tionally relaxed DNA.[30] The heuristic mechanism nicely explains results for CENU-treated DNA reported by others, including Babson and Reed's results for CENU deactivation of glutathione reductase,[31] Brent's results[32a] for alkylation of DNA and deactivation of an intracellular repair enzyme, and the sequential labeling of guanine-N_7 positions in DNA reported by Hartley et al.[29] In vitro experiments with polynucleotides [32b] and computer graphic studies[33] of the implications of the mechanism in Scheme II for CENU product distributions and the range of products formed in DNA that may affect tumor cell kill are being explored and will be reported elsewhere.

(31) Babson, J. R.; Reed, D. J. *Biochem. Biophys. Res. Commun.* **1978**, *84*, 754-756.
(32) (a) Brent, T. P. *Cancer Res.* 1986, *46*, 2320-2323. (b) Brent, T. P.; Buckley, N., unpublished results.
(33) Feuerstein, B. G.; Pattabiraman, N.; Marton, L. J., *Proc. Nat. Acad. Sci. U.S.A* 1986, 83, 5948-5952. Buckley, N.; Feuerstein, B. G.; Marton, L. J., manuscript in preparation.

Experimental Section

CENUs were dissolved in absolute ethanol to give concentrations of approximately 2 mg/mL. Ten or 20 μL of stock ethanol solution were added to microcuvettes containing 350 μL of 1 mM sodium cacodylate, 50 mM NaCl buffer (pH (pD) = 7) that had been preequilibrated in the electrically heated (37 ± 0.1 °C) block of a Gilford Model 2600 spectrometer. Five minutes after addition and mixing, 0 time readings were taken and reactions were followed for 1-2 half-lives. Rate constants were calculated as the slopes of plots of ln (A_t/A_0) vs. time, which assumes that $A_\infty = 0$.[6]

Acknowledgment. This work was supported in part by NIH program Project Grant CA-13525 and the Phi Beta Psi Sorority. I thank Professors John W. Larsen and John K. Snyder for helpful discussions and Burt G. Feuerstein, M.D., Ph.D., and Professors Leon M. Stock and Frank A. Carey for helpful comments on the manuscript.

Reactivity–Selectivity Relationships in Reactions of Ambident Nucleophiles with the Superelectrophiles 4,6-Dinitrobenzofuroxan and 4,6-Dinitro-2-(2′,4′,6′-trinitrophenyl)benzotriazole 1-Oxide[1]

Erwin Buncel* and Richard A. Renfrow

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

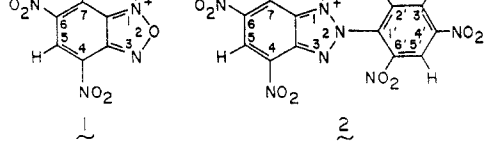
Michael J. Strauss

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

Received May 23, 1986

The reactions of 4,6-dinitrobenzofuroxan (1) and 4,6-dinitro-2-(2′,4′,6′-trinitrophenyl)benzotriazole 1-oxide (2) with aryl oxides and arylamines have been investigated. Phenoxide ion reacted with 1 to give a carbon-bonded adduct by reaction at C-7, but in contrast with the 1,3,5-trinitrobenzene (TNB) system, aniline reacted to give both nitrogen- and carbon-bonded adducts as observable species, depending on the reaction conditions. Reaction of 2 with phenoxide ion gave products arising solely from nucleophilic attack at C-1′ of the picryl moiety. Reaction of 2 with aniline also yielded a nitrogen-bonded adduct when carried out in the presence of 1 equiv of triethylamine as catalyst. Inhibiting the reactivity of aniline through ortho or *N*-methyl substitution resulted in the formation of C-7 carbon-bonded adducts of 2. These reactions generally involve kinetically preferred but reversible formation of a σ complex that is bonded via the heteroatom, followed by conversion to a carbon-bonded product of thermodynamic control. The extent to which the kinetically and thermodynamically preferred products can be observed is rationalized according to reactivity–selectivity arguments. The formation of carbon-bonded aniline complexes with 1, but not with TNB, is a result of the greater reactivity of the former (a superelectrophile). The observed regiochemistry in the reaction of nucleophiles with 2 depends on the stability of the adduct at the benzotriazole moiety (C-7) and the selectivity of the nucleophile for reaction at the benzotriazole (C-7) vs. the picryl moiety (C-1′). Decreased selectivity will result from an increase in thermodynamic driving force for the addition reaction (more negative ΔG_0) and/or, for exergonic reactions, a decrease in intrinsic barrier (i.e., decreased $\Delta G_0^{\ddagger}$). Decreased selectivity resulting from decreased intrinsic barriers will favor rapid formation of the products of thermodynamic control. Previous results with related systems are also rationalized on the basis of stability–selectivity relationships.

The recent discovery of the highly electrophilic nature of certain heteroaromatic substrates such as 4,6-dinitrobenzofuroxan (DNBF, 1) and 4,6-dinitro-2-(2′,4′,6′-trinitrophenyl)benzotriazole 1-oxide (PiDNBT, 2) has given new impetus to the study of the anionic σ complexes formed between nucleophiles and electron-deficient species.[4] Of particular interest recently has been the study of nucleophiles which are potentially ambidentate.[2,5-13] It



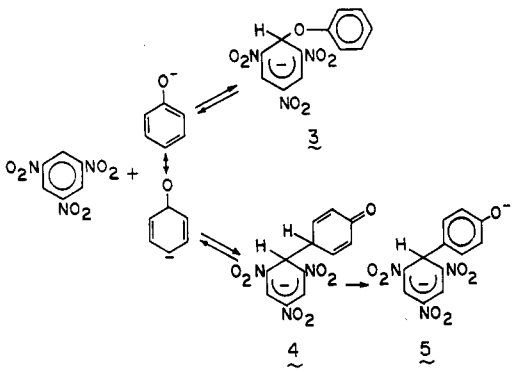
1 2

(1) Ambident Nucleophilic Reactivity in σ-Complex Formation. 6. Part 5: reference 2. Reactivity–Selectivity Correlations. 6. Parts 4 and 5: reference 3.

(2) Buncel, E.; Murarka, S. K.; Norris, A. R. *Can. J. Chem.* **1984**, *62*, 534.
(3) (a) Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* **1982**, *104*, 4896. (b) Buncel, E.; Wilson, H. *J. Chem. Educ.*, in press.
(4) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions. The Chemistry of Anionic Sigma Complexes*; Elsevier: Amsterdam, 1984.
(5) Strauss, M. J.; Renfrow, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1983**, *105*, 2473.
(6) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *Can. J. Chem.* **1983**, *61*, 1690.
(7) Terrier, F.; Debleds, F.; Halle, J. C.; Simonnin, M. P. *Tetrahedron Lett.* **1982**, *23*, 4079.
(8) Terrier, F.; Halle, J. C.; Simonnin, M. P.; Pouet, M. J. *J. Org. Chem.* **1984**, *49*, 4363.

