JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
*J. Phys. Org. Chem.* 2007; **20:** 369–374

(www.interscience.wiley.com) DOI: 10.1002/poc.1146

# Selectivity of nitro *versus* fluoro substitution in arenes in their reactions with charged *O*- and *S*-nucleophiles

**Irina A. Khalfina and Vladislav M. Vlasov***

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, 9 Lavrentjev Avenue, Novosibirsk 630090, Russia

*Received 20 July 2006; revised 22 September 2006; accepted 6 October 2006*

ABSTRACT: The relative mobility of nitro and fluoro substituents in 1,3-dinitro- and 1-fluoro-3-nitrobenzenes, 3,5-dinitro- and 3-fluoro-5-nitrobenzotrifluorides under the action of the nucleophiles $(2ArYH)\cdot K_2CO_3$ and $ArY^-K^+$ in solution and the nucleophiles $ArYH\cdot K_2CO_3$ (Y = O, S) under heterogeneous conditions was studied by a competitive method in DMF at 40–140 °C. The unique dependences of $\Delta\Delta H^{\neq}$ on $\Delta\Delta S^{\neq}$ and $\Delta\Delta H^{\neq}$ on $\Delta\Delta G^{\neq}$ were determined for all the substrates and nucleophiles. The dependence of the mechanistic pathway on the nucleophile is discussed. Two results are relevant to the reactions studied: (i) substituent effects in the nucleophiles $(2ArYH)\cdot K_2CO_3$ and $ArYH\cdot K_2CO_3$ on the activation entropies suggest that the entropy favours the displacement of nitro group; (ii) the negative signs of $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ for the reactions of the nucleophiles $ArY^-K^+$ indicate that the enthalpy determines the displacement of nitro group. It is concluded that the selectivity of the reactions with aryloxide and arylthioxide ions cannot be explained by the hard–soft acid–base principle only. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: aromatic nucleophilic substitution; nucleophilic reactivity; selectivity; compensation relationship; reaction mechanisms

## INTRODUCTION

It is well known that the selectivity of *ipso*-substitution in $S_NAr$ reactions depends on the nature of the nucleophile, and the comparison of hard and soft nucleophile reactivity (HSAB principle[1]) is a good method for predicting leaving mobility in these reactions.[2] As evident from previous data,[2,3] soft thiophenoxides substitute for a nitro group more rapidly than for fluorine in the reactions of 2-R- and 4-R-nitrobenzenes, 1-R-2,4- and 1-R-3,5-dinitrobenzenes, 1-R-4-trifluoromethylsulfonylbenzenes, 1-R-3,5-bis(trifluoromethylsulfonyl)benzenes, 3-R- and 4-R-phthalimides, 1-R- and 2-R-anthraquinones and 1-R-5-nitrothiophenes (everywhere R = $NO_2$, F) in comparison with hard oxygen nucleophiles. The activity series of the leaving groups $NO_2$ and F are attributable to the different polarizabilities of *O*- and *S*-anions.[2a]

Recently we found that the selectivity of the displacement of nitro and fluoro groups in the reactions of 1,3-dinitro- and 1-fluoro-3-nitrobenzenes, (**1** and **2**), 3,5-dinitro- and 3-fluoro-5-nitrobenzotrifluorides, (**3** and **4**), with phenols and thiophenols in the presence of potassium carbonate in DMF depends on the nature of the nucleophile.[4–6] It is worth noting that anhydrous potassium carbonate is widely used in organic synthesis as a non-nucleophilic agent for generating charged nucleophiles *in situ* in different nucleophilic reactions[7] including organic reactions under solid–liquid phase transfer catalysis conditions.[7a–d] We showed previously that phenols and thiophenols with $K_2CO_3$ in DMF form two types of nucleophiles as **5** and **6**.[4,8]

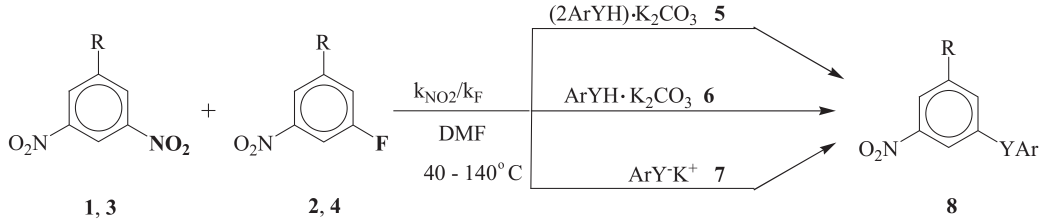
Nucleophile **6** characterised by IR and $^{19}F$ NMR spectra forms in the presence of an excess of solid $K_2CO_3$ (heterogeneous reaction conditions).[4] The other nucleophile **5** determined by IR, $^1H$, $^{13}C$ and $^{39}K$ NMR spectroscopy is obtained when the corresponding phenols or thiophenols and $K_2CO_3$ are kept in DMF at 70 °C, followed by filtration from the excess of solid $K_2CO_3$ (homogeneous reaction conditions).[8] Therefore, it was interesting to compare the selectivity of the displacement of nitro and fluoro groups in the reactions of **1** and **2**, **3** and **4** by action of nucleophiles **5**, **6** and standard nucleophile $ArY^-K^+$**7** under heterogeneous reaction conditions and in DMF solution.

