Ambident reactivity of aryloxide ions towards the super-electrophile, 4,6-dinitrobenzofuroxan. Kinetics, thermodynamics and stereoelectronic factors on regioselectivity†

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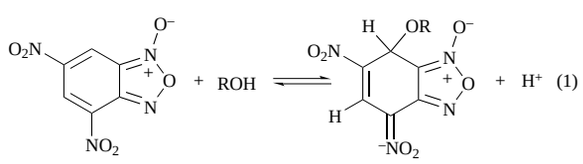
Reactions of the aryloxide ions, phenoxide (PhO^-) and 3,5-di-*tert*-butylphenoxide (3,5-DTBPhO$^-$), with the super-electrophilic heteroaromatic substrate, 4,6-dinitrobenzofuroxan (DNBF, 1), have been examined by 400 MHz ^{1}H NMR spectroscopy in acetronitrile–dimethoxyethane ([$^2H_3$]MeCN : [$^2H_{10}$]DME 1 : 1, v/v) as a function of varying temperature (−40 to 23 °C) and in dimethyl sulfoxide ([$^2H_6$]DMSO) at room temperature. We herein report the first observation and full characterization of the *O*-bonded σ-adduct (DNBF·OPh^-, 3a) formed by attack of PhO^-, acting as an *O*-nucleophile, at the C-7 super-electrophilic site of 1. No C-5 adduct was seen in the initial spectrum (−40 °C, [$^2H_3$]MeCN : [$^2H_{10}$]DME) or in subsequent monitoring of the reaction. These results suggest that PhO^- displays K7T7 regioselectivity towards DNBF wherein attack at the C-7 site is favoured by both kinetics and thermodynamics, comparable to the behaviour shown by PhO^- towards 2,4,6-trinitroanisole where the C-1 adduct is the product of both kinetic and thermodynamic control (*i.e.* K1T1 regioselectivity). Upon warming the reaction mixture to ambient, the C-7 *O*-adduct, DNBF·OPh^-, 3a, gives way to the more stable C-7 C-bonded σ-adducts (DNBF·*ortho*-$PhOH^-$ adduct, 4, and DNBF·*para*-$PhOH^-$ adduct, 5, in a ratio of *ca.* 1 : 6). The C-7 hydroxide adduct, DNBF·OH^-, 2a, and phenol are detected at this temperature. The *C*-adducts, 4 and 5, are the sole PhO^- adducts previously observed in the DNBF–PhO^- reaction system (in [$^2H_6$]DMSO at room temperature). When *C*-attachment is precluded by steric hindrance, as in the reaction of 1 with 3,5-DTBPhO^-, the C-7 DNBF·OPhDTB^- adduct, 3b, is observed by ^{1}H NMR spectroscopy even in [$^2H_6$]DMSO under ambient conditions. The results of the kinetics and thermodynamics of aryloxide adduct formation with DNBF, including the ambident reactivity found, are discussed with regard to stereoelectronic stabilization in the adducts and with comparison to relevant 4-nitrobenzofuroxan (NBF), 2-(nitroaryl)-4,6-dinitrobenzotriazole 1-oxides (2-Ar-4,6-DNBT) systems and to the normal electrophile, 1,3,5-trinitrobenzene (TNB).

Introduction

Studies of the interactions of nucleophilic reagents with polynitroaromatics and heteroaromatics have led to the discovery of a diverse number of species (π-complexes, and more notably radical anions,[1,2g] radical anion–radical pairs[1b,c] and anionic σ-adducts[2]) that have yielded valuable information concerning reaction mechanisms. Electron-deficient nitroaromatic and heteroaromatic compounds have been used for the identification of thiols[3] and amino (usually lysine) nucleophilic residues[4] in proteins. The anionic σ-adducts that have frequently been postulated as intermediates in these reactions have organic synthetic utility in their own right.[2a] The nitroaromatic and heteroaromatic substrates also serve as probes of ambident nucleophilic reactivity in anionic σ-adduct formation,[2] and, in this regard, our[5–7] and other groups[8] have been particularly interested in the reactivity of phenoxide ion (PhO^-) as an oxygen- and carbon-nucleophile towards 1,3,5-trinitrobenzene (TNB),[5,8] 2,4,6-trinitroanisole (TNA),[2a,6] and the 2-(nitroaryl)-4,6-dinitrobenzotriazole 1-oxide (2-Ar-4,6-DNBT)[7] series of ambident electrophiles. Recently, we have fully characterized the *O*-bonded anionic σ-adducts formed by PhO^- with 4-nitrobenzofuroxan (NBF)[9] and the normal reference electrophile, TNB,[10a] using ^{1}H NMR spectroscopy in the novel medium, acetonitrile–dimethoxyethane ([$^2H_3$]MeCN : [$^2H_{10}$]DME 1 : 1 v/v); this solvent system remains fluid to temperatures of −50 °C and, so, facilitated observation of these reactions at −40 °C. As a comparison of the reactivity of aryloxide ions towards NBF and TNB, we now report our findings on the reactivity of PhO^- and 3,5-di-*tert*-butylphenoxide (3,5-DTBPhO^-) with the super-electrophilic heteroaromatic, 4,6-dinitrobenzofuroxan (DNBF, **1**).

Current interest in the reactivity of **1** has been fuelled by the fact that this neutral 10 π-electron heteroaromatic substrate is a more powerful electrophile than such strong electrophiles as the *p*-nitrobenzenediazonium cation and the proton.[11] Thus, water and methanol react readily with **1** [eqn. (1)] to yield the C-7



1 R = H **2a**; R = CH_3 **2b**

hydroxide and methoxide adducts, **2a** and **2b**, respectively, which are 10^{10} times more stable than the analogous TNB·OH^- and TNB·OMe^- adducts that are only formed upon addition of hydroxide and methoxide ions.[1,2]

† For Part 52 of the series on anionic σ-complexes, see ref. 2(*h*). For Part 11 of the series on heteroaromatic super-electrophiles in σ-adduct formation, see ref. 24.

