# Intermediates in Nucleophilic Aromatic Substitution. 17.[1] Kinetics of Spiro Meisenheimer Complexes. Effect of Ring Size

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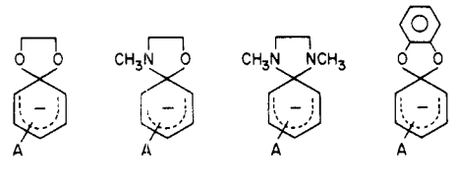
In the presence of base, 1-(3-hydroxypropoxy)-2,4,6-trinitrobenzene and 1-(3-hydroxypropoxy)-2,4-dinitrobenzene form the respective spiro Meisenheimer complexes with six-membered dioxane rings. On the other hand, 1-(4-hydroxybutoxy)-2,4,6-trinitrobenzene does not form a spiro complex but adds $OH^-$ to the 3 position of the aromatic ring, whereas in the case of 1-(4-hydroxybutoxy)-2,4-dinitrobenzene spiro complex formation and $OH^-$ attack on the aromatic ring appear to occur concurrently. Kinetic and equilibrium data on these reactions are reported. Spiro complex stability strongly decreases with increasing size of the spiro ring; this decrease is mainly due to a decrease in the rate of ring formation rather than ring opening, suggesting a complex-like transition state. The decrease in spiro complex stability with ring size is most pronounced with the 2,4,6-trinitrobenzene derivatives, least with the 2,4-dinitrobenzene derivatives, and intermediate with the 2,4-dinitronaphthalene derivatives known from the literature. This suggests that steric effects are important; in this comparison the changes from one system to another are mainly reflected in changes of the rate of ring opening rather than ring formation, suggesting a reactant-like transition state. A possible interpretation of this contradiction is that C–O bond formation and the turning of the *o*-nitro group(s) out of the plane of the aromatic ring have progressed to different degrees in the transition state. The question as to why spiro complex ring opening is much faster than methoxide ion departure from 1,1-dimethoxy Meisenheimer complexes is discussed. There are probably three factors which contribute; they are (a) difference in the basicity of the respective leaving groups, (b) relief of strain in the spiro complex, and (c) p–$\pi$ overlap of the lone pairs of the nonleaving oxygen with the C–O bond being broken. Hydronium ion catalyzed spiro complex ring opening, on the other hand, proceeds at about the same rate as hydronium ion catalyzed methoxide ion in departure from 1,1-dimethoxy Meisenheimer complexes. Possible reasons are discussed.

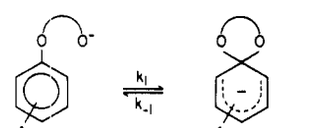
In our attempts to find model reactions which mimic C–O and C–N bond-forming and -breaking processes in $S_NAr$ reactions we have studied the kinetics of the equilibrium formation of a number of spiro Meisenheimer complexes of the type **1–4**;[1,2] A represents activating substituents. In order to



**1** 2d **2** 1,2c **3** 2b,2c **4** 2a

use these model reactions for the prediction of reactivities in *inter*molecular reactions, the intrinsic reactivity differences between inter- and intramolecular Meisenheimer complex forming reactions need to be known and understood.

It has commonly been observed that for nucleophiles of similar basicity the *intra*molecular addition is several orders of magnitude faster than *inter*molecular addition ($k_1 \gg k_2$, eq 1 and 2) and that the equilibrium constant for spiro com-



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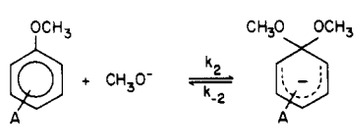