## RESULTS AND DISCUSSION

The relative mobility of nitro and fluoro substituents in two couples of substrates, **1** and **2**, **3** and **4**, was

---

**Correspondence to:* V. M. Vlasov, N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, 9 Lavrentjev Avenue, Novosibirsk 630090, Russia.
E-mail: vmvlasov@nioch.nsc.ru



**1, 2** R = H
**3, 4** R = $CF_3$

**a**. Y = O, Ar = $4\text{-}MeC_6H_4$
**b**. Y = O, Ar = Ph
**c**. Y = O, Ar = $4\text{-}ClC_6H_4$
**d**. Y = O, Ar = $3\text{-}NO_2C_6H_4$
**e**. Y = O, Ar = $4\text{-}AcC_6H_4$
**f**. Y = O, Ar = $4\text{-}CNC_6H_4$
**g**. Y = O, Ar = $3\text{-}NO_2\text{-}5\text{-}BrC_6H_3$
**h**. Y = S, Ar = $4\text{-}MeOC_6H_4$
**i**. Y = S, Ar = Ph
**j**. Y = S, Ar = $2\text{-}C_{10}H_7$
**k**. Y = S, Ar = $3\text{-}CF_3C_6H_4$
**l**. Y = S, Ar = $4\text{-}NO_2C_6H_4$

**Figure 1.** Scheme of the competitive displacement of nitro and fluoro groups in arenes **1**, **2** and **3**, **4** in their reaction with nucleophiles **5–7**

investigated by a competitive method[9] with a series of *O*-, **5a**,**d**,**g**, **6a–g**, **7a**,**d**,**g**, and *S*-nucleophiles, **5i**, **6h–l**, **7i**, in DMF at 40–140 °C (Fig. 1).

Fluoro-substituted substrates are compounds **2**, **4**. The selected temperature range ensured quantitative yields of the target products **8** and the absence of by-products. Nucleophiles **6** are readily generated *in situ* from the corresponding phenols and thiophenols in the presence of potassium carbonate under heterogeneous conditions.[4–6] At the same time nucleophiles **5** and **7** are obtained in DMF solution.[8] Clearly, it is difficult to compare kinetic data of heterogeneous and homogeneous processes. However, the competing technique may be useful for studying substrates exhibiting comparable reactivities, since the apparent reaction rate weakly depends on the rates of reaction steps other than the displacement steps.[10]

A better insight into the effects of the nucleophile structure on the displacement selectivity can be obtained from studies in which the reaction temperature is varied. The ratio $k_{NO_2}/k_F$ for the competitive reactions of **1**, **2** with **6a–d**,**i** and **3**, **4** with **5a**,**d**,**g**,**i**, **6a–l**, **7a**,**d**,**g**,**i** depends on temperature and changes from 0.57 to 116.2 (Table 1). The phenols and thiophenols under study give rise to linear relations between $\log(k_{NO_2}/k_F)$ and $1/T$ ($r = 0.999$; Fig. 2), obtained for the studied phenols and thiophenols, which means that the Arrhenius equation is valid for all the investigated reactions.

As can be seen from Table 1, the differences in the activation parameters ($\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$) calculated from the modified Eyring equation for competing reactions have positive signs, except for reactions of **3**, **4** with **7a**,**d**,**g**,**i** (entries 2, 4, 6, 8). The latter exhibit negative signs for $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$. Positive $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ suggest that the substitution of the nitro group in **1**, **3** is favoured by the entropy factor while the fluoro substitution in **2**, **4** is favoured by the enthalpy one. The opposite applies for $\Delta\Delta H^{\neq} < 0$ and $\Delta\Delta S^{\neq} < 0$: the nitro group displacement is preferred by enthalpy and the entropy favours the fluoro displacement. The $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values thus obtained (Table 1) are linearly related ($r = 0.999$; Fig. 3); this indicates a compensation relationship[11] for the reactions of all the substrates **1–4** and the whole series of nucleophiles **5–7** in homogeneous and heterogeneous conditions. The compensation regression was also estimated by the plot of $\Delta\Delta H^{\neq}$ *versus* $\Delta\Delta G^{\neq}$ (Fig. 4).[12] It is worth nothing that the $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values for the reactions of **1–4** with *S*-nucleophiles **5i** and **6i** are larger than those for the same reactions with *O*-nucleophiles **5a** and **6a** (Table 1, Figs 3 and 4, entries 1 and 7, 9 and 17, 22 and 25). At the same time there is almost no difference between the $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values for the reactions of **3**, **4** with both *O*- and *S*-nucleophiles **7** (Table 1, Figs 3 and 4, entries 2, 4, 6, 8). More interestingly the entropy contribution decreases from the reactions of *S*-nucleophiles **5i**, **6i** (negative $\Delta\Delta G^{\neq}$) to the reaction of *S*-nucleophile **7i** (positive $\Delta\Delta G^{\neq}$) (Table 1, entries 7, 8, 17, 25).

