Regioselectivity in the Reaction of Ambident Phenoxide Ion and Methoxide and Hydroxide Ions with 2,4,6-Trinitroanisole. Kinetic and Thermodynamic Control[1a]

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Abstract: 2,4,6-Trinitroanisole (TNA, **1**), as the archetypal electron-deficient aromatic that possesses a leaving group, reacts with alkoxide ions, including methoxide, in media that contain appreciable amounts of dipolar aprotic solvents to yield a 1,3 anionic σ-adduct as the product of kinetic control; the 1,3 adduct gives way over time to the thermodynamically more stable 1,1 adduct. This behavior, in which an initial 1,3 adduct isomerizes to a 1,1 adduct, is now classified as TC-1,1 (thermodynamic control favoring the 1,1 adduct) and has generally been taken to be ubiquitous. The present studies challenge this view. The salient features of the reaction of TNA with the ambident (O- and C-)nucleophile phenoxide, as studied by 400-MHz NMR spectroscopy, include initial formation of a 1,1 O-adduct, which only gives way at long times to a 1,3 para-bonded C-adduct of phenoxide. TNA is also intercepted by methoxide and hydroxide ions formed in situ through solvolytic pathways, which adhere to the TC-1,1 behavior. No 1,3 O-adduct of phenoxide is formed either prior to the 1,1 species or later in the reaction sequence. This fact is emphasized by low-temperature (-40 °C) NMR studies made possible by the introduction of the novel CD_3CN-glyme-d_{10} solvent system, where the 1,1 adduct is *the only species observed* (3 min after initiation of reaction). These observations are in accord with a system that obeys KC-1,1 regioselectivity (kinetic control favoring the 1,1 adduct), in which the 1,1 phenoxide O-adduct is both kinetically and thermodynamically favored. Four limiting TC and KC cases are considered, and the factors that favor one pattern of regioselectivity as compared to another are discussed with regard to the following: F-strain associated with approach of the nucleophile to C-1; stabilization afforded adducts by charge-separated canonical forms; stabilization of a later transition state for PhO^- attack at C-1, due to relief of strain in that transition state; ion pairing; geminal electronegative disubstitution; and, in particular, steric and stereoelectronic effects in antiperiplanar rotameric forms of the 1,1 O-adducts.

Nucleophiles interact with polynitroaromatics to give rise potentially to a diverse number of products: π-complexes, radical anions, radicals, and anionic σ-complexes.[2,3] The study of the formation and decomposition of σ-adducts has constituted a rich area of research not only because such adducts serve as models for the intermediates (or transition states) in nucleophilic aromatic substitution[2-6] but because of the interesting structure–reactivity relationships that have emerged from these studies.[7] Part of our recent effort has been directed toward the understanding of the reactions of ambident nucleophiles with electron-deficient aromatic and heteroaromatic compounds.[8] Among the most studied of reactions is that of anionic nucleophiles, mainly alkoxides, with picryl ethers and related substrates.[9]

In his classic work on the reaction of methoxide ion with 2,4,6-trinitroanisole (TNA, **1**) in dimethyl sulfoxide–methanol (95% DMSO–5% MeOH) solvent, Servis found[9c,d] that reaction occurred initially at both the C-1 and C-3 positions. With time, the 1,3 TNA·OMe^- adduct gave way to the thermodynamically more stable 1,1 adduct. Since then, this behavior has been elaborated in numerous picryl ether–alkoxide systems in solvents containing appreciable quantities of DMSO.[8e,9c-i] Thus, formation of a kinetically preferred 1,3 adduct that isomerizes to a more stable 1,1 adduct has been considered the general pattern of regioselectivity in the reaction of nucleophiles with 1-X-2,4,6-trinitrobenzenes.[10]

A wide variety of factors, kinetic and thermodynamic, have been cited to account for the rearrangement of 1,3 to 1,1 picryl adducts.[9i,11-14] These and other factors, notably stereoelectronic

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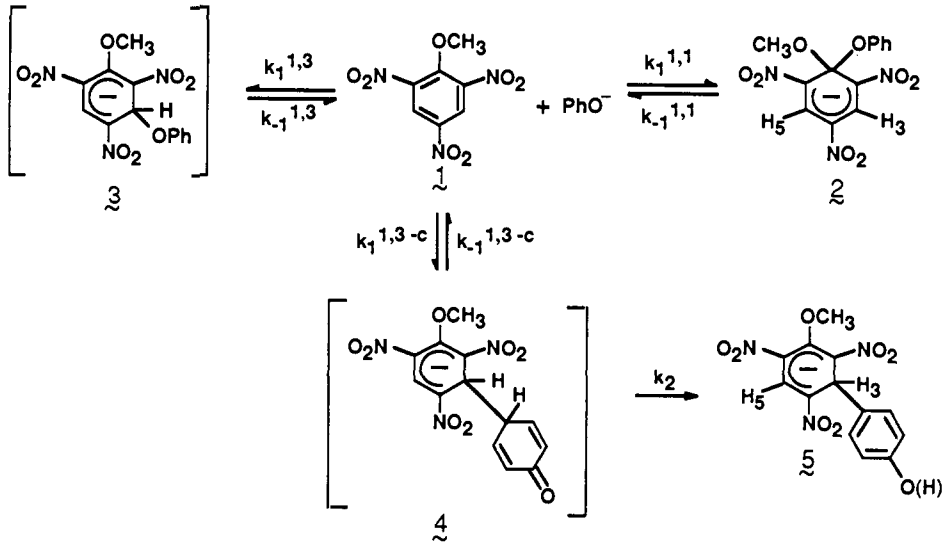
Scheme I



considerations, are evaluated in the Discussion section that follows.

We report herein the results of reaction of the ambident (C- and O-)nucleophile, phenoxide ion, with **1**. The salient feature of the reaction, whether in DMSO at ambient temperature or in the novel medium acetonitrile–dimethoxyethane (1:1 v/v, CD_3CN–glyme-d_{10}) at −40 °C, is that the 1,1 phenoxide oxygen-centered adduct is the product of kinetic control. While the carbon-centered phenoxide 1,3 adduct forms at later times, the 1,3 phenoxide O-complex is never observed. In contrast, methoxide, formed in situ or added separately to **1** in CD_3CN–glyme-d_{10} at low temperature, displays the standard kinetic regioselectivity for C-3 attack, followed by thermodynamic preference for 1,1 adduct formation. Hydroxide ion is also present under all conditions as a result of adventitious water in the solvents; the complexes and products that arise as a consequence will be described and their relationship in the overall reaction delineated.

Further insight is derived from the low-temperature experiments, experiments that are only now possible for these systems because of the introduction of the new solvent medium acetonitrile–glyme (CD_3CN–glyme-d_{10}), which solubilizes all of the reagents and products even at temperatures as low as −50 °C. It is these studies that permit us to draw the further conclusion that the 1,1 phenoxide O-adduct of **1** is the only phenoxide O-adduct formed in the TNA–PhO^- reaction system. It is in these studies that the 1,1 TNA·OPh^- adduct is observed as the first and only species to be formed at −40 °C. Careful monitoring of the low-temperature systems for extended periods of time also constitutes convincing evidence that the 1,1 TNA·OPh^- adduct is the thermodynamically favored O-adduct formed by PhO^- and **1**.

The results will be evaluated critically within the context of the four limiting cases that follow from the thermodynamic and kinetic constraints on these reactions.

Results

1. Reaction of 1 with Excess KOPh in DMSO. A 400-MHz ^1H NMR study yields the following observations (δ relative to tetramethylsilane or CD_2HSOCD_3 in ppm, J in hertz; see Table I). Addition of 1.4 equiv of KOPh in $(CD_3)_2SO$ to a $(CD_3)_2SO$ solution of **1** (9.099 (s, $H_{3,5}$), 4.051 (s, OCH_3)) results in the disappearance of the signals of the substrate and the simultaneous appearance of a set of singlets at 3.104 (3 H) and 8.599 (2 H), while a set of doublets is found at 8.373 (1 H, J = 1.80) and 6.142 (1 H, J = 1.80) with a related singlet a 3.772 (3 H). The former signals are consistent with resonances for the 1,1 TNA·OPh^- adduct, **2** (Scheme I), and the latter peaks are ascribed to the H_5 (8.373), H_3 (6.142), and C-1 OCH_3 (3.772) of a 1,3 TNA O-adduct. Although the 1,3 adduct might be presumed to be the 1,3 TNA·OPh^- adduct, **3**, on the basis of literature comparison to alkoxide adducts, we have recently found that the chemical shift of the sensitive sp^3-bound proton for the phenoxide O-adduct of 1,3,5-trinitrobenzene (TNB) is markedly different from those of

Table I. ^1H NMR Spectral Characteristics[a] of the Phenoxide Adducts of **1** in DMSO[b] and MeCN–Glyme (1:1)[c]

adduct	H_3	H_5	other
2[b]	8.599 (s)	8.599 (s)	3.104 (s, C-1 OCH_3)
2[c]	8.713 (s)	8.713 (s)	3.059 (s, C-1 OCH_3)
			6.640 (d, H_{ortho})
			6.914 (t, H_{para})
			7.120 (t, H_{meta})
5[b]	5.591 (d, J = 1.0)	8.389 (d, J = 1.0)	3.735 (s, C-1 OCH_3)
			6.985, 6.589[d] (A_2X_2 d,d, J = 8.53, C-3 *p*-HO-C_6H_4)
5[c,e]	5.629 (d, J = 1.30)	8.465 (d, J = 1.30)	3.807 (s, C-1 OCH_3)
			6.898, 6.490[d] (A_2X_2 d,d, J = 8.50, C-3 *p*-HO-C_6H_4)

[a] Chemical shifts are given in ppm measured at 400.1 MHz; coupling constants are in hertz. [b] $(CD_3)_2SO$ at ambient temperature. [c] CD_3CN–glyme-d_{10} (1:1 v/v) at −40 °C. [d] The hydroxyl peaks were not observed. [e] Determined at 25 °C.