0022-3263/87/1952-0488$01.50/0

Scheme I



has been found that phenoxide ion apparently reacts with 1,3,5-trinitrobenzene (TNB) as both an oxygen and carbon nucleophile (Scheme I),[10,11] but conflicting views have been expressed concerning the stability of the oxygen adduct.[12,13] However, aniline reacts with TNB only as a nitrogen nucleophile,[14,15] indicating that in this system aniline is not sufficiently activated to react via the carbon nucleophilic center. We anticipated that the more strongly electrophilic nature of 1 and 2, which have been termed superelectrophiles, might lower the energy barrier of reaction pathways utilizing the less reactive carbon nucleophilic site in the aniline system.

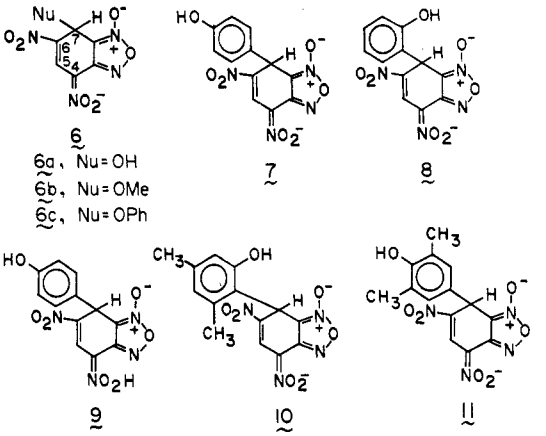
This behavior would be expected on the basis of reactivity–selectivity considerations. Thus, the relatively unreactive TNB electrophile reacts exclusively at the more nucleophilic nitrogen center of aniline, whereas the stronger electrophiles 1 and 2 should exhibit less selectivity toward the nitrogen center as opposed to the carbon center.

Previous studies have shown that 1 forms exceptionally stable complexes with hydroxide and alkoxide ions.[16,17] The greater stability of oxygen adducts of 1, relative to TNB, might facilitate the study of phenoxide–oxygen complexes of 1 and hopefully shed light on the existing controversy regarding observation of these species.[12,13]

Thus, the present study describes our results on the reactivities of 1 and 2 with phenoxides and anilines. The present work has enabled us also to reach an improved understanding of previous results in related systems,[18] on the basis of qualitative reactivity–selectivity relationships. Part of this work has been pusblished in the form of preliminary communications.[5,6] Related work has recently been published by Spear, Norris, and Read.[19,20]

Results

Reactions of DNBF (1) with Aryl Oxides. The addition of 1 equiv of 1 to a Me_2SO-d_6 solution of potassium phenoxide produced a deep orange solution. An NMR spectrum of the reaction mixture obtained within 2 min of mixing the reagents showed resonances at δ 5.44 (s), 8.74 (s), and 9.63 (br s), in addition to a multiplet in the aromatic region. These resonances are consistent with the carbon-bonded adduct 7. Additionally, a very small signal



at δ 5.7 could be detected in some experiments, which is consistent with H-7 of the ortho-bonded complex 8. The chemical shifts are close to those of corresponding protons in the analogous complexes derived from TNB.[12] More conclusive evidence for these strucutural assignments is provided by the observation that all resonances except for the hydroxy signal persisted for at least 1 week following addition of excess trifluoroacetic acid. This is in accord with previous observations on the stability of carbon-bonded aryl oxide complexes of TNB in acid media.[9,12] The oxygen-bonded adduct **6c** was not observed. If, however, the Me_2SO was wet or if the phenoxide was contaminated with hydroxide, resonances for the hydroxy adduct **6a** could be observed.

It was also found that phenol reacted with an equivalent amount of the potassium salt of the methoxy adduct **6b** in Me_2SO over several weeks to yield 7 and methanol. Following complete conversion to 7, no further changes in the spectrum occurred, even after 4 months.

A similar reaction sequence occurred in methanol. Reaction of 1 with an equivalent amount of potassium phenoxide in the presence of a 10-fold excess of phenol resulted in immediate precipitation of the methoxide adduct **6b**. After a suspension of this adduct was stirred with a 10-fold excess of phenol in methanol for several days, the carbon-bonded adduct 7 was isolated.

Although 7 is stable to decomposition in dilute acid, at high acid concentrations (>0.1 M, in methanol) the absorption maximum at 472 nm diminishes and a new absorbance is observed at 350 nm. Increasing the concentration of acid results in the disappearance of the absorption at 472 nm and an increase in that at 350 nm. These changes point to the formation of the nitronic acid 9, analogous to the species formed under similar conditions from the TNB adduct 5.[21] Partial neutralization of the solution regenerates the original spectrum.

No complex, either oxygen- or carbon-bonded, could be detected by NMR on mixing 1 with phenol in Me_2SO. However, addition of 1 equiv of Et_3N to the reaction mixture resulted in the complete formation of 7 within a few minutes. It was also found that anisole is totally unreactive toward 1. These results show that the phenoxide anion is indeed the reactive species involved in the formation of 7, and not phenol. Interestingly, addition of

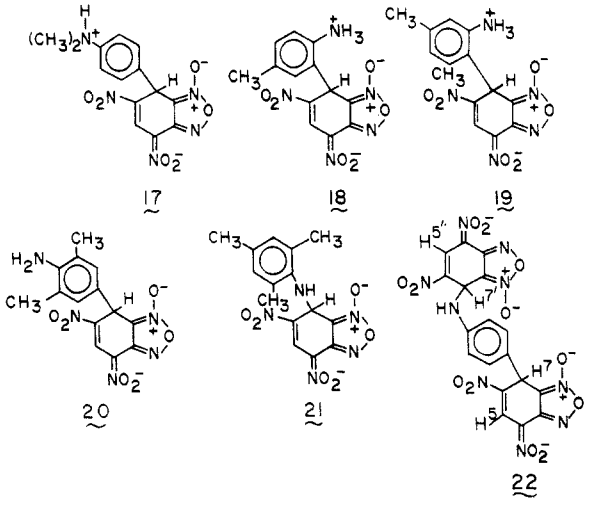
(9) Machacek, V.; Sterba, V.; Sterbova, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 2556.
(10) Buncel, E.; Webb, J. G. K. *J. Am. Chem. Soc.* **1973**, *95*, 8470.
(11) Shein, S. M.; Byval'kevich, O. G. *Zh. Org. Khim.* **1972**, *12*, 328.
(12) (a) Buncel, E.; Jonczyk, A.; Webb, J. G. K. *Can. J. Chem.* **1975**, *53*, 3761. (b) Buncel, E.; Moir, R. Y.; Norris, A. R.; Chatrousse, A. P. *Can. J. Chem.* **1981**, *59*, 2470.
(13) Shein, S. M.; Byval'kevich, O. G.; Khmelinskaya, A. D. *Zh. Org. Khim.* **1976**, *12*, 134.
(14) Buncel, E.; Eggimann, W. *J. Am. Chem. Soc.* **1977**, *99*, 5958.
(15) Buncel, E.; Eggimann, W. *J. Chem. Soc., Perkin Trans. 2* **1978**, *2*, 673.
(16) Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883.
(17) Norris, W. P.; Spear, R. J.; Read, R. W. *Aust. J. Chem.* **1983**, *36*, 297.
(18) Renfrow, R. A.; Strauss, M. J.; Cohen, S.; Buncel, E. *Aust. J. Chem.* **1983**, *36*, 1843.
(19) Spear, R. J.; Norris, W. P.; Read, R. W. *Tetrahedron Lett.* **1983**, *24*, 1555.
(20) Read, R. W.; Spear, R. J.; Norris, W. P. *Aust. J. Chem.* **1984**, *37*, 985.
(21) Buncel, E.; Eggimann, W. *Can. J. Chem.* **1976**, *54*, 2436.

