

The Influence of Nucleophile Substituents on the Orientation in the Reaction between 2,4-Difluoronitrobenzene and Lithium Phenoxides in Liquid Ammonia

Larisa Politanskaya,^[a] Evgenij Malykhin,^{*,[a]} and Vitalij Shteingarts^{*,[a]}

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The dependence of the orientation of aryloxydefluorination of 2,4-difluoronitrobenzene (**1**) (*o/p* ratio) by the action of X-substituted lithium phenoxides **2** (X = *p*-OMe, *p*-Me, *p*-Et, *p*-*i*Pr, *p*-*t*Bu, *m*-Me, H, *p*-F) in liquid ammonia in the temperature range from –55 to –35 °C has been investigated. The enthalpic preference for *ortho*-fluorine substitution decreases with weakening substituent electron-donating capability in the order: *p*-OMe > *p*-Me ≈ *p*-Et > *m*-Me > H ≥ *p*-F. The predominant fluorine substitution at the *ortho* position for X = *p*-Me, *p*-Et turns into a preference for substitution at the *para* position when X = *p*-*i*Pr, and this increases further on going to X = *p*-*t*Bu. PM3, AM1 and MNDO MO calculations

showed greater stability of the intermediate anionic σ -complexes formed on nucleophile addition at the *para* position, thus suggesting that the predominant *ortho* substitution manifested for X = *p*-OMe, *m*-Me, H, *p*-F and *p*-Alk = Me, Et is due to control over orientation by the charge distribution in the substrate. The substrate electronic structure, as a controlling factor, is probably changed by the relative stability of intermediate anionic σ -complexes on going to *p*-Alk = *i*Pr, *t*Bu, as a consequence of an enhancement of the substituent's electron-withdrawing nature with the increase in alkyl group polarizability in the order: *p*-Me ≈ *p*-Et < *p*-*i*Pr < *p*-*t*Bu.

Liquid ammonia has long been known as a perfect solvent in which to carry out reactions involving strong bases and nucleophiles, due to its endowing anionic species, such as amides and carbanions, with very high reactivity.^[1] However, its unprecedented suitability for aromatic nucleophilic substitution reactions, conventionally considered as proceeding via the intermediate formation of anionic Meisenheimer-type σ -complexes (S_NAr mechanism), has only been demonstrated as recently as in the last few years.^[2,3] Thus, the rate constant for the reaction of *p*-chloronitrobenzene with sodium phenylthiolate has been found to be $k \geq 3 \cdot 10^{-2}$ L/mol·s in liquid ammonia at –45 °C,^[2] compared with $4.8 \cdot 10^{-4}$ L/mol·s in 60% aqueous dioxane at 25 °C.^[4] The reaction of *o*- and *p*-fluoronitrobenzenes with alkoxides are 10^6 – 10^8 times faster in liquid ammonia^[3] than in the respective alcoholic media.^[5–8] Obviously, the reason for such an enhanced reactivity of nucleophiles in liquid ammonia lies in the combination of strong metal cation solvation^[9,10] and weak anion solvation,^[11] so that the situation is similar to that in bipolar aprotic solvents.^[12]

As well as the reaction rates, one aspect of the nature of liquid ammonia as a solvent is manifested in the factors governing the correlation of substitution rates at positions *ortho* and *para* to the nitro group (k_o/k_p): customarily a testing parameter for determining delicate details of nucleophilic substitution mechanisms in nitroarenes.^[3,5–8,13–17] In the alkoxydefluorination reactions of *o*- and *p*-fluoronitro-

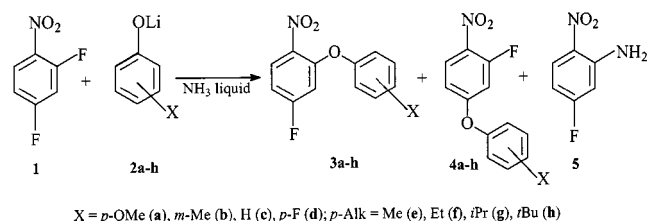
benzenes in AlkONa/AlkOH, the ratios of $k_o/k_p > 1$ observed for Alk = *i*Pr and Et and $k_o/k_p < 1$ for Alk = Me, based in both cases under entropic control,^[5,7,18] are changed to $k_o/k_p > 1$ under enthalpic control when changing to MeONa in liquid ammonia^[3] (the isokinetic temperature is raised from –130 °C to ca. 0 °C in going from MeOH^[19] to liquid ammonia^[3]). These findings have been interpreted^[3,15] as an indication that, at temperatures below 0 °C, solvation as a factor determining the relative stabilities of *ortho* and *para* substitution transition states for Alk = *i*Pr and Et in their respective alcohols^[8] is replaced in the case of MeONa in MeOH by the intrinsic structural characteristics of reactants, and the operation of structural factors, as the governing k_o/k_p , under entropic control in the last case, is changed by their operation under enthalpic control on going to liquid ammonia. Enthalpically controlled values of $k_o/k_p > 1$ have also been found^[15] for the reactions of 2,4-difluoronitrobenzene (**1**) with ROM (R = Me, Et, *i*Pr, Ph; M = Na, K) in liquid ammonia in the temperature range from –70 to –33 °C, becoming substituted by entropically controlled values of $k_o/k_p < 1$ at still higher temperatures (80–100 °C).