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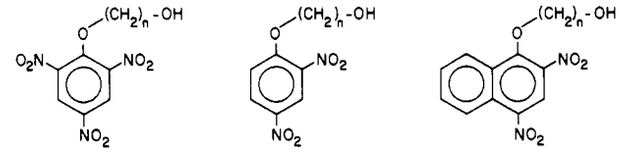
plex formation is several orders of magnitude higher than that for the intermolecular process ($K_1 \gg K_2$).[2,3] For example, for the spiro complex derived from 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene (**5a**) $k_1 \approx 4.8 \times 10^6\ s^{-1}$ [4] and $K_1 \approx 5.4 \times 10^7$ [4] in water, whereas for the formation of 1,1-dimethoxy-2,4,6-trinitrocyclohexadienate $k_2 = 17.3\ M^{-1}\ s^{-1}$ [5] and $K_2 = 1.7 \times 10^4\ M^{-1}$ [5] in methanol.[6] This greater facilitation of intramolecular reactions is consistent with general principles.[8,9]

Less well understood and perhaps contrary to expectation, ring opening of the (more stable) spiro complexes is considerably *faster* than methoxide ion departure from comparable complexes ($k_{-1} \gg k_{-2}$, typically by a factor of ~100 or more).[2,3] Since these observations referred to complexes with five-membered spiro rings of the type **1–4**, the first attempt to rationalize them was to invoke relief of steric strain in the five-membered ring.[3a] It appeared that a study of the effect of ring size on $k_1$ and $k_{-1}$ might shed more light on this problem. Thus we set out to investigate spiro complex formation from the parent compounds **5b, 5c, 6b**, and **6c** and to compare them with **5a**[3a] and **6a**,[2e] respectively. When our study was already underway we learned that Crampton and Willison[3b] were investigating **7b** and **7c**, with a similar purpose

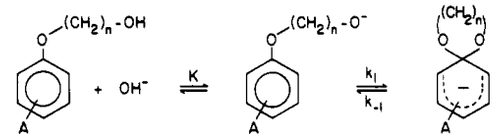


**5a** (n=2) **6a** (n=2) **7a** (n=2)
**5b** (n=3) **6b** (n=3) **7b** (n=3)
**5c** (n=4) **6c** (n=4) **7c** (n=4)

in mind. Some of our findings and conclusions reported here are similar to Crampton and Willison's,[3b] others deviate in important ways from theirs.

## Results

Spiro complex formation occurs in two steps, where the first step is a rapid equilibrium, as shown in eq 3. When $n = 2$ spiro



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complex formation is strongly favored over $OH^-$ attack on the aromatic ring. However, when $n = 3$ or 4 spiro complex stability is much lower and the possibility that complexes such

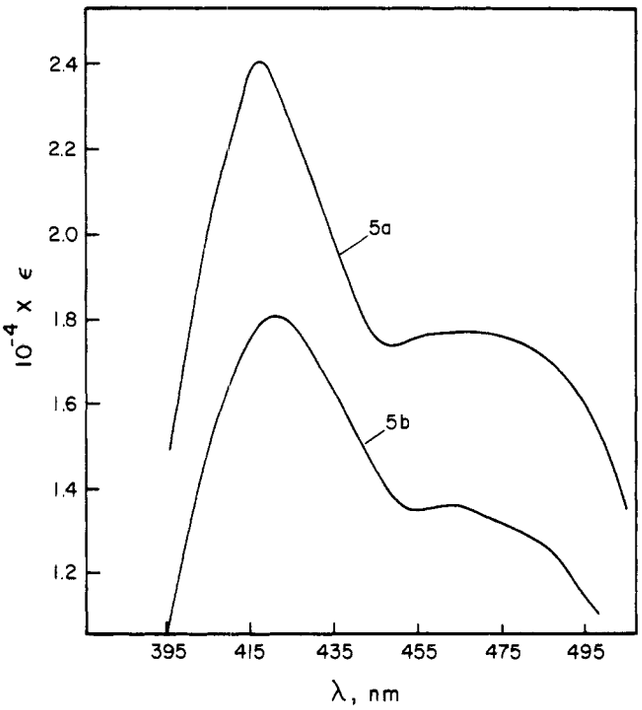
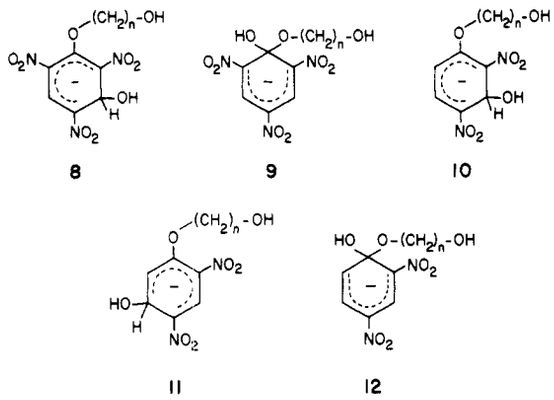