It was shown that electron-withdrawing substituents (EWS's) in **1–4** accelerate the replacement of the nitro group in the reaction with phenols in the presence of $K_2CO_3$ in DMF and the introduction of electron-releasing substituents (ERS's) into the aromatic ring of the nucleophiles **5**, **6** and **7** accelerates the replacement of the nitro and fluoro groups in **1–4**.[4] Moreover, the activation free energies, $\Delta G^{\neq}$, for the reactions of **1–4** with **6** (Table 2)[6] approach the $\Delta G^{\neq}$ range for typical $S_NAr$ reactions of weakly activated arenes with charged oxygen and sulphur nucleophiles.[13] Therefore, these facts indicate that the reactions of **1–4** occur via an $S_NAr$ mechanism,[4–6] but the TS structures for the rate-determining steps of the $\sigma$-complex formation are different (Fig. 5). The $S_NAr$ displacement with **1–4** and **5**, **6** is characterised by loose transition states $\mathbf{TS_1}$ and $\mathbf{TS_2}$. The assumed structures of $\mathbf{TS_1}$ and $\mathbf{TS_2}$ can be inferred

DOI: 10.1002/poc

**Table 1.** Relative leaving mobility of nitro and fluoro groups, $k(NO_2)/k(F)$, for reactions of **1–4** with **5**, **6** and **7** in DMF at 70 °C and Eyring parameters of these reactions

| Entry | Compounds | Nucleophile | $k(NO_2)/k(F)^a$ | $\Delta\Delta H^{\neq}$ $(kJ\,mol^{-1})^b$ | $\Delta\Delta S^{\neq}$ $(J\,mol^{-1}\,K^{-1})^b$ | $T\Delta\Delta S^{\neq}$ $(kJ\,mol^{-1})^{b,c}$ | $\Delta\Delta G^{\neq}$ $(kJ\,mol^{-1})$ | References |
|---|---|---|---|---|---|---|---|---|
| 1 | **3**, **4** | **5a** | $1.05 \pm 0.05$ | $15.4 \pm 0.4$ | $45.5 \pm 0.3$ | $15.6 \pm 0.1$ | −0.2 | [g] |
| 2 | **3**, **4** | **7a** | $0.57 \pm 0.01$ | $-6.7 \pm 0.3$ | $-24.2 \pm 0.3$ | $-8.3 \pm 0.1$ | 1.6 | [g] |
| 3 | **3**, **4** | **5d** | $1.52 \pm 0.03$ | $31.6 \pm 0.6$ | $95.6 \pm 2.1$ | $32.8 \pm 0.7$ | −1.2 | [g] |
| 4 | **3**, **4** | **7d** | $1.10 \pm 0.06$ | $-7.5 \pm 0.3$ | $-21.3 \pm 0.3$ | $-7.3 \pm 0.1$ | −0.2 | [g] |
| 5 | **3**, **4** | **5g** | $1.75 \pm 0.05$ | $39.8 \pm 0.8$ | $120.7 \pm 2.3$ | $41.4 \pm 0.8$ | −1.6 | [g] |
| 6 | **3**, **4** | **7g** | $1.34 \pm 0.05^d$ | $-8.1 \pm 0.4$ | $-20.7 \pm 0.6$ | $-7.1 \pm 0.2$ | −1.0 | [g] |
| 7 | **3**, **4** | **5i** | $2.18 \pm 0.04$ | $22.5 \pm 0.9$ | $72.0 \pm 2.9$ | $24.7 \pm 1.0$ | −2.2 | [g] |
| 8 | **3**, **4** | **7i** | $0.79 \pm 0.03$ | $-7.7 \pm 0.2$ | $-24.2 \pm 0.6$ | $-8.3 \pm 0.2$ | 0.6 | [g] |
| 9 | **3**, **4** | **6a** | $1.05 \pm 0.05$ | $15.4 \pm 0.2$ | $45.3 \pm 0.6$ | $15.5 \pm 0.2$ | −0.1 | 4 |
| 10 | **3**, **4** | **6b** | $1.11 \pm 0.01$ | $18.1 \pm 0.5$ | $52.9 \pm 1.4$ | $18.1 \pm 0.5$ | 0 | 4 |
| 11 | **3**, **4** | **6c** | $1.20 \pm 0.01$ | $21.8 \pm 0.4$ | $64.0 \pm 1.2$ | $21.9 \pm 0.4$ | −0.1 | 4 |
| 12 | **3**, **4** | **6d** | $1.38 \pm 0.02$ | $27.6 \pm 0.8$ | $83.6 \pm 2.5$ | $28.7 \pm 0.8$ | −1.1 | 4 |
| 13 | **3**, **4** | **6e** | $1.53 \pm 0.02$ | $75.0 \pm 0.4$ | $225.5 \pm 0.6$ | $77.3 \pm 0.3$ | −2.3 | 4 |
| 14 | **3**, **4** | **6f** | $1.58 \pm 0.02$ | $80.3 \pm 1.1$ | $241.3 \pm 3.4$ | $82.8 \pm 1.1$ | −2.5 | 4 |
| 15 | **3**, **4** | **6g** | $1.66 \pm 0.02$ | $91.6 \pm 6.2$ | $91.6 \pm 6.2$ | $94.4 \pm 3.3$ | −2.8 | 4 |
| 16 | **3**, **4** | **6h** | $6.73 \pm 0.47$ | $60.6 \pm 0.3$ | $184.4 \pm 1.0$ | $63.2 \pm 0.4$ | −2.6 | 5 |
| 17 | **3**, **4** | **6i** | $10.1 \pm 0.71$ | $69.1 \pm 2.8$ | $210.8 \pm 8.5$ | $72.3 \pm 2.9$ | −3.2 | 5 |
| 18 | **3**, **4** | **6j** | $14.9 \pm 1.04$ | $77.2 \pm 0.5$ | $235.6 \pm 1.4$ | $80.8 \pm 0.5$ | −3.6 | 5 |
| 19 | **3**, **4** | **6k** | $32.8 \pm 2.3$ | $94.1 \pm 0.5$ | $287.5 \pm 1.5$ | $98.6 \pm 0.5$ | −4.5 | 5 |
| 20 | **3**, **4** | **6l** | $116.2 \pm 8.13$ | 124.8 | 381.7 | 130.9 | −6.1 | 5 |
| 21 | **1**, **2** | **6a** | $1.23 \pm 0.01^e$ | $8.5 \pm 0.1$ | $23.5 \pm 0.3$ | $8.7 \pm 0.1^f$ | −0.2 | 6 |
| 22 | **1**, **2** | **6b** | $1.31 \pm 0.01^e$ | $10.5 \pm 0.1$ | $28.9 \pm 0.3$ | $10.7 \pm 0.1^f$ | −0.2 | 6 |
| 23 | **1**, **2** | **6c** | $1.40 \pm 0.01^e$ | $12.6 \pm 0.4$ | $34.8 \pm 1.1$ | $12.9 \pm 0.4^f$ | −0.3 | 6 |
| 24 | **1**, **2** | **6d** | $1.54 \pm 0.02^e$ | $16.3 \pm 0.2$ | $45.0 \pm 0.5$ | $16.7 \pm 0.2^f$ | −0.4 | 6 |
| 25 | **1**, **2** | **6i** | $0.76 \pm 0.1^d$ | $39.4 \pm 1.6$ | $109.3 \pm 4.8$ | $40.6 \pm 1.7^f$ | −1.2 | [g] |

