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Reactivity and selectivity control in the substitution reactions of nitro group and fluorine in 3-R-5-nitrobenzotrifluorides with aryloxide and arylthioxide ions

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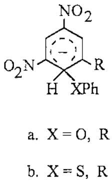
ABSTRACT: The relative mobility of nitro group and fluorine in 3,5-dinitro- and 3-fluoro-5-nitrobenzotrifluorides under the action of both phenols and thiophenols in the presence of potassium carbonate in DMF at 40–95 °C was studied by the competitive reactions method. Correlation analysis of the relative rate constants, k_{NO_2}/k_F, and the activation parameter differences, $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, of the competitive reactions was carried out. The displacement selectivity of the nitro group and fluorine depends on the nature of the nucleophile and is characterized by isokinetic ratios: the nitro group mobility increases compared with that of fluorine with increase in the reaction temperature and the decrease in the nucleophile basicity. There are good linear relationships between Brø nsted coefficient difference $\Delta\beta_{Nuc}$ and reciprocal temperature, $1/T$, enthalpy, $\Delta\Delta H^{\neq}$, and entropy, $\Delta\Delta S^{\neq}$, differences, suggesting isokinetic ratios in these reactions. The isokinetic temperatures are lower than the experimental temperature range, indicating that the displacement selectivity is controlled by entropy. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: aromatic nucleophilic substitution; nucleophilic reactivity; selectivity; linear free energy correlations; isokinetic ratio; substituted 3-R-5-nitrobenzotrifluorides

INTRODUCTION

Functionalization of arenes based on the reaction of nucleophilic displacement of hydrogen is limited by the synthesis only of *ortho* and *para* derivatives.[1] *Meta*-Substituted arenes are more readily obtained by *ipso* displacement of halogen (Cl, Br, I) in Cu-[2a] and Pd-catalyzed reactions,[2b] or of good leaving groups such as nitro group and fluorine.[3] The latter reactions are relatively rare,[3a] although it is known that the comparison of the displacement rates of the nitro group and fluorine in activated nucleophilic aromatic substitution reactions with soft sulfur and hard oxygen nucleophiles is a standard method reasonable for the prediction of leaving group mobility.[3a,,4a] As is evident from these data, soft thiophenoxides more rapidly substitute for a nitro group than for fluorine in the reactions of 4-nitro- and 4-fluoronitrobenzenes,[4b,c] 1-nitro- and 1-fluoro-2,4-dinitrobenzenes[4a] and 4-nitro- and 4-fluorophthalimido derivatives.[4d]

Here we compare the substitution reactions of the nitro group and fluorine in 3,5-dinitro- and 3-fluoro-5-nitrobenzotrifluorides, (**1** and **2**) with aryloxide and arylthioxide ions. It is known[1a,3a,5] that σ-complex formation at unsubstituted ring positions occur relatively rapidly and their stability depends strongly on the nature of the nucleophile. It is known that the phenoxide adduct **3a** has a lower stability[6a] than **3b** in DMSO.[6b] Nevertheless, the presence of the CF_3 group in **4a** and **b** and a solvent such as DMF, less favourable to their formation, should lower the stabilities of these adducts. Therefore, one might expect a slight effect on the stability of the σ-complex **4** on *ipso* substitution. It has been shown[7] that phenoxide **6b** and thiophenoxide **6i** (see Scheme 1) react readily with **1** and **2** to form derivatives **7b** and **i**, respectively, in quantitative yields. Hence we were interested in the possibility of observing the relative nitro group and fluorine mobility in *meta*-substituted arenes.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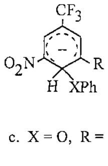
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a. X = O, R = NO_2 c. X = O, R = F

b. X = S, R = NO_2 d. X = S, R = F

RESULTS AND DISCUSSION

The relative nitro group and fluorine mobility in two substrates, **1** and **2**, was investigated by the competitive