Et_3N to a Me_2SO solution of phenol and TNB did not result in the formation of **5**.

The reaction of 3,5-dimethylphenol with **1** in the presence of 1 equiv of Et_3N immediately yielded the carbon-bonded adduct **10**. 2,6-Dimethylphenol gave **11** under the same conditions. Attempts to form a diadduct in which **7** would be bonded to another DNBF moiety, via the reaction of **7** with DNBF in the presence of 1 equiv of Et_3N, were unsuccessful.

Reaction of DNBF (1) with Arylamines. It was shown previously that while TNB does not react with aniline alone in Me_2SO, in the presence of a tertiary base (Et_3N, DABCO) reaction occurs to give only the N-bonded σ complex.[14,15] However, it was found in the present work that the addition of aniline alone to 1 equiv of **1** in Me_2SO results in the rapid formation of the zwitterionic carbon-bonded adduct **15**. When 2 equiv of aniline are used, the NMR spectrum after 2 min shows a 1:1 mixture of the nitrogen- and carbon-bonded adducts **13** and **16**. On standing, the signals due to **16** increase at the expense of those for **13**, the conversion being complete after 30 min. If the reaction between **1** and aniline in Me_2SO is carried out in the presence of 1 equiv of Et_3N, the adduct **13** is formed initially in greater proportion (9:1) and a longer period (ca. 36 h) is required for conversion to **16**.[5]

Carbon-bonded adducts were also obtained from the reactions of **1** in Me_2SO with *N,N*-dimethylaniline (**17**), *p*-toluidine (**18**), 3,5-dimethylaniline (**19**), and 2,6-dimethylaniline (**20**); see Table I. Several of the carbon-bonded arylamine complexes were isolated as the zwitterions or the potassium salts.



Reaction of **1** with 2,4,6-trimethylaniline in Me_2SO gave only the N-bonded adduct **21**, though formation of the latter occurred only on addition of Et_3N. The complex **22**, in which aniline is attached to two DNBF moieties via the carbon and nitrogen functionalities, was readily prepared by addition of **1** to **16** in Me_2SO in the presence of 2 equiv of Et_3N. Terrier reported similar complexes arising from the interaction of TNB with pyrroles.[22]

Reaction of PiDNBT (2) with Phenoxide. The reaction of **2** with phenoxide ion in Me_2SO as followed by NMR was found to lead to the rapid formation of picryl phenyl ether (**26**, Nu = OPh) in accord with nucleophilic displacement at C-1′. Thus, addition of 1 equiv of potassium phenoxide to **2** in Me_2SO-d_6 resulted in the instant disappearance of resonances for **2** and the subsequent appearance of signals corresponding to **26** (Nu = OPh).

(22) Halle, J. C.; Pouet, M. J.; Simonnin, M. P.; Debleds, F.; Terrier, F. *Can. J. Chem.* **1982**, *60*, 1988.

Table I. ^1H NMR Chemical Shifts (δ) for σ Complexes of 1 in Me_2SO-d_6

complex	H-5	H-7	other absorptions
6a	8.65	5.87	
6b	8.67	5.87	3.36 (s, 3 H, CH_3)
7	8.72	5.45	6.97 (m, 4 H, ArH), 9.63 (br s, 1 H, OH)
8		5.7	
10	8.70	5.52	2.52 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 6.44, 6.31 (poorly resolved AB, 2 H, ArH), 9.3 (br s, 1 H, OH)
11	8.73	5.65	6.75 (s, 2 H, ArH), 2.10 (s, 6 H, CH_3), 8.17 (br s, 1 H, OH)
13	8.74	6.08	6.9 (m, 5 H, ArH)
15	8.79	5.40	7.41, 7.26 (A_2B_2, 4 H, ArH, J = 8 Hz), 9.72 (br s, 3 H, NH_3)
16	8.78	5.18	6.96, 6.61 (A_2B_2, 4 H, ArH, J = 9 Hz)
17	8.76	5.40	7.51, 7.40 (A_2B_2, 4 H, ArH, J = 9 Hz), 3.12 (s, 6 H, CH_3), 9.49 (br s, 1 H, NH)
17a[a]	8.74	5.23	7.12, 6.79 (A_2B_2, 4 H, ArH, J = 8 Hz), 2.86 (s, 6 H, CH_3)
18	8.85	5.89	2.23 (s, 3 H, CH_3), 8.6 (very br s, 3 H, NH_3)
19	8.75	5.96	2.62 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 7.05, 6.91 (poorly resolved AB, 2 H, ArH), 9.52 (br s, 3 H, NH_3)
20	8.81	5.19	7.0 (s, 2 H, ArH), 2.12 (s, 6 H, CH_3)
21	8.73	583 (d, J = 9 Hz)	6.70 (s, 2 H, ArH), 2.10 (s, 3 H, CH_3), 2.04 (s, 6 H, CH_3), 4.23 (d, 1 H, NH, J = 9 Hz)
22	8.72	6.05 (d, J = 9 Hz)	8.79 (s, 1 H, H-5′), 5.17 (s, 1 H, H-7′), 6.94, 6.64 (A_2B_2, 4 H, ArH, J = 9 Hz), 6.35 (d, 1 H, NH, J = 9 Hz)

[a] Deprotonated **17**.

There was no evidence for the formation of a σ complex.

Reactions of PiDNBT (2) with Amines. When aniline (1 or 2 equiv) was used as the nucleophile, the displacement product **26** (Nu = NHPh) was rapidly formed. With 1 equiv of aniline, **25** was obtained in the protonated form **25H**. However, when equimolar amounts of aniline and triethylamine were reacted with 1 equiv of **2**, the signals for **2** were immediately (within 1 min) replaced with those for the N-bonded complex **23** (Nu = NHPh). Over the next 3 min the signals for **23** were replaced by signals for **25** and **26**.