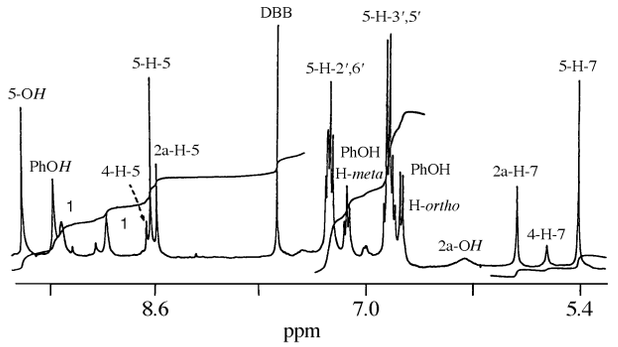


Fig. 1 ^{1}H NMR spectrum (downfield region; 5.4–9.6 ppm) of the DNBF–PhOK (1:1) reaction, recorded at *ca*. 3 min reaction time [$^2H_6$]DMSO at room temperature). The resonances that are highlighted are assigned to the C-7 adducts (*para* and *ortho* C-adducts and the hydroxide adduct). The singlet marked DBB represents 1,4-dibromobenzene, an internal integration standard.

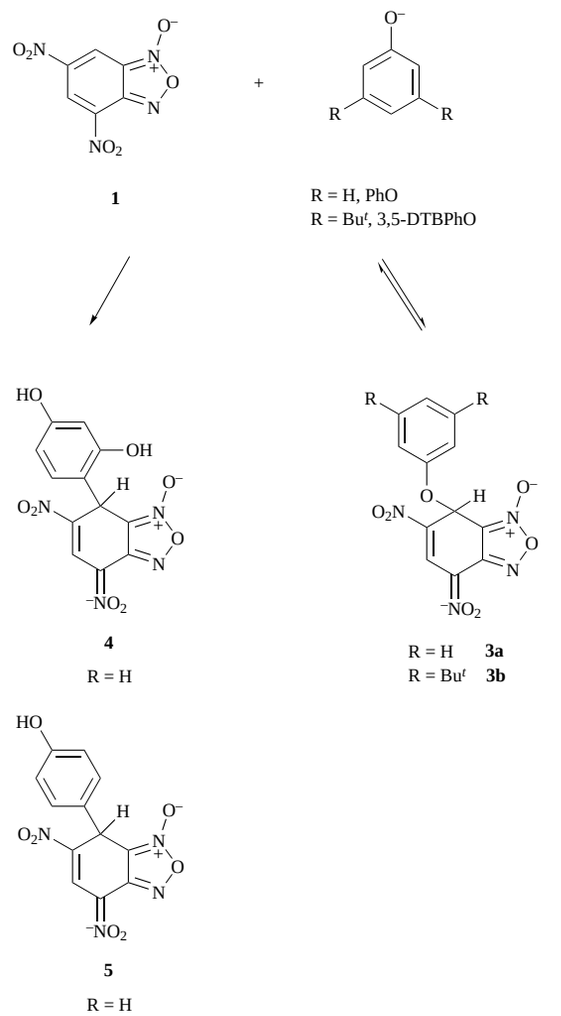
The ease of σ-adduct formation with **1** has enabled its use to assess the reactivity of weakly nucleophilic centres.[7b,12–14] In this context, **1** reacts according to a formal S_EAr mechanism[15] with the weakly nucleophilic benzene ring of 1,3,5-trimethoxybenzene;[14] similar facile substitution reactions proceed with π-electron rich heteroaromatics including indoles,[11] pyrrole, thiophene and furan.[16]

In the present paper, we describe the reaction of PhO^- and 3,5-DTBPhO$^-$ towards DNBF. For both anions we have been able to thoroughly characterize the oxygen-bonded anionic σ-adducts (*i.e.* **3a** and **3b** in Scheme 1) using 400 MHz ^{1}H NMR spectroscopy. The spectroscopic characteristics of the C-7 DNBF·OPh$^-$ adduct, **3a**, were acquired in MeCN–DME at −40 °C whereas the features of the C-7 DNBF·OPhDTB$^-$ adduct, **3b**, could be obtained in DMSO at ambient temperature. These results confirm our surmise that formation of *O*-adducts of PhO^- with **1** is kinetically favoured over formation of the corresponding *para* and *ortho C*-bonded adducts.[7b] Further, the regioselectivity shown by PhO^-, as an *O*-nucleophile, will be discussed in terms of patterns of regioselectivity previously classified for picryl ether systems.[6,17] The regioselectivity found depends partly on the stereoelectronic stabilization available to the relevant adducts and stereoelectronic factors affecting the kinetics and thermodynamics of adduct formation will be discussed. Finally, the enhanced stability of the DNBF *O*-adducts, as compared to corresponding *O*-adducts of NBF and TNB, reemphasizes the super-electrophilicity of **1** and allows us to draw comparisons between these systems and the 2-nitroaryl-4,6-dinitrobenzotriazole 1-oxide series that possesses both normal and super-electrophilic reaction sites.

Results

Reaction of 1 with 1 equiv. of phenoxide ion in DMSO

Addition of 1 equiv. of PhO^- (as potassium phenoxide solution, PhOK) in [$^2H_6$]DMSO to a [$^2H_6$]DMSO solution of DNBF **1** (final concentration: 0.09 M), immediately produced a deep-red solution. Fig. 1 shows a ^{1}H NMR spectrum of the reaction mixture acquired *ca*. 3 min after the reagents were mixed. Apparent in this first spectrum are resonances that represent three distinct σ-adducts. The H-7 proton in a given DNBF moiety is bound to an sp^3-hybridized carbon centre; the chemical shift of this signal is notably sensitive to the nature of the group attached to this position.[2,7,10] It is, therefore, significant that three different resonances are observed in the region of the spectrum typical for H-7 in a DNBF σ-complex,[10b,c] namely: δ 5.84 (21%), 5.62 (7%) and 5.40 (43%) with signals for the corresponding H-5 protons being found at δ 8.59, 8.66 and 8.64, respectively. On the basis of comparison with spectra recorded during our previous investigation of the DNBF–PhO^- reaction system in [$^2H_6$]DMSO,[7b] the resonances of the dominant σ-complex (*i.e.* those found at δ 5.40 and 8.64) could be attributed to the *para* C-bonded DNBF·$PhOH^-$ adduct, **5** (Scheme 1). Equally important, the phenoxy ring protons of **5**