Scheme II

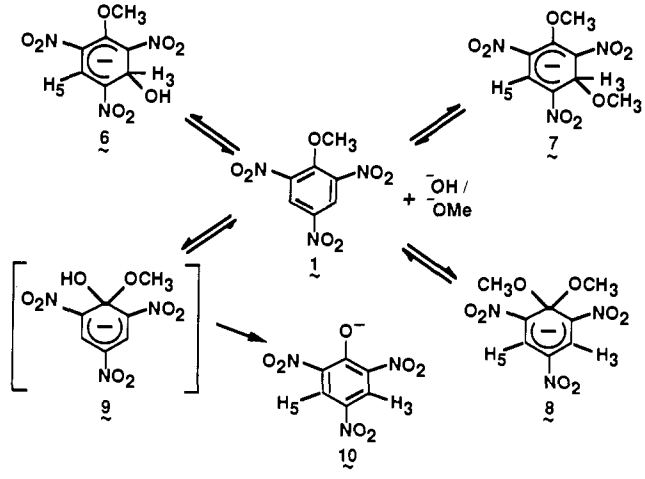


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Table II. ^{1}H NMR Spectral Characteristics[a] of the Hydroxide and Methoxide Adducts of **1** in DMSO[b] and MeCN–Glyme (1:1)[c]

adduct	H_3	H_5	other
6[b]	6.142 (d, J = 1.80)	8.373 (d, J = 1.80)	3.772 (s, C-1 OCH_3)[d]
6[e]	6.139 (br s)	8.374 (d, J = 1.90)	3.768 (s, C-1 OCH_3)
			5.519 (br s, O*H*)
6[c,f]	6.221 (d,d, J = 6.20, 1.90)	8.442 (d, J = 1.90)	3.834 (s, C-1 OCH_3)
			4.393 (d, J = 6.20, O*H*)
7[b]	6.124 (d, J = 1.93)	8.462 (d, J = 1.93)	3.815 (s, C-1 OCH_3)[g]
7[c]	6.116 (d, J = 1.90)	8.502 (d, J = 1.90)	3.824 (s, C-1 OCH_3)
			3.113 (s, C-3 OCH_3)
8[b]	8.612 (s)	8.612 (s)	3.012 (s, C-1 OCH_3's)
8[c,f]	8.773 (s)	8.773 (s)	3.055 (s, C-1 OCH_3's)

[a] Chemical shifts are given in ppm measured at 400.1 MHz; coupling constants are in hertz. [b] $(CD_3)_2SO$ at ambient temperature; species formed in situ (TNA–PhO^- system). [c] CD_3CN–glyme-d_{10} (1:1 v/v) at −40 °C. These are control experiments. [d] OH is not observed. [e] $(CD_3)_2SO$–H_2O 80 mol % DMSO, Me_4NOH. [f] 0 °C. [g] C-3 OCH_3 is obscured by peaks for MeOH, MeO^-, H_2O.

alkoxide and hydroxide analogs.[15] In fact, it appears general that the proton attached to the sp^3-hybridized carbon of aryloxide O-adducts is found 0.5–0.8 ppm downfield from the comparable proton of alkoxide or hydroxide adducts. Consequently, the peaks at 8.373, 6.142, and 3.772 are likely due to the 1,3 TNA·OH^- adduct, **6** (Scheme II). Further evidence for this assignment may be drawn from the control experiments, as given below.

Throughout the experiment the phenolic region (6.6–7.5) remains broad and unresolved, precluding observation of the attached aryloxyl protons of species such as **2**. Such broadness has been found in related systems[9c,d] and is indicative of the presence of paramagnetic species such as radicals, radical ions, etc., albeit in low concentration,[16] or of exchange processes. Note that the OH of the 1,3 TNA·OH^- adduct, **6**, is also unobserved, and so its state of ionization is uncertain.

Also in the downfield region, a singlet is found at 8.587 and is assigned to the ring protons of picrate anion ($PicO^-$, **10**) by comparison with an authentic sample. Further, signals ascribable to the 1,3 TNA·OMe^- adduct, **7**, on the basis of literature data[9e] are visible: 8.462 (1 H, d, J = 1.93, H_5), 6.124 (1 H, d, J = 1.93, H_3), and 3.815 (3 H, s, C-1 OCH_3). Acidification at this stage results in the disappearance of the resonances cited, except those due to MeOH, H_2O, and **10**, with concomitant restoration of the signals due to **1**. Acid lability is characteristic of O-adducts[8] and indicates that all of the peaks noted above are attributable to O-adducts formed by **1**.

Subsequent monitoring of the reaction reveals the following gradual changes over 7.5 h: within 15 min the signals for **2** have virtually disappeared while the resonances for **6** have increased in intensity. As the resonances of **7** decline, a new singlet at 8.612 and another at 3.012 appear and grow. These new peaks are assigned to the 1,1 TNA·OMe^- complex, **8**, and are in good agreement with literature values[9c-e] for the chemical shifts. Thus, the standard isomerization of **7** to **8** is confirmed. After 2 h, the first signs of another adduct are seen; its identification is only possible at longer times (vide infra; Table II).

Methanol and **10** observed in this study are the products of solvolytic processes involving **1** and adventitious water present in the medium (even after thorough treatment to remove water; see the Experimental Section) and are obtained via either an S_N2 type displacement or an S_NAr process or both.

$$1 + H_2O \rightarrow PicO^- + MeOH + H^+ \quad (1)$$

(15) Buncel, E.; Manderville, R. A. Unpublished work.
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MeOH so generated in the presence of excess PhO^- provides an equilibrium concentration of MeO^-

$$PhO^- + MeOH \rightleftharpoons PhOH + MeO^- \quad (2)$$

from which **7** and **8** are derived (eqs 2–4).

$$1 + MeO^- \rightleftharpoons 7 \quad (3)$$

$$1 + MeO^- \rightleftharpoons 8 \quad (4)$$

Similarly, equilibration between H_2O and PhO^- accounts for the appearance and growth of **6** with time.

Eventually the only complexes present are **8** and the previously unidentified adduct first observed at 2 h. The broad singlets at 8.389 and 5.591 are now assignable to the para-carbon-bonded 1,3 TNA·$ArOH^-$ adduct, **5**, on the basis[8,10] of the following: (i) the sp^3-bound proton at C-3 is upfield relative to the comparable peaks in the O-adducts, (ii) both peaks survive acidification, and (iii) an A_2X_2 pattern is displayed by the ring protons of the aryloxyl moiety of the complex (6.985, 6.589, 4 H, J = 8.53). The state of ionization of **5** is uncertain; no specific OH peak is found. By way of comparison, a C-adduct was previously characterized as the product of thermodynamic control in the reaction of TNB with PhO^- in MeOH–DMSO media at room temperature;[8a] the initial C-adduct in this system was also identified as the para-carbon-bonded complex. Recent evidence obtained from low-temperature NMR studies also shows that, where possible, C-adducts are the ultimate products of reaction of TNB with aryloxide anions.[15] It is noteworthy that neither the 1,3 ortho C-adduct nor the 1,1 TNA·$ArOH^-$ C-adducts (ortho or para) are observed in the present systems.

At this point (ca. 7.5 h), **6** has disappeared from the spectrum. The singlet due to **10** has also increased significantly in intensity. Clearly, **6** and **10** are linked, presumably by the rearrangement of **6** to a putative 1,1 TNA·OH^- adduct, **9**, whose rapid decomposition yields **10** and MeOH (Scheme II).

2. Reaction of 1 with Excess KOPh in MeCN–Glyme. To a solution of **1** in CD_3CN–glyme-d_{10} (1:1 v/v), cooled to −50 °C, was added a similarly cooled solution of KOPh in CD_3CN–glyme-d_{10}, such that the final concentration ratio of KOPh to substrate was 2:1. The initial spectrum taken at −40 °C shows the 1,1 TNA·OPh^- adduct, **2** (Scheme I), as the first species detected (Figure 1a). Even at this low temperature and with relatively rapid mixing (ca. 3 min before the first spectrum was recorded), peaks assignable to the 1,3 TNA·OPh^- adduct, **3**, *are not visible*, nor could such peaks—notably the upfield doublet expected for H_3 of **3**—be obscured by the peaks of the phenolic region, for at −40 °C exchange or radical formation is suppressed to the point where the phenolic region is well-resolved. Consequently, the full assignment of **2** in this novel, low-temperature solvent system is 8.713 (2 H, s, $H_{3,5}$), 7.120 (2 H, t, H_{meta}), 6.914 (1 H, t, H_{para}), 6.640 (2 H, d, H_{ortho}), and 3.059 (3 H, s, C-1 OCH_3). The spectrum also contains small peaks ascribable to **10** and **7** (Scheme II). Interestingly, the 1,3 TNA·$ArOH^-$ complex, **6**, is not initially observed (Figure 1a). On the other hand, peaks for excess PhO^- can be noted at 6.805 (2 H, t, H_{meta}), 6.403 (2 H, d, H_{ortho}), and 6.122 (1 H, t, H_{para}).

