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Influence of the nucleophile structure on the selectivity of the nitro group and fluorine displacement in S_NAr reactions

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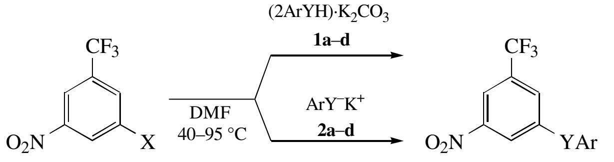
Temperature-dependent measurements according to the modified Eyring equation allowed the evaluation of the displacement selectivity of the nitro group and fluorine in the S_NAr reactions of 3-nitro-5-R-benzotrifluorides (R = NO_2, F) with the nucleophiles $(2ArYH)\cdot K_2CO_3$ and ArY^-K^+ (Y = O, S) in DMF solutions.

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 soft and hard nucleophile reactivity (HSAB principle) is a good method for predicting a leaving mobility in these reactions.[1] Taking into account that the energetics of the S_NAr reactions is a function of the leaving group and the nucleophile under other constant conditions,[2] there is an opportunity for a change of a nucleophile structure to control the displacement selectivity.

Recently, we found that a new type of nucleophiles as complexes $(2ArYH)\cdot K_2CO_3$ **1** is formed in the reactions of phenols and thiophenols with K_2CO_3 in DMF solutions.[3] We studied the displacement of the nitro group and fluorine in benzotrifluoride derivatives **3a**,**b** under the action of **1a**–**d**, phenolates **2a**–**c** and thiophenolate **2d** (for comparison) in DMF by a competitive reaction method (Scheme 1).[†] Earlier, it was shown that the substrate reactivity depends on the nucleophile type for the *meta* derivatives of nitrobenzene under heterogeneous reaction conditions.[4] The fluorine atom is only substituted in compound **3b**.

A better insight into the effects of nucleophile structure on displacement selectivity can be obtained from studies in which the reaction temperature is varied. The ratio of k_{NO_2}/k_F for the competitive reactions of **3a**,**b** with **1a**–**d** and **2a**–**d** depends on temperature and changes from 0.49 to 3.22 (Table 1) [*cf.* ref. 1(*c*)]. There is a linear relationship between the values of $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ ($r = 0.999$, $n = 8$) defined as a compensation effect.[5]



3a X = NO_2
3b X = F

4a–d

1, **2**, **4**: **a** ArY = 4-MeC_6H_4O
b ArY = 3-$NO_2C_6H_4O$
c ArY = 3-NO_2-5-BrC_6H_3O
d ArY = PhS

Scheme 1

The negative $\Delta\Delta H^{\neq}$ derives from $\Delta H^{\neq}_F > \Delta H^{\neq}_{NO_2}$, and then a lower activation barrier in the substitution of the nitro group, that is to say, the nitro group displacement is preferred by enthalpy. The opposite applies for $\Delta\Delta H^{\neq} > 0$: the enthalpy favours the fluorine displacement (Table 1). As for entropy, if it is assumed that a bimolecular substitution reaction is accompanied by a loss of activation entropy, $\Delta\Delta S^{\neq} < 0$ derives from $\Delta S^{\neq}_{NO_2} > \Delta S^{\neq}_F$: this means that the entropy loss in the nitro group displacement is larger than that of the fluorine one; thus, the entropy favours the fluorine displacement. The opposite

Table 1 Relative leaving mobility of the nitro group and fluorine, k_{NO_2}/k_F, differential activation parameters, $\Delta\Delta H^{\neq}$ and $T\Delta\Delta S^{\neq}$, and inversion temperature, T_{inv}, for the competitive reactions of compounds **3a**,**b** with nucleophiles **1a**–**d** and **2a**–**d** in DMF.