[a] Values have been corrected for a statistical factor where appropriate.

[b] $\Delta\Delta H^{\neq} = \Delta H^{\neq}(NO_2) - \Delta H^{\neq}(F)$ and $\Delta\Delta S^{\neq} = \Delta S^{\neq}(NO_2) - \Delta S^{\neq}(F)$ are calculated by the modified Eyring equation $\log[k(NO_2)/k(F)] = -\Delta\Delta H^{\neq}/2.303RT + \Delta\Delta S^{\neq}/2.303R$.

[c] At 70 °C.

[d] At 80 °C.

[e] At 120 °C.

[f] At 98 °C.

[g] This work.

from the influence of the isotope composition of the nucleophiles **6** obtained with phenols ArOH and ArOD, respectively; the substitution selectivity in competing reactions of **3** and **4** with **6** decreases on going from nucleophile **6** to its deuterium analogue.[6] The possibility of the formation of the intermediate complex (**IC**) (Fig. 6) between **1–4** and **5**, **6** can be ruled out, since these reactions are characterised by large values of $\Delta H^{\neq}$ (126–228 kJ mol$^{-1}$) and $\Delta S^{\neq}$ (−18 to 250 kJ mol$^{-1}$ K$^{-1}$) (Table 2).[6] These data contradict the concept involving formation of a $\sigma$-complex in the framework of the classical $S_N$Ar-mechanism.[13] In this case, the rate constants for the relative reactions are effective and the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are determined by both stages: the formation of **IC** and the following nucleophilic attack with the formation of $\mathbf{TS_1}$ or $\mathbf{TS_2}$, respectively (Fig. 6). The positive activation entropy, $\Delta S^{\neq}$, seems to be due to the higher degree of freedom in the loose $\mathbf{TS_1}$ and $\mathbf{TS_2}$ as compared with the more highly organised complexes **5** and **6** and **IC**. Recently, positive $\Delta S^{\neq}$ were found also for the reactions of benzoyl derivatives with hydroxide ion as a consequence of extensive OH$^-$ desolvation before the formation of the transition state.[14] It is also possible that the high sensitivity of $\Delta S^{\neq}$ and the low one of $\Delta G^{\neq}$ to the nucleophile structure (Table 2) are connected with the possibility for **5** and **6** to considerably change their geometry upon interaction with **1–4** leading to **IC**. Recently, it was shown on the basis of an *ab initio* study