When the solution is brought rapidly to 25 °C, the phenolic region again broadens to the extent that the H_3 resonances of **6** and **7** are buried by the peaks due to PhO^-, PhOH, and the phenoxyl group of **2**. However, these adducts can be identified from their downfield H_5 peaks. $PicO^-$, **10**, increases in intensity, and the trinitrocyclohexadienate singlet ($H_{3,5}$) of the 1,1 TNA·OMe^- adduct, **8**, is now also present at 8.773. (The assignment of the peaks of the TNA·OMe^- adducts, **7** and **8**, in this medium is outlined below.) The para C-adduct, **5**, can also be seen, with peaks at 8.465 (1 H, d, J = 1.30, H_5), an A_2X_2 spin system at 6.898 (2 H, d, J = 8.50) and 6.490 (2 H, d, J = 8.50) due to the attached aryloxyl ring, 5.629 (1 H, d, J = 1.30, H_3), and 3.807 (3 H, s, C-1 OCH_3). As in the DMSO ambient temperature experiment, at longer times (>8 h) the only species remaining in the reaction is the C-adduct, **5**, along with **10** and **8**, the 1,1 TNA·OMe^- adduct (see Figure 1b). Acidification at this point causes the disappearance of the resonances ascribable

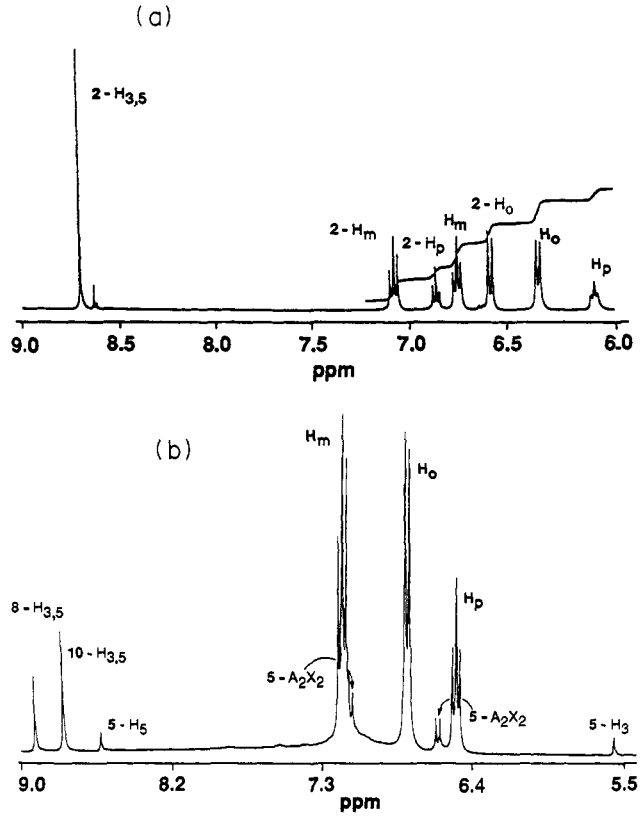


Figure 1. 400-MHz ^{1}H NMR spectrum in the 6.0–9.0 ppm region of the 2,4,6-trinitroanisole–phenoxide system (1:2) in CD_3CN–glyme-d_{10} taken after 3 min reaction time at –40 °C (a) Signals due to the O-bonded 1,1 TNA·OPh$^-$ adduct, **2**, and unreacted PhOK (H_m, H_o, and H_p) are apparent. The upfield region of the spectrum contains peaks due to the OCH_3 group of **2** (3.059) and solvent (glyme, 3.40 and 3.22; MeCN, 1.93). 400-MHz ^{1}H NMR spectrum in the 5.5–9.0 ppm region of TNA–PhOK (1:2) in CD_3CN–glyme-d_{10} following reaction at ambient temperature (12 h) (b). Present in the spectrum are signals due to the 1,3 para-carbon-bonded adduct, **5**, as well as the 1,1 TNA·OMe$^-$ adduct, **8**, picrate (**10**), and PhOH (H_m, H_o, and H_p). Located in the upfield portion of the spectrum are peaks due to the OCH_3 groups of **5** (3.807) and **8** (3.055) along with solvent.

to **8**, as expected for an alkoxide adduct, but those of **5** and **10** are unaffected.

A comment is warranted concerning the magnitude of chemical shifts in the two solvent systems. In general, resonances are recorded at positions further downfield in the CD_3CN–glyme-d_{10} system than in the $(CD_3)_2SO$ medium. For ring protons the shift difference amounts to 0.040–0.120 ppm; the effect on protons attached to sp^3-hybridized carbon centers is less pronounced (0.030–0.075 ppm). However, relationships between types of protons hold in this novel solvent system, as in $(CD_3)_2SO$. Hence, the H_3 proton of the carbon adduct, **5**, is found approximately 0.5 ppm upfield of the H_3 proton of the 1,3 TNA·OMe$^-$ adduct, **7**, regardless of solvent system.

When the TNA–PhO$^-$ system is observed at a constant –40 °C in CD_3CN–glyme-d_{10}, the sequence observed in the same solvent, as a function of temperature change, is preserved. Again, the 1,1 TNA·OPh$^-$ adduct, **2**, is essentially the only adduct formed initially. The phenolic region is well-resolved, and no peaks attributable to the 1,3 TNA·OPh$^-$ adduct, **3**, are seen either before or after the observation of the signals of **2**. Under these conditions, the 1,1 TNA·OPh$^-$ adduct, **2**, is the major species in the system even after 9 h.

It should be emphasized here that only through the use of this new medium could the 1,1 TNA·OPh$^-$ adduct be conclusively identified, for only in this medium is the phenolic region well-resolved.

3. Reaction of 1 with Equimolar KOMe in MeCN–Glyme. In order to aid in the assignment of the phenoxide system, particularly in the CD_3CN–glyme-d_{10} solvent system, several control studies were undertaken. Addition of equimolar potassium methoxide in methanol (1.025 M) to a CD_3CN–glyme-d_{10} solution of TNA, **1**, led to an initial spectrum at –40 °C that contained only a single species: the 1,3 TNA·OMe$^-$ adduct, **7**.

The spectrum is remarkably clean. It contains no peaks for picrate anion, **10**, or unreacted **1**. It is clear at this point that the 1,3 TNA·OMe$^-$ adduct, **7**, is unequivocally the product of kinetic control. The 1,1 adduct is not present. The spectrum consists of resonances at 8.502 (1 H, d, J = 1.90, H_5), 6.116 (1 H, d, J = 1.90, H_3), 3.824 (3 H, s, C-1 OCH_3), and 3.113 (3 H, s, C-3 OCH_3).

As the temperature is raised to 0 °C the 1,1 adduct, **8**, becomes the dominant species in the spectrum and then, at room temperature, the only adduct. Its spectrum contains peaks at 8.773 (2 H, s, $H_{3,5}$) and 3.055 (6 H, s, C-1 OCH_3's).

4. Reaction of 1 with Equimolar Me_4NOH in MeCN–Glyme. Addition of equimolar Me_4NOH (25 wt % in water) to a CD_3CN–glyme-d_{10} solution of **1** and subsequent monitoring at 0 °C shows peaks assignable to the 1,3 TNA·OH$^-$ adduct, **6**, at 8.442 (1 H, d, J = 1.90, H_5), 6.221 (1 H, d,d, J = 6.20, 1.90, H_3), 4.393 (1 H, d, J = 6.20, O*H*), and 3.834 (3 H, s, C-1 OCH_3).

Two points bear emphasis at this stage. First, the observation of coupling between the attached hydroxyl and the H_3 proton of **6** proves conclusively that the species is, in fact, the 1,3 TNA·OH$^-$ adduct. Equally clear is the fact that the rate of proton exchange from sites such as hydroxyl is relatively slow in the CD_3CN–glyme-d_{10} solvent system at 0 °C. The second major point is that the putative 1,1 TNA·OH$^-$ adduct, **9** (Scheme II), is not observed at any time, although peaks are noted for unreacted **1** and for **10**, PicO$^-$.

Increasing the temperature to 20 °C results in loss of the OH–H_3 coupling, although the 1,3 TNA·OH$^-$ adduct, **6**, is still visible in the spectrum and assignable by chemical shift data. Again, **9** is not present.

5. Reaction of 1 with Me_4NOH in DMSO. Reaction of **1** with OH$^-$ in $(CD_3)_2SO$ (equimolar Me_4NOH and **1**; 80 mol % $(CD_3)_2SO$) at room temperature leads to a complex spectrum that contains signals for unreacted **1**, as well as **10**, **7**, and **8**. These species can be readily assigned by comparison to literature data. Methanol is also present. Adducts and products, **7**, **8**, and **10**, likely arise from a sequence of reactions and equilibrations similar to those represented by eqs 1–4.

The 1,3 TNA·OH$^-$ adduct, **6**, can therefore be assigned partially through a process of elimination. Further, the resonances assignable to **6** are in reasonable agreement with expectations drawn from the relevant MeCN–glyme system. Thus, peaks are found at 8.374 (1 H, d, J = 1.90, H_5), 6.139 (1 H, broad s, H_3), 5.519 (1 H, broad s, O*H*), and 3.768 (3 H, s, C-1 OCH_3). Note that, consistent with the generalization concerning chemical shift in these solvents, the signals for the ring protons are upfield of the same signals in CD_3CN–glyme-d_{10}.