Addition of **1** equiv of 2,6-dimethylaniline to **2** resulted in disappearance of the signals for **2** and the concomitant appearance of resonances corresponding to the adduct **27**, in which the aniline is bonded via carbon. This σ complex did not react further. Reaction of **2** with *N,N*-dimethylaniline proceeds analogously to give **28**.

n-Butylamine was also reacted with **2** to provide comparison with the behavior of primary aromatic amines. Reaction of **2** with 2 equiv of *n*-butylamine led to immediate and complete formation of the C-7 adduct **23** (Nu = *n*-BuNH). The complex was converted to the displacement products **25** and **26** (Nu = *n*-BuNH) within 5 min, a rate comparable to that for conversion of the triethylammonium salt of **23** (Nu = PhNH).

Discussion

Ambident Reactivity of DNBF (1). O-Bonded vs. C-Bonded Complexes in Reaction with Phenoxide. It

Table II. ^{1}H Chemical Shifts (δ) for σ Complexes and Displacement Products in Reaction of 2 with Nucleophiles

Nu(H)	σ-complex 23				product 26		product 25
	H-5	H-7	H-3′	other	H-3	other	H-5, H-7[a]
$C_6H_5O^-$					9.32	7.30 (m, 5 H, ArH)	8.90, 8.84
$C_6H_5NH_2$ (1 equiv)					8.98	7.23 (m, 5 H, ArH), 10.25 (br s, 1 H, NH)	9.14, 8.94[b]
$C_6H_5NH_2$ (2 equiv)					8.98	7.23 (m, 5 H, ArH)	8.92, 8.84
$C_6H_5N(CH_3)_2$	8.79	5.57	9.26	7.43 (s, 4 H, ArH), 3.12 (s, 6 H, CH_3)			
2,6-$(CH_3)_2C_6H_3NH_2$	8.79	5.46	9.27	7.06 (s, 2 H, ArH), 2.29 (s, 6 H, CH_3)			
n-$BUNH_2$ (2 equiv)	8.81	5.55	9.41	aliphatic	8.99	6.8–7.8 (very br s, 2 H, NH_2^+), 1–1.9, 2.4–3.4 (n-Bu)	8.90, 8.82

[a] AB quartet, J = 2.5 Hz. [b] Protonated 25.

follows from the results that the reaction of phenoxide with DNBF occurs by a pathway analogous to the TNB–phenoxide reaction (Scheme I). Thus, attack by PhO^- via the oxygen center is kinetically preferred. The energy barrier for this process is lower than for attack via the carbon center since formation of the C adduct 4 requires disruption of aromaticity. However, whereas the O-bonded adduct 3 can revert to reactants, the initially formed C adduct 4 rapidly rearomatizes by proton loss to give the final product 5, making this pathway effectively irreversible. The C-bonded adduct is therefore obtained as the product of thermodynamic control.

Upon comparison of the DNBF and the TNB systems, it is noted that conversion of **6b** to **7** through reaction with phenol takes longer (weeks vs. hours) than the analogous conversion of the TNB–OMe^- adduct to **5**. This may be a reflection of the much greater stability of **6b**, although the difference in medium (Me_2SO in this work vs. 80:20 v/v Me_2SO–MeOH) is probably a contributing factor.

It is clear from the above results that an O-bonded phenoxide–DNBF complex could not be observed. The question remains, however, whether this results from an intrinsic instability of the oxygen adducts or from the ease of formation and thermodynamic stability of the C-bonded adduct. In light of previous results with 2,4,6-trimethylphenoxide and TNB, in which an O-bonded phenoxide complex was observed,[12b] it is probable that **6c** would be thermodynamically stable relative to reactants. However, the lack of success in formation of **6c** and of a diadduct corresponding to that derived from aniline (**22**) would tend to indicate that this stability is not large. A more detailed argument would take into account relative proton and carbon basicities of the various reactive species (phenoxide, aniline, triethylamine) in these systems, but we believe that the above qualitative explanation correctly describes the situation. It appears, therefore, that failure to observe oxygen adducts with **1** indicates that the anticipated added stability of the O-bonded DNBF complex **6c**, relative to that of the O-bonded TNB complex **3**, is compensated by the decreased barriers to carbon attack and the lesser selectivity of DNBF relative to TNB.

N-Bonded vs. C-Bonded Complexes in Reaction with Arylamines. The results are uniquely interpreted via Scheme II and the corresponding potential energy diagram in Figure 1, in which the nitrogen adduct **13** is formed in a rapid equilibrium, while formation of the carbon-bonded adducts **15** or **16** is slower but irreversible. A key feature of the scheme is that N attack leads initially to the unstable zwitterionic species **12** (K_1^{Nu} step), which must be deprotonated (K_1^H step) in order for the product **13** to be formed in observable quantity. Hence, formation of the N-bonded adduct can be either favorable or unfavorable depending on the base. The dotted curve in Figure 1 illustrates the situation when only 1 equiv of aniline is

Scheme II

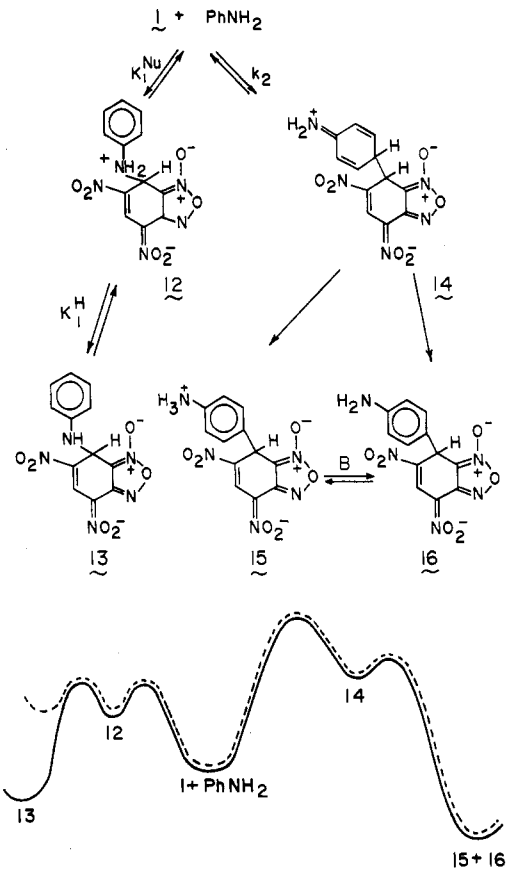


Figure 1. Free energy profile for reaction of 1 with aniline according to Scheme II. Dashed curves correspond to 1 equiv of aniline being used; solid curves, to 2 equiv of aniline.

used. The overall reaction to give **13** is unfavorable, since deprotonation of **12** requires an extra 1 equiv of aniline (or other base). However, formation of **15** or **16** can occur in the absence of added base. This is because rearomatization of the quinoid intermediate **14** can be effected by the product **16** and possibly by the solvent, as well as by unreacted aniline. The result is that formation of the C-bonded adduct is rapid. In the presence of excess base, formation of **13** becomes favorable, as shown by the solid curve in the PE diagram. In addition, increased strength and concentration of base slows the conversion of **13** to **16**. These factors permit detection of **13**.