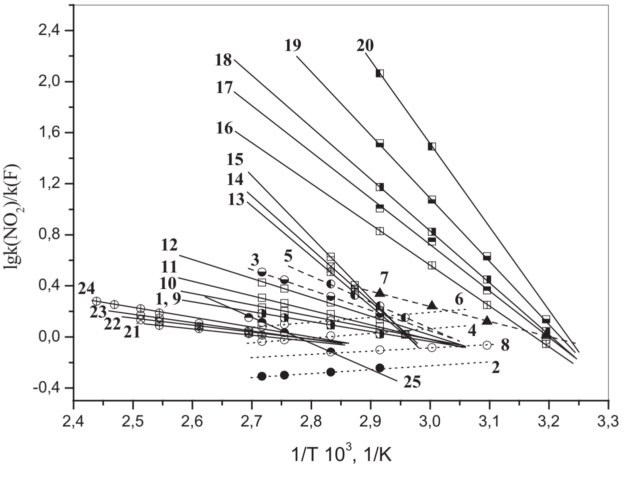


**Figure 2.** Eyring plots of $\log(k_{NO_2}/k_F)$*versus* 1/*T* for competitive reactions of compounds **1–4** with nucleophiles **5** (curves 1, 3, 5, 7), **6** (curves 9–25) and **7** (curves 2, 4, 6, 8) in DMF. The parameters of the lines are given in Table 1; the correlation coefficients for all lines are higher than 0.998

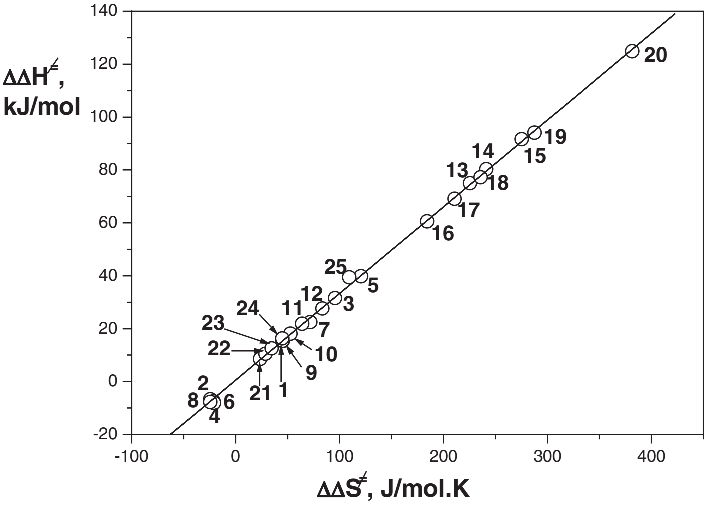


**Figure 3.** Compensation plot of $\Delta\Delta H^{\neq}$ *versus* $\Delta\Delta S^{\neq}$ for the competitive reactions of compounds **1** and **2** with nucleophiles **6**, compounds **3** and **4** with nucleophiles **5** and **7** in DMF. The identity of the numbers is the entry number of Table 1 ($\Delta\Delta H^{\neq} = 0.69 + 0.33\Delta\Delta S^{\neq}$, $r = 0.9997$, $s = 0.93$, $n = 25$)

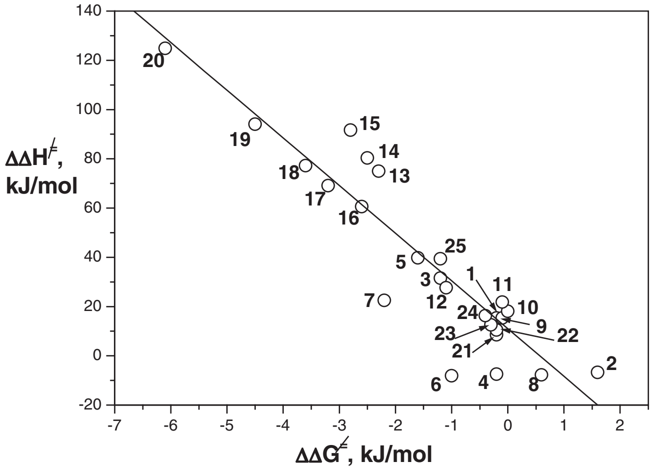


**Figure 4.** Compensation plot of $\Delta\Delta H^{\neq}$ *versus* $\Delta\Delta G^{\neq}$ for competitive reactions of compounds **1** and **2** with nucleophiles **6**, compounds **3** and **4** with nucleophiles **5** and **7** in DMF. The identity of the numbers is the entry number in Table 1 ($\Delta\Delta H^{\neq} = 11.0 - 19.4\Delta\Delta G^{\neq}$, $r = 0.944$, $s = 12.4$, $n = 25$)

that the interaction between negatively charged species and the $\pi$ system of an aromatic ring gives nucleophilically reactive complexes.[15]