This makes it worthwhile to study systematically the effects of diverse factors on the value and temperature dependence of k_o/k_p , so as to improve understanding of the influence of liquid ammonia as a solvent on the detailed mechanism of the reactions in question. Currently available experimental data do not allow one to judge in detail the relationship between the *o/p* ratio and the structural peculiarities of a reagent that can be used as a test case for the investigation of the effect of nucleophile structure on the character of transition states. For this purpose, the dependence of the *o/p* ratio on nucleophile steric characteristics

^[a] N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, Novosibirsk State University, Lavrentiev Ave. 9, Pirogova St. 2, Novosibirsk 630090, Russia
Fax: (internat.) + 7-383/234-4752
E-mail: shtein@nioch.nsc.ru
malykhin@nioch.nsc.ru

and ion association should be minimised. As for the steric factor, this requirement can be met by employing phenoxides containing varying substituents in positions *meta* and *para* to the nucleophilic centre. As regards ion association, Li^+ seems to be appropriate as a counter cation, since, reasoning by the increase in solvation of alkali metal cations by liquid ammonia in the order $\text{K}^+ < \text{Na}^+ \ll \text{Li}^+$,^[9,10] the regioselectivity observed for lithium phenolates is not believed to be dominated by ion association,^[14] particularly by chelate formation in the *ortho* substitution transition state (TS) (cf. ref.^[5–8,13]). In line with this assumption, the addition of bicyclohexyl-18-crown-6 resulted in a decreasing *o/p* ratio in the reaction of **1** with PhOK, but no change in this ratio in the case of PhOLi. Moreover, the dependencies of *o/p* ratio on a substituent X in the reactions of **1** with $\text{XC}_6\text{H}_4\text{OK}$ and with $\text{XC}_6\text{H}_4\text{OLi}$ are opposite.^[14]

The goal of this work was to determine the temperature dependence of the regioselectivity of phenoxydefluorination of 2,4-difluoronitrobenzene (**1**) with lithium phenoxides $\text{XC}_6\text{H}_4\text{OLi}$ (**2a–h**) [$\text{X} = p\text{-OMe}$ (**a**), *m*-Me (**b**), H (**c**), *p*-F (**d**); *p*-Alk = Me (**e**), Et (**f**), *i*Pr (**g**), *t*Bu (**h**)] in liquid ammonia (Scheme 1).



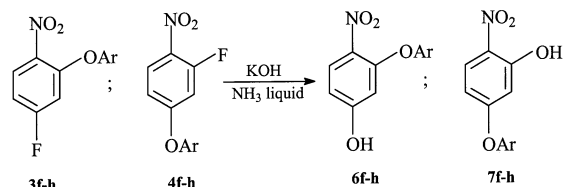
Scheme 1

Results and Discussion

The reactions were performed with **1** and **2**, taken in the ratio of 2:1, at -55 to -33 °C and quenched after reaching 30–50% conversion of phenoxide (10–30 min) by adding an excess of ammonium chloride. It was established that one fluorine atom only is replaced, to give the respective aryl 5-fluoro-2-nitrophenyl (**3a–h**) and aryl 3-fluoro-4-nitrophenyl (**4a–h**) ethers. In a parallel pathway, fluorine substitution by the amino group occurs in **1** at the position *ortho* to the nitro group, to form 3-fluoro-6-nitroaniline (**5**) in a maximum yield not exceeding 10% (according to the ^{19}F NMR spectroscopic data) after 30 min reaction time.

The ^{19}F NMR spectra of the reaction mixtures (C_6F_6 as internal reference) contained signals at $\delta \approx 62$ and 50 (belonging to aryloxydefluorination products), at $\delta = 60.3$ (belonging to **5**),^[20] and at $\delta = 50.9$ and 64.5 (belonging to the starting compound **1**). The positions of the product signals were practically invariant over the series of substituents (**a–h**) and had been anticipated for compounds **3** and **4**, respectively. The structures of the products **3a–e** and **4a–e** have been established previously.^[17] Attempts to separate **3f–h** and **4f–h** by chromatography failed, so that the structures of these compounds were assigned by treatment of the product mixtures with alkali in liquid ammonia, the corre-

sponding aryl 5-hydroxy-2-nitrophenyl ethers **6f–h** and aryl 3-hydroxy-4-nitrophenyl ethers **7f–h** having been isolated and characterized (Scheme 2).



Scheme 2

In Table 1, Table 2 and Table 3, the spectral and analytical data for **3**, **6** and **7** are summarized. In the IR spectra of **7f–h**, the hydroxy group absorptions exhibit low frequency shifts of ca. 100 cm^{-1} from their positions in the IR spectra of *p*-nitrophenols,^[21] including **6h**; this is typical for compounds with an intramolecular hydrogen bond.^[22] This peculiarity denotes mutual *ortho* location of nitro and hydroxy groups in **7f–h**, and in turn justifies the assignment of the aforementioned signals at $\delta \approx 50$, disappearing from the ^{19}F NMR spectra after hydroxydefluorination, to **4f–h**.