Importantly, the chemical shifts for **6** in this control experiment are in good agreement with the shifts for the species found in the TNA–PhO$^-$–DMSO system (vide supra) and previously assigned to **6**.

Discussion

1. Reaction Pathways. The range of nucleophiles present, carbon- and oxygen-centered, ambident and normal, and the range of behavior displayed by these nucleophiles in reaction with **1** provide an opportunity to draw a number of fundamental comparisons about regioselectivity in anionic σ-adduct formation. It is useful, then, to represent the diverse reaction pathways in two general schemes, even though the reactions illustrated by these schemes (Schemes I and II) occur simultaneously or within a limited time span.

If the focus is placed first on Scheme I, which displays the reaction of PhO$^-$ alone, it is clear that in $(CD_3)_2SO$ the first species observed from the reaction of PhO$^-$ with **1** is the 1,1 TNA·OPh$^-$ adduct, **2**. No 1,3 phenoxide complex, **3**, is detected in the beginning or later in the reaction. Consequently, a key question is

the following: Does **3** form prior to the first NMR observation and decompose too rapidly to detect?

First, the results of the low-temperature study in MeCN–glyme militate against this idea; the decomposition of **2** is slow, from ca. 15 min ($(CD_3)_2SO$, room temperature) to longer than 9 h (CD_3CN–glyme-d_{10}, −40 °C). With processes slowed to this extent it would seem likely that **3** could be detected in the first spectrum, if **3** forms at all. It is also germane to the discussion that, in their rapid stopped-flow UV–vis study of the reaction of **1** with PhO^-, Bernasconi and Muller[7e] also observed the 1,1 adduct, **2**, but did not detect the 1,3 analog, **3** (or the more slowly formed C-adduct, **5**). In the 50–90% DMSO–H_2O (v/v) media examined, the reaction proceeded to give the 1,3 TNA·OH^- adduct, **6**, instead and eventually yielded **10** (Scheme II). Hence, the 1,3 O-adduct, **3**, is not observed even with a fast kinetic technique. Reaction of PhO^- with **1** must lead to formation of **2** as the kinetically preferred complex. Since **3** is not observed later in any spectra, **2** is also the thermodynamically favored oxygen-centered phenoxide adduct.

The reactions of TNA with PhO^-, acting as an O-nucleophile, do not conform to the standard 1,3 to 1,1 isomerization pathway. The variance in behavior of the PhO^- system, detailed by Scheme I, is all the more striking because the "normal" regioselectivity is found in the same experimental systems for MeO^- (and, possibly, for OH^-, as will be discussed). Thus, in the low-temperature studies in MeCN–glyme, the 1,3 TNA·OMe^- adduct, **7** (Scheme II), forms concurrently with the 1,1 phenoxide O-adduct, **2**, although in significantly lower concentration. It would appear that **7** arises from solvolytic processes that generate MeO^-, OH^-, and methanol and involve adventitious water in the medium (eqs 1–4). In agreement with previous observations,[9c-e] **7** gives way to its 1,1 counterpart, **8**. At the same time, the 1,3 TNA·OH^- adduct, **6**, declines in favor of $PicO^-$, **10**, although quite slowly.

Both isomerization pathways (Scheme II) could be viewed as dissociative routes in which the kinetically preferred 1,3 adducts, **6** and **7**, decompose to **1** and the respective nucleophile. Reaction of the nucleophile at C-1, then, occurs to yield **8** in the case of **1** and MeO^- and to yield the putative 1,1 TNA·OH^- complex **9** in the case of **1** and OH^-. Rapid expulsion of MeOH from **9** would account for the inability to observe the 1,1 TNA·OH^- (or 1,1 TNA·O^-) adduct and is consistent both with the slow growth of **10** over time, notably in the DMSO system, and with a recent proposal of Bernasconi and co-workers concerning the decomposition of **9** to **10**.[17] It might be argued that MeOH and **10** arise directly from **1** and any of the available nucleophiles (PhO^-, OH^-, or MeO^-) via S_NAr displacement on the methoxy group of **1**. Alternatively, water itself may act as the nucleophile in attack at C-1 and subsequent S_NAr displacement.[18] It is important, then, to note that in the reaction of equimolar MeO^- with **1** in MeCN–glyme the initial spectrum did not contain peaks due to **9** or **10** or MeOH. The spectrum at −40 °C consisted solely of the 1,3 MeO^- adduct, **7**. We favor the pathway shown in Scheme II for formation of **10** via **9**.

While comparison of the three reactions (**1** with OH^-, MeO^-, and PhO^-) on a rigorous basis is hampered by the varying amounts of OH^- and MeO^- present (dependent as these concentrations must be on the amount of adventitious water),[19] a kinetic and thermodynamic ranking of the O-adducts can be proposed. Since **7**, and in some systems the 1,3 TNA·OH^- adduct, **6**, form along with the 1,1 TNA·OPh^- adduct, **2**, it follows that these three species

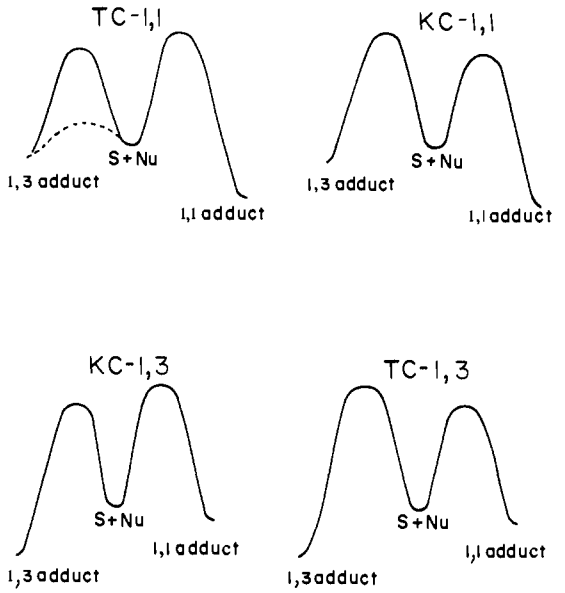


Figure 2. Qualitative free energy profiles showing the different patterns of behavior in terms of kinetic control (KC-1,1; KC-1,3) and thermodynamic control (TC-1,1; TC-1,3) in σ-complex formation between polynitroaromatic substrates and nucleophiles. The different classes of regioselectivity (TC-1,1, KC-1,3, etc.) are described in the text.

are the kinetically preferred O-adducts formed from **1**. Given the limited amount of water that is present,[19] observation of **6** and **7** also indicates that MeO^- and OH^- are significantly more reactive than PhO^- in both solvent systems studied. The thermodynamically favored O-adducts, then, are **8**, **9** (or **10**, in accord with Scheme II; vide supra), and **2**, respectively. Clearly, **2** is the product of both kinetic and thermodynamic control.

The regioselectivity shown by MeO^- in the formation of **7** and its subsequent rearrangement to **8**, whether as a parallel process in the reaction of **1** with PhO^- or as found in the control experiments, emphasizes that the processes involving **2** are not artifacts of the method of study or of the medium.

The final thermodynamic product in the PhO^- reaction is not an O-adduct, but the 1,3 para C-adduct, **5**; it is the result of the ambident reactivity of PhO^- displayed in Meisenheimer adduct formation in this and related reactions.[7,8]

The various isomerization pathways observed in, and inferred for, these systems will now be examined on a more general basis.

2. Classification of Behavior. Discussions of the factors that influence the regioselectivity observed in these processes have focused mainly on picryl ether–alkoxide interactions. The course of the reaction usually found is the initial formation of the 1,3 O-complex followed by appearance of the 1,1 O-adduct as the thermodynamic product, which eventually is the sole product.

The qualitative free energy profile for this sequence is given as TC-1,1 (thermodynamic control favoring the 1,1 adduct) in Figure 2. A quantitative profile has been determined for **7** and **8** in MeOH by Bernasconi[9i] and by Terrier[4d] in DMSO–MeOH. However, TC-1,1 (as shown in Figure 2) represents a generalized case and as such is qualitative. For clarity, energy differences in this and the other profiles are exaggerated.

In TC-1,1 the observed kinetic order corresponds to the condition $k_1^{1,3} > k_1^{1,1}$ (forward rate constants for formation of the 1,3 and 1,1 adducts, respectively), while the thermodynamic order, $K^{1,1} > K^{1,3}$, implies the condition $k_{-1}^{1,3} > k_{-1}^{1,1}$ for the breakdown of the respective complexes. Examples of this behavior include **1** with MeO^- and other picryl ether + RO^- systems, including those reactions that involve TNA analogs in which one or two nitro groups have been replaced by a variety of substituents such as SO_2CF_3, CN, Cl, or ring nitrogen.[9d-i,20] The reaction of alk-

(17) Bernasconi, C. F.; Fassberg, J.; Killiom, R. B., Jr.; Schuck, D. F.; Rappoport, Z. *J. Am. Chem. Soc.* **1991**, *113*, 4937.

(18) Castilho, P. C. M. F.; Crampton, M. R.; Yarwood, J. *J. Chem. Res. S* **1990**, 394.