Scheme 1

appear in the δ 6.74–7.16 region, while the phenolic OH resonates at δ 9.54. The identity of the minor product whose signals are located at δ 5.62 and 8.66 is consistent with formation of the *ortho C*-bonded adduct, **4**,[7b] whereas peaks at δ 5.84 and 8.59 stem from production of the DNBF·OH^- adduct, **2a**.[18]

The presence of adventitious water in the [$^2H_6$]DMSO solvent, coupled with general base catalysis by phenoxide ion, accounts for the formation of **2a** and phenol (PhOH). Note that the H-7 signals ascribed to the *C*-adducts (δ 5.62, 5.40) appear upfield of the H-7 signal assigned to the DNBF·OH^- adduct (δ 5.84). This is in accord with the effect of the greater electronegativity of the oxygen centre in **2a** on the chemical shift of H-7 of this adduct as compared to the electronegativity of the attached *C*-centres in **4** and **5**. The assignment of the C-7 signals of the carbon adducts is also consistent with the chemical shift data recently reported for a series of carbon adducts of DNBF formed by nitrocarbanion attack at C-7.[10c]

Few changes in the spectra of the system were noted over a 2 h period. Upon acidification (5 μl trifluoroacetic acid; TFA) peaks attributed to the *C*-bonded adducts, **4** and **5**, remain unchanged, while the resonances belonging to the DNBF·OH^- adduct, **2a**, decreased in intensity, but did not vanish. These observations support the present assignments. Thus, anionic σ-adducts formed by C-attack of PhO^- on any electron-deficient substrate are generally stable to acid, while *O*-adducts formed

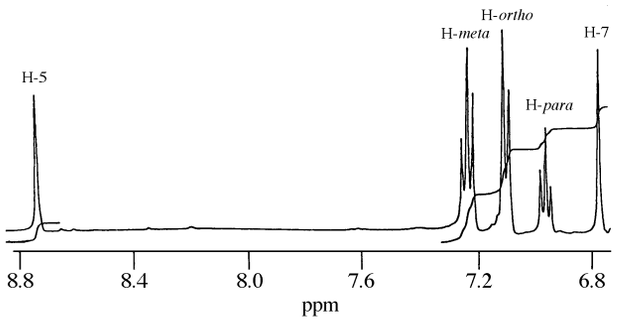


Fig. 2 ^{1}H NMR spectrum (aromatic region; 6.8–8.8 ppm) of the DNBF–PhOK (1:1) reaction, recorded at *ca.* 3 min reaction time ([$^2H_3$]MeCN–[$^2H_{10}$]DME at −40 °C). The spectrum contains the resonances ascribed to the phenoxide C-7 DNBF·OPh$^-$ *O*-adduct, **3a**.

from normal electrophiles such as TNB and TNA are acid-labile.[1,2,5–7,9,10a] On the other hand, even *O*-centred adducts of DNBF are acid stable‡ relative to the corresponding TNB complexes. In this regard, the C-7 DNBF·OMe$^-$ adduct does not decompose even at a pH of 5, whereas the TNB·OMe$^-$ complex readily reverts to TNB and methanol at *ca.* pH 7.[19] In fact, the DNBF ring is such a powerful electron sink that the DNBF·OH$^-$ adduct is quite acidic (pK_a = 1.5 in 90% DMSO–H_2O).[20]

In [$^2H_6$]DMSO (ambient temperature), signals that could be ascribed to formation of the C-7 DNBF·OPh$^-$ adduct, **3a** (Scheme 1) were not observed, in agreement with our previous investigation.[7b] Moreover, no C-5 *O*- or *C*-adducts of **1** could be observed either initially or throughout the period of observation. To detect these putative species, the reaction was repeated in [$^2H_3$]MeCN:[$^2H_{10}$]DME (1:1 v/v) at reduced temperatures.

Reaction of 1 with equimolar phenoxide ion in MeCN–DME

To a solution of DNBF in [$^2H_3$]MeCN–[$^2H_{10}$]DME (1:1, v/v) cooled to −40 °C was injected a similarly cooled solution of phenoxide ion (PhOK in the same medium; final concentrations *ca.* 0.1 M). Fig. 2 reproduces the initial spectrum of the reaction mixture as recorded at −40 °C (acquired within approximately 3 min of mixing). Remarkably, the spectrum was clean and the intense resonances could be assigned to a single complex, the C-7 *O*-bonded DNBF·OPh$^-$ adduct, **3a**, having peaks at δ 8.77 (H-5, s), 7.24 (H-*meta*, m), 7.10 (H-*ortho*, m), 6.96 (H-*para*, m) and 6.78 (H-7, s). As in previous cases, the integrals supported the assignments made. As expected from our previous studies of electrophile–aryloxide systems,[9,10a,21] the chemical shift of the sensitive sp^3-attached H-7 proton in **3a** (δ 6.78) was found downfield (*ca.* 0.9 ppm) with respect to its counterpart proton in the C-7 DNBF·OH$^-$ adduct, **2a**, (δ 5.84)[18] or the C-7 DBNF·OMe$^-$ adduct, **2b**, (δ 5.87),[1,10b] which reflects the electron-withdrawing nature of the phenyl group.[9]

As in the DMSO experiment, there was no evidence for the formation of a C-5 *O*-centred DNBF·OPh$^-$ adduct even in this initial spectrum. However, comment need be made here about the assignment of adducts as C-7 rather than C-5 since reaction at the C-5 centre could give rise to a spectrum similar to that obtained from attack at C-7 (*i.e.* giving an upfield signal at *ca.* 5–7 ppm and a downfield signal at *ca.* 8.5–8.8 ppm). Chemical shift evidence, though not conclusive, is helpful in making the assignment. The proton at the site of attachment undergoes a major upfield shift while the proton bound to the remaining sp^2 centre undergoes only a small upfield shift. In the case of the C-7 methoxide adduct of **1**, whose assignment was conclusively demonstrated through ^{1}H, ^{13}C and ^{15}N NMR studies, involving selective isotopic labelling, the upfield shift of H-7 was 3.38 ppm (*i.e.* δ 9.27 for DNBF–H-7 −δ 5.89 for H-7 of DNBF·OMe$^-$) whereas the upfield shift of H-5 was only 0.25 ppm (δ 8.95 for DNBF–H-5 −δ 8.70 for H-5 of DNBF·OMe$^-$).[10b] Based on comparison with the picryl ether systems[2,17] attachment of a phenoxy group to a ring site is expected to cause an upfield shift of *ca.* 2.5 ppm. Thus, attachment at C-7 should yield a signal at δ 6.77 and attachment at C-5 should yield a signal at δ 6.45. The signal found in the DNBF–PhO$^-$ system at δ 6.78 is, therefore, likely due to H-7 and the adduct is a C-7 DNBF·OPh$^-$ adduct and not a C-5 adduct. Further support for the assignment will emerge in the Discussion.

