An Unexpected Ring Protonation in Meisenheimer Complex Formation

Richard A. Manderville*,† and Erwin Buncel*

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

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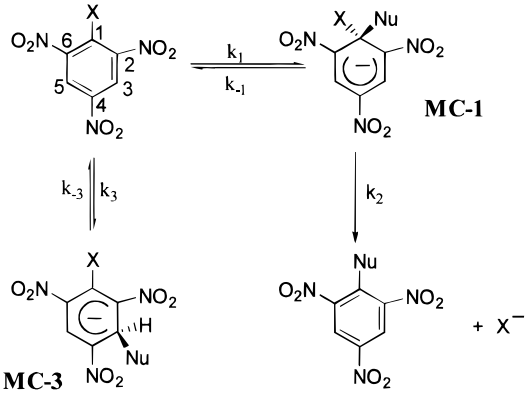
The reactions of *N*,*N*-dimethylpicramide (DMP) with phenoxide and 2,6-di-*tert*-butylphenoxide ions have been monitored by ^{1}H and ^{13}C NMR spectroscopy in dimethyl sulfoxide at room temperature. Both aryloxide nucleophiles react at the unsubstituted (C-3) position of DMP to produce *para* carbon-bonded σ-adducts (Meisenheimer complexes, **1** and **3**, respectively). Surprisingly, acidification of these Meisenheimer complexes led to a ring protonation resulting in production of nitro tautomers (**2** and **4**) with a sp^3-bound NO_2 group at the C-2 position. For **4**, the C-2 nitro tautomer of the 2,6-di-*tert*-butylphenoxide adduct of DMP (**3**), a pK_a value of 6.2 was determined in aqueous solution. Insight into electronic factors that could provide a driving force for ring protonation was derived from examination of the ^{13}C NMR parameters of the Meisenheimer complexes and the C-2 nitro tautomers. These parameters were consistent with the notion that the C-2 protonation stemmed from charge transfer interactions from the C-1 NMe_2 substituent to the C-2 NO_2 group ("enamine") and the attendant relief in steric strain upon conversion of the C-2 center from sp^2 to sp^3.

Introduction

Anionic σ-adducts, also termed Meisenheimer complexes,[1] arise from covalent bond formation between nucleophiles (Nu:$^-$) and electron deficient nitroaromatic compounds.[2] For 1-X-2,4,6-trinitrobenzene substrates (Scheme 1), isomeric Meisenheimer complexes (i.e., MC-1 and MC-3) can result from nucleophilic attachment at C-1 and C-3, respectively. When X is a good leaving group, MC-1 decomposes to give 1-Nu-2,4,6-trinitrobenzene derivatives, which are representative of the S_NAr mechanism of nucleophilic aromatic substitution.[3] However, if X is a poor leaving group, then both MC-1 and MC-3 may be detected depending on solvent and temperature.

In a classic study of the reaction of 2,4,6-trinitroanisole (TNA) with methoxide ion in 90% dimethyl sulfoxide (DMSO)−10% methanol, Servis[4] was able to detect both MC-1 and MC-3 by ^{1}H NMR. Initially, peaks due to MC-3 were dominant, but with time these resonances gave way to peaks ascribed to MC-1. Since then this pattern of kinetically preferred MC-3 formation and thermodynamically favored MC-1 formation has been documented in numerous picryl ether−alkoxide reaction systems.[5] We have classified this regioselectivity as K3T1 (kinetic preference for reaction at the 3-position but thermodynamic preference for formation of the C-1 adduct).[6,7]

Scheme 1. Reaction Pathways for 1-X-2,4,6-trinitrobenzene Substrates



In our studies of regiochemistry in σ-adduct-forming reactions involving phenoxide ions as nucleophiles,[6,7] we have demonstrated a wide range of reactivity and regioselectivity in Meisenheimer complex formation. For example, the reaction of TNA with phenoxide ion (PhO$^-$) as an oxygen-centered nucleophile yields the MC-1 O-adduct as the product of both kinetic and thermodynamic control, which corresponds to K1T1 regioselectivity.[6] At extended periods of observation a *para* carbon-centered C-3 adduct of phenoxide was noted as the ultimate product of thermodynamic control. Thus, the behavior of PhO$^-$ as a C-nucleophile follows the K3T3 pattern of regioselectivity. In contrast, the reaction of 2,4,6-trimethylphenoxide (mesitoxide, MesO$^-$) with TNA displays K1T3 reactivity.[7] In this system, oxygen attack at C-1 is favored kinetically, but over time the C-1 adduct is replaced by C-3 MesO$^-$ and C-1,3 di(MesO$^-$) O-adducts; C-adduct formation is precluded here due to the *o*- and *p*-methyl groups of mesitoxide.

† Current address: Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109-7486.