The regioselectivity of phenoxydefluorination of **1** was determined from the ratio of integral intensities of the ^{19}F NMR signals at $\delta \approx 62$ and 50, belonging to isomers **3** and **4**, respectively. The data listed in Table 4 and 5 characterize the dependence of *o/p* ratio on the nature of a substituent in the nucleophile, over the temperature range of -33 to -55 °C. It can be seen that the proportion of the *ortho* substitution product increases with decreasing electron-donating capability of the substituent in the nucleophile (i.e., on passing along the substituent series from *p*-OMe to *p*-F) and decreasing temperature (Table 4). The latter finding, in conjunction with the *o/p* ratio of > 1 , suggests that the regioselectivity is controlled by enthalpy over the temperature range from -55 to -33 °C. For *p*-methyl- and *p*-ethylphenoxides (**2e,f**), the proportion of *ortho* substitution also increases with decreasing temperature, which, together with the *o/p* value of > 1 , indicates enthalpic control of regioselectivity over the temperature range used (Table 5). For *p*-Me and *p*-Et, *ortho* substitution is enthalpically more advantageous than *para* substitution, the isokinetic temperature lying above -33 °C. In contrast, when *p*-isopropyl- and *p*-tert-butylphenoxides (**2g** and **2h**) are used as nucleophiles, the isokinetic temperature shifts into the range from -33 to -55 °C. This fact is illustrated by the alteration of *o/p* ratio from > 1 at -33 °C to < 1 at -55 °C, and corresponds to the change from entropically controlled regioselectivity to that controlled by enthalpy upon lowering the temperature, with *para* substitution of fluorine becoming more preferred (Figure 1).

The differences between the activation parameters of phenoxydefluorination of **1** at the positions *ortho* and *para* to the nitro group were calculated by the least-squares method, from the temperature dependencies of the *o/p* ratio (more than 6 values at various temperatures). The activation parameters are given in Table 6 and 7. The differences in the enthalpies and entropies of activation for fluorine substitution by the action of lithium phenoxide at the *ortho*

Table 1. ^1H and ^{19}F NMR spectroscopic data for substituted aryl nitrophenyl ethers **3f**, **3g**, **6h**, and **7f–h**

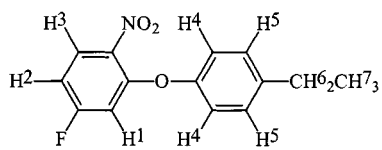
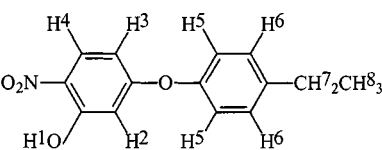
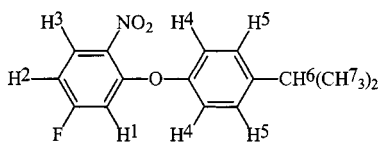
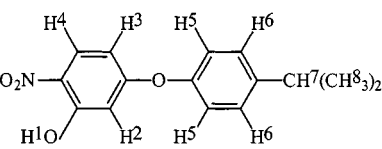
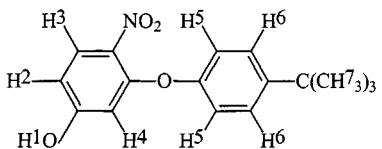
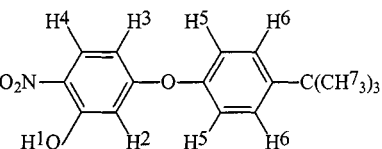
										
