.3(NO_2), 1(F)][d]	–	–	35
	8	RbF	DMSO	150	0.3	–	58	–	35, 174
	9	RbF	DMSO	25	–	3.12×10^{-4}	–	–	177
	10	KF	DMSO	185	4.5	–	–	38	178
	11	Bu_4NF	THF	20–25	1.5	–	100	25	179
3-NO_2	12	RbF	DMSO	150	0.3	–	17.4	–	35
	13	KF	NMP[e]	180	48	–	40–45	–	125

Table 9 (continued).

R	Entry	Reagent	Reaction conditions	Temperature /°C	Time /h	k_2^{Cl} /litre mol^{-1} s^{-1} [$k_{rel} = k_2^X/k_2^{Cl}$]	Yield (%) at X		Ref.
							NO_2	Cl (F)	
	14	KF	Sulfolane, PDC [f]	200	72	–	70	–	180
	15	KF	Sulfolane, PDC, Me_4NCl	160	8	–	94	–	181
	16	KF	Sulfolane, PDC, Ph_4PBr	180	3	–	89	–	182
	17	KF	Sulfolane, PDC, Ph_4PBr	220	5.5	–	–	16 [g]	182
	18	Me_4NF	DMSO	100	4	–	70	–	183
	19	$Me_4NF \cdot HF$	DMA [h]	140	2	–	66	–	184
4-CN	20	RbF	DMSO	150	0.3	–	81	–	35
	21	RbF	DMSO	165	0.25	–	50	30	175
	22	CsF	DMSO	80	0.33	1.58×10^{-7}	7	–	176
	23	KF	DMSO	180	0.16	–	75	–	185
	24	KF	DMI [i]	290	2	–	–	91	186
2-CN	25	RbF	DMSO	150	0.3	–	86	–	35, 174
	26	KF	DMI	290	2	–	–	76	186
	27	Me_4NF	DMSO	80	1	–	100	–	183, 187
2-CF_3	28	Me_4NF	DMSO	80	24	–	95	–	187
2-CHO	29	Me_4NF	DMSO	80	1	–	60	–	187
3-CN	30	KF	Sulfolane, PDC, Ph_4PBr	210	2.5	–	86	–	182
	31	KF	DMI	290	8	–	–	70	186

[a] The activities of groups X relative to chlorine, determined from competitive reactions. [b] $k_2^{NO_2}$ (25 °C). [c] k_2^F. [d] The activities of groups X relative to fluorine. [e] NMP is *N*-methylpyrrolidone. [f] PDC is phthaloyl chloride. [g] 1-Chloro-3-fluorobenzene is also formed (yield 27%). [h] DMA is *N*,*N*-dimethylacetamide. [i] DMI is 1,3-dimethylimidazolidin-2-one.

reactions of 1,4-disubstituted benzenes **1**, **31** and **32** with $Rb^{18}F$ (DMSO, 150 °C) changes in the following order: $NO_2 > F \gg Cl$ (Table 9, entry 1).[35] However, the activities of the nitro group and fluorine in an analogous reaction of 1,2-disubstituted benzenes **2** and **3** are markedly approximated (entry 7).[35] A comparison of the activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) for the substitution of the nitro group and fluorine in compounds **1** and **32** under the action of the ^{18}F-labelled fluoride ion in DMSO showed that the selectivity of substitution of these groups (k^{NO_2}/k^F ratio) is controlled by the entropy of activation.[176, 177] Obviously, in this case, too, the substitution of the nitro group in compound **1** is characterised by an earlier transition state on the reaction coordinate than the substitution of fluorine in compound **32** (*cf.* Refs 154 and 155). At the same time, the substitution of the nitro group in 1,4-dinitro- (**1**) and 1-cyano-4-nitrobenzenes (**22**) under the action of the fluoride ion in DMSO (entries 4 and 21) is subject to enthalpy control despite the fact that a decrease in the electrophilicity of the substrate **22** results in a more positive value of $\Delta S^{\neq}$ in comparison with compound **1** (see Ref. 176).

The data listed in Table 9 corroborate the fact that fluorodenitration is an efficient procedure for the introduction of fluorine into the aromatic ring in both activated (entries 2, 4, 8, 11, 20, 21, 23, 25, 27–29) and low-reactive substrates (entries 13–16, 18, 19 and 30).

Some synthetic implications of reactions of complex chloro(nitro)aromatic compounds with the fluoride anion are presented in Table 10; these are analysed in subsequent paragraphs with regard to the previously established kinetic, thermodynamic and

Table 10. Activities of the leaving groups NO_2 and Cl in reactions of chloronitroarenes with the fluorine ion resulting in fluoroarenes.