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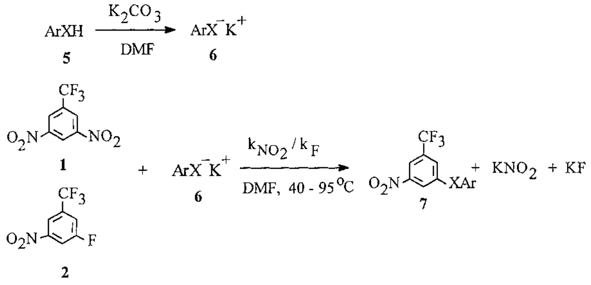

a. $X = O, Ar = 4\text{-}MeC_6H_4$
b. $X = O, Ar = Ph$
c. $X = O, Ar = 4\text{-}ClC_6H_4$
d. $X = O, Ar = 3\text{-}NO_2C_6H_4$
e. $X = O, Ar = 4\text{-}AcC_6H_4$
f. $X = O, Ar = 4\text{-}CNC_6H_4$
g. $X = O, Ar = 3\text{-}NO_2\text{-}5\text{-}Br\text{-}C_6H_3$
h. $X = S, Ar = 4\text{-}MeOC_6H_4$
i. $X = S, Ar = Ph$
j. $X = S, Ar = 2\text{-}C_{10}H_7$
k. $X = S, Ar = 3\text{-}CF_3C_6H_4$
l. $X = S, Ar = 4\text{-}NO_2C_6H_4$

Scheme 1

reactions method[8] with a series of aryloxide ions, **6a**–**g**, and arylthioxide ions, **6h**–**l**, in DMF at 40–95 °C (Scheme 1). Nucleophiles **6a**–**l** are readily generated *in situ* from phenols and thiophenols **5a**–**l** in the presence of potassium carbonate. The high acidity of **5a**–**l** in aprotic dipolar solvents[9] allows the generation of **6a**–**l** under the action of K_2CO_3[4d,10] to avoid the formation of by-products.[11] We were able to show that not all reactions lead to the formation of by-products under the experimental conditions adopted and involve the processes shown in Scheme 1.

Taking into account that the S_NAr substitution reactions with anionic nucleophiles and different leaving groups can involve isokinetic relationships,[12] the relative reactivity of **1** and **2** was investigated with nucleophiles **6a**–**l** over a wider range of basicity (pK 12.2–18.9 for **5a**–**g** and 5.5–11.2 for **5h**–**l** in DMSO;[9] the correlation of pK^{DMF} with pK^{DMSO} for phenols and thiophenols[9c] supports the fact that the relative acidities of **5** are similar in both solvents). The experimental data in Table 1 show that the displacement selectivity of the nitro group and fluorine depends on the reaction temperature and the nucleophile basicity. The temperature dependence of the displacement selectivity can be analyzed according to the Eyring equation [Eqn. (1)] for the two reaction paths.

$$log(k_{NO_2}/k_F) = -\Delta\Delta H^{\neq}/2.303RT + \Delta\Delta S^{\neq}/2.303R \qquad (1)$$

where $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ are the difference in the enthalpy and entropy of activation for nitro group and fluorine substitution reactions, respectively. From all the experimental data a linear correlation between $1/T$ and displacement selectivity $\log(k_{NO_2}/k_F)$ is observed. In this case, temperature-dependent measurements on the basis of Eqn. (1) allow the evaluation of displacement selectivity in terms of differential enthalpy and entropy of activation (Table 1). There are good correlations between $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ for both sets of nucleophiles (Fig. 1). These correlations are known as isokinetic relationships, and the slope of the linear plot is known as the isokinetic temperature, β.[13] These values are 58 and 53 °C for the reactions with ArO^- and ArS^-, respectively (Fig. 1); they are lower than the experimental temperature range. This means that the displacement selectivity in each case is controlled by entropy.[13] In this case, there exists a temperature range where $T\Delta\Delta S^{\neq} > \Delta\Delta H^{\neq}$. The positive $\Delta\Delta S^{\neq}$ values (Table 1) mean that the $\Delta S^{\neq}$ values in the displacement reaction of the nitro group are less negative than those of fluorine. This suggests that reactions of **2** with both ArO^- and ArS^- are more highly organized than those of **1** with the same nucleophiles.[14] It is important to emphasize that entropy control has a larger influence for ArS^- than for ArO^-. In view of the excellent leaving group abilities of the nitro group and fluorine, it is likely that the proximity of both the nitro group and ArS^- as two bulky groups should increase the