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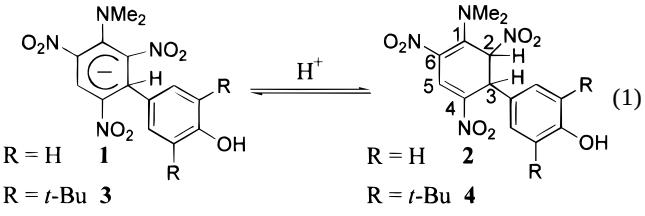
Table 1. ^{13}C NMR Spectral Characteristics[a] of the PhO$^-$ and 2,6-DTBPhO$^-$ σ-Adducts (1 and 3) and the C-2 Nitro Tautomers (2 and 4) of DMP, with DMP and the C-3 Hydroxide Adduct 5 in DMSO[b]

	C-1	C-2	C-3	C-4	C-5	C-6	NMe	other
DMP	141.2	142.4	126.2	135.8	126.2	142.4	42.5	
1	150.4	131.5	41.0	116.8	130.5	116.8	43.5	115.3, 127.1, 135.2, 156.9
3	150.8	132.9	41.2	115.8	130.0	116.8	43.3	138.9, 122.6, 135.7, 152.5, 34.5, 30.3
5	150.1	134.7	63.0	118.0	130.6	119.6	44.0	
2	153.5	82.9	42.8	116.2	130.3	121.7	47.4, 42.8	116.2, 128.6, 132.5, 157.7
4	153.8	83.1	43.2	116.1	129.9	122.1	47.1, 42.7	140.1, 123.2, 132.8, 154.3, 34.6, 30.1

[a] Chemical shifts are given in ppm measured at 100 MHz. [b] DMSO-d_6 at ambient temperature.

The present study involves the reactions of two aryloxide nucleophiles, namely, phenoxide ion (PhO$^-$) and 2,6-di-*tert*-butylphenoxide ion (2,6-DTBPhO$^-$), toward the 1-X-2,4,6-trinitrobenzene substrate *N*,*N*-dimethylpicramide (DMP, with X = NMe_2 in Scheme 1). Previously, the reaction of DMP with methoxide ion was shown to follow the K3T3 pattern of regioselectivity;[8,9] the lack of C-1 σ-adduct formation presumably reflects the steric bulk of the C-1 NMe_2 substituent. This characteristic of methoxide reactivity toward DMP prompted us to consider study of its reactions with aryloxide nucleophiles, since our recent studies[6,7] indicated a kinetic preference for O-attachment by aryloxides at C-1 of 1-X-2,4,6-trinitrobenzene substrates. In the current study, both aryloxide nucleophiles are potentially ambident, as O- and C-nucleophiles, although 2,6-DTBPhO$^-$ is highly hindered about the O-center. As C-nucleophiles, PhO$^-$ may react via either *ortho* or *para* C-centers, while 2,6-DTBPhO$^-$ is limited to reaction via the *para* carbon.

In this article we report the results of monitoring these DMP-ArO$^-$ systems in dimethyl sulfoxide-d_6 (DMSO-d_6) at ambient temperature using ^{1}H and ^{13}C NMR spectroscopy. These reaction conditions favored detection of C-adduct formation, and both nucleophiles displayed reactivity via the *para* C-center to produce the corresponding C-3 Meisenheimer complexes. Thus, as C-nucleophiles both aryloxides react with DMP according to K3T3 regioselectivity. While these findings may have been anticipated, what was not anticipated, and constitutes the focus of this paper, was a C-2 ring protonation of the resulting C-3 Meisenheimer complexes in acidic media to furnish C-2 nitro tautomers (eq 1). These results are discussed in terms of electronic factors which follow from consideration of ^{13}C NMR chemical shifts of the C-3 σ-adducts and nitro tautomers.



R = H **1** R = H **2** R = *t*-Bu **3** R = *t*-Bu **4** (1)

Results

1. Reaction of *N*,*N*-Dimethylpicramide (DMP) with Phenoxide and 2,6-Di-*tert*-butylphenoxide in DMSO. Addition of 1 equiv of PhOK in DMSO-d_6 via a syringe into an NMR tube containing a DMSO-d_6 solution of DMP (final concentrations 0.1 M) resulted in a deep red solution. Inspection of the initial ^{1}H NMR spectrum (obtained ca. 3 min after mixing) revealed resonances consistent with formation of a single Meisenheimer complex, the *para* C-bonded C-3 phenoxide adduct, **1**, characterized by the following resonances: δ 9.26 (1H, s, O*H*), 8.44 (1H, s, H5), 6.89 and 6.60 (4H, A_2X_2, J = 7.7), 5.95 (1H, s, H3) and 2.76 (6H, s, NMe_2). Subsequent monitoring of the reaction over a 2 h period revealed no further change in the acquired spectra. To ascertain that the species present was in fact **1**, 5 μL of trifluoroacetic acid (TFA) was added to the reaction mixture as C-adducts of PhO$^-$ are known to be resistant to acid, while O-adducts decompose.[8,9] Unexpectedly, upon acidification the contents changed in appearance from deep red to bright orange. The ^{1}H NMR spectrum of the resulting orange solution displayed resonances consistent with formation of the C-2 nitro tautomer **2**. Signals for **2** were found at δ 9.64 (1H, br s, O*H*), 8.50 (1H, s, H5), 7.06 and 6.74 (4H, A_2X_2, J = 8.6), 6.53 (1H, d, J = 2.5, H2), 5.33 (1H, d, J = 2.5, H3), 3.14 (3H, s, NMe), and 3.31 (3H, s, NMe).