Compound	Entry	Reagent	Reaction conditions	Temperature /°C	Time /h	Reaction products	Yield (%)	Ref.
2-NO_2-4-$ClC_6H_3CO_2Me$	1	Me_4NF	DMSO	80	1.5	2-F-4-$ClC_6H_3CO_2Me$	76	183, 187
	2	$R_3NMeF \cdot 2H_2O$ [a]	DMSO	100	2	2-F-4-$ClC_6H_3CO_2Me$, 2-NO_2-4-$FC_6H_3CO_2Me$	50, 6	188
	3	KF	DMSO, Ph_4PBr	130	27	2-F-4-$ClC_6H_3CO_2Me$, 2-NO_2-4-$FC_6H_3CO_2Me$	72, 1	189
4-NO_2-2-$ClC_6H_3CO_2Me$	4	Me_4NF	DMSO	80	3	4-F-2-$ClC_6H_3CO_2Me$	44	187
	5	KF	DMSO, Ph_4PBr	130	24	4-F-2-$ClC_6H_3CO_2Me$	60	189
2-NO_2-4-ClC_6H_3CN	6	KF	DMSO, Ph_4PBr	130	0.5	2-F-4-ClC_6H_3CN	100	189
4-NO_2-2-ClC_6H_3CN	7	KF	DMSO, Ph_4PBr	130	1	4-F-2-ClC_6H_3CN, 2,4-$F_2C_6H_3CN$	90, 10	189
2-NO_2-4-$ClC_6H_3CF_3$	8	KF	DMSO, Ph_4PBr	130	20	2-F-4-$ClC_6H_3CF_3$	31	189
4-NO_2-2-$ClC_6H_3CF_3$	9	KF	DMSO, Ph_4PBr	130	5	4-F-2-$ClC_6H_3CF_3$	48	189
2-NO_2-4-$ClC_6H_3SO_2CF_3$	10	KF	DMSO, Ph_4PBr	130	0.5	2-F-4-$ClC_6H_3SO_2CF_3$, 2,4-$F_2C_6H_3SO_2CF_3$	64, 26	189
4-NO_2-2-$ClC_6H_3SO_2CF_3$	11	KF	DMSO, Ph_4PBr	130	0.1	4-F-2-$ClC_6H_3SO_2CF_3$, 2,4-$F_2C_6H_3SO_2CF_3$	78, 5	189
	12	Bu_4NF	THF	78	0.5	4-F-2-$ClC_6H_3SO_2CF_3$	98	189
2-NO_2-4-$ClC_6H_3NO_2$	13	$R_3NMeF \cdot 2H_2O$	DMSO	60	0.1	2-F-4-$ClC_6H_3NO_2$ + + 2-F-5-$ClC_6H_3NO_2$	95	188

Table 10 (continued).

Compound	Entry	Reagent	Reaction conditions	Temperature /°C	Time /h	Reaction products	Yield (%)	Ref.
2-NO_2-6-ClC_6H_3CN (**84**)	14	RbF	DMSO	150	0.3	2-F-6-ClC_6H_3CN, 2-NO_2-6-FC_6H_3CN (**33**)	55, 17	35, 174
	15	Bu_4NF	THF	25	1.5	2-F-6-ClC_6H_3CN, 2,6-$F_2C_6H_3CN$	75, 25	179
	16	$Me_4NF \cdot HF$	DMA	60	3	2-F-6-ClC_6H_3CN	84	184
4-$ClC_6H_4SO_2C_6H_4NO_2$-4	17	$R_3NMeF \cdot 2H_2O$	DMSO	100	0.5	4-$ClC_6H_4SO_2C_6H_4F$-4	75	188
3,5-$(NO_2)_2$-4-$ClC_6H_2CF_3$	18	KF	Sulfolane, TPDF [b]	150	2	5-NO_2-3,4-$F_2C_6H_2CF_3$	70	181
1,2,4-$(NO_3)_3C_6H_3$ (**58**)	19	KF	Sulfolane, PDC, Me_4NCl	160	1.5	3,4-$F_2C_6H_3$ NO_2	51	181
3-NO_2-4-$ClC_6H_3CF_3$	20	KF	Sulfolane, PDC, Ph_4PBr	180	7	3,4-$F_2C_6H_3CF_3$	65	181
3-NO_2-4-ClC_6H_3CN	21	KF	Sulfolane, PDC, Ph_4PBr	180	2	3,4-$F_2C_6H_3CN$	65	182
3-NO_2-6-ClC_6H_3CN	22	KF	Sulfolane, PDC, Ph_4PBr	220	8	2,5-$F_2C_6H_3CN$	25	182
$C_6Cl_5NO_2$ (**75**)	23	KF	DMF	150	4	C_6Cl_5F	10	178
2,3,5,6-$Cl_4C_6HNO_2$ (**85**)	24	Bu_4NF	THF	25	1.5	2,3,5,6-Cl_4C_6HF	70	179
	25	Me_4NF	MeCN	50	3	2,3,5,6-Cl_4C_6HF	86	187
2,3,4,5-$Cl_4C_6HNO_2$	26	$R_3NMeF \cdot 2H_2O$	DMSO	100	0.1	2,3,4,5-Cl_4C_6HF	84	188
2,4-$(NO_2)_2C_6H_3CO_2Me$	27	Me_4NF	DMSO	60	1	2-NO_2-4-$FC_6H_3CO_2Me$, 4-NO_2-2-$FC_6H_3CO_2Me$	66, 20	183, 187
2,4-$(NO_2)_2C_6H_3CF_3$	28	Me_4NF	DMSO	80	4	4-NO_2-2-$FC_6H_3CF_3$, 2,4-$F_2C_6H_3CF_3$	63, 31	187
2,4-$(NO_2)_2C_6H_3CN$	29	Me_4NF	DMSO	80	0.2	2,4-$F_2C_6H_3CN$	100	187
1,3,5-$(NO_2)_3C_6H_3$	30	KF	Sulfolane, PDC	180	12	3,5-$F_2C_6H_3NO_2$	77	180
3,5-$(NO_2)_2C_6H_3CO_2Me$	31	RbF	DMSO	150	0.3	5-NO_2-3-$FC_6H_3CO_2Me$	34	35
N-Methyl-4-nitrophthalimide	32	KF	–	300	5	*N*-methyl-4-fluorophthalimide	28	190
4-Nitrophthalic anhydride	33	KF	–	220	2	4-fluorophthalic anhydride	62	191