3f		7f								
										
3g		7g								
										
6h		7h								
Com- pound	Solvent	¹ H- and ¹⁹ F NMR chemical shifts, δ [p.m.]								Coupling constants, <i>J</i> [Hz]
		H ¹	H ²	H ³	H ⁴	H ⁵	H ⁶	H ⁷	H ⁸ (F ¹)	
3f	CD ₂ Cl ₂	6.65	6.86	8.04	7.29	7.03	2.69	1.26	61.29	<i>J</i> (F,H ¹) 7.3, <i>J</i> (F,H ²) 10.0, <i>J</i> (F,H ³) 5.8, <i>J</i> (H ¹ ,H ²) 2.8, <i>J</i> (H ² ,H ³) 9.4, <i>J</i> (H ⁴ ,H ⁵) 8.6, <i>J</i> (H ⁶ ,H ⁷) 7.5
3g	[D ₆] acetone	6.72	6.98	8.17	7.30	7.04	2.88	1.21	61.62	<i>J</i> (F,H ¹) 7.8, <i>J</i> (F,H ²) 10.1, <i>J</i> (F,H ³) 6.1, <i>J</i> (H ¹ ,H ²) 2.8, <i>J</i> (H ² ,H ³) 9.0, <i>J</i> (H ⁴ ,H ⁵) 8.7, <i>J</i> (H ⁶ ,H ⁷) 7.2
6h	[D ₆] acetone	9.80	6.72	8.01	6.40	7.49	7.02	1.32		<i>J</i> (H ² ,H ³) 8.8, <i>J</i> (H ² ,H ⁴) 2.5, <i>J</i> (H ⁵ ,H ⁶) 8.6
7f	[D ₆] acetone	10.71	6.47	6.63	8.12	7.34	7.09	2.68	1.24	<i>J</i> (H ² ,H ³) 2.5, <i>J</i> (H ³ ,H ⁴) 9.6, <i>J</i> (H ⁵ ,H ⁶) 8.5, <i>J</i> (H ⁷ ,H ⁸) 7.4
7g	CD ₂ Cl ₂	9.91	6.30	6.40	8.08	7.12	6.83	2.75	1.09	<i>J</i> (H ² ,H ³) 2.6, <i>J</i> (H ³ ,H ⁴) 9.1, <i>J</i> (H ⁵ ,H ⁶) 8.5, <i>J</i> (H ⁷ ,H ⁸) 8.0
7h	CD ₂ Cl ₂	10.66	6.32	6.43	7.88	7.28	6.85	1.16		<i>J</i> (H ² ,H ³) 2.6, <i>J</i> (H ³ ,H ⁴) 9.5, <i>J</i> (H ⁵ ,H ⁶) 8.5

Table 2. IR data

Compound	IR spectra, $\tilde{\nu}$ [cm^{-1}]		CH (Alk)	C–O–C	NO_2	Other bonds
	OH	CH (Ar)				
3f		3030–3100	2930, 2870	1270	1520, 1335, 840, 740	1075 (C–F)
3g		3030–3110	2940, 2870	1270	1520, 1340, 830, 745	1080 (C–F)
6h	3350 s.	3030–3100	2960, 2865	1270	1510, 1340, 840, 745	
7f	3235 w.	3030–3120	2970, 2870	1270	1510, 1335, 840, 755	
7g	3220 m.	3030–3110	2970, 2865	1270	1520, 1330, 840, 750	
7h	3200 m.	3050–3110	2960, 2860	1270	1520, 1320, 830, 740	

and *para* positions of **1** ($\Delta\Delta H_{\text{olp}}^\ddagger = -0.9 \text{ kJ/mol}$, $\Delta\Delta S_{\text{olp}}^\ddagger = -1.1 \text{ J} \times \text{mol}^{-1}\text{K}^{-1}$) are considerably smaller than the corresponding values for the reaction of **1** with sodium phenoxide ($\Delta\Delta H_{\text{olp}}^\ddagger = -4.4 \text{ kJ/mol}$, $\Delta\Delta S_{\text{olp}}^\ddagger =$

$-11.9 \text{ J} \times \text{mol}^{-1}\text{K}^{-1}$).^[15] This is in line with the previous conclusion^[14] of a minimal contribution to regioselectivity by chelation observed for lithium phenoxides as compared with other alkali metal cations.

Table 3. Exact values of molecular ion masses

Compound	Formula	M ⁺ (found)	M ⁺ (calcd.)
3f	C ₁₄ H ₁₂ FNO ₃	261.0799	261.0801
3g	C ₁₅ H ₁₄ FNO ₃	275.0954	275.0958
6h	C ₁₆ H ₁₇ NO ₄	287.1132	287.1157
7f	C ₁₄ H ₁₃ NO ₄	259.0840	259.0844
7g	C ₁₅ H ₁₅ NO ₄	273.1003	273.1001
7h	C ₁₆ H ₁₇ NO ₄	287.1150	287.1157

Table 4. *o/p* ratios in the reaction of 2,4-difluoronitrobenzene (**1**) with XC₆H₄OLi (**2a–d**) in liquid ammonia

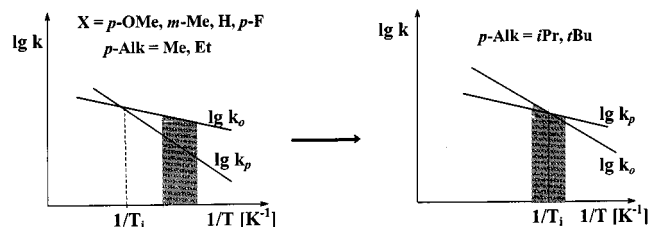
T [°C]	<i>p</i> -OMe	<i>m</i> -Me	H	<i>p</i> -F
–33	1.12 ^[a]	1.28	1.36	1.49
–55	1.20	1.37	1.45	1.58

^[a] The deviations of *o/p* ratios do not exceed 0.02.

Table 5. *o/p* ratios in the reaction of 2,4-difluoronitrobenzene (**1**) with *p*-AlkC₆H₄OLi (**2e–h**) in liquid ammonia

T [°C]	Me	Et	<i>i</i> Pr	<i>t</i> Bu
–33	1.23 ^[a]	1.24	1.03	1.14
–55	1.30	1.40	0.93	0.96

^[a] The deviations of *o/p* ratios do not exceed 0.02.