**Figure 1.** Spectra of the spiro complexes derived from **5a** ($\lambda_{max}$ 416 nm, $\epsilon$ 24 000) and **5b** ($\lambda_{max}$ 418 nm, $\epsilon$ 18 000[10]).

as **8–12** may be formed in competition with the respective spiro complex needs to be considered.



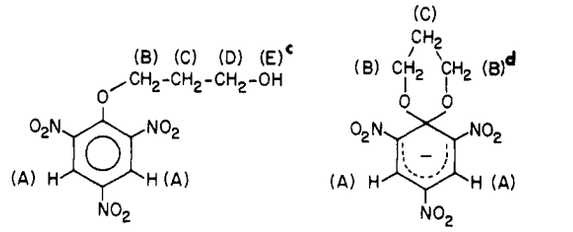

Another consequence of the lower spiro complex stability is that the parent substrate is present in significant concentration at equilibrium, which makes hydrolysis of the parent, to form picrate or 2,4-dinitrophenolate ion, respectively, an important side reaction.

**1-(3-Hydroxypropoxy)-2,4,6-trinitrobenzene (5b).** Addition of dilute NaOH to an aqueous solution of **5b** rapidly produces a short-lived species with a visible spectrum typical of Meisenheimer complexes. The color fades fairly rapidly due to conversion into picrate ion, which makes it necessary to record the spectrum in the stopped-flow spectrophotometer. The spectrum is shown in Figure 1; it is very similar to that of the spiro complex derived from **5a**[10] (also in Figure 1), suggesting that **5b** in fact forms a spiro complex.

$^1$H NMR data in $Me_2SO$-$d_6$, where the complex is much more stable than in aqueous solution, are also consistent with the structure of a spiro complex; they are summarized in Table I. It needs to be pointed out, however, that $^1$H NMR proof in $Me_2SO$ is not definite proof that the same complex also forms in aqueous solution, although it is very suggestive evidence.

Further evidence comes from kinetic measurements. Kinetics was studied in the stopped-flow apparatus, as a function

Table I. $^1$H NMR Shift Data on 5b and Its Spiro Complex in $Me_2SO$-$d_6$[a,b]




| | | |
|---|---|---|
| $H_A$ | 9.13 (s, 2) | 8.34 (s, 2) |
| $H_B$ | 4.31 (t, 2) | 4.08 (t, 4) |
| $H_C$ | 1.87 (q, 2) | 2.08 (q, 2) |
| $H_D$ | 3.50 (t, 2) | |
| $H_E$ | 3.87 (s, 1) | |

[a] Chemical shifts ($Me_4Si$ as internal standard); s = singlet, t = triplet, q = quintuplet; numbers in parentheses indicate relative intensities. [b] For NMR data in chloroform see ref 34. [c] Registry no., 56228-38-7. [d] Registry no., 63018-32-6.