[a] R_3N is hexamethylenetetramine (urotropin). [b] TPDF is tetrafluorophthaloyl fluoride.

topological peculiarities. High yields of fluoro derivatives can be achieved by varying the source of the fluoride ion (Table 9, entries 11, 18, 19, 28 and 29), solvents and traps for the leaving nitrite ion (Table 9, entries 15, 16 and 30).[164]

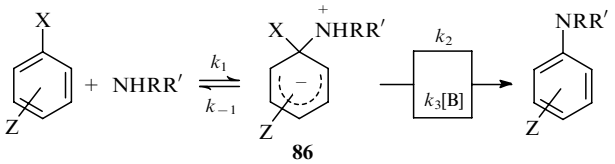
The lower activity of chlorine in comparison with the nitro group (Table 9, entries 11, 17, 21, 30 and 31) allows selective fluorodenitration in nitrochloroarenes where these substituents are additionally activated by an electron-withdrawing group (Table 10, entries 1–17). Under these conditions, the effect of the phase-transfer catalyst on the exchange of the nitro groups and chlorine is more pronounced in weakly polar aprotic solvents than in strongly polar solvents.[192] Using the reaction of 2-chloro-6-nitrobenzonitrile (**84**) with KF as an example, a number of solvents were tested to ensure the highest selectivity of substitution of the nitro group in comparison with chlorine: DMSO > NMP > sulfolane > MeCN > 1,2-dimethoxyethane (1,2-DME).[193] The order of substitution of the NO_2 and Cl groups in chloronitroarenes containing no activating group changes to the opposite (Table 10, entries 18–22). In this case, both functional groups are substituted for fluorine.[164]

In polychloronitroarenes, the rate of substitution of the nitro group increases under the action of the fluoride ion due to both its exit from the plane of the aromatic ring and the inductive effect of chlorine (entries 24–26).[179] Naturally, the fluorodenitration reaction proceeds especially smoothly in nitroarenes where the nitro group is activated by more than one electron-withdrawing substituent (entries 27–33).

The relative nucleofugicities of the nitro group and chlorine within the same molecule were studied using semi-empirical methods (AM1 and PM3) for the reaction of 2,4-dichloronitrobenzene (**81**) with a free fluoride ion and a fluoride ion bound to the counterion Me_4N^+. A comparison of the transition state enthalpies for these reactions demonstrated a certain preference for fluorodenitration in the case of the free fluoride ion,[194] whereas fluorodechlorination occurs preferentially with Me_4N^+ as a counterion. In addition, it was found experimentally[187, 194] that the effect of the solvent on the predominant substitution of the nitro group or chlorine under the action of Me_4NF in 2,3,5,6-tetrachloronitrobenzene (**85**) can be used for estimating the contribution of solvation effects to the structure of the transition states of these reactions.

VI. Reactions with amines

Among other neutral nucleophiles used for aromatic substitution of the nitro group and halogens, only amines have been studied in detail.[1, 165, 195–199] In contrast to reactions with charged nucleophiles, S_NAr reactions with primary and secondary amines can be catalysed by bases; the role of a base can be played by the second molecule of the amine.