The reaction between DMP and 2,6-DTBPhO$^-$ in DMSO-d_6 mimicked the reactivity observed in the DMP−PhO$^-$ system. Admixture of potassium 2,6-di-*tert*-butylphenoxide and DMP in DMSO-d_6 (0.1 M) again led to a deep red solution. The ^{1}H NMR spectrum (acquired ca. 3 min after mixing) indicated *para* C-attack by 2,6-DTBPhO$^-$ at C-3 of DMP, and the resulting σ-adduct displayed resonances at δ 8.32 (1H, s, H5), 6.94 (2H, s), 6.78 (1H, br s, OH), 5.95 (1H, s, H3), 2.83 (6H, s, NMe_2), and 1.28 (18H, s, *t*-Bu). Addition of 5 μL of TFA to the DMSO solution of **3** resulted in formation of the C-2 nitro tautomer **4**, in accord with eq 1. The ^{1}H NMR resonances of **4** were noted at δ 8.54 (1H, H5), 7.05 (1H, s, O*H*), 6.97 (2H, s), 6.59 (1H, d, J = 2.0, H2), 5.37 (1H, d, J = 2.0, H3), 3.30 (3H, s, NMe), 3.10 (3H, s, NMe) and 1.36 (s, *t*-Bu).

Further confirmation of structure of the C-2 nitro tautomers **2** and **4** and their respective precursors **1** and **3** was obtained through ^{13}C NMR spectroscopy. The ^{13}C NMR spectral characteristics of the pertinent species are listed in Table 1. Parameters for **1**, **2**, and **3** were obtained from the 1:1 mixture of DMP and the respective aryloxides in DMSO-d_6, as described. Parameters for the nitro tautomer **4** were obtained from examination of an isolated sample, which was obtained as a yellow-orange solid after recrystallization from ethyl acetate/petroleum ether (see Experimental Section). To facilitate ^{13}C NMR peak assignments, ^{13}C NMR parameters of the C-3 DMP·OH$^-$ adduct **5**, and the 1,3,5-trinitrobenzene (TNB)−*para* C-adduct of phenoxide, **6**,[10] were also recorded in DMSO-d_6 at ambient temperature. The hydroxide adduct **5** was prepared from reaction of DMP (0.1 M) in 70

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(11) ^{13}C NMR assignments for the NO_2-bearing carbons (C-2, C-4, and C-6) of **1** and **3** were aided, in part, by line broadening of the resonance at ca. 132 ppm. This observation was taken as evidence of exchange processes (i.e., protonation) and so was assigned to C-2. The peaks at ca. 117 ppm were then assigned to C-4 and C-6, which is consistent with delocalization of the negative charge at these positions.

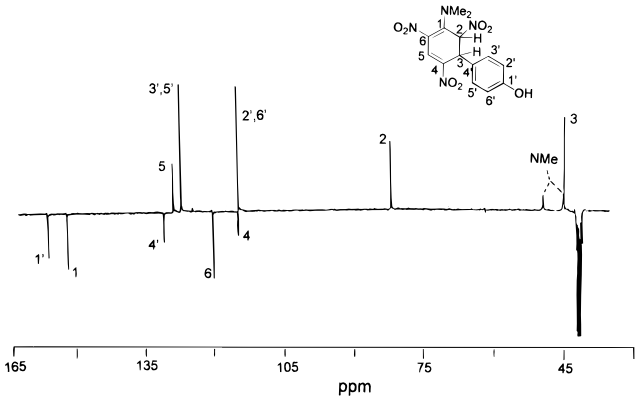
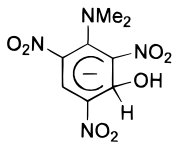


Figure 1. ^{13}C NMR spectrum of the C-2 nitro tautomer **2** in DMSO-d_6 at ambient temperature.

mol % DMSO-d_6 −30 mol % D_2O/H_2O with equimolar tetramethylammonium hydroxide (Me_4NOH).



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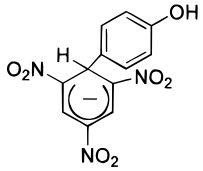

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Inspection of Table 1 shows that for the C-3 aryloxide C-adducts of DMP (**1** and **3**) C-2 resonates at ca. δ 132 ppm, while the other two carbon atoms bearing NO_2 groups (C-4 and C-6) resonate at ca. 117 ppm.[11] This observation is consistent with the notion that the C-4 and C-6 carbon atoms bear a greater percentage of negative charge.

Figure 1 shows the ^{13}C NMR spectrum of the C-2 nitro tautomer **2** in DMSO-d_6, obtained after acidification (5 μL of TFA) of the Meisenheimer complex **1**, which was generated from admixture of DMP and PhO^-. The C-2 carbon resonates at δ 82.9 ppm, which is ca. 49 ppm upfield from the corresponding resonance in the precursor **1**. This shift is consistent with the change in hybridization (sp^2 to sp^3) of the C-2 carbon upon acidification and is closely similar to the value (79.1 ppm) reported by Ejchart for Cα of $(CH_3)_2CHNO_2$.[12a] [see also ref 12b]. Other changes that were noted include the shifting of the NMe_2 methyl resonances. In the anion **1**, this group was represented by a sharp peak at 43.5 ppm (Table 1), while for **2** the methyl resonances were observed as two broad peaks at δ 47.4 and 43.0 (Figure 1).