(19) Every effort was made to minimize the amount of water present in the solvent. The method advocated by Burfield (Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966), namely, sequential treatment with 4A molecular sieves, was used in the drying of $(CD_3)_2SO$; this method is claimed to produce solvent that contains only 10 ppm of water. However, given the well-known hygroscopicity of DMSO, it is not surprising that varying and significantly higher amounts of water would be present in our systems, introduced in the process of preparing samples from the dry $(CD_3)_2SO$. On this basis the water content of the DMSO likely ranged from 10 ppm to 0.26 wt % (Burfield, D. R.; Smithers, R. H. *Ibid.*).

(20) (a) Terrier, F.; Morel, J. *J. Org. Chem.* **1976**, *41*, 3892. (b) Terrier, F.; Millot, F.; Schaal, R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1192. (c) Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010.

oxides[9j,21a] and sulfites[21b] with 2,4,6-trinitrobenzyl chloride similarly conforms to TC-1,1 behavior.

In view of the present results, it has become clear that the scope of classification should be broadened. These other possibilities, depicted in Figure 2 according to thermodynamic control (TC) or kinetic control (KC)[22] for the 1,1 and 1,3 adducts, are now discussed briefly.

The inverse of TC-1,1, which exhibits kinetic preference for the 1,1 complex and favors the 1,1 → 1,3 isomerization process, is labeled as TC-1,3. This reaction sequence corresponds to the following relationships: $k_1^{1,1} > k_1^{1,3}$, $K^{1,3} > K^{1,1}$, and consequently, $k_{-1}^{1,1} > k_{-1}^{1,3}$. Two examples can be found in the literature that demonstrate TC-1,3 behavior. Thus, in the reaction of CN^- with **1**, Norris observed both the 1,3 and 1,1 TNA·CN^- adducts by ^1H NMR spectroscopy.[23] Of the 70% of complexes formed at −30 °C, $^4/_5$ existed as the 1,3 species, while the 60% TNA complexed at −6.5 °C existed as the 1,3 adduct to the extent of $^{17}/_{20}$. With increased temperature both complexes decomposed to unidentified products, but the 1,3 adduct remained in the system after the 1,1 adduct had disappeared. The 1,3 complex is, therefore, the more stable of the two, and the 1,1 complex converts into its 1,3 isomer as required by the TC-1,3 classification. Similar behavior was reported by Biggi and Pietra for the reaction of EtSNa with picryl ethyl sulfide.[24] Recent work by Crampton and Stevens[25] agrees with the observed preference for C-1 attack by ethanethiolate and thioglycolate anions on picryl ethyl ether (2,4,6-trinitrophenetole) by NMR measurements, but offers an alternative explanation based on kinetic results in aqueous DMSO (vide infra).

KC-1,1 represents a situation in which the 1,1 complex is both kinetically and thermodynamically preferred over the 1,3 adduct. The prevailing kinetic conditions are $k_1^{1,1} > k_1^{1,3}$ and $k_{-1}^{1,1} < k_{-1}^{1,3}$, which gives rise to the relationship $K^{1,1} > K^{1,3}$. Importantly, examples can be found of systems that conform to the KC-1,1 behavior. Such systems include 2,4,6-trinitrobenzaldehyde–CN^-,[26a] TNA–N_3^-,[26b] and 2,4,6-trinitrobenzyl chloride–OH^-.[26] Interestingly, even when the C-1 position is occupied by a polymeric ether, as in the case of the picryl ether of poly(ethylene glycol), reaction with *n*-propylamine appears to follow the KC-1,1 pattern.[26d] Definitive conclusions in some of these systems would be premature, because an ambiguity arises from possible rate constants of widely different magnitudes. If in TC-1,1 behavior the kinetic conditions $k_1^{1,3} \gg k_1^{1,1}$ and $k_{-1}^{1,3} \gg k_{-1}^{1,1}$ both hold, as represented by the dotted lines in Figure 2 (TC-1,1), then it may not be possible to observe the 1,3 complex because of the time scale of the experiments employed. The results would give the illusion of KC-1,1 behavior. In this regard, Fyfe and co-workers[26e] in their study of the reaction of various ratios (1:2, 1:3, 1:4) of *n*-butylamine with **1** by a relatively rapid flow NMR method at −40 °C in DMSO–MeOH (1:1) only definitively identified the 1,1 TNA·$NHBu^-$ adduct, even though the initial spectrum was acquired within 0.44 s. Clearly, whether the NMR technique is rapid (0.44 s)[26e] or slow (ca. 3–10 min),[26a-d] discrimination between TC-1,1 and KC-1,1 would be difficult. A similar point can be made with regard to cases KC-1,3 and TC-1,3.[25]

The present NMR results, at both ambient and low temperature for ***1*** *reacting with* PhO^-*, can be satisfactorily described as KC-1,1 behavior alone.* KC-1,3 behavior[22] corresponds to both kinetic and thermodynamic preference for the 1,3 adduct over the 1,1 adduct, and the following relationships hold: $k_1^{1,3} > k_1^{1,1}$, $k_{-1}^{1,3} < k_{-1}^{1,1}$, and so $K^{1,3} > K^{1,1}$. We have found no clear examples of KC-1,3 reactivity in the literature. The acetonate anion, for instance, reacts with picryl phenyl ether or 2,4,6-trinitrophenetole in DMSO to yield only a 1,3 adduct,[9e] but under alkaline reaction conditions these adducts are formed irreversibly. The first kinetic condition for KC-1,3 is met, but the relative stability of the two adducts is uncertain.

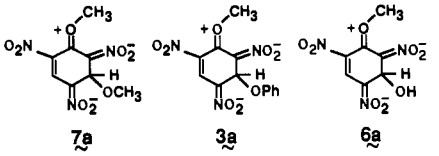
It should be stressed that while **1** reacts with MeO^- and other alkoxides in accordance with TC-1,1[9c-e] it apparently reacts with N_3^- in accordance with KC-1,1[26b] and with CN^- in accordance with TC-1,3.[26a] The results of the present study similarly highlight the full range of reactivity: PhO^- as an O-nucleophile reacts with **1** according to the KC-1,1 pattern, but with MeO^-, and likely with OH^-, according to the TC-1,1 pattern. It is striking that the seemingly small change in the nucleophile attendant with replacement of the alkoxide with phenoxide affects the kinetics and thermodynamics in a fundamental way that warrants further scrutiny.

The factors that account for the various patterns of regioselectivity will now be discussed qualitatively. This approach has been found useful in explaining the reactions of PhO^- with 2,4,6-trinitrophenyl[8b] and other related systems.[9f,11-14]

3. Factors That Determine the Regioselectivity in O-Nucleophile Reactions with 1. (a) Kinetic Factors. (i) **F-Strain.** Steric hindrance to approach of the nucleophile, F-strain, has been invoked to account for the kinetic preference of C-3 attack by RO^-.[11,27,28] PhO^- as a planar nucleophile may align itself so as to minimize the F-strain of C-1 attack. The difference between attack at C-1 versus C-3 would be reduced and the reaction would tend toward KC-1,1 or TC-1,3 regioselectivity. Similarly, one factor in the reaction of **1** with the linear ion, CN^-, is that CN^- can align itself to minimize F-strain.[22] This rationale seems incomplete in itself, however, since monotonic increases in the bulk of groups at C-1 in a series of 1-X-2,4,6-trinitrobenzenes do not result in a changeover in regioselectivity of ethoxide ion.[28]

Interestingly, the C-1 position of a picryl ether bears higher positive charge density than the C-3 position on the basis of ^{13}C NMR evidence[29,30] and theoretical calculations.[31,32] As such, the oxygen-centered nucleophiles, including PhO^- acting as an O-nucleophile, might be expected to prefer attack at C-1, while the softer nucleophiles, including PhO^- acting as a C-nucleophile, would preferentially attack the softer C-3 position.

(ii) **Charge-Separated Canonical Forms.** The argument here is that in the case of the transition state (TS) that leads to the 1,3 adduct there would be a contribution from a resonance structure that involves through-conjugation from the C-1 methoxy to the C-4 nitro group (e.g., **7a**), analogous to this type of charge separation in TNA itself. This interaction would not be possible in 1,1 adduct formation.[9f,i] The result: kinetic preference for



7a **3a** **6a**

1,3 adduct formation in the TNA–MeO^- system. This reasoning could not account for a decreased kinetic preference for 1,3 adduct formation in the phenoxide reaction system, since there is little

(21) (a) Brooke, D. N.; Crampton, M. R.; Corfield, C. G.; Golding, P.; Hayes, G. F. *J. Chem. Soc., Perkin Trans. 2* **1981**, 526. (b) Brooke, D. N.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1850.

(22) In accord with a suggestion from a referee, the cases labeled KC-1,1 and KC-1,3 could be designated product development control, where the more stable product is also formed fastest. For simplicity, KC-1,1 and KC-1,3 have been retained, focusing on the kinetic control in these cases.

(23) Norris, A. R. *Can. J. Chem.* **1969**, *47*, 2895.

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(25) Crampton, M. R.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1097.

(26) (a) Buncel, E.; Norris, A. R.; Proudlock, W. *Can. J. Chem.* **1968**, *46*, 2759. (b) Caveng, P.; Zollinger, H. *Helv. Chim. Acta* **1967**, *50*, 861. (c) Crampton, M. R.; Routledge, P. J.; Golding, P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 939. (d) Dust, J. M.; Harris, J. M. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 1875. (e) Fyfe, C. A.; Damji, S. W. H.; Koll, A. *J. Am. Chem. Soc.* **1979**, *101*, 951. (f) Clapp, L. B.; Lacey, H.; Beckwith, G. G.; Srivastava, R. M.; Muhammad, N. *J. Org. Chem.* **1968**, *33*, 4262.