Table 1. Relative leaving mobility of the nitro group and fluorine, k_{NO_2}/k_F, for reactions of **1** and **2** with **6a–1** in DMF at various temperatures and the Eyring parameters of these reactions

	k_{NO_2}/k_F									
Compound	40 °C	50 °C	60 °C	70 °C	75 °C	80 °C	90 °C	95 °C	$-\Delta\Delta H^{\neq}$ (kJ mol^{-1})[a]	$\Delta\Delta S^{\neq}$ (J mol^{-1} K^{-1})[a]
6a	—	—	—	1.05	—	1.23	1.41	1.52	15.4 ± 0.2	45.1 ± 0.6
6b	—	—	—	1.11	—	1.35	1.58	1.70	18.1 ± 0.5	52.9 ± 1.4
6c	—	—	—	1.20	—	1.51	1.84	2.02	21.8 ± 0.4	64.0 ± 1.2
6d	—	—	—	1.38	—	1.86	2.39	2.66	27.6 ± 0.8	83.6 ± 2.5
6e	—	—	—	1.53	2.24	3.23	—	—	75.0 ± 0.4	225.5 ± 0.6
6f	—	—	—	1.58	2.34	3.55	—	—	80.3 ± 1.1	241.3 ± 3.4
6g	—	—	—	1.66	2.54	4.25	—	—	91.6 ± 6.2	275.3 ± 9.4
6h	0.88	1.78	3.63	6.73	—	—	—	—	60.6 ± 0.3	184.4 ± 1.0
6i	1.03	2.31	5.57	10.1	—	—	—	—	69.1 ± 2.8	210.8 ± 8.5
6j	1.11	2.82	6.71	14.9	—	—	—	—	77.2 ± 0.5	235.6 ± 1.4
6k	1.37	4.27	11.9	32.8	—	—	—	—	94.1 ± 0.5	287.5 ± 1.5
6l	—	—	31.0	116.2	—	—	—	—	124.8	381.7

[a] Calculated from Eqn. (1), where $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{NO_2} - \Delta H^{\neq}_F$ and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{NO_2} - \Delta S^{\neq}_F$.

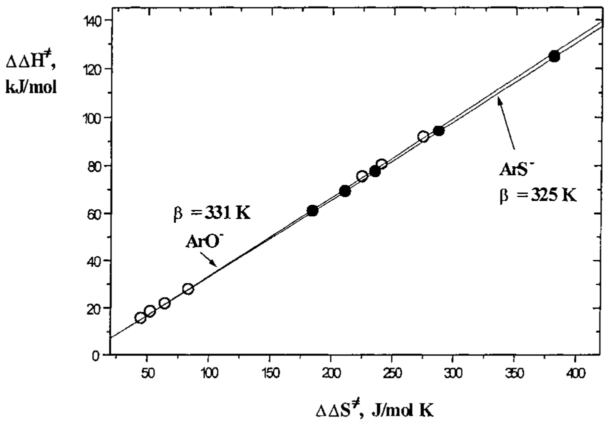

Figure 1. Plots of $\Delta\Delta H^{\neq}$ vs $\Delta\Delta S^{\neq}$ for the reaction of **1** and **2** with ArO^- (**6a**–g) and ArS^- (**6h**–l) ($\Delta\Delta H^{\neq} = -0.42 + 0.331\Delta\Delta S^{\neq}$, $r = 0.999$, $s = 0.25$ for ArO^-; $\Delta\Delta H^{\neq} = +0.51 + 0.325\Delta\Delta S^{\neq}$, $r = 0.999$, $s = 0.04$ for ArS^-)