The Meisenheimer complexes (**1** and **3**) were also characterized by UV−visible spectroscopy by diluting the NMR samples in DMSO. The anions showed two broad bands at 426 and 498 nm in a ratio of 2.4:1. Acidification with TFA (2 μL) produced spectra with λ_{max} at 402 and 434 nm in a 1.14:1 ratio. The hypsochromic (blue) shift for the C-2 nitro tautomers (**2** and **4**) relative to the σ-adducts (**1** and **3**) was consistent with the color change noted in the NMR experiments (*vide supra*).

2. Determination of Acidity Constant (pK_a) for the C-2 Nitro Tautomer 4. Scheme 2 shows the equilibria resulting on addition of alkoxides ions (RO^-) to the C-2 nitro tautomer **4**. The first equilibrium (K_1) involves conversion of **4** into the σ-adduct **3**. The second step (K_2) is a deprotonation of the phenolic OH to form the dianion **7**, while the third equilibrium (K_3) involves formation of the trianion **8** through covalent attachment of RO^-.

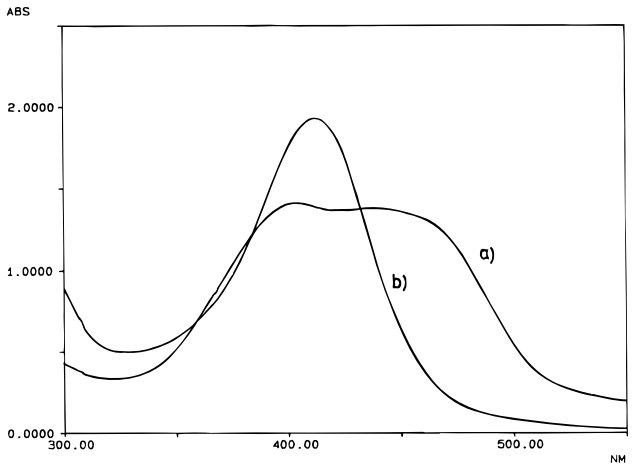
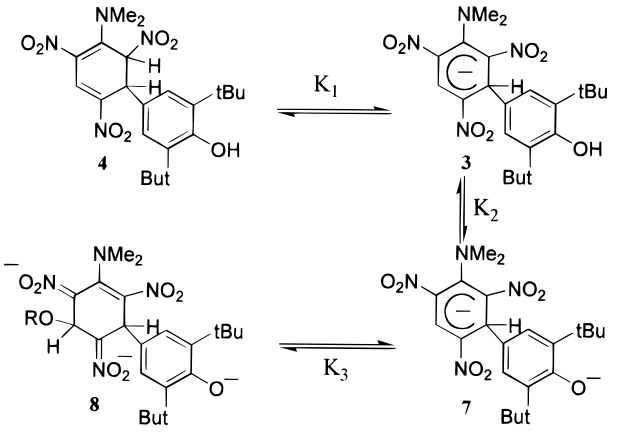


Figure 2. UV−visible spectra of the C-2 nitro tautomer **4** in 0.1 M HCl (curve a) and in 0.1 M KOH (curve b). The curve b spectrum corresponds to the C-3,3 diadduct **8** (Scheme 2); see text for details.

Scheme 2. Reaction of Base (RO^-) with the C-2 Nitro Tautomer 4



For processes analogous to K_2 in Scheme 2, much data has been previously obtained.[13] In the present system, the *para* substituent of the 2,6-di-*tert*-butylphenol is the negatively charged DMP^- moiety. This substituent is expected to be electron-withdrawing by analogy with previous studies,[14] and comparison with 2,6-di-*tert*-butylphenols possessing *para* Br, COO^-, or SO_3^- groups[13] suggests a pK_a range of 10.4−10.8 for the phenolic dissociation (K_2) in Scheme 2.

The K_3 step (Scheme 2) involves formation of the diadduct **8**. C-3,3 diadducts of this type for the reaction of substituted nitroaromatics with nucleophiles have been previously characterized.[8,15] Generally, these species show a single absorption maximum in the 410−430 nm region.[8] Figure 2 shows UV−visible spectra of the C-2 nitro tautomer **4** in 0.1 M HCl (curve a) and in 0.1 M KOH (curve b) containing 3.2 vol % methanol; in 0.1 M

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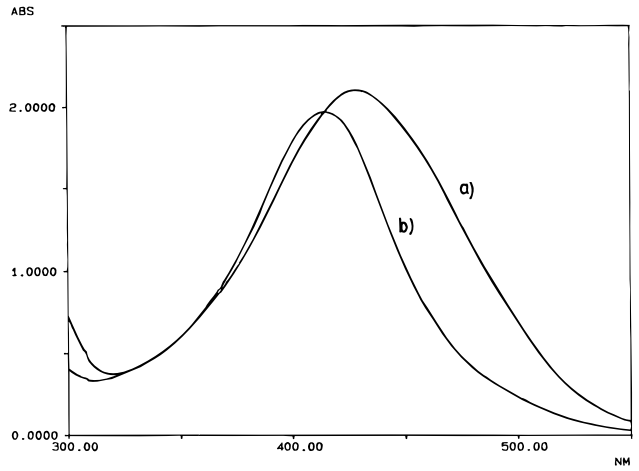

Figure 3. UV−visible spectra of the C-3 DMP·2,6-DTBPhO⁻ C-adduct **3** (curve a) and the C-3,3 diadduct **8** (Scheme 2); see text for details.