Further monitoring of the reaction, by allowing the temperature to rise in 5 °C increments after *ca.* 30 min, revealed that the signals attributed to **3a** were dominant in the spectra recorded from −40 °C up to −20 °C. Above this temperature peaks that belong to the *para C*-bonded DNBF·PhO$^-$ adduct, **5**, began to increase in intensity, coupled with the appearance of small signals identified as belonging to the *ortho C*-bonded DNBF·PhO$^-$ adduct and the decline in intensity of those assigned to **3a**. At 0 °C, peaks due to **3a** had completely vanished in favour of those ascribed to the *C*-adducts **4** and **5**. On further warming to ambient temperature (*ca.* 23 °C), and at longer times (>2 h), the only species that remained in solution were the *C*-adducts, **4** and **5**, and the DNBF·OH$^-$ adduct, **2a**, *i.e.* the same final products observed in the DMSO experiment. At no time during this sequence could signals attributable to a C-5 phenoxide *O*- or *C*-adduct be observed.

The interaction of DNBF with PhO$^-$ at low temperatures in MeCN–DME as described above, has confirmed the apparent kinetic preference for *O*-attachment in reactions of DNBF, **1**, with aryloxide nucleophiles. In an attempt to examine *O*-adduct formation in DMSO at ambient temperature, the reaction of **1** with 3,5-di-*tert*-butylphenoxide ion (3,5-DTBPhO$^-$) was examined. In this system, *C*-attachment is sterically inaccessible owing to the bulky *tert*-butyl groups that would be expected to block attack involving the positions either *ortho* or *para* to the aryloxyl oxygen;[9] such a condition should favour detection of any *O*-adducts.

Reaction of 1 with equimolar 3,5-di-*tert*-butylphenoxide ion in DMSO

Injection of 1 equiv. of a [$^2H_6$]DMSO solution of 3,5-di-*tert*-butylphenoxide ion (as 3,5-DTBPhOK) into an NMR tube that contained a [$^2H_6$]DMSO solution of **1** (final concentration 0.1 M) yielded a deep red mixture. Assessment of the first spectrum revealed that signals attributable to formation of the C-7 aryloxide *O*-adduct, **3b** (Scheme 1), were present (43%). In [$^2H_6$]DMSO (ambient temperature) the ^{1}H NMR signals of **3b** are as follows: δ 8.66 (H-5, s), 7.01 (H-4′, t, *J* 1.5 Hz), 6.71 (H-7, s), 6.68 (H-2′,6′, d, *J* 1.5 Hz) and 1.19 (Bu^t groups, s). Again, the integral ratios supported the assignments made. The downfield shift of the H-7 resonance at 6.71 ppm accords with expectations derived from characterization of the C-7 DNBF·OPh$^-$ adduct, **3a**, in [$^2H_3$]MeCN–[$^2H_{10}$]DME and from related systems,[9,10a,20] corrected for the slight solvent-dependency of these chemical shifts.[6] Other peaks in the spectrum belong to 3,5-DTBPhOH (47%) and the C-7 DNBF·OH$^-$ adduct; these arise from equilibration of the aryloxide with adventitious H_2O in the [$^2H_6$]DMSO medium.[6,7b] After 30 min reaction time, resonances ascribed to **3b** were no longer present in the spectrum. Instead, the spectrum contained signals for **2a**, 3,5-DTBPhOH and unmodified substrate, **1**.

In a separate experiment, the reaction mixture was acidified (5 μl TFA) after acquisition of the initial spectrum. Subsequent spectra showed that the signals ascribed to the C-7 DNBF·OPhDTB$^-$ adduct, **3b**, had disappeared completely, whereas resonances belonging to the hydroxide complex, **2a**, remained. This observation demonstrates the superior thermodynamic

‡ A referee has noted that equilibrium protonation of **2a** could involve protonation on the C(4)–NO_2 group.

Table 1 ^{1}H NMR spectroscopic characteristics[a] of the anionic σ-adducts of DNBF, **1**, in [$^2H_6$]DMSO[b] and [$^2H_3$]MeCN:[$^2H_{10}$]DME (1:1 v/v)[c]

Adduct	H-7	H-5	Other signals (δ/ppm; *J*/Hz)
2a[b]	5.83, s	8.59, s	6.23 (br, s, OH)
3a[c]	6.78, s	8.77, s	7.10 (m, 2 H, H-*ortho*), 7.24 (m, 2 H, H-*meta*), 6.96 (m, 2 H, H-*para*)
3b[b]	6.71, s	8.66, s	7.01 (t, *J* 1.5, 1 H, H-*para′*), 6.68 (d, *J* 1.5, 2 H, H-*ortho′*), 1.19 (s, 18 H, 3′,5′-di-Bu^t).
4[b]	5.62, s	8.66, s	Obscured.[d]
5[b]	5.40, s	8.64, s	7.16, 6.74 (A_2X_2 d,d, partly obscured),[d] 9.54 (br s, OH)

[a] Chemical shifts are measured at 400.1 MHz. [b] Determined in [$^2H_6$]-DMSO at ambient temperature. [c] Determined in [$^2H_3$]MeCN:[$^2H_{10}$]-DME AT −40 °C. [d] Signals due to the ring protons of PhO^-/PhOH, as well as those of the ring protons of the attached phenoxyl moieties of **4** and **5** overlap, *cf.* Fig. 1.

stability of the DNBF·OH^- adduct, **2a**, as compared to the aryloxide *O*-adduct, **3b**.