(27) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.

(28) Cooney, A.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1973.

(29) Olah, G.; Mayr, H. *J. Org. Chem.* **1976**, *41*, 3448.

(30) Farnum, D. G. *Adv. Phys. Org. Chem.* **1975**, *11*, 123.

(31) Strauss, M. J.; Fleischman, S.; Buncel, E. *J. Mol. Struct. (THEOCHEM)* **1985**, *121*, 37.

(32) Nudelman, N. D.; MacCormack, P. *J. Chem. Soc., Perkin Trans. 2* **1987**, 327.

to differentiate structure **3a** from structures **6a** and **7a**.

Moreover, the argument considers only the stabilization imparted to the TS although, clearly, the 1,3 adducts themselves would also be stabilized. Hence, the generality of this factor is questionable.

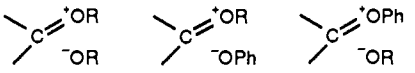
(iii) Transition-State Structure: The Effect of Strain. Although PhO^- has been shown to be a better nucleofuge than MeO^- by a factor of 4.5×10^6 in their reactions with **1** (i.e., breakdown of **8** in Scheme II versus **2** in Scheme I), PhO^- is also a better nucleophile toward **1** *in water* than MeO^- *in MeOH* by a factor of 2.9.[7e,33] In aprotic media, as in the present study, nucleophilic reactivity might be expected to mirror the Bronsted basicities of the nucleophiles.[34,35] In this regard, PhOH goes from a pK_a of 10.0 in H_2O to 18.0 in DMSO, while MeOH goes from a pK_a of 15.5 in H_2O to 29.0 in DMSO.[36] Thus, in going from a hydroxylic solvent to DMSO (and, presumably, MeCN–glyme), MeO^- becomes an even better nucleophile and an even worse nucleofuge than PhO^-. Significantly, H_2O, the conjugate acid of OH^-, has a pK_a of 32 in DMSO;[36] OH^- should be the most reactive nucleophile, in a Bronsted sense, in aprotic solvents. The observation that the 1,3 TNA·OH^- adduct, **6**, is formed concurrently with **2** in DMSO (although later in MeCN–glyme) is an indication of the high reactivity of OH^-, considering that the initial OH^- concentration is certainly less than that of PhO^-.[19]

On the basis of these considerations, the reactions of MeO^- with **1** should be generally faster ($> k_1^{1,1}$ *and* $k_1^{1,3}$) and involve an earlier TS than the reactions of PhO^- with the same substrate. There is, then, a kinetic role for the relief of internal steric strain at C-1 for the PhO^- adduct but not for the MeO^- adduct.[11,13,14] In the MeO^- adducts, the TS involved in formation of the adducts is sufficiently early that the relief of strain that accompanies formation of the 1,1 adduct (conversion of an sp^2 to an sp^3 center at C-1)[13,14] affects the overall thermodynamics but not the kinetics. In the PhO^- sequence, however, the relatively late TS means that the 1,1 adduct TS resembles the product (C-1 sp^3-hybridized). Strain is reduced in the TS, and hence the TS for formation of **2** would be stabilized relative to the TS for formation of **8**. The TS for formation of the 1,3 adducts (**3** and **7**) would involve the same strain found in the substrate[13,14] and in the adducts themselves. Thus, there would be a kinetic preference for C-1 over C-3 attack.

The thermodynamic effect of the same relief of strain also partially accounts for the stability of the 1,1 adducts relative to the 1,3 adducts.[11] In order for TC-1,1 behavior to be found, many 1,1 adducts must be more stable than their 1,3 counterparts. For the regioselectivity observed in the KC-1,1 pattern to exist, however, the only change required from the TC-1,1 case is that attack at C-1 becomes kinetically favorable.

(b) Thermodynamic Factors. (i) **Ion Pairing.** Ion pairing involving the counterion of the nucleophile with oxygens of the dialkoxy 1,1 complex (including those of the *o*-nitro groups) occurs in hydroxylic solvents or co-solvent media. This preferential ion pairing stabilizes the 1,1 complexes at the expense of the 1,3 isomers[12,28] and no doubt contributes to the observation of TC-1,1 regioselectivity in some systems. Elimination of ion pairing through the use of crown ethers has not been found to convert TC-1,1 behavior into any of the other patterns of reactivity cited.[12b] Anions are generally desolvated in DMSO, and cations, conversely, are well-solvated.[34] Under these aprotic conditions (extended also to the MeCN–glyme medium), it is reasonable to assume that minimum ion pairing of K^+ with the 1,1 complexes, **2** and **8**, would occur. Lack of ion pairing would favor the 1,3 complexes over their 1,1 counterparts. However, this effect alone is not sufficient to change the pattern; **7** still rearranges to **8** in our systems.

(ii) **Geminal Electronegative Disubstitution.** Geminal disubstitution has been advanced as a factor that stabilizes 1,1 complexes relative to the 1,3 analogs.[8b,9i,25,37] If the efficacy of this stabilization is diminished, then TC-1,1 thermodynamics could move in the direction of TC-1,3 and KC-1,3. The mode of stabilization afforded by geminal disubstitution may be a type of anionic hyperconjugation,[38] i.e., contribution of a canonical form such as **11** in the case of a geminal dialkoxy derivative, R′R″C-$(OR)_2$, and similarly for other electronegative groupings. To the extent that 1,1 dialkoxy adducts can be considered as structural analogs of acetals, this factor would stabilize a 1,1 adduct relative to a 1,3 adduct. For an unsymmetrical 1,1 alkoxy–phenoxy



11 **12** **13**

adduct, such as **2**, the canonical form **12** would be stabilizing, but form **13** could not make as large a contribution to the overall hybrid. In **12** the negative charge could be further delocalized into the aryl ring, but **13** places the positive charge adjacent to the electronegative aryl moiety.[39] The influence of these conflicting factors on the stabilization provided **2** by the structures **12** and **13** as compared to that afforded **8** by **11** is difficult to assess, although generally disubstitution by two different groups at the geminal position has been associated with reduced overall stabilization.[8b,23] We believe, however, that the relevance of contributing forms **12** and **13** is better discussed from a molecular orbital viewpoint, as follows.

(iii) Stereoelectronic and Steric Effects at the C-1 Position. The structural similarity between acetals and 1,1 dialkoxy Meisenheimer complexes such as **8** has been noted previously,[40,41] and the recent work of Kirby[41,42] is particularly pertinent in this context. Thus, a prototypal electronic symmetrical acetal such as a 2-alkoxytetrahydropyran prefers a conformation in which the exocyclic alkoxyl is axial. This is considered to result from the stabilizing donation of lone pair electron density from the ring oxygen to the σ^* orbital of the antiperiplanar C–OR bond simultaneous with n–σ^* donation to the acetal ring C–O bond from the exocyclic OR oxygen. This is a thermodynamic factor, and in the present systems, if the 1,1 adducts, **2** or **8**, can achieve such antiperiplanar (lone pair to OR) conformations, stabilization results. (These conformations place groups gauche or synclinal to one another.)

Clearly, it is essential for stereoelectronic stabilization that the adducts preferentially take up the required antiperiplanar conformation(s) (or that such a conformation be readily accessible by minimal rotation about a single bond). Inspection of the antiperiplanar conformations shows that one form places both substituents on the same side of a plane drawn through the CH_3–O–C–OR bonding axis (conformer SS for the same side), while the others place the groups on opposite sides (conformer OS for opposite sides and its enantiomer RS for reverse sides (not shown)) of this plane (COR = COPh for **2** and $COCH_3$ for **8**). Conformer SS involves considerable steric congestion[7e,40] between the methyl and R group, as well as lone pair–lone pair repul-

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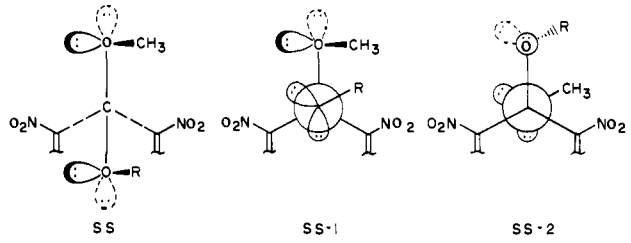
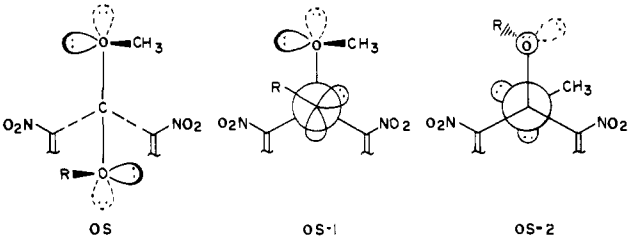
sion,[43,44] as can be readily seen in the two Newman projections: one is obtained from sighting down the RO–C bond, SS-1, and the other from sighting down the C–OCH_3 bond, SS-2. Conformer OS, which minimizes these gauche steric interactions, would likely be preferred, particularly by **2**. (See also ref 8b for a discussion of conformations of 1,1 O-bonded aryloxyl adducts.)