If the nucleophilic carbon sites of the aniline are blocked, as with 2,4,6-trimethylaniline, then only the N-bonded adduct forms. It is noteworthy that 2,4,6-trimethylaniline does not add to DNBF except in the presence of a relatively strong base such as Et_3N, whereas aniline requires only a second 1 equiv of aniline to form an N-bonded

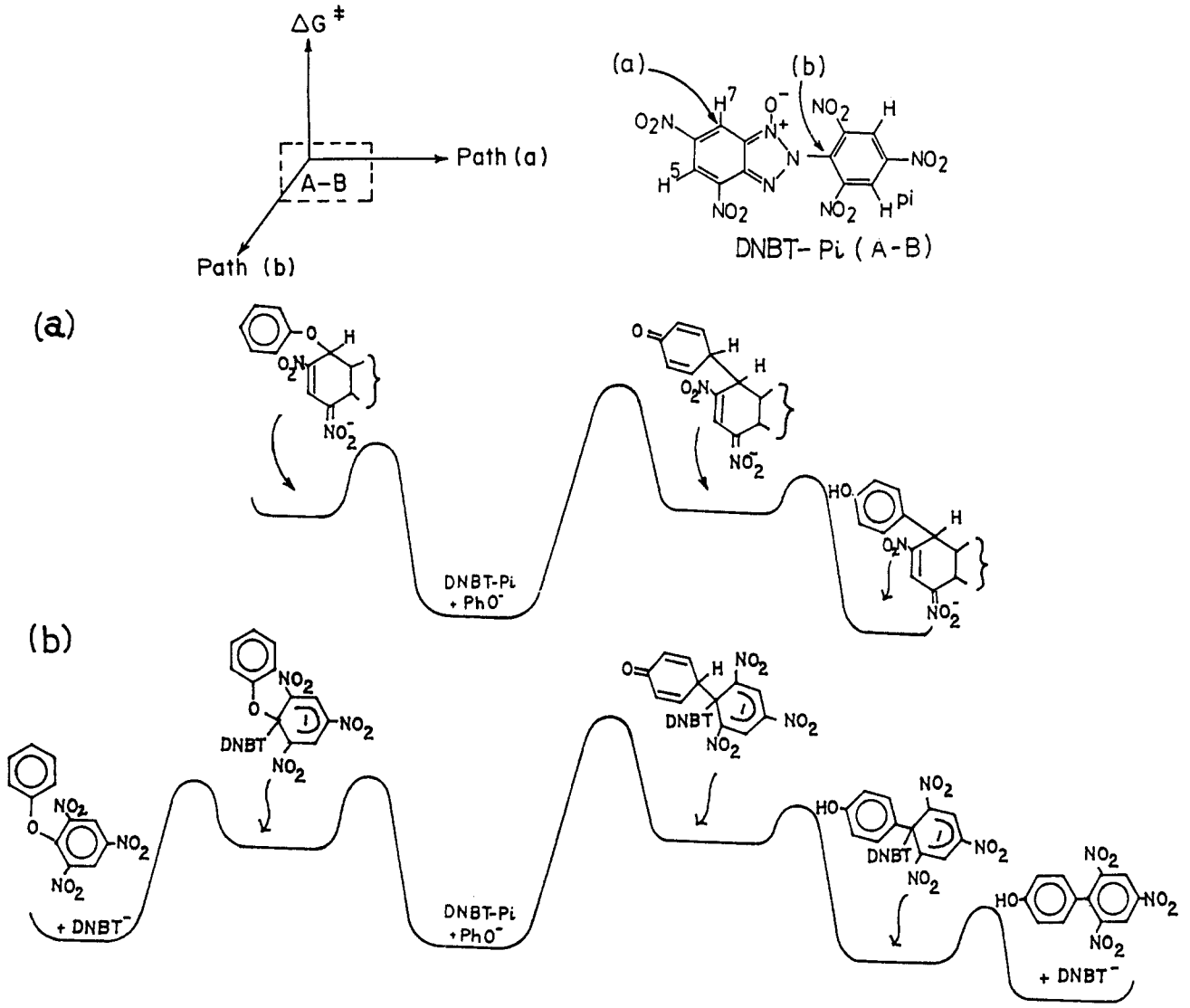


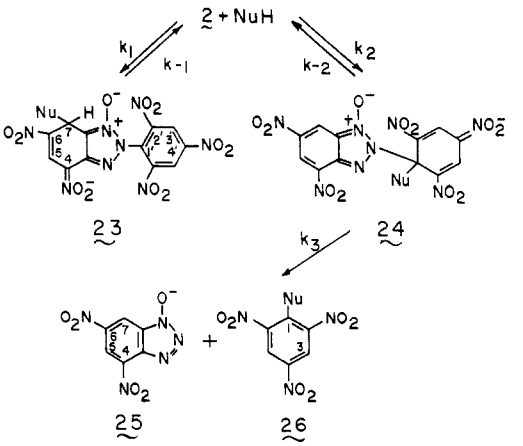
Figure 2. Schematic free energy profiles for reaction of **2** with phenoxide ion as an ambidentate nucleophile. Pathway a corresponds to nucleophilic attack at C-7; pathway b, to attack at C-1′.

adduct. This behavior suggests significant destabilization of **21** relative to **13** as a result of steric interactions between the ortho methyl groups and the dinitrobenzofuroxan moiety. A similar destabilization has been found in the behavior of mesidine toward TNB, where σ complex formation does not occur even in the presence of triethylamine.[23]

The formation of C-bonded adducts in addition to N-bonded adducts is in accord with the expectation mentioned earlier that, relative to TNB, the increased reactivity in the DNBF system leads to decreased selectivity among the nitrogen and carbon nucleophilic centers.

Ambident Reactivity of PiDNBT (2). σ Complex Formation vs. S_NAr Displacement. The substrate **2** is similar to **1** with regard to electrophilic properties of the benzotriazole moiety. However, **2** contains the picryl moiety as an additional site for attack by nucleophiles, as shown in Scheme III. We have already reported that C-7 and C-1′ of **2** are reactive sites toward certain nucleophiles.[18] Thus in the reaction of **2** with phenoxide and aniline we have multidentate reactants in both electrophilic and nucleophilic components. A key requirement is that addition at C-1′ occurs more slowly than addition at C-7 but is effectively irreversible. The breakdown of **24** to

Scheme III



products is expected to be rapid, in part because of the accompanying relief of steric strain between the benzotriazole and picryl moieties and in part because of the favorable nucleofugality of **25** as a leaving group. It has been reported[24] that the parent 1-hydroxybenzotriazole forms salts with aniline, while the dinitro species **25** should

(23) Renfrow, R. A. M.S. Thesis, University of Vermont, 1982.

(24) Deorha, O. S.; Sareen, S. P. *J. Indian Chem. Soc.* **1964**, *41*, 793.

be considerably more acidic.