As follows from Fig. 2, the displacement selectivity of nitro and fluoro groups, $\log(k_{NO_2}/k_F)$, in the reaction of **3**, **4** with oxygen nucleophiles **5a**,**d**,**g**, **6a–g** (curves 1, 3, 5, 7, 9–15) is lower than that in the same reaction with sulphur nucleophiles **5i**, **6h–l** (curves 7, 16–20) in line with the HSAB principle.[1] On passing to the reaction of **1**, **2** with oxygen nucleophiles **6a–d** (Fig. 2, curves 21–24) and sulphur nucleophile **6i** (Fig. 2, curve 25), the relative mobility of the nitro and fluoro groups is very close for both types of nucleophiles. However, the displacement selectivity of nitro and fluoro groups in the reaction of **3**, **4** with *O*-nucleophiles **7d**,**g** can exceed that in the same reaction with *S*-nucleophile **7i** (Fig. 2, curves 4, 6, 8). Evidently, the influence of the larger polarizability of sulphur nucleophiles[16] does not always determine the larger displacement selectivity of nitro and fluoro groups compared with that for the oxygen ones.[2] Recently, it was found that the selectivities of the reactions of carbocations

**Table 2.** Calculated activation parameters for the reactions of nitro and fluoro displacement in arenes **1–4** by reaction with nucleophiles **6** in DMF[6]

| Compound | Nucleophile | $\Delta H^{\neq}$ (kJ mol$^{-1}$) | $\Delta S^{\neq}$ (J mol$^{-1}$ K$^{-1}$) | $T\Delta S^{\neq}$ (kJ mol$^{-1}$)[a] | $\Delta G^{\neq}$ (kJ mol$^{-1}$) |
|---|---|---|---|---|---|
| **3** | **6a** | 212 | 250 | 86 | 126 |
| **4** | **6a** | 197 | 205 | 70 | 127 |
| **3** | **6d** | 154 | 66 | 23 | 131 |
| **4** | **6d** | 126 | −18 | 6 | 132 |
| **1** | **6a** | 228 | 240 | 89[b] | 139 |
| **2** | **6a** | 220 | 217 | 80[b] | 140 |
| **1** | **6d** | 160 | 52 | 19[b] | 141 |
| **2** | **6d** | 144 | 7 | 3[b] | 141 |

[a] At 70 °C.
[b] At 98 °C.

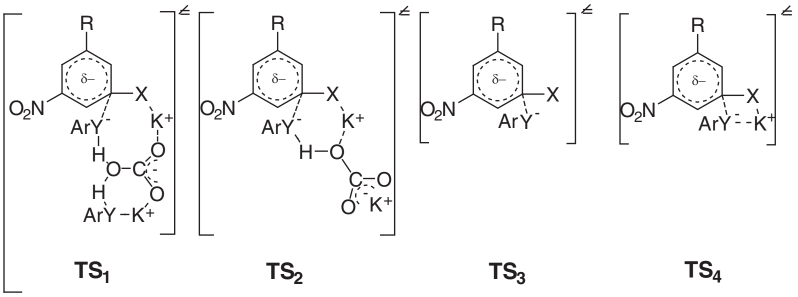


**Figure 5.** Assumed structures for the transition states of attack of nucleophiles **5** onto **3**, **4** (**TS$_1$**), nucleophiles **6** onto **1–4** (**TS$_2$**), nucleophiles ArY$^-$ onto **3**, **4** (**TS$_3$**) and nucleophiles **7** onto **3**, **4** (**TS$_4$**)

with ambident thiocyanate ion, ($k_S/k_N$), and nitrite ion, ($k_N/k_O$), cannot be explained by the HSAB principle.[17]

Usually the nitro group is an extremely good nucleofugic group, much better than fluoro group, when a more polarizable reagent such as thiophenoxide is used. This fact is well explained by taking into account the intervention of repulsion (or London forces) phenomena between the nucleophile and the nucleofugic group in the transition state **TS$_3$** (Fig. 5). When the nucleophile is softer, larger, and more polarizable, it can efficiently make the new bond at a larger distance, minimising these phenomena.[2a,b] But in the case of **TS$_1$** and **TS$_2$**, an additional factor determining the length of the new bond is a steric strain in the cycle.

It is noted that the reactions of nucleophiles **7** with arenes **3**, **4** can go through the formation of the highly organised **TS$_3$** or **TS$_4$** without the preliminary **IC** step (Fig. 6) because the same reactions are characterised by negative $\Delta S^{\neq}$ values.[13] **TS$_4$** implies the assistance of potassium-phenoxide (thiophenoxide) 'ion-pair'.[18] Probably, the length of the new bond in the tight transition state **TS$_4$** is controlled by the cycle strain and there is a compensation for repulsion phenomena between the different oxygen and sulphur nucleophiles and the leaving group in the cyclic **TS$_4$** (*cf.* Ref. 2a). The latter interpretation can be suggested for the decrease in the displacement selectivity of nitro and fluoro groups in **3**, **4** in their reaction with **7i**.