86

The experimental second-order rate constant k_A is calculated from the conventional mechanism of S_NAr reactions with amines at a steady-state concentration of the σ-complex **86**:[1, 195, 196]

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]}.$$

Depending on the ratio of the rate constants k_1, k_{-1}, k_2 and $k_3[B]$ in reactions with amines, the following variants are possible:

(a) if $k_2 + k_3[B] \gg k_{-1}$, there is no catalysis and $k_A = k_1$, *i.e.*, the formation of the σ-complex **86** is the limiting step;

(b) if $k_2 + k_3[B] \ll k_{-1}$, the rapid formation of the intermediate **86** is followed by the rate-determining step of its decomposition, and the expression for k_A appears as $k_A = k_1 \times k_2/k_{-1} + k_2 \times k_3[B]/k_{-1}$, which predicts that the basic catalysis will be characterised by a linear dependence of k_A *vs* [B];

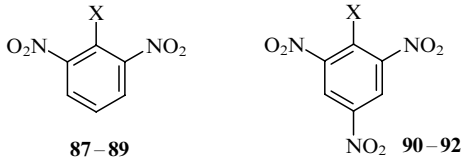
(c) if $k_2 + k_3[B] \approx k_{-1}$, the dependence of k_A on [B] will be more complex, *viz*., at low [B], the dependence of k_A on [B] will be linear, whereas at high [B] it will reach a plateau where $k_A = k_1$. Depending on the nature of the aromatic compound, the amine, the base and the solvent, different substitution mechanisms of the nitro group, fluorine and chlorine in arenes under the action of amines will be realised,[1, 195, 196, 200, 201] as a result of which the substitution rate constant k_A for these groups will change substantially.

The data on the relative activities (rate constants k_A) of the nitro group, fluorine and chlorine in various arenes under the action of primary and secondary amines in protic, aprotic polar and nonpolar solvents are given in Table 11. The activity series of the leaving groups in reactions of 1,4-disubstituted nitrobenzenes **1**, **31** and **32** with piperidine in aprotic dipolar solvents appear as: F ≫ NO_2 > Cl (Table 11, entries 1–3). This order is obviously preserved in reactions of more electrophilic 1-X-2,4-dinitrobenzenes (**57**, **58**, **60**) with piperidine in both protic (MeOH) and aprotic polar solvents (MeCN): F > NO_2 ≫ Cl (entries 10 and 11). Presumably, this order of the relative activities of the leaving groups is observed in the absence of the amine catalysis where $k_A = k_1$ and the formation of the intermediate **86** is the limiting step.[1, 211, 217]

At the same time, the differences in the activities of the nitro group, fluorine and chlorine in reactions of compounds **1**, **31** and **32** with piperidine in aprotic weakly polar solvents are less apparent, and the order of their activities varies from F > Cl > NO_2 (Table 11, entry 4) to F > NO_2 > Cl (entry 5). The activity series of the leaving groups on going to more electrophilic arenes **57**, **58** and **60** in reactions with piperidine under identical conditions appear to be different: NO_2 > F > Cl (entries 12 and 13).

The reason for such variations in the relative activities of these groups is the change of the limiting step of the reaction. If the reaction of compounds **58** and **60** with piperidine in benzene is not subject to catalysis by the amine, the formation of the σ-complex **86** is the limiting step of the reaction.[205, 213] The reaction of 1-fluoro-2,4-dinitrobenzene (**57**) is catalysed by piperidine.[211, 214] This is confirmed by the observation of a kinetic isotope effect in a reaction where deuteriopiperidine [214] and the ^{18}F-labelled starting compound **57** were used.[218] Obviously, in this case the decomposition of the σ-complex of the type **86** is the limiting step of this reaction.[211, 214] A comparison of k_A values for the substitution of fluorine and chlorine in reactions of compounds **57** and **58** with piperidine revealed that the k_A^F/k_A^{Cl} ratio was rather small.[211, 214] Quite probably, the small values of the $k_A^{NO_2}/k_A^{Cl}$ and k_A^F/k_A^{Cl} ratios in the reactions of nitrobenzenes **1** and **32** with this amine also suggest that the decomposition of the σ-complex **86** is the limiting step in the substitution of the nitro group and fluorine (entries 4 and 5).

The relative activities of the leaving groups in reactions of di- and trinitrobenzenes **57**, **58** and **60** with the primary aromatic amine, *viz*., aniline, in ethanol decrease in the following order: NO_2 > F > Cl,[209] which becomes NO_2 ≫ F ≫ Cl for an analogous reaction of more electrophilic arenes, *viz*., 2,6-dinitro- (**87**–**89**) and 2,4,6-trinitrobenzenes **90**–**92** (entries 16 and 17).



87–**89** **90**–**92**

X = NO_2 (**87**, **90**), F (**88**, **91**), Cl (**89**, **92**).

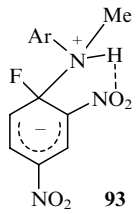
Table 11. Activities of the leaving groups X (X = NO_2, F, Cl) in reactions of substituted arenes ArX with amines.