Entry	Nucleophile	k_{NO_2}/k_F[a]						T_{inv}/°C	$\Delta\Delta H^{\neq}$/ kJ mol^{-1} [b]	$T\Delta\Delta S^{\neq}$/ kJ mol^{-1} [b,c]
		65 °C	70 °C	75 °C	80 °C	90 °C	95 °C			
1	**1a**	—	1.05±0.05	—	1.24±0.04	1.41±0.0	1.53±0.03	45	15.4±0.4	15.6±0.1
2	**2a**	—	0.57±0.01	—	0.53±0.03	0.50±0.02	0.49±0.03		–6.7±0.3	–8.3±0.1
3	**1b**	—	1.52±0.03	—	2.07±0.10	2.80±0.01	3.22±0.09	62	31.6±0.6	32.8±0.7
4	**2b**	—	1.10±0.06	—	1.02±0.05	0.95±0.01	0.92±0.01		–7.5±0.3	–7.3±0.1
5	**1c**	1.42±0.04	1.75±0.05	2.12±0.10	2.60±0.01	—	—	66	39.8±0.8	41.4±0.8
6	**2c**	—	1.46[d]	—[e]	1.34±0.05	1.25±0.05	1.20±0.01		–8.1±0.4	–7.1±0.2
7	**1d**	1.74±0.03[f]	2.18±0.04	1.03±0.01[g]	1.32±0.05[h]	—	—	40	22.5±0.9	24.7±1.0
8	**2d**	0.86±0.04[f]	0.79±0.03	1.03±0.06[g]	0.94±0.05[h]	—	—		–7.7±0.2	–8.3±0.2

[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] Calculated value. [e] It is not determined because of the low reactivity of **3a**,**b**. [f] At 60 °C. [g] At 40 °C. [h] At 50 °C.

holds for $\Delta\Delta S^{\neq} > 0$: the entropy now favours the nitro group displacement (Table 1). In all cases, there is a temperature range where $|T\Delta\Delta S^{\neq} > \Delta\Delta H^{\neq}|$ for the competitive reactions of **3a**,**b** with **1a**–**d** and **2a**,**d** and $|\Delta\Delta H^{\neq} > T\Delta\Delta S^{\neq}|$ for the same reactions with **2b**,**c** (Table 1). Thus, a change of the nucleophile structure leads to an inversion of the reaction control: **1a**–**d** and **2a**,**d** favour the entropy control, whereas **2b**,**c** act in favour of the enthalpy one. These data suggest that reactions of **3b** with nucleophiles **1a**–**d** are more highly organised than those of **3a** with the above nucleophiles (*cf.* ref. 6). Besides, the relative mobility of the nitro group and fluorine in the reaction of **3a**,**b** with hard oxygen nucleophiles **2b**,**c** can exceed that in the same reaction with soft sulfur nucleophile **2d** (Table 1) (Figure 1, curves *4*, *6* and *8*). However, the displacement selectivity of nitro group and fluorine in the reaction of **3a**,**b** with oxygen nucleophiles **1a**–**c** at ≤ 70 °C is lower than that in the same reaction with sulfur nucleophile **1d** (HSAB principle[1]) (Figure 1, curves *1*, *3*, *5* and *7*). Evidently, the influence of the larger polarizability of the sulfur nucleophiles[7] is not always responsible for the larger displacement selectivity of the nitro group and fluorine compared with that for the oxygen one.[1]

The corresponding Eyring plots of $\log(k_{NO_2}/k_F)$ *vs.* $1/T$ give two intersecting lines for two related nucleophiles compared at a point defined as the inversion temperature T_{inv} (Figure 1). The T_{inv} represents the interconversion temperature between the reactions of these two types of nucleophiles. At temperatures lower than T_{inv}, the mobility of the nitro group relative to the fluorine atom is higher for nucleophiles **2a**–**d**, while at temperatures higher than T_{inv} it is higher for nucleophiles **1a**–**d**.

Note that the negative and positive values of the differential Brönsted and Hammett coefficients $\Delta\beta_{Nuc} = \beta_{Nuc}(NO_2) - \beta_{Nuc}(F)$, $\Delta\rho = \rho(NO_2) - \rho(F)$ from the $\log(k_{NO_2}/k_F)$ (at 80 °C)–p$K(\sigma)$[4(b)] relationships for the reactions of **3a**,**b** with **1a**–**c** and **2a**–**c** suggest greater sensitivity of the replacement of the fluorine atom to the substituent in both types of the nucleophiles, as compared to the replacement of the nitro group. The close values of $\Delta\beta_{Nuc}$ (–0.06 and –0.05) and $\Delta\rho$ (0.25 and 0.32) for **1a**–**c** and **2a**–**c**, respectively, also suggest that the sensitivity of the relative mobility of the leaving groups has a small dependence on the nucleophile structure and the steps of nucleophilic attack of the reactions studied are not different in principle.