entropy of activation $\Delta S^{\neq}{}_{NO_2}$ compared with $\Delta S^{\neq}{}_F$ for fluorine in **2** and ArS^-. A similar comparison for the less bulky ArO^- should lead to a smaller increase in $\Delta S^{\neq}{}_{NO_2}$ compared with $\Delta S^{\neq}{}_F$. The latter can be associated also with better solvation of ArS^- relative to ArO^- in DMF,[15] although ArS^- is more poorly solvated than ArO^- by hydrogen-bonding solvents,[15] since entropy control increases for more delocalized and more solvated anions ArO^-, **6e**–g (Table 1). It should be noted that the $\Delta S^{\neq}$ term does not depend on the leaving group for the reactions of 4-fluoro- and 4-chloronitrobenzenes with 9-phenylfluorenide ion in DMSO.[14] It is likely that the steric difference between fluorine and chlorine as leaving groups in S_NAr reactions is smaller than that between fluorine and a nitro group in the reaction with soft, highly delocalized nucleophiles.[4a] Hence the S_NAr displacement of **1** is characterized by a transition state earlier along the reaction coordinate than those for **2**, owing to the soft–soft interaction. The proximity effects work in the same directions.

The negative $\Delta\Delta H^{\neq}$ values mean that the $\Delta H^{\neq}{}_{NO_2}$ term is smaller than $\Delta H^{\neq}{}_F$, that is, the enthalpy of activation works in favor of displacement of the nitro group, in particular for ArS^- (Table 1). It is likely that one factor which helps arylthioxide ions is the favorable soft–soft interaction between the polarizable sulfur atom and the highly polarizable nitro group as a leaving group.[4]

Isokinetic relationships were suggested by the analysis of the displacement selectivity k_{NO_2}/k_F in terms of differential Brø nsted coefficients $\Delta\beta_{Nuc}$ and reciprocal temperatures $1/T$ (Table 2, Fig. 2). The isokinetic temperatures are 49, 67 and 29 °C for the reactions of **1** and **2** with ArO^- (**6a–d**), ArO^- (**6e–g**), and ArS^- (**6h–1**), respectively. They are close to the isokinetic temperatures obtained from Eqn. (1). It is important to emphasize two peculiarities following from data in Table 2 and Fig. 2. First, the negative values of $-\Delta\beta_{Nuc} = \beta_{Nuc}(NO_2)$ $\beta_F(F)$ indicate a smaller dependence of the rate constant for nucleophile attack on the basicity in the case of the nitro group displacement, in particular for ArS^-. The latter is consistent with related work where the reasons for the very low values of β_{Nuc} for thiolate addition to α-nitrostilbenes,[16] methoxybenzylidene Meldrum's acid[16] and trinitro-aromatic compounds[15] have been found and discussed. The major factor is the greater polarizability of the ArS^- ions which is responsible for their high carbon basicity relative to their proton basicity.[16] The latter can explain the increased negative values of $\Delta\beta_{Nuc}$ for the reactions of **1** and **2** with ArO^- (**6e–g**), having a more delocalized structure and a larger polarizability.[15] Despite the small $\Delta\beta_{Nuc}$ values, it is important to note the trend for their changes from 0.02 to 0.22 passing from ArO^- (**6a–g**) to ArS^- (**6h–1**) (Table 2). Therefore, the different line slopes for ArO^- in Fig. 2 are as a trend for the related anions with different charge delocalization and polarizability. The isoselective temperature is 71 °C, which is in the experimental region. On going from the isoselective temperature to a higher or lower value gives an inversion of the displacement selectivity (Fig. 2).

Hence the selectivity of the nitro group and fluorine displacement in the reactions of *meta*-substituted arenes with phenoxide and thiophenoxide ions is controlled by the entropy of activation. The linear correlations allow the prediction of increasing of nitro group displacement

Table 2. Differences in the Brønsted coefficients, $\Delta\beta_{Nuc} = \beta_{Nuc}(NO_2) - \beta_{Nuc}(F)$, from the dependence of log (k_{NO_2}/k_F) vs pK for the reaction of **1** and **2** with **6a–l** at various temperatures[a]