KOH solution a single absorption maximum is observed at 413 nm. To further identify this species, the reaction of tetramethylammonium hydroxide (Me_4NOH) in methanol (25 wt % solution) with **4** (0.06 M) was monitored by ^1H NMR spectroscopy in CD_3OD.

Addition of 1 equiv of Me_4NOH (ca. 11 μL) to a solution of **4** produced peaks attributable to the σ-adduct **3** (K_1, Scheme 2). Further addition of Me_4NOH (ca. 2 equiv more) resulted in the appearance of new signals at δ 6.83 (2H, s), 6.23 (1H, s, H5), 5.87 (1H, s, H3), 2.82 (3H, s, NMe), 2.74 (3H, s, NMe), and 1.16 (18H, s, *t*-Bu). These peaks were consistent with formation of a C-3,3 diadduct, such as **8** (R = H or CH_3, Scheme 2). Figure 3 shows UV−visible spectra in H_2O (obtained by dilution of the NMR samples) of the σ-adduct **3** (curve a) and the diadduct **8** (curve b). The σ-adduct **3** showed a broad absorption at 429 nm,[16] while the diadduct **8** shows a sharper absorption at 413 nm. This absorption for **8** corresponds to the maxima observed for the tautomer **4** in 0.1 M KOH (Figure 2, curve b) and suggested strongly that **4** was converted into the diadduct **8** in 0.1 M KOH. However, solutions of **4** in 0.1 M TRIS·HCl ranging from pH 8.0 to 9.0 showed a single broad absorption at 429 nm for **3** (Figure 3). Hence, using UV−visible spectroscopy it was possible to monitor the conversion of the C-2 nitro tautomer **4** into the σ-adduct **3** and determine a pK_a value for the K_1 equilibrium in Scheme 2.

The pK_a for deprotonation of the C-2 nitro tautomer **4** was measured at 25 °C in 0.1 M aqueous buffer solutions containing 3.2 vol % methanol using the recommended spectrophotometric procedure.[17] The methanol cosolvent was necessary to enhance the solubility of **4**. The spectra of **4** were acquired in 0.1 M HCl and in 0.1 M buffer solutions (succinic acid·HCl, KH_2PO_4/Na_2HPO_4 and TRIS·HCl, see Experimental Section) of pH 5.0−8.2. The λ_{max} of **3** at 429 nm was used as the analytical wavelength, and the relevant absorption data are given in Table 2. Using this procedure, the pK_a of the nitro tautomer **4**, as determined from the equation pK_a = pH + log I,[17] was estimated as 6.22 ± 0.08 (95% confidence interval).

Table 2. UV−Visible Absorption Data for the C-2 Nitro Tautomer 4 as a Function of pH for Determination of pK_a[a]

pH	A_{429}[b]	$(A_{A^-} - A_{429})$	$(A_{429} - A_{HA})$	log I[c]
1.0	1.72			
5.04	1.75	0.55	0.03	1.26
5.79	1.90	0.40	0.18	0.35
5.98	1.95	0.35	0.23	0.18
6.16	1.99	0.31	0.27	0.06
6.37	2.04	0.26	0.32	−0.09
6.58	2.15	0.15	0.43	−0.46
7.58	2.27	0.03	0.55	−1.26
8.20	2.30			

[a] All buffer solutions contained 3.2 vol % MeOH. [b] Absorbance at λ_{max} of the σ-adduct **3**. [c] I is the ionization ratio, $I = (A_{A^-} - A_{429})/(A_{429} - A_{HA})$; p$K_a$ = pH + log I.

Discussion

Reaction Pathways in σ-Complex Formation. In the present study, the reactions of *N*,*N*-dimethylpicramide (DMP) with the aryloxide nucleophiles, phenoxide (PhO^-) and 2,6-di-*tert*-butylphenoxide (2,6-DTBPhO⁻), were monitored by NMR spectroscopy in dimethyl sulfoxide at ambient temperature. Reaction with both nucleophiles proceeded cleanly to give the respective *para* C-bonded Meisenheimer complexes (**1** and **3**) from attachment at C-3 of DMP. No oxygen-bound adducts of PhO^- and no products resulting from C-1 attachment were observed. Thus the C-3 C-bonded adducts **1** and **3** are thermodynamically preferred and may also be kinetically favored, although the kinetic properties in these systems are difficult to assess under the present experimental conditions (DMSO-d_6, ambient temperature, first spectrum acquired ca. 3 min after mixing the reagents).