The potential energy profile for the reaction of **2** with an ambident nucleophile such as phenoxide ion is shown in Figure 2 in simplified form so as to represent the reaction pathways at the two electrophilic centers. Pathway a represents attack at C-7 while pathway b corresponds to attack at C-1′. In pathway a there is illustrated the kinetic preference for O attack and the thermodynamic preference for C attack; this profile is also applicable to phenoxide attack on TNB (Scheme I) or DNBF. In pathway b the initially formed O adduct can expel the 4,6-dinitrobenzotriazole leaving group ($DNBT^-$), leading to formation of the oxygen displacement product shown on the left-hand branch of the profile. Also, since the two electrophilic sites in the reactant are dissimilar, the energy barriers in the upper and lower diagram will in general not be equal, and only the starting materials can be taken as the common reference point. The following discussion bears further on the profiles of Figure 2.

Reactivity–Selectivity. Considerations based on reactivity–selectivity[3,25] suggest that less reactive (more selective) nucleophiles will tend to form σ complexes at the benzotriazole moiety (C-7), while more reactive (less selective) nucleophiles will react initially at both sites (C-7, C-1′). The rate of the overall conversion of the C-7 complex **23** to displacement products **25** and **26** will therefore depend on both the stability of the C-7 complex (K_1) and on the selectivity of the nucleophile as given by the ratio k_1/k_2. These two criteria arise because of the effectively irreversible nature of C-1′ attack caused by the k_3 step being very fast.

These relationships are more clearly seen by considering the reactants (**2** + NuH) as steady-state intermediates for the conversion reaction (i.e., **23** → **25** + **26**) and considering the formation of **24** as effectively irreversible (i.e., ignoring the k_{-2} and k_3 steps). The rate of conversion is then given by $-d[\mathbf{23}]/dt = k_{obsd}[\mathbf{23}]$, where

$$k_{obsd} = k_{-1}k_2/(k_1 + k_2) \quad (1)$$

A decrease in K_1 must involve a decrease in k_1, an increase in k_{-1}, or both. According to eq 1 all of these will enhance k_{obsd}. Similarly, a decrease in selectivity requires a decrease in k_1, an increase in k_2, or both. Again all of these factors will enhance k_{obsd}.

In general, these parameters are not independent. For example, an increase in k_1 is usually linked to an increase in k_2 and K_1. Furthermore, according to the RSP an increase in K_1 will lower the selectivity. Thus, in many cases a change in reactivity will give rise to opposing effects. Consequently, the net effect on the rate of conversion from the C-7 adduct **23** to displacement products (**25**, **26**) may be small (e.g., when the reactivity of the nucleophile is changed by varying a remote substituent).

However, a change in the nucleophile can conceivably alter the rates of the reactions (k_1, k_{-1}, k_2) without affecting the thermodynamics (K_1, ΔG_0). This could occur if the *intrinsic rates* (k_0, defined as k_1 when $K_1 = 1$) were different for the two different nuclephiles.[26,27] Such a situation could occur if the reacting center were altered, for example, by changing the nucleophilic atom from O to S.

Pross[25] has pointed out that reactions that do not obey a rate–equilibrium relationship (i.e., that have different intrinsic rates) are not expected to display a reactivity–selectivity effect. However, we have shown[28] that varying

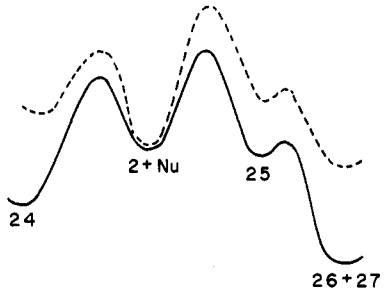


Figure 3. Free energy profile for reaction of **2** with nucleophiles, illustrating effect of adduct **24** stability.

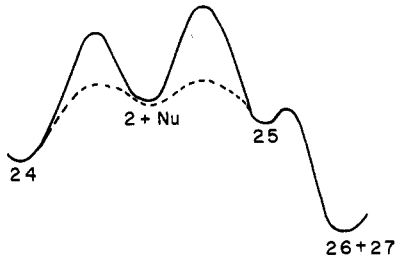
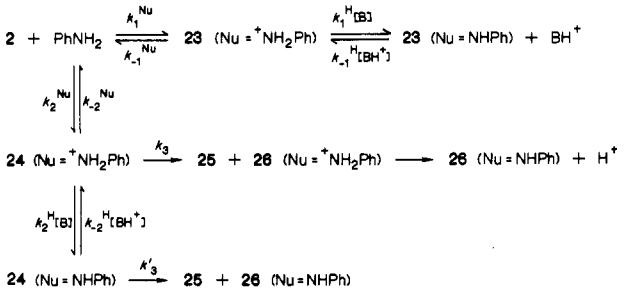


Figure 4. Free energy profile for reaction of **2** with nucleophiles, illustrating effect of varying the intrinsic barriers.

Scheme IV



the intrinsic barriers ($\Delta G_0^{\ddagger}$) for a pair of reactions can affect the selectivity between them (see also ref 29). Specifically, for a pair of fairly exergonic reactions, decreasing $\Delta G_0^{\ddagger}$ decreases the selectivity.

Hence the selectivity of nucleophiles for attack at C-7 and C-1′ can be altered both by changing the thermodynamics of the reaction (ΔG_0) and by varying the intrinsic rate. In the latter case, decreasing selectivity will increase the rate of conversion of C-7 adduct to displacement products, while in the former case the effect of decreased selectivity is opposed by the increased thermodynamic stability of the adduct.

For the C-7 adduct to be observed, the formation of the complex must be favorable ($K_1 > 1$). Furthermore, the rate of conversion to products must also be fairly slow. Thus, unless K_1 is very large, the selectivity must also be high (k_1/k_2 large). Figures 3 and 4 illustrate the effects of adduct stability and selectivity on the potential energy profile for Scheme II. Figure 3 illustrates the effect of stabilizing the adduct **23** (dashed line less stable adduct, solid line more stable adduct). Figure 4 compares the profiles of reactions that have the same thermodynamics (ΔG_0) but different intrinsic barriers ($\Delta G_0^{\ddagger}$) and selectivities (k_1/k_2).

Since phenoxide does not give rise to observable complexes from attack at C-7, it follows that K_1 is small, the selectivity is small, or both occur. This is not surprising, since the present work points to only moderate or small stability for oxygen-bonded phenoxide complexes (i.e., K_1

(25) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *14*, 69.
(26) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.
(27) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.
(28) Renfrow, R. A.; Buncel, E., to be submitted for publication.
(29) Shaik, S. S. *Can. J. Chem.* **1986**, *64*, 96.

small). Moreover, since phenoxide is poorly solvated in Me_2SO, nucleophilic attack requires relatively little solvent reorganization. Consequently $\Delta G^{\ddagger}$ for phenoxide O attack is expected to be small and the electivity (k_1/k_2) low.