Ar	Entry	Amine	Solvent	Temperature /°C	k_A^{Cl} /litre mol^{-1} s^{-1}	$k_{rel} = k_A^X/k_A^{Cl}$ at X		Ref.
						NO_2	F	
4-$NO_2C_6H_4$	1	$C_5H_{10}NH$	DMSO	50	6.6×10^{-5}	8.7	412	202
	2	$C_5H_{10}NH$	DMSO	50	2.28×10^{-5}	6.7	325	203
	3	$C_5H_{10}NH$	MeCN	50	5.5×10^{-6}	3.4	209	203
						(2.6) [a]	–	204
	4	$C_5H_{10}NH$	MeCOEt	50	9.3×10^{-6}	0.25	24	203
	5	$C_5H_{10}NH$	$MeCO_2Et$	50	0.32×10^{-6}	5.6	134	203
2-$NO_2C_6H_4$	6	$C_5H_{10}NH$	C_6H_6	25	1.44×10^{-4} (see [b])	–	–	205
				60	1.05×10^{-5}	–	–	206
	7	$C_5H_{10}NH$	n-C_6H_{14}	27.4	1.67×10^{-4} (see [b])	–	–	207
	8	Pr^iNH_2	$C_6H_5CH_3$	60	1.71×10^{-5} (see [c])	–	–	208
2,4-$(NO_2)_2C_6H_3$	9	$PhNH_2$	EtOH	50	2.69×10^{-4}	188	62	209
	10	$C_5H_{10}NH$	MeOH	0	1.95×10^{-3}	207	769	210
	11	$C_5H_{10}NH$	MeCN	15	0.291	–	375	211
				25	0.422	–	214	212
	12	$C_5H_{10}NH$	$MeCO_2Et$	15	0.183	–	85	211, 213
	13	$C_5H_{10}NH$	C_6H_6	15	4.0×10^{-2}	–	92	211, 213
				25	8.05×10^{-2}	143	29	205, 214
	14	4-$MeOC_6H_4NH_2$	C_6H_6	30	0.21×10^{-5}	–	33	215
	15	4-$MeOC_6H_4NHMe$	C_6H_6	30	0.43×10^{-5}	–	0.3	215
2,6-$(NO_2)_2C_6H_3$	16	$PhNH_2$	EtOH	50	1.98×10^{-4}	1646	44	216
2,4,6-$(NO_2)_3C_6H_2$	17	$PhNH_2$	EtOH	50	3.34	1260	100	209

[a] The experimental value for the nitro group was calculated relative to chlorine. [b] Substitution of the nitro group. [c] Substitution of fluorine.

For polynitroarenes, the higher activities of the nitro group (compounds **60**, **87** and **90**) and fluorine (compounds **57**, **88** and **91**) in comparison with chlorine (compounds **58**, **89** and **92**) are due to the fact that the limiting step of these reactions is the formation of the σ-complex **86**.[1, 10, 199, 205] The activity of the nitro group in compounds **87** and **90** is higher than that of fluorine (compounds **88** and **91**) due to the steric effect of two *ortho*-nitro groups in the vicinity of the reaction centre (*cf.* entries 9, 16 and 17).[216] The weaker spatial effect of a primary amine in comparison with the secondary amine causes a reversal of the relative activities of the nitro group and fluorine in reactions of compounds **60** and **57** with aniline and piperidine in alcohols where the formation of the intermediate **86** (entries 9 and 10) is the limiting step.[217] Moreover, steric effects in amines can even change the limiting step of the substitution in arene **57** with a small-sized leaving group (the fluoride ion). Thus the reaction of the ^{18}F-labelled compound **57** with 2-methylaniline (DMSO, 30 °C) manifests a pronounced kinetic isotope effect which suggests the abstraction of the fluoride ion at the rate-determining step.[219] However, no such effect is observed in an analogous reaction with 4-methylaniline where the formation of the σ-complex **86** is the limiting step[219] (*cf.* Ref. 220). Naturally, the steric effects of primary and secondary amines in their reactions with arenes in weakly polar media disappear, if the decomposition of the σ-complex **86** is the limiting step. The low values of the k_A^F/k_A^{Cl} ratio in reactions of compounds **59** and **60** with piperidine and 4-anisidine in benzene where the former undergoes catalysis by the corresponding amine (entries 13 and 14) is supporting evidence for this hypothesis.[214, 215]

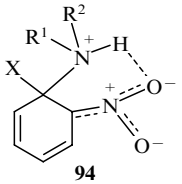
The reasons for the higher activity of fluorine in reactions of arenes with amines in weakly polar media in comparison with chlorine under conditions of basic catalysis were discussed in some recent publications.[199] The formation of a hydrogen bond with the amino group is a possible explanation for the faster abstraction of the fluoride ion from the σ-complex **86**. This means that the abstraction of the fluoride ion requires an additional molecule of the amine, *i.e.*, a catalytic step takes place.[199] This is confirmed by a decrease in the activity of fluorine in comparison with chlorine in reactions of halogeno-2,4-dinitrobenzenes **57** and **58** with *N*-methyl-4-anisidine in benzene; the efficiency of catalysis in the reaction of compound **57** (X = F) with a secondary amine markedly decreases due to increased stability of the intermediate **93**.[215]