These results appear to be consistent with previous work on the interactions of DMP with nucleophiles where C-3 adduct formation has been the only process reported.[8,9] Clearly the bulky NMe_2 group reduces the equilibrium constant for C-1 adduct formation. This factor is especially apparent for reaction with aryloxide nucleophiles which typically show a kinetic preference for attack at C-1 of 1-X-2,4,6-trinitrobenzene substrates.[6,7,18] For example, when X = F or Cl, both PhO^- and 2,6-DTBPhO⁻ react at C-1. Reaction with PhO^- proceeds via the oxygen center to give picryl phenyl ether,[18,19] while 2,6-DTBPhO⁻ furnishes 2,6-di-*tert*-butyl-4-picrylphenol as the major product.[18] The fact that C-3 adduct formation in the picryl halide/2,6-DTBPhO⁻ systems is not the dominant pathway indicates that the forward rate constant for MC-1 is favored over the corresponding rate constant for MC-3. However, this situation is clearly not the case for alkoxide/1-X-2,4,6-trinitrobenzene systems where C-3 adduct formation always precedes MC-1 (if the C-1 adduct is in fact formed) regardless of the nature of the X substituent.[5] This finding is generally explained in terms of F-strain, through steric hindrance to approach of the alkoxide nucleophiles for attachment at the substituted C-1 site.[5,18]

The thermodynamic preference for C-3 C-adduct formation by the aryloxide nucleophiles with DMP is in accord with evidence, both from calculations[20] and product distributions in the vicarious nucleophilic substitution

(16) The loss of resolution in the UV spectra of the σ-adduct **3** in going from pure DMSO (λ_{max} 426 and 498, 2.4:1) to H_2O (λ_{max} 429) may be attributable to changes in charge distribution and ion-pairing of the σ-adduct. For a discussion on this subject, see: Crampton, M. R.; Khan, H. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1103.

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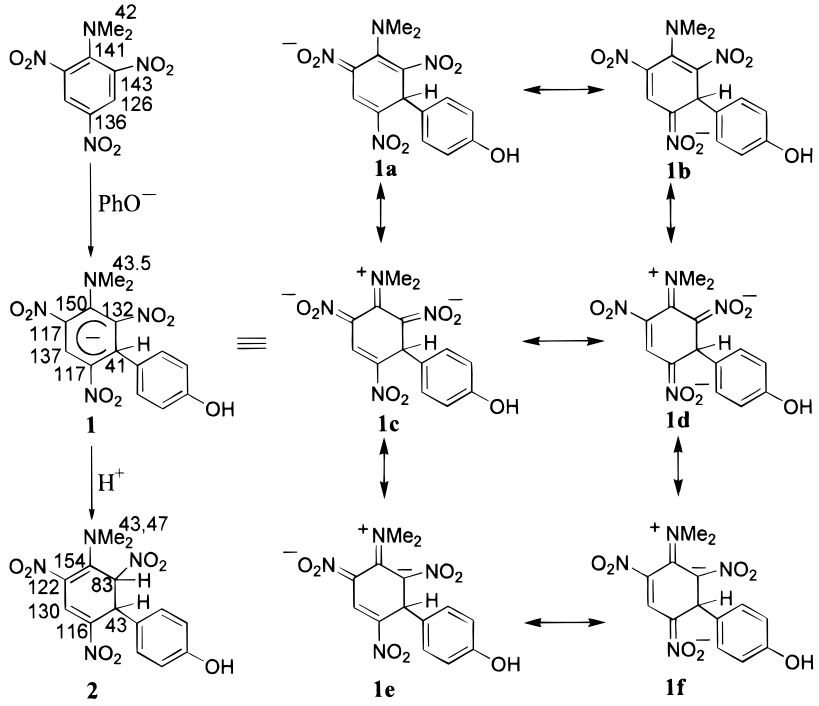
Scheme 3. Formation and Protonation of σ-Adduct 1 and Its Resonance Structures



(VNS) reaction,[21] which suggest that carbon nucleophiles form their most stable σ-adducts from attack at an unsubstituted position. Further, the C-3 Meisenheimer complexes benefit from through-conjugation from the NMe_2 substituent to the trinitrocyclohexadienate ring system.[22] Such a factor has been explored by Sinha and Yates[23] who have evaluated the electronic properties of planar versus twisted *p*-nitroaniline derivatives using electro-optical absorption (electrochromism) methods. They concluded that significant conjugation exists in the *N*,*N*-dimethylnitroaniline compounds even when the donor (NMe_2) or acceptor (NO_2) groups are twisted by more than 60° from the plane of the benzene ring, as a result of the very strong electron-donating ability of the NMe_2 group.

Origin of Protonation Behavior of the σ-Complexes. In the present system, the degree of electron transfer from the C-1 NMe_2 group to the trinitrocyclohexadienate ring in the various C-3 adducts can be evaluated by scrutiny of the ^{13}C NMR parameters (Table 1). The ensuing discussion focuses on the data shown in Scheme 3 together with resonance structures depicting this electron transfer.

Formation of **1** from its precursor DMP is accompanied by upfield shifts of the C-2, C-4, and C-6 carbons. This is in accord with previous observations[2] that in σ-complex formation negative charge from the nucleophile becomes delocalized onto nitro groups at the C(2), C(4), and C(6) positions with respect to the position of attachment of the nucleophile. However in the present case the oxygens of the C(2)-NO_2 group will be forced considerably out of plane of the benzene ring and hence less charge is delocalized onto this position. Next, one finds that the C-4 and C-6 carbons resonate at the same δ value whereas normally the position *para* to the attachment of the nucleophile (C-6 in this case) carries the most negative charge and resonates furthest upfield. The present observation is, once again, explicable as being due to lack of coplanarity of the C(6)-NO_2 group as a result of steric hindrance with the NMe_2 functionality.