Rotamer OS may be similarly divided into component Newman projections. Antiperiplanar arrangements of these (OS-1, OS-2) are apparent; in OS, one nonbonding pair of electrons of one ether oxygen is antiperiplanar to the C–O bond of the other group (OS-1) and vice versa (OS-2).



In consideration of the accessibility of these rotamers to the various adducts, it is obvious that none of the 1,3 adducts can be approximated by acetals and none of the 1,3 adducts would be stabilized by the thermodynamic anomeric effect. However, further examination of models (Darling or Fieser) of the doubly antiperiplanar conformations (SS, RS, OS) shows that, with the possible exception of SS, **8** can readily take up the required conformations (or intermediate rotameric forms that would still provide some stabilization) and likely only **8** partakes of full stereoelectronic stabilization. This is not the case with **2**. Steric and lone pair–aryl π-cloud repulsion make it difficult for **2** to be accommodated by any of the doubly antiperiplanar structures.

It seems likely that forms that permit stereoelectronic stabilization through a single n–σ^* interaction would be significantly populated along the rotameric continuum, although inspection suggests that only the OS form of the doubly antiperiplanar conformations would be populated. If this is the case, then even a single n–σ^* interaction (in combination with other thermodynamic factors) appears to be sufficient to stabilize a 1,1 adduct, relative to its 1,3 analog.[45]

It is important to recognize that changes in relative stability between 1,1 and 1,3 adducts only require a change in stability of the 1,1 species. With the single exception of the stabilization afforded 1,3 adducts by charge-separated resonance structures (cf. 2a (ii) above), the only factors that pertain to the stability of either of the types of adducts involve the 1,1 adduct alone.

4. O- versus C-Attack of PhO^- on 1. The eventual stable product of reaction of **1** with PhO^- is a para-carbon-centered complex, **5**. In this context, the O-adduct, **2**, can be viewed as the kinetically preferred phenoxide adduct, while the C-centered adduct, **5**, is the ultimate product of thermodynamic control. The partition between a kinetically favored O-adduct and a thermodynamically preferred C-adduct is in accord with previous results in the TNB–PhO^- system at room temperature where no O-adduct is spectrally observable and where only the para- and ortho-bonded C-adducts are spectrally observable.[8a,d,46] The result also agrees with our recent low-temperature NMR studies in which the TNB·OPh^- O-adduct was observed, unequivocally, for the first time. As the temperature was raised, the phenoxide O-adduct gave way to the carbon-bonded species.[15]

O-adduct formation occurs via a single step, whereas C-adduct formation plausibly involves two steps. In the first step, a quinoidal complex, **4** (Scheme I), is formed. This process would be expected to be slow compared to O-adduct formation since it requires the disruption of the aromaticity of the phenoxyl ring. Recently, Crampton and co-workers determined the intrinsic reactivity (in the Marcus sense[47]) of several carbanions and methoxide in their attack at unsubstituted ring positions (C-3) of 2,4,6-trinitrotoluene.[48] In this study, it was found that highly delocalized ions such as those derived from nitroalkanes were inherently less reactive than methoxide by approximately 4 orders of magnitude in intrinsic rate constant (k_0). Solvent and structural reorganization were invoked as the reasons for the relatively low rate constants for attack by nitroalkyl carbanions.[48] Similar structural reorganization would be expected to accompany the reaction of PhO^- as a carbon nucleophile with **1**. On the other hand, the rearomatization step that follows (Scheme I) is rapid because aromaticity is restored. Note that the quinoidal intermediate, **4**, has not been detected in this reaction nor have related intermediates been observed in comparable reactions.[7,8,46]

In essence, two pathways are available for decomposition of the quinoidal intermediate, **4**. If $k_1^{1,3\text{-C}}$ (the forward rate constant for formation of **4**) is the rate-determining coefficient, then the quinoidal intermediate, once formed, may either decompose again to starting material or proceed to the 1,3 C-adduct, **5** (Scheme I). The rate constant for formation of **5** (k_2) represents rearomatization for the attached phenoxyl ring and might be expected to be fast on those grounds alone. However, decomposition of **4** back to TNA and PhO^- ($k_{-1}^{1,3\text{-C}}$) also leads to rearomatization. The salient point is that rearomatization and concomitant formation of **5** are presumably a base-catalyzed process, while decomposition (**4** → **1** + PhO^-) is unimolecular. In an alkaline reaction system, the k_2 forward rearomatization should be the favored process.[49] Thus, k_2 is larger than $k_{-1}^{1,3\text{-C}}$, and $k_1^{1,3\text{-C}}$, the constant for formation of **4**, is clearly the rate-determining coefficient in the sequence of formation of the C-centered adduct, **5**.

Comparison with the other forward rate coefficients for formation of the phenoxide O-complex would give the order $k_1^{1,1}$(**2**) > $k_1^{1,3\text{-C}}$(**5**). While it is difficult to place the other O-adducts (**6**–**9**) on the list, it seems likely that all of the forward rate constants for formation of the O-adducts are greater than $k_1^{1,3\text{-C}}$ for the

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(44) In the diagrams shown (SS and OS), the lone pairs are shown as sp^3 hybrids with the minor lobes omitted for clarity. More accurately, lone pairs of π- and σ-symmetry, n_π and n_σ, respectively, should be used since these are of different energies. However, for our purposes, the sp^3 representation will yield a qualitatively similar result. See also ref 43, pp 135–136.

(45) An alternative explanation has been re-introduced for the *decomposition* of acetals, namely the principle of least nuclear motion. Since the discussion is restricted to the thermodynamic stability of the 1,1 adducts and not the pathways for decomposition of these adducts, the thermodynamic anomeric effect is not at odds with the principle of least nuclear motion. See: Sinnot, M. L. The Principle of Least Nuclear Motion and the Theory of Stereoelectronic Control. *Adv. Phys. Org. Chem.* **1988**, *24*, 114.

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(49) Three cases can be evisaged: (a) the quinoidal adduct is more stable than the starting material and is of comparable stability to **5**; (b) the quinoidal adduct, **4**, is less stable than either starting material, **1** and PhO^-, or **5**, and k_2 is much larger than the reverse rate constant for decomposition of **4** back to **1** and PhO^-, $k_{-1}^{1,3\text{-C}}$; and (c) **4** is less stable than **1**, PhO^-, and **5**, but k_2 and $k_{-1}^{1,3\text{-C}}$ are comparable in magnitude. Case a is highly improbable; **4** is not an aromatic compound, while **1** and PhO^- are and **5** contains an aromatic moiety. Case b has been explored in the text. Case c results in a partitioning of **4** between reversion to starting material and forward rearomatization to **5**. The position of this partitioning process will depend upon how close $k_{-1}^{1,3\text{-C}}$ and k_2 are in size and on the relative stability of **1** and PhO^- as compared to **5**.

reasons cited. Regardless, the forward rearomatization step, k_2, is effectively irreversible and, consequently, confers superior thermodynamic stability on the C-centered phenoxide complex, **5**.

On the basis of the present results for the TNA–PhO^- systems, it is reasonable to anticipate that an O-bonded adduct would be detected in the TNB–PhO^- system, as well as the C-adduct(s), even in DMSO solvent at room temperature.[46,15] On the other hand, real differences separate the two systems. It is germane to the discussion to note, then, that the equilibrium constant for formation of the 1,1 TNA·OMe^- adduct is greater than the comparable constant for formation of the TNB·OMe^- adduct.[4d] A similar difference in stability would favor formation of the O-adduct in the TNA–PhO^- system as compared to the TNB–PhO^- system.

The fact that only a 1,3 C-bonded PhO^- adduct is obtained, rather than a 1,1 adduct, is in accord with a more favorable steric approach at C-3 as compared to C-1 for PhO^- attacking as a C-nucleophile. Such steric hindrance at C-1 is either diminished for PhO^- acting as an O-nucleophile or outweighed by other favorable kinetic factors (vide supra). In the case of 2,4,6-trinitrobiphenyl reacting with PhO^-, we also observed only the 1,3 C-bonded adduct.[7b] In conjunction with steric considerations it should be reemphasized that C-3 is the softer center of the substrate (as compared to C-1) and PhO^- is relatively soft as a C-nucleophile.

Conclusions

The results of these studies on the course of the reactions of **1** with the ambident nucleophile, PhO^-, and the normal nucleophiles, MeO^- and OH^-, permit us to draw the following conclusions.

1. The 1,1 phenoxide O-adduct, 1,1 TNA·OPh^-, is kinetically favored and is first observed in the NMR spectrum at ambient temperature in DMSO and even more clearly at −40 °C in MeCN–glyme. The 1,3 O-adduct in the TNA–PhO^- system is not observed.

2. The final phenoxide product in the TNA–PhO^- system is the para 1,3 C-adduct, **5**. The irreversibility of formation of **5** confers upon it superior thermodynamic stability; **5** is the ultimate product of thermodynamic control.

3. For the phenoxide O-adducts, **2**, the 1,1 O-adduct, is both kinetically and thermodynamically preferred. This regioselectivity is classified as KC-1,1.[22]

4. Although the proportions differ with the differing media and the amount of adventitious water in the media,[19] the 1,3 TNA·OH^- complex, **6**, and the 1,3 TNA·OMe^- adduct, **7**, are formed simultaneously with the 1,1 phenoxide O-adduct, **2**. In the case of the latter, it rearranges to the 1,1 TNA·OMe^- adduct, **8**, whereas the former decomposes to picrate anion, $PicO^-$. The pathway for rearrangement of the 1,3 TNA·OH^- adduct to $PicO^-$, **10**, invokes an intermediate 1,1 TNA·OH^- adduct that yields **10** via expulsion of methanol.