93

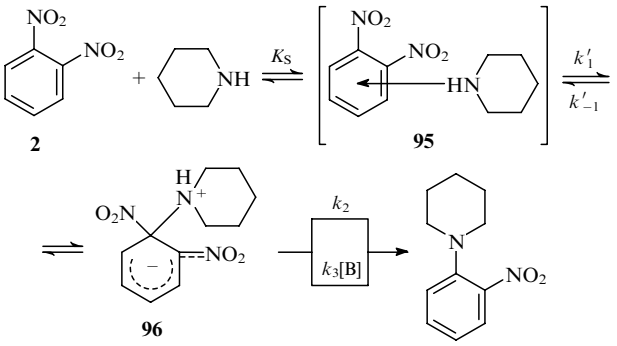
The formation of a molecular complex of an arene and an amine that is more reactive than the arene itself may be regarded as yet another reason for the higher activity of fluorine in comparison with chlorine under catalytic conditions. This is supported by high negative values of ρ obtained in the analysis of the Hammett equation for the reaction of compound **57** with substituted anilines.[199] Both molecular complexes of reactants and aniline dimers, which are more reactive nucleophiles[221, 222] may be formed on the reaction coordinate of compounds **57** and **58** with aniline in a weakly polar solvent.

It should be emphasised that the activities of the nitro group, fluorine and chlorine in *ortho*-substituted benzenes **2**–**4** exceed those of the *para*-substituted compounds **1**, **32** and **33** in reactions with piperidine in weakly polar solvents due to intramolecular solvation in the transition state of the reaction, *i.e.*, in the intermediate **94** (Table 11, entries 4, 5 and 6).[1, 206, 208]



94

The reactions of compounds **2**–**4** with amines are not catalysed by a base and the formation of the σ-complexes **86** is the limiting step.[205, 206, 208] In contrast, similar reactions of compounds **1**, **32** and **33** are catalysed by a base and decomposition of the corresponding σ-complexes is the limiting step. The amine-catalysed reaction of 1,2-dinitrobenzene (**2**) with piperidine in non-polar n-hexane is an exception.[207] The kinetics of this reaction involves the equilibrium constant K_S for the formation of the n–π electron-donor complex **95** prior to the formation of the σ-complex **96**; the decomposition of the latter is the limiting step of this reaction (entry 7).[207] Recently, it has been shown that no complexes of the type **95** are formed upon substitution of benzene for n-hexane, which results in the deceleration of the reaction of arene **58** with amines.[223]

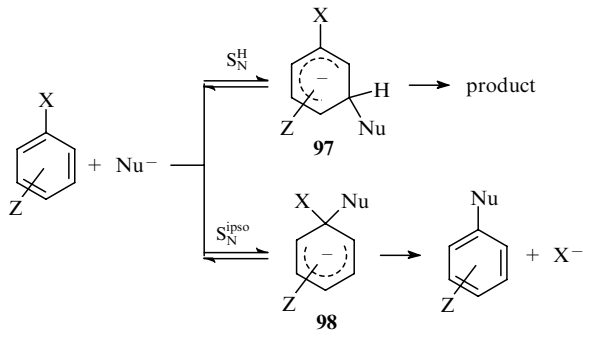


Thus, the substitution reactions of the nitro group, fluorine and chlorine in arenes under the action of amines under various reaction conditions are multistep processes. In-depth studies of their mechanisms in weakly polar and nonpolar media are currently under way.[224–228] Such reactions are also being investigated for five-membered heterocycles, *e.g.*, thiophene derivatives.[229, 230]

VII. The role of the reaction mechanisms

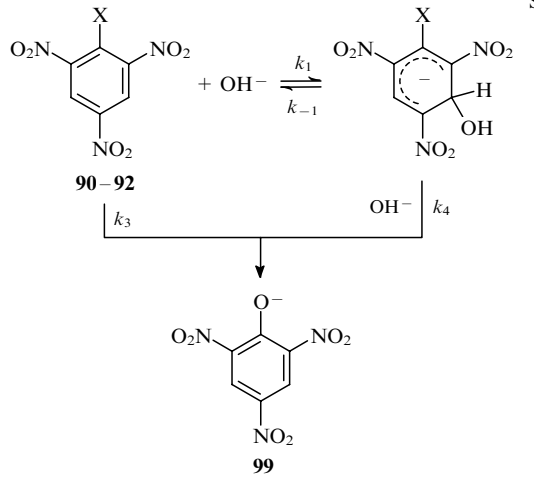
Although the nucleophilic substitution mechanism S_NAr (addition–elimination) in arenes and heteroarenes has become classical in organic chemistry long ago,[1, 7, 10, 11] some alternative mechanisms can also be used. These may be divided into several groups, *viz.*, electron-transfer reactions (SET),[3] photochemical reactions,[6, 231–233], vicarious hydrogen substitution reactions (VNS),[2, 9] *kine*- and *tele*-substitutions,[6, 234] ring opening–closure reactions, mainly for heterocyclic compounds (ANRORC)[2, 64] and reactions catalysed by transition metals.[235, 236]