Hence the differential entropy of activation determines the selectivity of the nitro *versus* fluoro displacement in the reactions of *meta*-substituted arenes with phenols and thiophenols in the presence of potassium carbonate. At the same time the nitro group displacement by phenoxides can be favoured over that by thiophenoxides contrary to the HSAB principle. The compensation relationship (Fig. 3) gives a possibility to estimate the influence of the nucleophile structure on the mechanistic details in the classical S$_N$Ar reaction.

## EXPERIMENTAL

GLC analysis of the reaction mixtures was performed on an LKhM-72 chromatograph (heat conductivity detector; 4000 × 0.4 mm column packed with 15% of SKTFT-803 on Cromaton-W; carrier gas helium; linear oven temperature programming from 70 to 270 °C at a rate of 10 deg min$^{-1}$). The products were quantitatively determined by the absolute calibration technique using preliminary plotted calibration curves and were identified by addition of authentic samples. Commercial DMF was dried over 4 Å molecular sieves and distilled under reduced pressure over CaH$_2$. Commercial phenols, thiophenol, **1** and **2**, were purified by standard procedures. Starting compounds **3**, **4**, **7a**,**d**,**g**,**i** were synthesised according to previously published procedures.[4,19,20] The reaction products **8a**,**d**,**g**,**i** were obtained in quantitative yields by reaction of **1–4** with the corresponding phenols and thiophenols in the presence of K$_2$CO$_3$ in DMF at 98 °C and characterised by IR, $^1$H and $^{19}$F NMR and mass spectroscopy.[4,19] Preliminary it was shown that the products **8a**,**d**,**g**,**i** were stable under the experimental conditions.[4,19]

### Kinetic measurements

The kinetic runs and the preparation of solutions of nucleophiles **5a**,**d**,**g**,**i** and **7a**,**d**,**g**,**i** were performed under purified argon atmosphere. Competition reactions of the

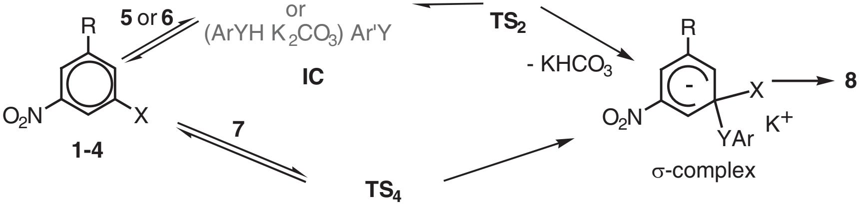


**Figure 6.** The proposed steps of the S$_N$Ar mechanism for the reactions of substrates **1–4** with nucleophiles **5–7**

DOI: 10.1002/poc

two substrates **1**, **2** or **3**, **4** with nucleophiles **5a**,**d**,**g**,**i**, **6i** and **7a**,**d**,**g**,**i** were carried out with equal molar concentrations of **3** and **4** or **1** and **2**, those of the nucleophile being five times smaller. In every case, **8a**,**d**,**g**,**i** are the only products, as shown by GLC analyses. Performing of the competition reactions in large excess of **1**–**4** relative to nucleophile is more favourable to obtain $k_{NO_2}/k_F$ values constant along the reaction progress.[8,19] In such a case, pseudo-first-order kinetics prevail.[9] These conditions ensured that the ratios of reacted **3**, **4** or **1**, **2** were directly proportional to the ratio of the second-order rate constants for each reaction according to the equation:[9,21]

$$\frac{k_{NO_2}}{k_F} = \log[A_0] - \log[A_t]/\log[B_0] - \log[B_t]$$

where $[A_0]$, $[B_0]$, $[A_t]$ and $[B_t]$ are the initial concentrations and the concentrations at reaction time *t*, respectively, of **3** and **4** or **1** and **2**.

The procedure for the determination of the relative reactivity of compounds **1**, **2** towards nucleophile **6i** in DMF is described in a previous work.[5]

**Determination of the relative reactivity of compounds 3, 4 towards nucleophiles 5a,d,g,i, and 7a,d,g,i in DMF (typical kinetic procedure).** $K_2CO_3$ (0.4 g, 2.9 mmol) was added to 2.0–4.5 mL of a 10% solution of the corresponding phenol or thiophenol (2.0 mmol) in DMF. The mixture was stirred for 3 h at 70 °C, cooled, and the excess of $K_2CO_3$ was filtered off on a glass filter (16th pore size) and washed with 0.2 mL of DMF on the filter. The filtrate obtained (0.1–0.2 mL) or 0.2–0.3 mL of 10% solution of **7a**,**d**,**g**,**i** (0.1 mmol) was added to 2.2 mL of a 10% solution of **3** (0.5 mmol) and **4** (0.5 mmol), the solution was stirred at definite temperature for 3–4 h, cooled and analysed by GLC. The reported relative constants are average values of several determinations.