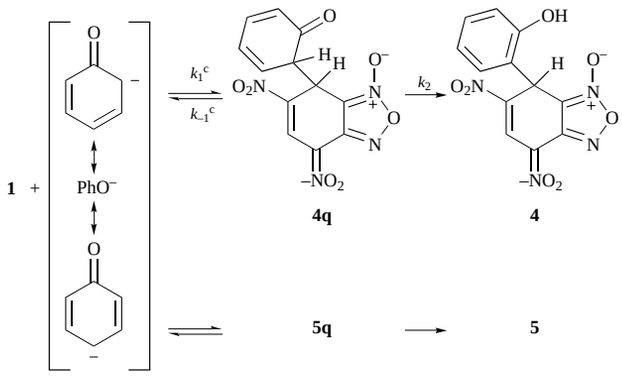
The present study has confirmed our earlier expectations[6] that, under appropriate conditions, aryloxide *O*-adducts of a range of electrophiles, including TNB,[10] NBF[9] and, now, DNBF, could be detected and fully characterized. The ^{1}H NMR chemical shifts of the σ-adducts observed in the present study are summarized in Table 1. The nature of the ambident reactivity of the aryloxide nucleophiles, as well as those factors that account for observation of the C-7 *O*-adducts including stereoelectronic stabilization, as compared to the C-5 regioisomeric adducts, will be considered below with appropriate comparisons to related reaction systems.

Discussion

Oxygen- *versus* carbon-reactivity

In our previous NMR (100 MHz) investigation of phenoxide reactivity towards the super-electrophile, DNBF, **1**, in [$^2H_6$]-DMSO at ambient temperature,[7b] evidence for *O*-attack was not obtained; no DNBF·OPh^- adduct was observed under these conditions. However, formation of an *O*-centred adduct would be expected to be kinetically preferred over *C*-adduct formation. Thus, *O*-attack by PhO^- occurs *via* a single step, whereas formation of a *C*-adduct plausibly proceeds in two steps. As shown in Scheme 2 (for formation of the *ortho* *C*-adduct) the first step (k_1^C) involves attachment of the phenoxy ring to DNBF and formation of a quinoidal adduct (**4q**). The loss of aromaticity concomitant with formation of the quinoidal *C*-adduct, as well as structural and solvent reorganization, combine to indicate that this step should be slow.[5–7a,21] Both the reverse step (decomposition of the quinoidal adduct, **4q**, back to starting materials, k_{-1}^C) and the forward tautomerization step (k_2^C) that would generate the *C*-adduct (**4**, in this case) result in restoration of aromaticity and on these grounds both steps would be expected to be fast. However, the k_2^C step represents a bimolecular reaction, involving base, and would be expected to be favoured over the unimolecular decomposition (k_{-1}^C) under the alkaline conditions of this study. In any case, further reaction of the quinoidal adduct is likely to be rapid since the quinoidal adduct itself is not observed in this study or related ones.[5–7a,21] The rearomatization that occurs in the second step, k_2^C, confers effective irreversibility on the overall process of *C*-adduct formation and establishes the *C*-adduct as the product of thermodynamic control on the DNBF·PhO^- reaction system.

In summary, the lack of success in observing the *O*-bonded adduct, **3a**, was presumed to arise not from any abnormally high kinetic barrier to its formation but could be attributed to its transient nature. Therefore, its transformation into the *ortho* and *para* *C*-adducts, **4** and **5**, occurs too rapidly to permit characterization by ^{1}H NMR spectroscopy in DMSO at room



Scheme 2

temperature, even though the first spectrum was acquired within *ca.* 3 min of mixing the reagents.[7b]

This ^{1}H NMR investigation has confirmed our earlier suppositions. Even with the superior spectroscopic sensitivity available in the present study (400 *versus* 100 MHz instruments), no PhO^- *O*-adduct of DNBF, **1**, was seen in the initial spectrum obtained in [$^2H_6$]DMSO at room temp. (*cf.* Fig. 1). However, by altering the solvent system to [$^2H_3$]MeCN:[$^2H_{10}$]DME (1:1 v/v) NMR measurements could be made at reduced temperatures (−40 °C).[6,9,10a,22] Now, *O*-attachment is spectrally observable and the C-7 DNBF·OPh^- *O*-adduct, **3a**, is the only species detected in the initial spectrum (Fig. 2). The fact that no *C*-adduct was produced at −40 °C clearly establishes the kinetic preference for *O*-attachment in reactions of ambident aryloxide *O*- and *C*-nucleophiles with **1**.

It is interesting to compare these results obtained with the super-electrophile, DNBF, to the observations gleaned from the 2-(nitroaryl)-4,6-dinitrobenzotriazole 1-oxide series (2-Ar-DNBT). These novel electron-deficient substrates contain both a super-electrophilic centre, C-7, and a normal electrophilic site, C-1′. Reaction of 2-(2′,4′,6′-trinitrophenyl)-4,6-dinitrobenzotriazole 1-oxide (Pi–DNBT) with PhO^- (DMSO, room temperature) led only to displacement of the picryl moiety (*i.e.* formation of phenyl 2,4,6-trinitrophenyl ether); no C-7 *O*- or *C*-phenoxide adduct was seen, nor was a C-1′ adduct noted although displacement at C-1′ would reasonably proceed through such a species.[7b–d] It is pertinent to note that the C-7 centre in the 2-Ar-DNBT series has been ranked between the comparable site in TNB and DNBF in order of increasing electrophilicity.[7] When the reactivity of the C-1′ site was reduced (by successive removal of nitro groups from the 2-aryl moiety) C-7 carbon-centred adducts, *para* and *ortho*, could now be observed, but the product of C-7 *O*-attack was still not detected.[7a] This comparison also supports the previous arguments concerning the relative stability of phenoxide *O*-adducts, even when such adducts are formed with super-electrophiles.