It is known that the formation of σ-complexes of the type **97** at nonsubstituted positions of activated aromatic rings proceeds much faster and the stabilities of these complexes strongly depend on the nature of the nucleophile, the substrate and some other factors.[1, 2, 5, 9, 25, 44, 148] Therefore, S_N^H and S_N^{ipso} substitutions always compete with one another due to the reversibility of formation of the σ-complexes **97** and **98**.



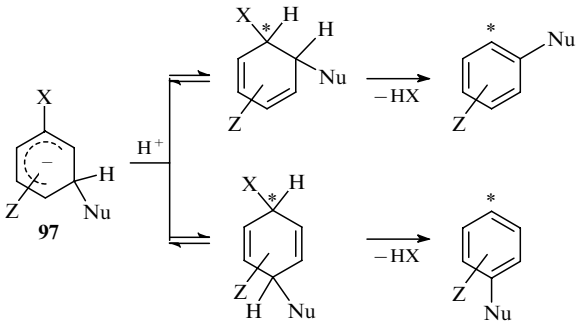
If σ-complexes of the type **97** can be transformed further (*e.g.*, according to VNS or an oxidative route[2,9]), the S_N^H route will prevail over S_N^{ipso} substitution. Such a competition has already been discussed in this review (Sections III – V) (see also Ref. 237). It is of note that steric and electronic factors can also influence the regioselectivity of substitution of the nitro group, fluorine and chlorine.[5,20] Thus compounds **90** and **92** react with the hydroxide ion in water more readily according to the S_N^H route than according to the S_N^{ipso} route, whereas picryl fluoride **91** undergoes preferably *ipso*-substitution in this reaction.[238,239] Presumably, the stereoelectronic effects in the reaction of compound **91** with the hydroxide ion in the *ipso*-position favour fast formation of the picrate ion **99** (Scheme 3).[5,20]

Scheme 3



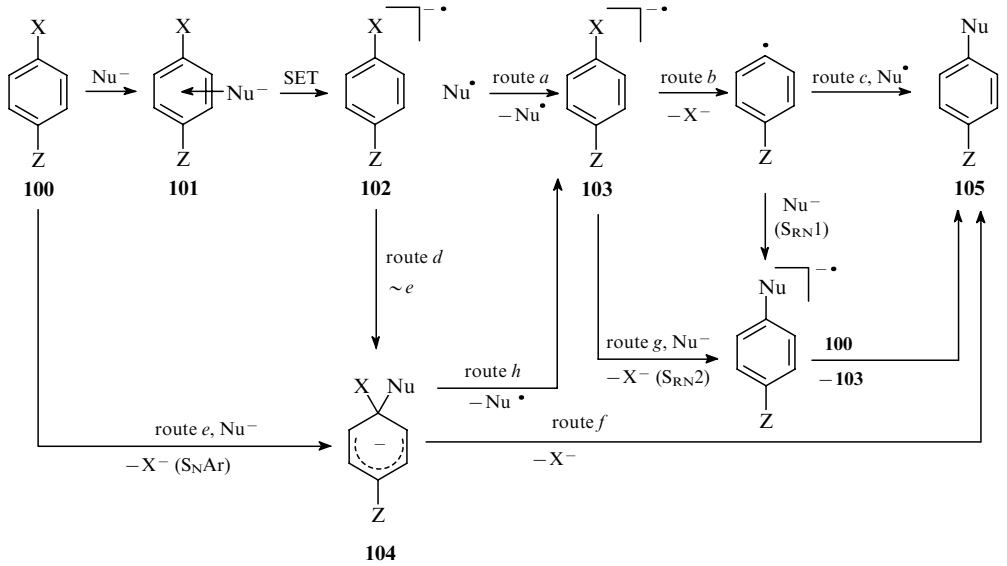
Compound	X	k_1/litre mol^{-1} s^{-1}	k_3/litre mol^{-1} s^{-1}
90	NO_2	1450	140
91	F	50	750
92	Cl	6	0.40

Steric effects in a nucleophile may become crucial as regards the regioselectivity of substitution. Thus compounds **3** and **4** react with the 2-phenylthio-1,3-dithiane carbanion exclusively according to the VNS mechanism.[240] Recently, it has been shown that the S_N^H substitution becomes prevalent over S_N^{ipso} substitution in reactions of 1,3-dinitrobenzene (**66**) and its 5-fluoro- and 5-chloro derivatives with potassium methoxide with an increase in the excess of the nucleophile relative to the substrate.[241] The competition between the S_N^{ipso} and S_N^H routes may result in *kine*- and *tele*-substitution due to faster conversion of the σ-complex of the type **97**. Various *kine*- and *tele*-substitution reactions of the nitro group were generalised in the reviews.[6,234]