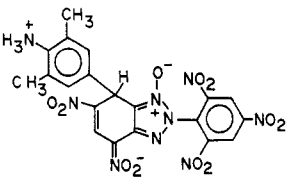
Competing Pathways in the Reaction of PiDNBT with Arylamines. In the case of the anilines (Scheme IV), formation of the N-bonded C-7 adduct **23** (Nu = NHPh) entails two steps: attack to form a zwitterionic intermediate followed by its deprotonation. The PE profile (not shown) for the aniline reaction (and other amine reactions) is of the same form as that for the reaction of aniline with DNBF (Figure 1), with C-7 attack corresponding to the left-hand branches and C-1′ attack corresponding to the right-hand branch. Clearly then, when only 1 equiv of $PhNH_2$ is used, the overall equilibrium constant ($K_1 = K_1^{Nu}K_1^{H}[B]/[BH^+]$) will be small because there is insufficient base to effect deprotonation. In addition, it is likely that the rate of C-7 complex formation will be slow, due to a low $k_1^{H}[B]$ value, since the corresponding deprotonation step was found to be rate-limiting in the $TNB/PhNH_2/R_3N$ system.[14] The rate of formation of the displacement products, however, is expected to be relatively fast. This is because deprotonation of the intermediate zwitterion is anticipated to be unnecessary (i.e., $k_3 > k_2^{H}[B]$), owing to the favorable nucleofugality of the benzotriazole moiety. The combination of these two factors is in accord with the experimental result, i.e. that the C-7 adduct is not seen under these conditions.

With 2 equiv of aniline, one would expect C-7 complex formation to be more favorable, both kinetically and thermodynamically, due to the increased value of $k_1^{H}[B]$. However, the results indicate that formation of the complex is still not sufficiently favored under these conditions to permit its detection. Use of a stronger base will enhance $k_1^{H}[B]$ still further, and accordingly, reaction of **2** with a mixture of 1 equiv each of aniline and Et_3N permits observation of the C-7 complex (**23**, Nu = NHPh).

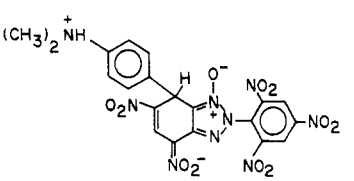
Carbon vs. Heteroatom Attack in Reaction of PiDNBT with Arylamines and Aryl Oxides. It is interesting that, in the reactions of **2**, attack by phenoxide and aniline occurs exclusively through oxygen and nitrogen, respectively, in view of the ease of formation of carbon-bonded adducts with **1**. The present results also contrast with the recent work with 1-phenyl-2,4,6-trinitrobenzene where phenoxide attack at C-1 was not observed, only carbon attack at C-3 of the TNB moiety being observed.[2]

The failure to observe carbon-bonded adducts in the PiDNBT systems results from a higher energy barrier for carbon attack than for attack by oxygen or nitrogen (cf. Figures 1 and 2, pathways a and b). This is in part a consequence of the disruption of aromaticity in the phenoxide and aniline moieties. In addition to this structural reorganization, one would expect attack by more electronegative nucleophilic centers to be more favorable in Me_2SO.[30] These considerations, coupled with the irreversibility of C-1′ attack noted above, explain the absence of carbon-bonded adducts in these systems. In the cases of **1** and 1-phenyl-2,4,6-trinitrobenzene, however, the electrophile lacks a good leaving group. Thus oxygen or nitrogen addition is reversible, permitting the thermodynamically preferred attack via carbon to take place (cf. Figure 2, pathway a).

It follows from the above argument that one can enhance the selectivity for attack at the benzotriazole moiety, and via the carbon nucleophilic center, by raising the barrier to oxygen or nitrogen attack at C-1′. Such is the case for reaction of **2** with 2,6-dimethylaniline and *N,N*-dimethylaniline, in which the transition state leading to displacement is extremely sterically hindered. In these reactions, the overall equilibrium constant for carbon adduct formation and the selectivity for C-7 vs. C-1′ attack are extremely large, and hence these processes give rise to very stable C-7 carbon-bonded adducts **27** and **28**.[6]



27



28

Reaction of PiDNBT with *n*-Butylamine. The greater basicity of *n*-butylamine compared with aniline would be expected to result in greater thermodynamic stability for the C-7 adduct, but the increased reactivity of *n*-butylamine might also be expected to decrease the selectivity between C-7 and C-1′ attack. The fact that the *n*-butylamine C-7 adduct is converted to displacement products at about the same rate as the triethylammonium salt of the aniline adduct **23** (Nu = NHPh) suggests that any increase in stability of the C-7 complex is offset by the faster rate of addition to C-1′.

Reaction of PiDNBT with Other Nucleophiles. The above discussion and Scheme III can be used to rationalize the behavior of **2** toward other nucleophiles. Previous work showed that ethanethiol and diethylamine (2 equiv) both form stable σ complexes that convert to displacement products quite slowly.[18] Both these nucleophiles have K_1 values large enough to permit observation of the C-7 complex. More importantly, their rates of addition to C-1′ are very slow (since on the one hand un-ionized EtSH is a relatively poor nucleophile toward TNB, for example, and on the other hand Et_2NH is appreciably sterically hindered); they are relatively unreactive and hence are expected to be selective for C-7 attack.

It was also found[18] that methoxide ion adds to **2** to give an observable C-7 complex, but this goes on to form the displacement products **25** and **26** much more rapidly. As with *n*-butylamine, although the K_1 value for this nucleophile is very favorable, its reactivity is also quite large. Thus, its selectivity is expected to be relatively low, and its rate of addition to the picryl moiety rapid.

Thiophenol does not give observable σ complexes with **2**.[18] Presumably this is because K_1 is of moderate magnitude,[31] while addition to C-1′ is rapid. If the actual reactive species is the thiophenoxide anion, as seems plausible, then it will show low selectivity by analogy with phenoxide.

Alternate Reaction Pathways in Reactions of PiDNBT. Although it is conceivable that C-5 and C-3′ in **2** could be alternate sites for reaction, such products have not been observed in the present work. In the case of C-3′ addition it would be expected that such adducts would be less favorable than adducts to the benzotriazole moiety (C-5, C-7). Although 4-nitrobenzofuroxan gives evidence of reaction at C-5 as well as C-7,[32,33] there has been no report so far of similar behavior with **1** or **2**.

(30) Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133.

(31) Thiols and thiophenols are known to add to **1** in Me_2SO to yield stable σ complexes.[23]

(32) Terrier, F.; Chattrousse, A. P.; Millot, F. *J. Org. Chem.* **1980**, *45*, 2666.

(33) Buncel, E.; Chuaqui-Offermanns, N.; Norris, A. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 415.

An additional pathway could involve formation of a dianionic adduct through addition of NuH at C-7 and C-1′ simultaneously. This is unlikely to have been formed to a significant extent under our conditions, involving largely use of 1 equiv of nucleophile. The main effect of this reaction, if it exists, would be to increase the rate of formation of the displacement products, since the C-1′ sites of both the substrates **2** and the C-7 adduct **23** would be available for attack by nucleophiles to yield **25** and **26**. Hence, the conditions necessary to observe the C-7 adduct would not be affected by the existence of this pathway when equimolar amounts of reactants are used. However, use of excess nucleophile would drastically shorten the lifetime of the C-7 adduct and prevent its observation.