Further confirmation of the formation of aryloxide *O*-adducts of DNBF, as well as assistance in the spectroscopic assignment of the phenoxide *O*-adduct of **1**, was obtained from examination of the DNBF–3,5-DTBPhO^- reaction system in DMSO (room temp.). In the 3,5-di-*tert*-butylphenoxide nucleophile the sites *ortho* and *para* to the oxygen centre are sterically blocked, the kinetic barrier (k_1^C, Scheme 2) to formation of the thermodynamically favoured *C*-adduct(s) is substantially raised, while that for *O*-attack is left unchanged. Now, *O*-attachment of the aryloxide nucleophile can be observed in [$^2H_6$]DMSO at ambient temperature. Significantly, the DNBF·OPhDTB^- σ-adduct, **3b**, was present in solution throughout the period of observation (*ca.* 30 min). This contrasts with the results recorded in the NBF–3,5-DTBPhO^- system[9] and the TNB–3,5-DTBPhO^- reaction system,[10] both examined in DMSO. In the TNB reaction, diaryl ether for-

mation through NO_2 group displacement, as well as competitive TNB·OH^- adduct formation made identification and structural elucidation of the TNB·OPhDTB$^-$ complex less definitive than in the current DNBF–3,5-DTBPhO$^-$ study. In the reaction of 3,5-DTBPhO$^-$ with NBF,[9] σ-adduct formation could not be detected in DMSO at ambient temperature as a result of the intervention of a rapid deoxygenation pathway. This decomposition, in which the sp^3-bound proton (H-7) of the adduct is transferred to the 1-oxide oxygen which may subsequently be lost, has been observed previously as a competitive process in the reaction of methoxide with NBF[23] and in the reaction of Pi-DNBT with isopropoxide ion.[24] In the case of the NBF and TNB reactions with 3,5-DTBPhO$^-$, however, the aryloxide *O*-adducts could be seen and their structural features assigned using the low temperature medium (MeCN–DME). Even under these conditions the σ-adducts exhibited relatively short lifetimes.[9,10a]

Clearly, the ease of observation of the DNBF·OPhDTB$^-$ *O*-adduct arises from a number of factors. First, formation of the *O*-adduct in this system benefits from the super-electrophilicity of DNBF[11] as compared to TNB or even NBF. Importantly, if *C*-adduct formation were not blocked sterically, then the process of *C*-adduct formation would also be enhanced by using **1** relative to TNB (see below). This super-electrophilicity has been attributed to the relatively low aromaticity of the heteroaromatic, as well as the intrinsic electron-withdrawing ability of the furoxan moiety as compared to a standard nitro group (as in TNB).[1a,2a,b] Secondly, adducts formed by DNBF are generally more stable than their TNB counterparts. If the absolute energy of the activation barrier for the deoxygenation step, which is observed in various NBF and 2-Ar-DNBT systems but not in the DNBF reactions, remains approximately constant the greater stability of the DNBF adducts translates into a higher kinetic barrier to decomposition by this pathway for the adducts formed by **1**.

In view of the present low temperature NMR studies, the inability to detect the *O*-bonded C-7 DNBF·OPh$^-$ adduct, **3a**, in DMSO can be rationalized by considering the high reactivity of DNBF towards carbon nucleophiles in DMSO-rich media.[11–14,16] For example, neutral electron-rich benzenes like 1,3,5-trimethoxybenzene or 3,5-dimethoxyaniline readily form *C*-adducts with DNBF,[13,14] and kinetic studies on *C*-attachment of 3,4-diaminothiophene towards **1**[25] have established a high value for the forward rate constant, k_1, of the order of *ca.* 9×10^5 dm^3 mol^{-1} s^{-1} in 50% H_2O–50% DMSO. This value compares very favourably with the forward rate coefficient for *O*-attack on DNBF by hydroxide ion,[19,20] which under similar conditions has been determined to be $k_1 = 3.3 \times 10^5$ dm^3 mol^{-1} s^{-1}. Thus, the intrinsically low stability of phenoxide oxygen-centred adducts[6,17,22] that has been partly linked to the superior leaving group ability of aryloxides,[26] coupled with the decreased activation barrier to *C*-adduct formation by unhindered *C*-nucleophiles with **1**, would account for our inability to detect the *O*-adduct, **3a**, in DMSO, even though its formation is kinetically favoured (based on our low temperature NMR study).

Classification of regioselectivity of phenoxide *O*-attack with 1

A full range of regioselectivity is exhibited in the reaction of nucleophiles with 2,4,6-trinitroanisole and related picryl ethers: K3T1 (TNA–MeO$^-$), K1T1 (TNA–PhO$^-$, where PhO$^-$ acts as an *O*-nucleophile), K3T3 (TNA–PhO$^-$, where PhO$^-$ acts as a *C*-nucleophile) and K1T3 (TNA·OMes$^-$).[22,26–29] Here K1T3 represents kinetically favoured formation of a C-1 adduct but thermodynamic preference for C-3 adduct formation; the other designations are derived similarly. In fact, these patterns of regioselectivity have been found in a large number of systems and have been reviewed recently.[17]

The classification of regioselectivity may be profitably extended to the related heteroaromatic systems. In a hypothetical case, then, attack of a nucleophile at C-5 of DNBF, **1**, to form a C-5 adduct could be kinetically preferred while attack of the same nucleophile at C-7 could be thermodynamically preferred. This situation would be analogous to the K3T1 behaviour found in the TNA–MeO$^-$ and related systems. The regioselectivity could be designated K5T7, as previously suggested[17] and a qualitative energy–reaction coordinate profile (based on the quantitative energy profiles for the TNA–MeO$^-$ system)[2b,30] proposed (Fig. 3). In agreement with the designation, the forward rate constant for attack at C-5 would be greater than that for attack at C-7, *i.e.* $k_5 > k_7$. The greater thermodynamic stability attributed to the C-7 adduct would require that the equilibrium constant for formation of the C-7 adduct be larger than that for formation of its C-5 counterpart; $K_7 > K_5$. Based on the TNA–MeO$^-$ model system, it is also likely that the reverse rate constants for decomposition of the adducts, k_{-5} and k_{-7}, respectively, would bear the following relationship to one another: $k_{-5} > k_{-7}$.