Figure 1. Temperature dependence of the regioselectivity in the reaction of **1** with XC₆H₄OLi (*p*-Alk C₆H₄OLi)

It follows from these data that, firstly, the substitution of the *ortho*-fluorine atom is more preferable in terms of enthalpy than that of the *para*-fluorine atom and, secondly, that this tendency weakens in the order: *p*-OMe > *m*-Me > *p*-Me ≈ *p*-Et > H ≈ *p*-F (Table 6). As well as this, the enthalpic advantage moves from *ortho* to *para* substitution on going along the alkyl substituent series from Me and Et to *i*Pr and *t*Bu (Table 7). Thus, the absolute values of $\Delta\Delta H_{olp}^\ddagger$ and $\Delta\Delta S_{olp}^\ddagger$ increase in the order: Me ≈ Et < *i*Pr < *t*Bu.

Table 6. The differences between the *ortho* and *para* activation parameters ($\Delta\Delta H_{olp}^\ddagger$ and $\Delta\Delta S_{olp}^\ddagger$) for the reaction of 2,4-difluoronitrobenzene (**1**) with XC₆H₄OLi in liquid ammonia

X	<i>p</i> -OMe	<i>p</i> -Me	<i>p</i> -Et	<i>m</i> -Me	H	<i>p</i> -F
$\Delta\Delta H_{olp}^\ddagger$ ^[a]	–2.1±0.2	–1.7±0.2	–1.7±0.3	–1.4±0.3	–0.9±0.2	–0.9±0.1
[kJ/mol]						
$\Delta\Delta S_{olp}^\ddagger$ ^[a]	–8.3±0.1	–5.3±0.1	–5.2±0.1	–3.8±0.1	–1.1±0.1	–0.5±0.1
[J/mol × K]						

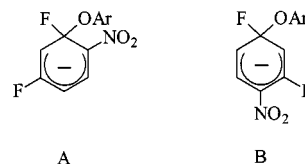
^[a] $\ln(o/p) \approx \ln(k_o/k_p) = \ln(A_o/A_p) - [(\Delta E_o - \Delta E_p)/R] \times 1/T$; $\Delta\Delta H_{olp}^\ddagger = \Delta\Delta E_{olp}^\ddagger$; $\Delta\Delta S_{olp}^\ddagger = R\ln(A_o/A_p)$.

Table 7. The differences between the *ortho* and *para* activation parameters ($\Delta\Delta H_{olp}^\ddagger$ and $\Delta\Delta S_{olp}^\ddagger$) for the reaction of 2,4-difluoronitrobenzene (**1**) with *p*-AlkC₆H₄OLi in liquid ammonia

Alk	Me	Et	<i>i</i> Pr	<i>t</i> Bu
$\Delta\Delta H_{olp}^\ddagger$ ^[a]	–1.7±0.2	–1.7±0.3	1.7±0.1	2.7±0.2
[kJ/mol]				
$\Delta\Delta S_{olp}^\ddagger$ ^[a]	–5.3±0.1	–5.2±0.1	7.4±0.1	12.0±0.1
[J/mol × K]				

^[a] $\ln(o/p) \approx \ln(k_o/k_p) = \ln(A_o/A_p) - [(\Delta E_o - \Delta E_p)/R] \times 1/T$; $\Delta\Delta H_{olp}^\ddagger = \Delta\Delta E_{olp}^\ddagger$; $\Delta\Delta S_{olp}^\ddagger = R\ln(A_o/A_p)$.

The TS structure for the reaction under study may more closely resemble either an anionic cyclohexadienyl intermediate (σ -complex) or the starting reactants. In the former case, the ratio of *ortho* to *para* substitution rates in **1** under enthalpic control should correlate with the relative stabilities of σ -complexes **A** and **B** (Figure 2). In the second case, it is reasonable to apply reactivity indices associated with the electronic structure of **1**. Let us consider both possibilities.

Figure 2. Structures of the intermediate anionic σ -complexes

Calorimetric measurements^[23] indicate a higher stability for anionic σ -complexes formed by 1-methoxy-2- and -4-nitronaphthalenes and 2,4- and 2,6-dinitroanisoles with MeONa in methanol when the nitro group is located *para* rather than *ortho* to the geminal methoxy groups (in both cases, $\Delta\Delta H_{olp}^0 = 21$ kcal/mol). Quantum chemical calculation^[24] of the enthalpies of formation of the anionic intermediates of S_NAr reactions also indicates a slightly higher stability for the structures with a nitro group located *para* rather than *ortho* to the sp³-hybridized carbon atom. Thus, according to ab initio calculations with the STO-3G basis set, the difference between the energies of cyclohexadienyl anions with their nitro groups situated *ortho* and *para* to the sp³-hybridized carbon atom is as small as 2.09 cal/mol.^[25] Semiempirical calculation of the enthalpies of formation of the anionic σ -complexes derived from *o*- and *p*-fluoronitrobenzenes and an amide ion gives the following values: $\Delta\Delta H_{olp}^0 = -1$ kcal/mol (CNDO), -3 kcal/mol (INDO), and 5 kcal/mol (MNDO).^[24] According to the MNDO re-

sults, which are considered the most reliable,^[24] the σ -complex formed by nucleophile addition to the position *para* to the nitro group is more stable.