Aromatic nucleophilic substitution reactions are characterised by an immense diversity of intermediates formed (Scheme 4). Introduction of a nitro group into the aromatic ring significantly facilitates the formation and increases the stability of the corresponding radical anions because of a decrease in their LUMO energy. As a rule, *para*-substituted aryl halides **100** (X and/or Z = Hal) produce intermediate structures **101** and **102** and then free radical anions of the type **103**, which undergo fragmentation into aryl radicals and halide ions and can serve as substrates for $S_{RN}1$ reactions (routes *a* + *b*).[3,242–244] The $S_{RN}1$ mechanism is uncommon for nitro- and halogenonitroarenes. It was shown that substitution of fluorine and chlorine in compounds **57** and **58** under the action of a sterically hindered ethyl α-cyanophenylacetate carbanion in DMSO is induced by a solvated electron and occurs according to the $S_{RN}1$ mechanism.[245] Previous studies have

Scheme 4



shown [246, 247] that substitution of fluorine and chlorine in compounds **31** and **32** under the action of ethyl cyanoacetate carbanion in DMSO follows a non-chain radical mechanism (routes *a* + *c*) (*cf*. Ref. 105). However, it is believed [248] that in the latter case the reactions proceed presumably with an electron transfer (route *d*) with an intermediate formation of the radical pair **102** inside the solvent cage. Subsequent coupling of the radical anion and the radical inside the cage yields the σ-complex **104**. The S_NAr mechanism (route *e*) cannot be excluded either.[248]

There is a great body of evidence in favour of the *ipso*-substitution mechanism in nitro- and halogenonitroarenes under the action of charged and neutral nucleophiles, which proceeds *via* an intermediate n–π donor–acceptor complex of the type **101**. This is followed by an electron transfer resulting in the formation of the radical pair **102**.[242, 243, 249–251] The further fate of the radical pair **102** depends largely on the nature of the nucleophile, although its further conversion according to the route *d* + *f* prevails.[251] Since the routes *d* and *e* leading to the formation of the reaction product **105** are kinetically indistinguishable, the S_NAr substitution mechanism is not ruled out either.[248] If the radical pair **102** leaves the solvent cage, free radical anions of the type **103** can be detected by ESR.[244, 249–252] The hypothesis that these radical anions lie on the coordinate of nucleophilic $S_{NR}2$ substitution of the nitro group, fluorine and chlorine (route *g*) [253, 254] met sound criticism on kinetic,[255, 256] electrochemical [256, 257] and theoretical grounds.[3, 243] Most probably, the formation of radical anions of the type **103** and the substitution *via* the σ-complex **104** may occur in parallel and independently of one another.[244] Using the reaction of 1,4-dinitrobenzene **1** with the cyanide ion in oxygen-free DMF as an example, it was shown that the radical anions **103** can be generated by homolytic fragmentation of the σ-complex **104** (route *h*) [258] (*cf*. Ref. 257). Therefore, the *ipso*-substitution of the nitro group, fluorine and chlorine in nitro- and halogenonitroarenes follows mainly the SET or the S_NAr mechanism (routes *d*, *e* and *f*) (*cf*. Ref. 259).

Photochemical substitution reactions of fluorine and chlorine in arenes have been reviewed previously;[231] their mechanisms strongly depend on the nature of the arene and the nucleophile. However, photosubstitution of the nitro group in arenes has been little studied. It was shown [231] that the reaction of 4-nitroanisole with glycine ethyl ester occurs upon an attack of the substrate in the excited state by the nucleophile (the S_NAr^* mechanism).[260] The SET mechanism is realised to a lesser degree [260] (*cf*. Ref. 261). It is of note that photochemical transformations are more efficient for S_N^H substitution reactions in nitroarenes which proceed according to the VNS mechanism.[232, 233]

Reactions according to the ANRORC mechanism are mostly related to S_N^H rather than S_N^{ipso} substitution.[2, 63] The S_N^{ipso} reactions catalysed by transition metals (Cu, Ni, Pd, *etc*.), are of extreme importance and are being developed dynamically; they were studied mostly for the substitution of chlorine, bromine and iodine.[168, 235, 236, 262–265]

* * *

A vast body of evidence has been accumulated on the activities (including relative activities) of the nitro group, fluorine and chlorine in aromatic nucleophilic substitution reactions in relation to the structure of the substrate, the type of the nucleophile and the medium and the reaction mechanism. This review is an attempt at a state-of-the-art generalisation of the results obtained in this area. The need for such generalisation is due to the fact that significant progress in the development of methods for functionalisation of arenes has become possible owing to the use of convenient nucleophilic *ipso*-substitution reactions ($S_N^{ipso}Ar$).

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