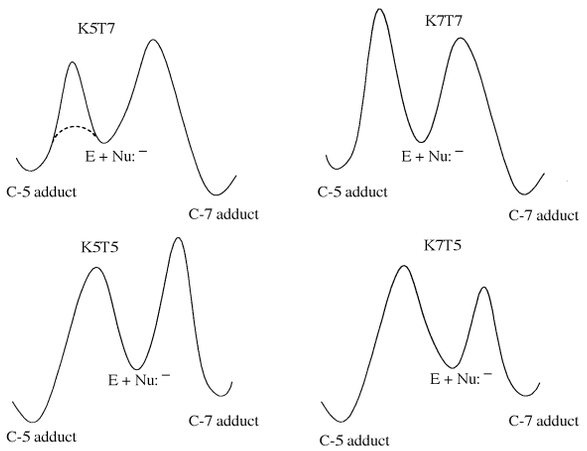


Fig. 3 Qualitative comparative energy–reaction coordinate diagrams that describe four general patterns of regioselectivity. Kinetic barriers and relative stabilities are exaggerated for clarity. K5T7 represents systems in which formation of the C-5 adduct is the product of *kinetic control*, but the C-7 adduct is the *thermodynamic product*. In the K7T7 profile the C-7 adduct is favoured by both kinetics and thermodynamics. In the same way, K5T5 represents the situation where the C-5 adduct is doubly preferred: by kinetics and by thermodynamics. K7T5 profile describes the inverse behaviour from that indicated by K5T7; now, the C-7 adduct is favoured kinetically, but the C-5 adduct is the most stable product. These profiles, derived from consideration of the regioselectivity found in picryl ether–nucleophile systems,[17] are now extended to DNBF systems and are further described in the text.

In the DNBF–ArO$^-$ systems, whether the investigation was undertaken at room temp. in [$^2H_6$]DMSO as in the DNBF–3,5-DTBPhO$^-$ case, or at low temperature in MeCN–DME as in the DNBF–PhO$^-$ reaction, no C-5 adducts were observed. Under the most sensitive experimental regime, only C-7 *O*-adducts were detected as the products of kinetic control. Recall that with NBF, alkoxides do form C-5 adducts as kinetic products that give way to their more stable C-7 analogues.[1,23] Conversely, neither C-5 aryloxide *O*- nor *C*-adducts of NBF were observed even at low temperature and it has been argued that the corresponding C-7 *O*-adducts are the products of both kinetic and thermodynamic control.[9] Further, the literature contains only one tentative report of formation of a transient C-5 adduct formed by **1** and azide ion that gave way over time in favour of a C-7 adduct; conversion of **1** to 2,4,6-trinitroaniline was apparently also a competitive process in this system.[18] Apparently observation of a C-5 adduct in the DNBF systems is rare, and when coupled with our inability to observe C-5 ⟶ C-7 isomerization in the NBF–ArO$^-$ systems, argues in favour of designating the regioselectivity

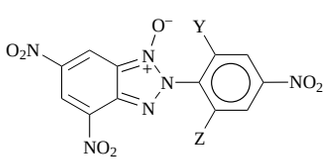
found in the current systems for both *O*- and C-aryloxide nucleophiles as K7T7. Nonetheless, very rapid attack at C-5 and rapid rearrangement could mimic K7T7 behaviour and make a K5T7 system appear to fit the K7T7 description (dotted line in K5T7 profile, Fig. 3). Consequently, although we strongly favour the classification of the regioselectivity in this system as K7T7 we cannot rule out the possibility that it is merely a 'pseudo-K7T7' system.

One factor that could account for both the kinetic and thermodynamic preference apparently shown is the efficacy of through-conjugation to the 4-nitro group (*cf*. structures **3–5**). Previously, this stabilization by through-conjugation was advanced as a rationale for the K7T7 regioselectivity displayed by aryloxide nucleophiles with NBF.[9] Regardless of the structure of the electrophile, if a relatively later transition state (TS) obtains for aryloxides[26] as compared to alkoxides[31] (based on 60% C–O bond formation between PhO^- and TNA at C-1[26] relative to 45% C–O bond formation between MeO^- and TNA at C-1[31]) then the TS for C-7 attack on DNBF should also partake of the stabilization afforded by through-conjugation to the 4-NO_2 group. Thus, the TS for C-7 attack is stabilized relative to the TS for C-5 attack and, at the same time, the C-7 adduct is stabilized relative to its C-5 counterpart. K7T7 regioselectivity results.

Comparison of the current systems with the TNA–ArO^- systems previously examined bears consideration. In the TNA systems it was deduced that the stability of C-1 adducts was intimately tied to the degree of stereoelectronic stabilization provided by the n–σ* interaction in these adducts, which are geminally disubstituted with electronegative groups.[6,22,27] On the other hand, DNBF is unsubstituted at the C-7 position and similar n–σ* stabilization of the resultant DNBF·OPh^- adduct, **3a**, is not possible. In fact, our studies of the NBF–ArO^- systems[9] and the TNB–ArO^- systems[10a] clearly show that the preferred alignment of the attached aryloxy group at C-7/C-2 in the aryloxide *O*-adduct is one which places the p-type lone pair orbital of the oxygen coplanar with the aryl ring of the attached aryloxyl moiety. This arrangement permits conjugation (p–π) of the oxygen with the aryl ring and, unless precluded by highly unfavourable steric congestion, dictates the conformational preferences of the adduct.[9,10a] It is reasonable to suggest that the preferred structures of the DNBF aryloxide adducts reported herein also arise from this stabilizing p–π stereoelectronic effect.§

Ortho versus para C-attachment by phenoxide ion

Formation of the *para C*-bonded C-7 DNBF·$PhOH^-$ adduct, **5**, has been found to be favoured over formation of the *ortho* C-7 DNBF·$PhOH^-$ adduct, **4**, by a ratio of *ca.* 6:1 in the current study. This observation is consistent with the findings of studies of phenoxide *C*-attachment to TNB,[5,10] where, again, formation of the *para*-isomeric *C*-adduct is preferred. Interestingly, in our previous investigations of phenoxide reactivity towards 2-(2′,4′-dinitrophenyl)- and 2-(4′-nitrophenyl)-4,6-dinitrobenzotriazole 1-oxides (DNP–DNBT, **6**, and NP–DNBT, **7**, respectively) the



Y = H, Z = NO_2 **6**
Y = H, Z = H **7**

§ We note the contribution by Professor N. S. Zefirov to the understanding of stereochemistry of stereoelectronic effects on the conformations of ring systems.[33–35]

C-7 *ortho-C* and C-7 *para-C* adducts were found to form in a statistical 2:1 ratio.[7a]

Although reaction *via* the *ortho* positions of phenoxide ion as compared to *para C*-attack is favoured by statistics, it should be re-emphasized that *ortho* and *para* sites are not inherently equal in their potential nucleophilicity. In this context, the ^{13}C chemical shift of signal of the *para* carbon of potassium phenoxide is 12.7 ppm upfield of that for the *ortho* carbons in this nucleophile.[10] This observation may be attributed to a greater shielding of the *para* carbon relative to the *ortho* carbons as a result of the greater partial negative charge density that resides at the *para* position[36] and which could be expected to render the *para* site more nucleophilic than a given *ortho* site. In this sense, a less than statistical ratio for *ortho*/*para* attack could be expected in reactions of phenoxide ion as a *C*-nucleophile.