Experimental Section

Materials and Methods. Methanol was distilled from barium oxide. Me_2SO was stirred with calcium hydride and distilled under nitrogen. Me_2SO-d_6 was dried by storing over molecular sieves. Acetonitrile was distilled from P_2O_5. The phenols and amines used were recrystallized or distilled.

4,6-Dinitrobenzofuroxan (DNBF, **1**) was prepared by nitration of benzofuroxan.[34] 4,6-Dinitro-2-picrylbenzotriazole 1-oxide (PiDNBT, **2**) was prepared as described previously.[18] Anhydrous potassium phenoxide was prepared by the method of Kornblum.[35] The potassium salt of the methoxy adduct **6b** was obtained from **1** and KOH[36] or KOPh in methanol.

NMR measurements were obtained at 100 and 60 MHz on JEOL MH-100 and Varian EM-360 spectrometers, respectively, with tetramethylsilane (Me_4Si) as internal reference. UV–vis spectra were recorded with a Perkin-Elmer Model 402 spectrometer. ESR spectra were recorded with a Varian E-4 spectrometer.

The present studies have shown that the NMR shifts reported in our previous communications dealing with aspects of this work[5,6,18] were too large by a factor of 1.024 due to calibration problems.

Reaction of 1 with Potassium Phenoxide. To an NMR tube containing 32 mg of **1** in 0.5 mL of Me_2SO was added 18 mg (1 equiv) of anhydrous PhOK. The tube was shaken and placed in the probe of the spectrometer, and the spectrum was recorded within 7 min. Subsequent spectra revealed no change over several hours, whereupon trifluoroacetic acid (TFA) was added, the NMR tube shaken, and the spectrum again recorded. This reaction was also carried out with a variation in which 45 mg of **1** was added to 26.5 mg (1 equiv) of PhOK dissolved in 0.5 mL of Me_2SO-d_6 and the spectrum recorded after 1 min.

Reaction of DNBF–Methoxide Adduct 6b with Phenol in Me_2SO. To an NMR tube containing 79 mg of **6b** in 0.5 mL of Me_2SO-d_6 was added 30 mg of phenol. The spectrum was recorded periodically over 5 weeks and again after 5 months.

Reaction of 1 with Aniline and Triethylamine and Generation of the Bis(aniline) Adduct 22. A 21-μL portion of aniline and 32 μL of Et_3N were dissolved in 0.5 mL of Me_2SO-d_6. To this was added 57 mg (1.1 equiv) of **1**, the tube shaken, and the spectrum recorded after 30 s. After 24 h, when no further changes were observed in the spectrum, another 57 mg of **1** was added. The spectrum showed only slight broadening of the resonances for DNBF and the NH_3 moiety. Another 36 μL (1.1 equiv) of Et_3N was added and the spectrum recorded.

Reaction of 2 with Potassium Phenoxide. To an NMR tube containing 28 mg of **2** in 0.5 mL of Me_2SO-d_6 was added 8.5 mg of solid anhydrous PhOK. The tube was shaken and placed in the probe of the spectrometer and the recording of the spectrum begun within 2 min. Spectra were recorded continuously for 30 min and at intervals over the next 5 h.

Reaction of 2 with Aniline and Triethylamine. On the side of an NMR tube containing 14 mg of **2** in 0.5 mL of Me_2SO-d_6 was carefully placed 2.9 μL of aniline and 4.5 μL of Et_3N. The tube was shaken and placed in the probe of the spectrometer and the spectrum recorded after 1 min. Spectra were recorded continuously for 25 min and at invervals over the next 24 h. Several 2.5-μL (1-equiv) aliquots of TFA were added; the NMR tube was shaken and the spectrum recorded after each addition.

Isolation of DNBF Complexes. Preparation of the Potassium Salt of 7. The potassium salt of **6b** (0.4 g) was added to 2.0 g (15 equiv) of phenol dissolved in 10 mL of methanol and the resultant mixture stirred for 5 days. Reaction was monitored by removing 5-μL aliquots of the supernatant, diluting, and recording the visible spectrum both before and after acidification with 10 μL of TFA. The appearance of an absorption at 472 nm that was stable to acidification was indicative of formation of **7**. After 5 days, the solution was diluted with an equal amount of 1 M acetic acid/methanol, and the precipitated solid was collected by filtration, washed with methanol and anhydrous ether, and dried in vacuo to give 0.32 g (66%) of an orange powder: mp >300 °C with slow discoloration above 160 °C, explodes at 165° C on rapid heating.

Preparation of the Potassium Salt of 16. **16** was prepared in a manner analogous to **7**. To a suspension of 0.4 g of **6b** in 10 mL of methanol was added a 10-fold excess (1.26 g) of aniline and 10 μL of TFA. After 24 h, a UV–vis spectrum showed the reaction to be complete. The red solid was filtered, washed with methanol and ether, and dried in vacuo to yield 0.34 g (70%) of a red powder; explodes at 190 °C.

Preparation of the Potassium Salt of 17a. **17a** (i.e., deprotonated **17**) was prepared in the same manner as **16** from 1.64 g of *N*,*N*-dimethylaniline to give 0.35 g (67%) of a brown powder: mp >300 °C with slow discoloration above 235 °C; explodes at 235 °C on rapid heating.

Preparation of the Zwitterionic Complex 15. To 0.4 g of **1** suspended in 10 mL of methanol was added 0.16 g (1 equiv) of aniline. Within a few minutes the DNBF had disappeared and an orange precipitate formed. This was filtered, washed with methanol and ether, and dried in vacuo to give 0.52 g (92%) of **15**; explodes at 198 °c.

Acknowledgment. Support of this research by the Natural Sciences and Engineering Research Council of Canada (E.B.) and the Naval Surface Weapons Center at Silver Springs, MD (M.J.S.), is gratefully acknowledged.

Registry No. **1**, 5128-28-9; **2**, 87604-86-2; **6a**, 57891-85-7; **6b**, 91948-45-7; **7**, 105563-82-4; **8**, 105563-83-5; **10**, 105582-44-3; **11**, 105563-84-6; **13**, 105563-85-7; **15**, 105563-86-8; **16**, 105563-87-9; **17**, 105563-88-0; **17a**, 105563-89-1; **18**, 105563-90-4; **19**, 105563-91-5; **20**, 105563-92-6; **21**, 105563-93-7; **22**, 105597-50-0.

(34) Drost, P. *Justus Liebigs Ann. Chem.* **1899**, *49*, 307.
(35) Kornblum, M.; Lurie, A. P. *J. Am. Chem. Soc.* **1959**, *81*, 2705.
(36) Boulton, A. J.; Clifford, D. P. *J. Chem. Soc.* **1965**, 5414.