However, clearly, the chemical shifts found in adduct **1** will reflect the superposition of both the increased charge density originating from nucleophilic addition and electron transfer from the NMe_2 moiety. For the sake of simplicity and as a first approximation, one could assume that because of the lack of coplanarity of C(2)-NO_2 the negative charge originating from the nucleophile resides largely on the C-4 and C-6 NO_2 groups (i.e., resonance structures **1a** and **1b**). Hence the upfield shift of C-2 by 11 ppm on going from DMP to adduct **1** could be considered as due to electron transfer from NMe_2, or "through conjugation", as denoted by the resonance structures **1c** and **1d**, bearing in mind our assumption as above and recalling the results of Sinha and Yates[23] on conjugation between NMe_2 and NO_2 groups.

The resonance structures **1e** and **1f** denote that on acidification of **1** protonation takes place at C-2. In discussing the rationale for C-2 protonation in this system, it is noteworthy that the C(4)- and C(6)-NO_2 groups form part of a conjugated system, as is apparent in considering the pairs **1a** ↔ **1b**, **1c** ↔ **1d**, **1e** ↔ **1f**. On the other hand the C(2)-NO_2 is isolated in that sense and can be considered as part of an extended enamine system with the NMe_2 moiety; this would account for the observed C(2)-protonation of **1**. As well, protonation at C-2 with the attendant conversion of the sp^2 center into an sp^3 carbon will result in appreciable relief of steric strain, as is evident on inspection of structures **1c** and **1d**.

With regard to the above discussion, it is interesting to note that reaction of TNB with enamines affords N,C-cyclo diadducts that are also characterized by a ring

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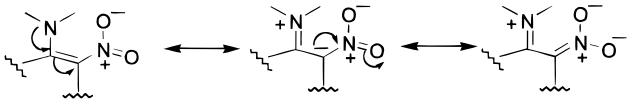
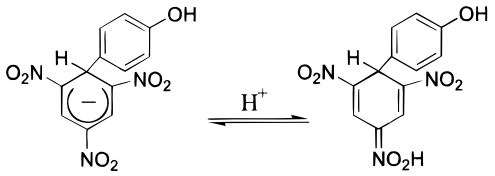


protonation at C-2.[24] However, in contrast to the present observation of carbon protonation, it was found in a previous study[25] that the phenoxide C-adduct of 1,3,5-trinitrobenzene **6** is protonated in aqueous H_2SO_4 or HCl on oxygen to give the nitronic acid derivative **9** for which a pK_a of −1.2 was found. This contrasting behavior can be understood on the basis that in **6** the nitro group is part of a conjugated system, whereas in **1** the C(2)-NO_2 is isolated as discussed above.

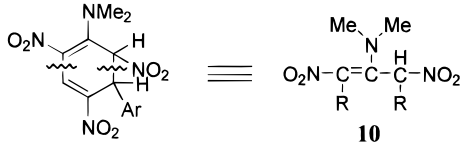


(2)

6 **9**

pK_a Relationships. For the present C-2 nitro tautomers **2** and **4**, a pK_a of ca. 6.2 was determined in aqueous solutions. Since **2** and **4** are carbon acids activated by an α-NO_2 group, comparison can be made to the nitroalkane family of acids. This class of carbon acids has been extensively studied, and interestingly, as the length of the alkyl chain increases, so does the acidity.[26] For example, nitromethane has a pK_a of 10.2 at 25 °C in water, nitroethane (pK_a = 8.60), and 2-nitropropane (pK_a = 7.74).

To compare the present system to the nitroalkane family of acids, it is informative to view the C-2 nitro tautomers as the straight chain derivative **10**, a structure which illustrates that the group attached to the acidic $CHRNO_2$ center is an alkene possessing the NMe_2 and NO_2 substituents. If these substituents are replaced by hydrogen atoms, one obtains 3-nitropropene (CH_2=$CHCH_2NO_2$) which has a pK_a of 5.22 in water at 25 °C.[27] Noting that the C-2 nitro tautomer **4** has a pK_a ca. 6.22, it follows that introduction of the NMe_2 and NO_2 substituents decreases the acidity by ca. 1 pK_a unit.



10

To assess the origin of this reduction in acidity for the tautomer **4** relative to 3-nitropropene, structural aspects of the conjugate acid/base pair in each deprotonation step may be considered. For 3-nitropropene, deprotonation leads to a conjugated, resonance stabilized nitronate anion, which would account for the greater acidity. However, in the present case, both the acid **4** and the base (*σ*-adduct) **3** are conjugated systems due to resonance forms between the C-1 NMe_2 group and the ring NO_2 groups (*vide supra*). In fact, inspection of the ^{13}C NMR parameters (Table 1) indicates a greater degree of charge transfer from the NMe_2 group to the trinitrocyclohexadienate ring in **4** compared to **3**. Thus, upon acidification of **3** the C-1 carbon resonance shifts downfield by ca. 3 ppm, while the NMe resonances are shifted downfield by ca. 1.8 ppm (subtraction of the NMe resonance of the *σ*-adduct **3** from the average of the two NMe resonances in the tautomer **4**, Table 1, **3** versus **4**). These chemical shift changes are consistent with an increase in charge transfer from the C-1 NMe_2 substituent upon conversion of the C-2 center from sp^2 to sp^3 and provide a rationale for the C-2 ring protonation of C-3 C-bonded aryloxide *σ*-adducts of DMP.