	Temperature (°C)							
Parameter	40	50	60	70	75	80	90	95
$-\Delta\beta_{Nuc}{}^b$	—	—	—	0.026	—	0.040	0.051	0.054
$-\Delta\beta_{Nuc}{}^c$	—	—	—	0.020	0.031	0.067	—	—
$-\Delta\beta_{Nuc}{}^d$	0.061	0.122	0.161	0.220	—	—	—	—

[a] pK (DMSO) of **5a–l** from Ref. 9.
[b] For the reaction of **1** and **2** with **6a–d**, $r = 0.999$, $s = 0.001$–0.005.
[c] For the reaction of **1** and **2** with **6e–g**, $r = 0.994$–0.999, $s = 0.001$–0.004.
[d] For the reaction of **1** and **2** with **6h–l**, $r = 0.996$–0.999, $s = 0.006$–0.02.

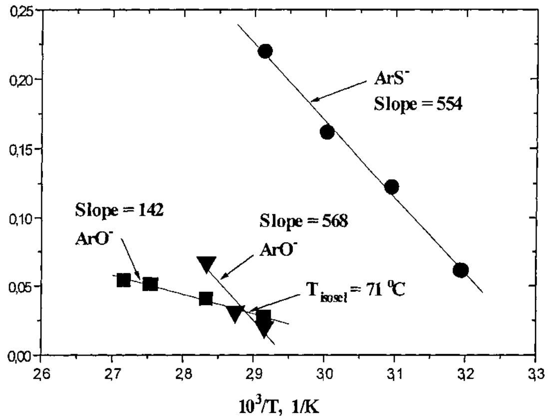

Figure 2. Plots of $\Delta\beta_{Nuc}$ vs $1/T$ for the reaction of **1** and **2** with ArO^- (**6a**–**d**), ArO^-, (**6e**–**g**) and ArS^- (**6h**–**l**) [$\Delta\beta_{Nuc} = -0.44 + 142/T$, $r = 0.995$, $s = 0.002$ for ArO^- (**6a**–**d**); $\Delta\beta_{Nuc} = -1.67 + 568/T$, $r = 0.954$, $s = 0.011$ for ArO^- (**6e**–**g**); $\Delta\beta_{Nuc} = -1.83 + 554.1/T$, $r = 0.997$, $s = 0.007$ for ArS^- (**6h**–**l**)]

with increasing reaction temperature or decreasing nucleophile basicity. The nitro group displacement by thiophenoxides is favored over that by phenoxides.

EXPERIMENTAL

Compounds **1** and **2** were available from previous work.[7] Compounds **5a**–**1**, potassium carbonate and DMF were of the purest grades commercially available. All reaction products **7a**–**1** were preparatively isolated and characterized by microanalyses and IR and NMR spectroscopy. The kinetic runs were performed under a purified argon atmosphere. Competition reactions of the two substrates **1** and **2** with nucleophiles **5a**–**1** were carried out with identical molar concentrations of **1** and **2** that of the nucleophile being five times smaller. These conditions ensured that the ratios of reacted **1** and **2** were directly proportional to the ratio of the second-order rate constants for each reaction according to the equation[8]

$$k_{NO_2}/k_F = \log[A_0] - \log[A_t]/\log[B_0] - \log[B_t] \qquad (2)$$

where $[A_0]$, $[B_0]$, $[A_t]$ and $[B_t]$ are the initial concentrations and the concentrations after a reaction time t, respectively, of **1** and **2**.

General kinetic procedure. The phenol or thiophenol **5a**–**1** (0.018 mmol) and K_2CO_3 (0.021 mmol) were added to a stock solution of **1** (0.091 mmol) and **2** (0.091 mmol) in DMF (1 ml). The reaction time was 2–3 h and the reaction was then stopped by addition of the reaction mixture to 1.2 M hydrochloric acid and chloroform at 0–5 °C. The chloroform layer was washed with water and dried and the solvent was evaporated. The residue was examined by GLC (Hewlett-Packard HP5890) calibrated with standards to determine the concentrations of reacted **1** and **2**. The reported relative constants are average values ±7% of several determinations.

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