Furthermore, steric factors play a role in determining the feasibility of σ-adduct formation with *ortho*-substituted benzenes[37] and we have previously invoked increased steric hindrance for phenoxide as an *ortho* nucleophile[5,6] to account partly for the observed preference for *C*-adduct formation *via* the *para* carbon of PhO^-. In the present case of the DNBF–PhO^- system, steric hindrance between the flanking NO_2 group and furoxan ring with phenoxide can either raise the rate determining kinetic barrier to formation of the *ortho* quinoidal intermediate, **4q** (lower k_1^C, Scheme 2), or lead to a decrease in the rate of tautomerization (lower k_2^C) that yields the *ortho C*-adduct, **4**. If the decrease in k_2^C is great enough, then the process that results in decomposition of **4q** back to **1** and PhO^- (k_{-1}^C) may even become competitive with the forward rate process that yields adduct **4**. By whatever mechanism steric hindrance influences the rate of reaction for *ortho C*-attack as compared to *para C*-reaction, the result is the same: nucleophilic attack *via* the *para* carbon becomes the favoured process in the DNBF–PhO^- system.

In conclusion, the current study of the regioselectivity of aryloxide ambident *O*- and *C*-nucleophilic attack on DNBF extends our understanding to super-electrophilic heterocycles and shows the generality of the classification scheme (Fig. 3), and is in accord with our analysis of stereoelectronic effects in these systems.[17]

Experimental

Materials and methods

4,6-Dinitrobenzofuroxan (DNBF, **1**) was prepared by nitration[38] of benzofuroxan (Aldrich) and recrystallized from ethyl acetate, mp 172 °C. [$^2H_3$]MeCN, [$^2H_6$]DMSO and [$^2H_{10}$]DME (Merck or CDN) were dried by treatment with 4 or 3 Å molecular sieves prior to use, as advocated by Burfield.[39] 1,4-Dibromobenzene (DBB integral standard, Eastman) was recrystallized from ethanol, mp 89 °C. Potassium ethoxide (KOEt) solutions were prepared from freshly cut potassium metal and dry EtOH (distilled from Mg turnings) under N_2 and standardized against potassium hydrogen phthalate (phenolphthalein indicator). Phenol (BDH) was distilled under vacuum and stored and handled in an Ar-filled glovebox. 3,5-Di-*tert*-butylphenol (Aldrich) was purified by recrystallization from light petroleum. Melting points were measured on a Thomas-Hoover capillary apparatus and were not corrected. Potassium phenoxide (PhOK) and potassium 3,5-di-*tert*-butylphenoxide (3,5-DTBPhOK) were prepared from the purified phenol and standard KOEt and EtOH in a dry box; excess EtOH was evaporated under a stream of N_2 and the solid dried under vacuum.

NMR experiments

The NMR experiments were carried out on a Bruker AM-400 spectrometer (operating at 400.1 MHz) in [$^2H_3$]MeCN:[$^2H_{10}$]DME (1:1 v/v) and in [$^2H_6$]DMSO. In the mixed solvent

system, residual CD_2HCN served as chemical shift standard (^1H: δ 1.93 ppm) and lock signal, while spectra recorded in [$^2H_6$]DMSO were referenced to the $CD_2\mathbf{H}SOCD_3$ peak (δ 2.50 ppm). Chemical shifts are given in ppm; coupling constants are reported in Hz. Wilmad PP-507 NMR tubes (5 mm) were used in all experiments. Stock solutions and NMR tubes were capped with rubber septa and swept out with N_2 prior to injection of the reactants by means of a syringe.

Representative room temperature experiment in DMSO. Transfer of 100 μl of a [$^2H_6$]DMSO stock solution of DNBF (**1**, 0.5 M) into an NMR tube that contained solvent (295 μl) and DBB (5 μl from a 1 M stock solution) afforded the initial sample. DBB functioned as the internal integral standard and was present in any experiment where the singlet for the aromatic ring did not overlap with signals for adducts. Injection of 1 equiv. of 3,4-DTBPhOK (100 μl of a 0.5 M stock solution) initiated the reaction. ^1H NMR spectra were recorded at various intervals but generally as rapidly as possible (*i.e.* within 3 min) at the start of the reaction and then at progressively longer intervals as the reaction proceeded. The system was typically monitored until no further change could be detected in the recorded spectrum.

In a separate experiment, acidification of the reaction mixture (5 μl TFA) was performed after acquisition of an initial spectrum. Spectra of the acidified solution were recorded immediately following the addition of trifluoroacetic acid (within 3 min).

Typical low temperature NMR experiment in MeCN–DME (1:1 v/v). The PhOK stock solution (in [$^2H_3$]MeCN:[$^2H_{10}$]-DME 1:1 v/v) was injected into an NMR tube and the solution then frozen by immersion in liquid N_2. To this frozen solution was injected 1 equiv. of DNBF solution (prepared in the same solvent). The resultant frozen mixture (final volume: 500 μl; 0.1 M in both components) was placed in a dry ice–acetone bath, which had been maintained at −50 °C. Once the contents of the tube had thawed at −50 °C, the components were mixed by rapid inversion of the tube. The contents were then frozen again by immersion of the tube in liquid N_2. The sample was transferred to the spectrometer probe (−40 °C) and spectra were recorded at various intervals. A standard sequence was: 3, 5, 7 and 9 min and then as warranted by the observed changes in the acquired spectrum. At the same time the temperature of the probe was gradually raised to ambient.

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