Experimental Section

Materials. All common solvents and reagents were purchased from commercial sources and used without further purification. Melting points were determined using a Thomas-Hoover melting point apparatus and are reported without correction. The NMR spectra of starting materials and products were recorded in DMSO-d_6; chemical shifts are given in parts per million (ppm) relative to the residual DMSO-d_5 H peak (*δ* 2.50 ppm) and coupling constants are reported in hertz (Hz).

N,*N*-Dimethylpicramide (DMP) was prepared by adding an excess of dimethylamine in ethanol to an ethanolic solution of picryl chloride (1.75 g, 7 mM) as previously reported.[8] Recrystallization from ethanol to constant melting point and subsequent drying in vacuo produced 1.44 g (80%) of DMP, mp 137−138 °C (lit. mp 138 °C (8)). ^1H NMR: *δ* 8.84 (2H, s) and 2.89 (6H, s, NMe_2). The potassium aryloxide salts were prepared according to the method of Kornblum and Laurie.[28] Potassium phenoxide (PhOK) was obtained as a colorless solid. ^1H NMR: 6.67 (m, 2H, H-*meta*), 6.03 (d, 2H, H-*ortho*) and 5.82 (1H, t, H-*para*). Potassium 2,6-di-*tert*-butylphenoxide (2,6-DTBPhOK) was a lime green solid. ^1H NMR: 6.58 (2H, d, *J* = 7.3, H-*meta*), 5.57 (1H, t, *J* = 7.3, H-*para*), and 1.32 (18H, s, *t*-Bu).

C-2 Nitro Tautomer 4. DMP (0.5 g, 2 mmol) was dissolved in 30 mL of DMSO, and to this stirred solution was added a DMSO solution of 2,6-DTBPhOK (0.42 g, 1.7 mmol). The resulting deep red mixture was stirred at room temperature for 30 min and then poured into a beaker containing 200 mL of 0.1 N HCl. The orange precipitate was collected, dried under vacuum, and recrystallized from ethyl acetate/petroleum ether to yield the C-2 nitro tautomer **4** (0.76 g, 95.5%), mp 200−201 °C dec. ^1H NMR: *δ* 8.54 (1H, s, H5), 7.05 (1H, s, O*H*), 6.97 (2H, s, H-*meta*), 6.59 (1H, d, *J* = 2.0, H2), 5.37 (1H, d, *J* = 2.0, H3), 3.30 (3H, br-s, NMe), 3.10 (3H, br-s, NMe), and 1.36 (18H, s, *t*-Bu). ^{13}C NMR: 154.3, 153.8, 140.1, 132.8, 129.9, 123.2, 122.1, 116.1, 83.1, 47.1, 43.2, 42.7, 34.6, and 30.1 ppm. Anal. Calcd for $C_{22}H_{30}N_4O_7$: C, 57.1; H, 6.5; N, 12.1. Found: C, 56.7; H, 6.3; N, 12.0.

NMR Experiments. NMR measurements were made with a Bruker AM-400 spectrometer operating at 400 MHz (^1H) and 100 MHz (^{13}C). The spectrometer was adjusted as previously reported.[6] ^{13}C NMR spectra were acquired using the *J*-modulated (JMOD) pulse sequence.[29] Wilmad pp-507 NMR tubes (5 mm) were used in all experiments. All stock solutions and NMR tubes were capped with rubber septa and swept out with N_2 prior to injection of the reactants.

pK_a Determination. The pH measurements were obtained at 25 °C on a Beckman F71 digital pH meter using standard glass electrodes. Calibration was done using commercial buffers (BDH, pH 4.00, 7.00 and 10.00, all ± 0.01). The following buffers were used for the given pH range: succinic acid·HCl (pH 5.00−6.30), KH_2PO_4/Na_2HPO_4 (6.40−7.60), and tris(hydroxymethyl)aminomethane (TRIS)·HCl (pH 7.80−8.80). Each buffer solution was prepared by mixing the

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appropriate quantity of reagent into a 100 mL volumetric flask and diluting the mixture to 100 mL with decarbonated water.[30] The pHs of these buffer solutions were checked after the spectral measurements and were found to vary by no more than ±0.01 pH unit. All spectra were acquired on a Cary 3 UV−visible spectrophotometer fitted with a thermostated cell compartment at 25 °C using a standard matched pair of 1 cm quartz cells. The sample and reference cells were filled with 3.00 mL of buffer solution, and to the sample cell was added 100 μL of the stock solution of **4** in methanol. The final composition of the solvent in the sample cell was kept constant at 3.2:96.8 methanol:water (v/v), and the final volume was 3.1 mL. UV−visible spectra were recorded by the overlay method in the wavelength range of 300−550 nm.

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