In order to estimate the relative stabilities of isomeric σ -complexes forming only in the course of aryloxydefluorination of **1**, we calculated the formation enthalpies for the structures **A** and **B**, with Ar = Ph, using semiempirical PM3, AM1, and MNDO methods.^[26] The initial parameters for the cyclohexadienyl fragments were obtained by the geometric optimization of σ -complexes, formed by *p*- and *o*-fluoronitrobenzenes with an amide ion, in terms of MNDO approximation.^[24] According to these calculations, the most stable structures are those in which the mutual arrangement of bonds between the four-coordinated carbon and the fluorine atoms, and between the oxygen atom and the phenyl ring, corresponds to an antiperiplanar conformation (cf. ref.^[27]). The data presented in Table 8 show the structure **B** to be preferred by a formation enthalpy value of 2.11 to 2.91 kcal/mol, depending on the calculation procedure. To estimate the effects exerted by the substituents in the phenyl ring on $\Delta\Delta H^0_{olp}$, we calculated the formation enthalpies for the structures **A** and **B**, using the PM3 method. The data presented in Table 9 show no regular correlation between the identity of the substituent and the $\Delta\Delta H^0_{olp}$ value, the structure **B** being preferred in all cases.

Table 8. Calculated enthalpies of formation (ΔH^0) of structure **A** and **B** (Ar = Ph)

Parameter	PM3	AM1	MNDO
ΔH^0 (A) [kcal/mol]	−139.16	−120.33	−111.99
ΔH^0 (B) [kcal/mol]	−142.07	−123.10	−114.10
$\Delta\Delta H^0_{olp}$ [kcal/mol]	2.91	2.77	2.11

Table 9. PM3 enthalpies of formation (ΔH^0) of structures **A** and **B** with various substituents in the aryl fragment

Parameter	<i>p</i> -OMe	<i>p</i> -Me	<i>m</i> -Me	H	<i>p</i> -F
ΔH^0 (A) [kcal/mol]	−176.67	−148.24	−148.27	−139.16	−184.86
ΔH^0 (B) [kcal/mol]	−179.61	−151.16	−151.27	−142.07	−187.51
$\Delta\Delta H^0_{olp}$ [kcal/mol]	2.94	2.82	3.00	2.91	2.65

Steric hindrance, arising from the phenoxy group, to a coplanar arrangement of the nitro group and pentadienyl fragment in the structure **A** could be a factor responsible for its smaller relative stability. However, according to crystallographic data,^[28] the nitro groups in the σ -complex of 2,4,6-trinitrophenetole with potassium ethoxide are coplanar with the ring. Therefore, the above hindrance can scarcely be significant. Another factor of the same nature lies in the fact that a fluorine atom, situated adjacent to the nitro group in structure **B**, can hinder coplanarity of the nitro group with the pentadienyl moiety. However, taking into account that the effective radius of fluorine is small and the solvating ability of liquid ammonia toward anions is weak,^[11] and hence that an increase in the effective size

of the nitro group due to local interaction with solvent molecules should not be considerable, the contribution of this factor is probably insignificant. On the other hand, mutual electrostatic repulsion between nitro group and fluorine atom, as structural units bearing partial negative charges, may be important. In any case, both their steric and electrostatic interactions favor structure **A**. However, on the whole, we cannot judge with certainty the contribution of a particular structural factor to the relative stability of the structures **A** and **B**, and the real stability difference between isomeric σ -complexes seems not great, so their relative stability might change on variation of structure. Nonetheless, in general, the above data suggest the σ -complex-like TS approximation to be more probably in favor of *para* substitution than *ortho* substitution.

That is why one must also take into account the fact that the experimentally observed enthalpic preference for *ortho* substitution for X = *p*-OMe, *m*-Me, H, *p*-F; *p*-Me, *p*-Et, and the dependence of $\Delta\Delta H^{\neq}_{olp}$ and $\Delta\Delta S^{\neq}_{olp}$ values on a substituent in the nucleophile may originate from a structural similarity of the aryloxydefluorination TS to the starting compounds **1** and **2** rather than to the intermediate σ -complexes. In the context of this approximation, it is reasonable to consider reactivity indices relating to the electronic structure of the initial compound **1**. Table 10 gives the calculated charges on the carbon atoms that are electrophilic centers in **1**. As expected, the positive charge on the carbon atom *ortho* to the nitro group exceeds that for the *para* carbon atom that would provide the enthalpic preference for the nucleophilic attack, proceeding via the reactant-like TS, at the *ortho* position of **1**. The occurrence of such a TS is favored by the high reactivity of anionic nucleophiles in liquid ammonia,^[2,3] thanks to their lack of significant specific solvation and association with a counter cation. It seems reasonable to assume that a fluorine atom attached to the carbon atom attacked by a nucleophile, because of its strong electron-withdrawing inductive effect, also acts in favor of the “early” TS. This is supported by the inversion of the signs of both $\Delta\Delta H^{\neq}_{olp}$ and $\Delta\Delta S^{\neq}_{olp}$ (vide supra), as well as by the substantial increase in $\Delta H^{\neq}$ value for halogen substitution reactions of *p*- and *o*-halogenonitrobenzenes with charged nucleophiles, on going from fluorine to other halogens, while the $\Delta S^{\neq}$ values remain almost unchanged.^[3,5–7]