The results obtained suggest that the reactions of **1a**–**d** and **2a**–**d** follow the S_NAr mechanism, but the structures of transition states for the rate-determining steps of the σ-complex formation are different. The S_NAr substitution with **1a**–**d** is characterised by an earlier transition state on the reaction coordinate than the substitution with **2a**–**d** (*cf.* ref. 11).

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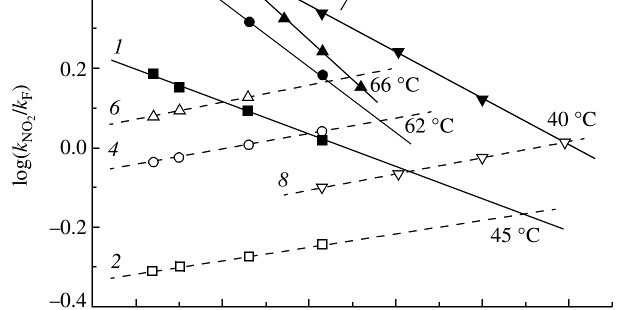

Figure 1 Eyring plots of $\log(k_{NO_2}/k_F)$ *vs.* $1/T$ for the competitive reactions of compounds **3a**,**b** with nucleophiles **1a**–**d** (curves *1*, *3*, *5* and *7*) and **2a**–**d** (curves *2*, *4*, *6* and *8*) in DMF. The identity of the lines is given as the entry in Table 1; the correlation coefficients for all lines is not worse than 0.998.

[†] GLC analysis of the reaction mixtures was performed on an LKhM-72 chromatograph (thermal conductivity detector; 4000×0.4 mm column packed with 15% SKTFT-803 on Cromaton-W; carrier gas, helium; linear oven temperature programming from 70 to 270 °C at a rate of 10 K min^{-1}). The components were quantitated by the absolute calibration technique using preliminary plotted calibration curves and identified by the addition of authentic samples. Commercial DMF was dried over 4 Å molecular sieves and distilled under reduced pressure over CaH_2. Commercial phenols and thiophenol were purified by standard procedures. Starting compounds **2a**–**d**, **3a**,**b** were synthesised according to published procedures.[4,8,9] Reaction products **4a**–**d** were obtained in quantitative yields by the interaction of **3a**,**b** with a corresponding phenol or thiophenol in the presence of K_2CO_3 in DMF at 98 °C and characterised by IR, ^{1}H NMR and ^{19}F NMR spectroscopy and mass spectrometry.[7] It was shown that products **4a**–**d** were stable under experimental conditions.[4(b),8] The operation with nucleophiles **1a**–**d** and **2a**–**d** were performed in a purified argon atmosphere. Competition reactions of substrates **3a**,**b** with nucleophiles **1a**–**d** and **2a**–**d** were carried out with equal molar concentrations of **3a** and **3b**. Performing of the competition reactions in a large excess of **3a**,**b** relative to nucleophile is more favourable to receive the k_{NO_2}/k_F values not changing as the reaction progresses.[10] In such a case, pseudo-first-order kinetics prevail.[10(a)] These conditions ensured that the ratios of reacted **3a**,**b** were directly proportional to the ratio of the second-order rate constants for each reaction according to the equation[10]

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

where $[A_0]$, $[B_0]$, $[A_t]$ and $[B_t]$ are the initial concentrations and the concentrations after a reaction time t, respectively, of **3a** and **3b**.

Determination of the relative reactivity of compounds **3a**,**b** *towards nucleophiles* **1a**–**d** and **2a**–**d** *in DMF (typical kinetic procedure).* K_2CO_3 (0.4 g, 0.1 mmol) was added to 2.0–4.5 ml of a 10% solution of a corresponding phenol or thiophenol (2.0 mmol) in DMF. The mixture was stirred for 3 h at 70 °C and cooled. An excess of K_2CO_3 was filtered off on a glass filter and washed with 0.2 ml of DMF. The filtrate obtained (0.1–0.2 ml) or 0.2–0 3 ml of a 10% solution of **2a**–**d** (0.1 mmol) was added to 2.2 ml of a 10% solution of **3a** (0.5 mmol) and **3b** (0.5 mmol), the solution was stirred for 3–4 h, cooled and analysed by GLC. The reported relative constants are the average values of several determinations.

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