5. For the methoxide adducts, **7** is kinetically favored, but **8** is the product of thermodynamic control. This regioselectivity is classified as TC-1,1. For the hydroxide adducts, **6** is the product of kinetic control, but **10** is the ultimate product. On the plausible assumption that the 1,1 adduct, **9**, is intermediate between **6** and **10**, the 1,1 TNA·OH^- adduct is the thermodynamically favored hydroxide *adduct*. This regioselectivity is, then, also classified as TC-1,1.

6. KC-1,1 behavior[22] in the TNA–PhO^- system arises from an increase in $k_1^{1,1}$ for the formation of **2** relative to $k_1^{1,3}$ for the formation of **3**. While $k_{-1}^{1,1}$ may increase as a result of decreased anomeric stabilization of the 1,1 adduct, the increase in $k_1^{1,1}$ must more than counter any increase in $k_{-1}^{1,1}$, so that overall $K^{1,1}$ remains larger than $K^{1,3}$. The increase in $k_1^{1,1}$ for **2** (as compared to **8**) is a function of a combination of factors: reduced F-strain at C-1 (for PhO^- as compared to MeO^-) and relief of steric strain in the relatively late TS for formation of **2** (where hybridization at C-1 has progressed substantially toward sp^3). The magnitude of $k_{-1}^{1,1}$ for **8**, the 1,1 TNA·OMe^- adduct, is smaller than the same rate coefficient for **2**, because **8** can partake of full stereoelectronic stabilization, whereas **2** cannot.

Experimental Section

Materials and Procedures. Potassium phenoxide was prepared in an N_2-filled drybox from recrystallized PhOH and standard KOMe–MeOH; excess MeOH was evaporated in a stream of N_2 and the solid KOPh was dried in vacuo (<1 Torr), mp > 220 °C (lit. mp 285–289 °C[50]). $(CD_3)_2SO$, CD_3CN, and glyme-d_{10} (MSD) were dried by sequential treatment with 4A molecular sieves.[19] 1,4-Dibromobenzene (DBB; Eastman) was recrystallized twice from EtOH and dried in vacuo. Trifluoroacetic acid (TFA; Aldrich) was used without further purification. Picryl chloride was prepared either by nitration of 2,4-dinitrochlorobenzene (Eastman), according to the method of Frankland and Garner,[51] or by reaction of pyridinium picrate with $POCl_3$,[52] mp 83 °C (lit. mp 83 °C[51]). 2,4,6-Trinitroanisole (TNA, **1**) was prepared by literature methods.[53] Melting points were measured on a Thomas-Hoover capillary apparatus and were not corrected.

NMR Experiments. NMR experiments were recorded on a Bruker AM-400 MHz spectrometer equipped with a standard $^1H/^{13}C$ probe. Standard Wilmad PP-507 NMR tubes were used. In all of the NMR experiments the NMR tubes were swept out with N_2 prior to addition of reagents. The reagent solutions were prepared under N_2.

(a) A Representative Room-Temperature Experiment in DMSO. A solution of the substrate in $(CD_3)_2SO$ (ca. 0.133 M in 1 mL) was prepared. CD_2HSOCD_3 present in the solvent served as the chemical shift reference (2.500 ppm relative to TMS), and DBB functioned as the internal integration standard. An initial sample was prepared by injection of the substrate solution (**1**, 75 μL), DBB stock solution (5 μL of a 0.445 M solution), and $(CD_3)_2SO$ (400 μL) into an NMR tube. This solution was scanned first to ascertain the purity of the reagents. Injection of the relevant quantity of KOPh (14 μL for 1.4 equiv) initiated the reaction. Spectra were recorded at various intervals, generally as rapidly as possible (within 2.5 min) at the start of the reaction and then at progressively longer intervals as the reaction proceeded. After the final spectrum had been acquired and the system did not appear to have changed from the penultimate to the final spectrum, TFA (5 μL) was injected into the tube and the spectrum recorded again. All spectra were plotted (10.5–0 ppm), the peaks were integrated, and the chemical shifts of all pertinent peaks were obtained from the computer printout. The spectrometer was routinely adjusted as follows: spin rate = 25 rps; repetition delay = 2.0 s; acquisition time = 2.982 s; pulse width = 5 μs (with a pulse angle of 45°); sweep width = 5500 Hz; 32000 data points; temperature = ambient (21 ± 2 °C). Early in the experiment, 16 transients per FID were collected, but later 32 or more transients were acquired. These conditions sufficed to obtain the spectra reported herein (see Figure 1). Chemical shifts and coupling constants are reported to one figure less than the computer printout.

In a separate experiment, 1.4 equiv of KOPh was added to the NMR tube containing **1** in solution. After acquisition of an initial spectrum, TFA (5 μL) was added to the tube, and the spectrum was again recorded.

(b) Low-Temperature NMR Experiments in MeCN–Glyme (1:1). Typically the excess (2:1) KOPh was dissolved in a 1:1 (v/v) mixture of CD_3CN and glyme-d_{10}. This solution was injected into an N_2-swept NMR tube, and the solution was frozen by immersion of the tube in liquid N_2. To the frozen solution was injected the substrate, **1**, in the solvent. The resulting mixture was placed in a dry ice–acetone bath at −50 °C. The contents of the tube were allowed to mix and the tube was again immersed in liquid N_2. The sample was transferred to the spectrometer probe (−40 °C), and spectra were recorded at various intervals, a standard sequence being 3, 5, 7, and 9 min and then as warranted by the observed changes. At the same time, the temperature of the NMR probe was gradually raised.

In separate experiments, the spectrum was recorded rapidly (within 2.5 min) at −40 °C, heated to 0 °C, and then returned to −40 °C to quench any higher temperature reaction. The spectra recorded are consistent with those obtained by the gradual warming sequence and those obtained by leaving the sample at a constant −40 °C for long periods of time (>15 h).

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Mechanistic Studies on the Base-Promoted Addition of Lithiopinacolonate to Several Aromatic Carbonyl Compounds in Nonhydroxylic Solvents†

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Abstract: An investigation of the reaction of lithium enolates with carbonyl compounds is continued by determining kinetic data for the aldol reaction of lithiopinacolonate with *o*- and *p*-methylbenzaldehyde in methylcyclohexane-d_{14} at −80 °C using rapid injection proton NMR spectroscopy. The data were fit to a second-order reaction model with half-lives of 43.2 and 12.7 s, respectively. The NMR spectra showed no evidence of free radicals participating in the CIDNP phenomenon. The question of electron transfer as a feasible mechanism was tested using Eberson's criterion of estimating the barrier to single electron transfer (SET) from the free energy of single electron transfer using the redox potentials of the reactants and Marcus theory. These values were obtained using cyclic voltammetry and second-harmonic ac voltammetry in tetrahydrofuran and acetonitrile at room temperature. In comparison to the observed free energy of activation, calculated from the observed rate at −80 °C, the electrochemical free energy of single electron transfer is sufficiently endergonic to eliminate the single electron transfer pathway according to this criterion. The same type of analysis was utilized for both the aldol reaction of lithiopinacolonate with benzophenone and its Claisen condensation with ethyl 4-nitrobenzoate in THF at room temperature. By this criterion, single electron transfer is also not a feasible process for either of these reactions. Three cyclizable probes were utilized to test further for a SET pathway in the aldol reactions and the Claisen condensation, namely, 7-iodo- and 7-bromo-2-methoxy-2-heptenenitrile and 8-iodo-3-methyl-3-octene. No cyclized products were found in any of the reactions tested. However, as expected, cyclized products were produced from reaction of the probes with tributyltin hydride and AIBN. Bulk electrolysis of the cyclizable probes leads to a complex mixture of products including the expected cyclized ones. None of the (admittedly questionable) criteria applied here to these reactions of lithiopinacolonate with these carbonyl electrophiles gave diagnostic evidence for an electron-transfer mechanism instead of the familiar nucleophilic addition. These results say nothing about the actual (free or aggregated) state of the lithium enolate in the transition structure.

Introduction

The addition of anionic reagents to carbonyl groups ranks in a leading position among the most useful reactions in chemistry. In recent years the power and adaptability of these reactions has been increased enormously by the use of lithium reagents in nonpolar media at low temperatures. Thanks to structural studies in a number of laboratories,[1-5] it is now established beyond doubt that most organolithiums exist in solution under synthetic conditions as clearly defined aggregates. A wide range of complex structures such as ion pairs, triple ions, dimers, tetramers, hexamers, octamers, and mixed aggregates of various types have been authenticated in crystal structures[2a-d,6-10] and in some cases related directly to those in solution.[2a,4b,f,5,6b,9,10] Several studies from this laboratory[5b-d] have dissected the thermochemistry of carefully chosen aldol reactions and related their thermodynamics to the structure changes. However, at this point, little definitive evidence is available about the mechanisms of aldol type reactions under modern synthetic conditions.

The traditional mechanisms proposed for such reactions[11-20] have involved the direct addition of the nucleophilic anion to the carbonyl electrophile usually through a six-membered chair transition state involving the metal cation as an organizing component of the ring. The state of aggregation, if any, of the organoalkali in the transition state is a widely recognized additional

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