## REFERENCES

1. Pearson RG. *Chemical Hardness*. Wiley: New York, 1997.
2. (a) Bartoli G, Todesco PE. *Acc. Chem. Res.* 1977; **10**: 125–132; (b) Bunnett JF, Merritt WD, Jr. *J. Am. Chem. Soc.* 1957; **79**: 5967–5969; (c) Williams FJ, Donahue PE. *J. Org. Chem.* 1978; **43**: 250–254.
3. (a) Vlasov VM. *Russ. Chem. Rev.* 2003; **72**: 681–703; (b) Vlasov VM. *Usp. Khim.* 2003; **72**: 764–786.
4. (a) Khalfina IA, Vlasov VM. *Russ. J. Org. Chem.* 2002; **38**: 47–58; (b) Khalfina IA, Vlasov VM. *Zh. Org. Khim.* 2002; **38**: 56–67.
5. Vlasov VM, Khalfina IA. *J. Phys. Org. Chem.* 2000; **13**: 630–633.
6. (a) Khalfina IA, Vlasov VM. *Russ. J. Org. Chem.* 2005; **41**: 978–983; (b) Khalfina IA, Vlasov VM. *Zh. Org. Khim.* 2005; **41**: 999–1005.
7. (a) Sasson Y, Bilman N. *J. Chem. Soc. Perkin Trans. 2* 1989; 2029–2033; (b) Landini D, Penso M. *J. Org. Chem.* 1991; **56**: 421–423; (c) Albanese D, Landini D, Maia A, Penso M. *J. Mol. Cat. A: Chemical* 1999; **150**: 113–131; (d) Albanese D, Landini D, Lupi V, Penso M. *Eur. J. Org. Chem.* 2000; 1443–1449; (e) Bessard F, Crettaz R. *Tetrahedron* 2000; **56**: 4739–4745; (f) Jonckers THM, Maes BUW, Lemiere GLF, Dommisse R. *Tetrahedron* 2001; **57**: 7027–7034; (g) Ma D, Xia C. *Org. Lett.* 2001; **3**: 2583–2586.
8. (a) Khalfina IA, Beregovaya IV, Vlasov VM. *Russ. J. Org. Chem.* 2003; **39**: 1104–1115; (b) Khalfina IA, Beregovaya IV, Vlasov VM. *Zh. Org. Khim.* 2003; **39**: 1175–1186.
9. Bunnett JF. In *Investigation of Rates and Mechanisms of Reactions, Part 1*, Bernasconi CF (ed.). Wiley: New York, 1986.
10. Kiperman SL. *Osnovy khimicheskoi kinetiki v geterogennom katalize (Principles of Chemical Kinetics in Heterogeneous Catalysis)*. Khimiya: Moscow, 1979.
11. Liu L, Guo QX. *Chem. Rev.* 2001; **101**: 673–695.
12. (a) Krug RR, Hunter WG, Grieger RA. *J. Phys. Chem.* 1976; **80**: 2341–2351; (b) Exner O. *Chem. Commun.* 2000; 1655–1656.
13. (a) Ho KC, Miller J, Wong KW. *J. Chem. Soc. B* 1966; 310–314; (b) Miller J. *Aromatic Nucleophilic Substitution*. Elsevier: Amsterdam, 1968; (c) Bazzano F, Mencarelli P, Stegel F. *J. Org. Chem.* 1984; **49**: 2375–2377; (d) Gomes PCB, Vichi EJS, Moran PJS, Neto A, Maroso ML, Miller J. *Organometallics* 1996; **15**: 3198–3203.
14. El Seoud OA, Ferreira M, Rodrigues WA, Ruasse M-F. *J. Phys. Org. Chem.* 2005; **18**: 173–182.
15. Mascal M, Armstrong A, Bartberger MD. *J. Am. Chem. Soc.* 2002; **124**: 6274–6276.
16. (a) Bernasconi CF, Killion RB, Jr. *J. Am. Chem. Soc.* 1988; **110**: 7506–7512; (b) Bernasconi CF, Ketner RJ, Chen X, Rappoport Z. *J. Am. Chem. Soc.* 1998; **120**: 7461–7468.
17. (a) Loos R, Kobayashi S, Mayr H. *J. Am. Chem. Soc.* 2003; **125**: 14126–14132; (b) Tishkov AA, Schmidhammer U, Roth S, Riedle E, Mayr H. *Angew. Chem. Int. Ed.* 2005; **44**: 4623–4626.
18. (a) Jones P, Harrison R, Wynne-Jones L. *J. Chem. Soc. Perkin Trans. 2* 1979; 1679–1685; (b) Gopalakrishnan G, Hogg JL. *J. Org. Chem.* 1984; **49**: 1191–1195.
19. (a) Khalfina IA, Rogozhnikova OYu, Vlasov VM. *Russ. J. Org. Chem.* 1996; **32**: 1328–1333; (b) Khalfina IA, Rogozhnikova OYu, Vlasov VM. *Zh. Org. Khim.* 1996; **32**: 1371–1377.
20. (a) Kornblum N, Lurie AP. *J. Am. Chem. Soc.* 1959; **81**: 2705–2715; (b) Kornblum N, Boyd SD, Ono N. *J. Am. Chem. Soc.* 1974; **96**: 2580–2587.
21. Ingold CK. *Structure and Mechanism in Organic Chemistry*. Cornell University Press: Ithaca–London, 1969.

DOI: 10.1002/poc