Table 10. Calculated charges [a. u.] on the carbon atoms bearing fluorine atoms in positions *ortho* and *para* to the nitro group in compound **1**

Atom	PM3	AM1
<i>ortho</i>	+0.191	+0.196
<i>para</i>	+0.151	+0.167
Δq_{olp}	0.040	0.029

Owing to the above-mentioned weak solvation of anions by liquid ammonia, it is not unreasonable to expect the nucleophilicity of substituted phenoxides in liquid ammonia to change in parallel with their gas phase basicity: i.e., in the order *p*-F < H < *m*-Me < *p*-Me < *p*-OMe.^[29] The

increase in nucleophile reactivity makes the TS more reactant-like, so that the charge density distribution in **1** would be an increasingly significant factor in the difference between the activation parameters for *ortho*- and *para*-aryloxydefluorination, thus enhancing the enthalpic preference for *ortho* substitution. The change of $\Delta\Delta H^{\ddagger}_{olp}$ from -0.9 to -2.1 kJ/mol on going from $X = p\text{-F}$ to $X = p\text{-OMe}$ is in line with this prediction. Conversely, the increase in the electron-accepting capability of a substituent in the phenoxide is expected to diminish the enthalpic advantage of *ortho* substitution, even as far as reversing the *olp* ratio, as indeed occurs, for example, on going from sodium methoxide to sodium phenoxide in their respective reactions with *o*- and *p*-fluoronitrobenzenes in methyl alcohol ($\Delta\Delta H^{\ddagger}_{olp} = -0.5$ kcal/mol for MeO^- and $+3.3$ kcal/mol for PhO^-).^[5]

It is known^[29] that *p*-alkylphenoxides display a variation of gas phase acidity in the order $\text{Me} < \text{Et} < i\text{Pr} < \text{H} < t\text{Bu}$,^[29] thus illustrating the weakening of the electron-donating influence of the alkyl substituent and its trend towards a change to an electron-withdrawing one with the branching at the alkyl α -carbon atom; i.e. the increase in the alkyl polarizability is unfavorable for phenoxide basicity. Accordingly, if one assumes for the above reasons that alkylphenoxide nucleophilicity in liquid ammonia should follow the same sequence, the inversion of $\Delta\Delta H^{\ddagger}_{olp}$, concomitant with passing from *p*-Me and *p*-Et to *p*-*i*Pr and *p*-*t*Bu (Table 7), would suggest the growth of the intermediate-like character of TS, to the detriment of its reactant-like character, as caused by weakening phenoxide nucleophilicity. Such a view is consistent with the $\Delta\Delta H^{\ddagger}_{olp}$ values for the reactions of **1** with PhOLi and $p\text{-FC}_6\text{H}_4\text{OLi}$ (ca. -0.9 kJ/mol), $p\text{-iPrC}_6\text{H}_4\text{OLi}$ ($+1.7$ kJ/mol), and $p\text{-tBuC}_6\text{H}_4\text{OLi}$ ($+2.7$ kJ/mol). Thus, the *p*-*i*Pr and *p*-*t*Bu substituents manifest as electron-withdrawing ones, diminishing phenoxide nucleophilicity in the reaction in question: this is similar to their influence on the phenol dissociation equilibrium in the gas phase. If so, for the reactions between **1** and **2a–f**, the *olp* ratios are apparently determined by factors inherent in the “early” TS, first of all by the charge density distribution in **1**, which is characterized by the greater proportion of positive charge in the position *ortho* to the nitro group, as compared to the *para* position. Decreasing nucleophilicity on passing to **2g** and **2h** makes the TS more closely similar to the intermediate σ -complexes, and heightens the influence of those factors inherent in the “late” TS. It is suggested that this is the reason for the inversion of the correlation of TS energies in favor of *para* substitution.

Conclusion

The results given in this paper, together with other data,^[3,15,17] are believed to explain the significant difference in the detailed mechanisms of fluorine nucleophilic substitution in positions *ortho* and *para* to the nitro group by the action of anionic nucleophiles in liquid ammonia, as well as, probably, in aprotic bipolar solvents on one hand, and

in distinctly protic, particularly hydroxylic, solvents on the other.^[5–8] Specifically, as a result of conferring charged nucleophiles with considerably higher activity, TSs are expected to be generally more reactant-like in solvents of the first type than in solvents of the second. As a consequence, any decrease in nucleophile activity due to structural reasons may change the correlation of activation parameters of competing reactions and regioselectivity, in compliance with the strengthening intermediate-like character of the TS.

Experimental Section

General Methods and Materials: The ^{19}F NMR spectra were recorded with a Bruker WP-200 SY instrument in 50% Et_2O and 5% $[\text{D}_6]\text{acetone}$ solutions, using C_6F_6 as an internal standard. The ^1H NMR spectra were recorded with a Bruker WP-200 SY instrument in 5% $[\text{D}_6]\text{acetone}$ and CD_2Cl_2 solutions, using $[(\text{CH}_3)_3\text{Si}]_2\text{O}$ as an internal standard. – IR spectra were recorded with a UR-20 instrument in KBr tablets (0.25% by weight). – Exact values of molecular ion masses were measured by high-resolution mass spectrometry with a Finnigan MAT-8200 machine. 2,4-Difluoronitrobenzene (**1**) was prepared according to the literature procedure.^[30] Phenol, *m*-cresol, *p*-cresol, *p*-ethylphenol, *p*-fluorophenol, *p*-methoxyphenol, *p*-isopropylphenol, and *p*-*tert*-butylphenol were commercially available. Liquid ammonia was purified by dissolving metallic sodium in it, with subsequent distillation into the reaction flask at -40 °C. Metallic lithium and potassium were purified from their oxide films and weighed directly before loading into the reaction flask.

General Procedure for the Preparation of Lithium Phenoxides in Liquid Ammonia: To liquid ammonia (75 mL) at -40 °C was added lithium metal (0.02 g), with stirring. $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (ca. 0.005 g) was added to the obtained dark blue solution, which was stirred until lithium amide formation was complete, concomitant with decolorization. To generate the lithium phenoxide, one equivalent (relative to lithium amide) of phenol was added (concentration 0.04 mol/l).

General Procedure for the Interaction of 2,4-Difluoronitrobenzene (1) with Lithium Phenoxide in Liquid Ammonia: To a thermostatted (± 0.5 °C) solution of lithium phenoxide, prepared as described above, was added **1** (1 g). It was stirred for 10 and 20 min for $X = p\text{-OMe}$, *m*-Me, *p*-Me, and *p*-Et; and for 20 and 30 min for $X = p\text{-F}$, H, *p*-*i*Pr, and *p*-*t*Bu, at -33 and -55 °C, respectively. To determine temperature dependencies, not less than 6 experiments were carried out for each compound at fixed temperatures (error ± 0.5 °C), with a step of ca. 5 °C. The reaction mixture was poured into a stirred suspension of ammonium chloride (ca. 2 g) in diethyl ether (100 mL) cooled to -50 °C. After the ammonia had evaporated, the mixture was diluted with water (50 mL) and extracted with diethyl ether (2×50 mL). The combined ether extracts were washed with 5% aqueous NaOH solution (2×50 mL), then with water (50 mL), and dried with MgSO_4 . The mixture of reaction products obtained after solvent evaporation (1.1–1.2 g for $X = \text{H}$, *p*-F, *m*-Me, *p*-Me; and 1.2–1.3 g for $X = p\text{-OMe}$, *p*-Et, *p*-*i*Pr, *p*-*t*Bu), was analyzed by ^{19}F NMR.

General Procedure for the Separation of 3 and 4 from other Reaction Products: A mixture of **1**, **3**, and **4** was purified by column chromatography (silica gel 40–140 μ , hexane), followed by evaporation of **1** in vacuum (5 Torr with 70 °C bath), to give a mixture of **3** and **4**.

General Procedure for the Interaction of a Mixture of 3 and 4 with Potassium Hydroxide in Liquid Ammonia: To a stirred solution of

potassium metal in liquid ammonia (concentration 0.2 mol/l) at $-40\text{ }^{\circ}\text{C}$, containing ferric chloride (ca. 0.005 g), was added dropwise an equimolar amount of water. After formation of a potassium hydroxide suspension, a mixture of **3** and **4** (concentration 0.1 mol/l) was added, and the reaction mixture was stirred at $-35\text{ }^{\circ}\text{C}$ for 4 h. The reaction was quenched by pouring the mixture into a stirred suspension of ammonium chloride (ca. 5 g) in diethyl ether (150 mL) cooled to $-50\text{ }^{\circ}\text{C}$. After the ammonia had evaporated, the mixture was washed with 20% aqueous KOH solution ($2 \times 100\text{ mL}$), then with water (50 mL), and dried with MgSO_4 . According to ^{19}F NMR spectroscopic data, the corresponding mixtures of **3** and **4** contained mainly isomers **3f** and **3g**, which were isolated by TLC [Silufol® UV-254 plates, hexane/diethyl ether (9:1), $R_f = 0.9\text{--}0.7$]. The combined alkaline, aqueous solution was neutralized with sulfuric acid (to $\text{pH} = 6$) and extracted with diethyl ether ($2 \times 100\text{ mL}$). The ether extract was washed with water and then dried with MgSO_4 . After solvent evaporation, **6** and **7** were isolated by TLC (Silufol® UV-254 plates, benzene, $R_f = 0.9\text{--}0.7$ and $0.5\text{--}0.15$, respectively).

The spectral characteristics of new compounds **3f**, **3g**, **6h**, and **7f–h** are presented in Table 1, Table 2 and Table 3.

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