**Table III. Rate and Equilibrium Constants and Solvent Isotope Effects for the Reaction of NaOH with 5b in Water[a]**

| | 15.1 °C | 25.0 °C | 35.1 °C |
|---|---|---|---|
| $Kk_1(H_2O)$, $M^{-1}$ $s^{-1}$ | 11.2 ± 0.3 | 19.7 ± 0.1 | 36.3 ± 0.8 |
| $k_{-1}(H_2O)$, $s^{-1}$ | 0.41 ± 0.04 | 0.87 ± 0.04 | 1.84 ± 0.1 |
| $KK_1(H_2O)$, $M^{-1}$ | 27.3 ± 3.0 | 22.6 ± 1.1 | 19.7 ± 1.5 |
| $Kk_1(D_2O)$, $M^{-1}$ $s^{-1}$ | | 26.6 ± 0.50 | |
| $k_{-1}(D_2O)$, $s^{-1}$ | | 0.69 ± 0.04 | |
| $KK_1(D_2O)$, $M^{-1}$ | | 38.6 ± 1.0 | |
| $Kk_1(H_2O)/Kk_1(D_2O)$ | | 0.74 ± 0.02 | |
| $k_{-1}(H_2O)/k_{-1}(D_2O)$ | | 1.26 ± 0.13 | |
| $KK_1(H_2O)/KK_1(D_2O)$ | | 0.585 ± 0.05 | |

[a] $Kk_1$ from slope of plot of $1/\tau$ vs. [NaOH]; $k_{-1}$ from intercept of same plot; $KK_1$ from $Kk_1/k_{-1}$.

of [NaOH] at constant ionic strength, maintained by NaCl. Substrate concentration was always small compared to base concentration, thus assuring pseudo-first-order conditions. Based on the scheme of eq 3 the rates must obey:

$$\frac{1}{\tau} = \frac{Kk_1[\text{NaOH}]}{1 + K[\text{NaOH}]} + k_{-1} \quad (4)$$

where $1/\tau$ is the reciprocal relaxation time or pseudo-first-order rate constant for the approach to equilibrium.

Our data, collected in $H_2O$ at three different temperatures, and in $D_2O$ at one temperature, are summarized in Table II.[11] Plots of $1/\tau$ vs. [NaOH] (not shown) are linear, indicating that eq 4 simplifies to

$$1/\tau = Kk_1[\text{NaOH}] + k_{-1} \quad (5)$$

because of $K$[NaOH] $\ll 1$ even at the highest concentrations (0.4 M) used. From slopes and intercepts, the $Kk_1$ and $k_{-1}$ values summarized in Table III are obtained.

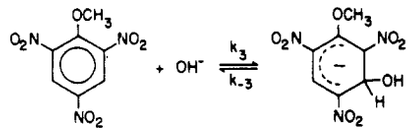
The linear concentration dependence of $1/\tau$ would, in principle, also be consistent with a reaction of $OH^-$ with **5b** to form **8** ($n$ = 3) or **9** ($n$ = 3). Apart from the $^1$H NMR evidence in favor of a spiro complex, **8** ($n$ = 3) and **9** ($n$ = 3) are unattractive alternatives for the following reasons. If the rate and equilibrium parameters referred to the formation of **8** ($n$ = 3), they would be expected to be very similar to those for

**Table VI. Rate and Equilibrium Constants and Solvent Isotope Effects of the Reactions of NaOH with 5c and with 2,4,6-Trinitroanisole in Water at 25 °C[a]**

| | 5c[b] | TNA |
|---|---|---|
| $k_3(H_2O)$, $M^{-1}$ $s^{-1}$ | 5.38 ± 0.50 | 7.37 ± 0.50 |
| $k_{-3}(H_2O)$, $s^{-1}$ | 8.40 ± 0.30 | 8.90 ± 0.20 |
| $K_3(H_2O)$, $M^{-1}$ | 0.64 ± 0.03 | 0.83 ± 0.04 |
| $k_{-3}(D_2O)$, $s^{-1}$ | 5.50 ± 0.2 | 5.18 ± 0.15 |
| $k_{-3}(H_2O)/k_{-3}(D_2O)$ | 1.53 ± 0.08 | 1.72 ± 0.08 |

[a] $K_3$ determined spectrophotometrically, with assumed $\epsilon$ 20 000 at 495 nm; $k_{-3}$ from average of three $1/\tau$ values at [NaOH] = 0.01 to 0.06 M; $k_3$ from $K_3k_{-3}$. [b] Rate and equilibrium constant are believed to refer to formation of 8 ($n$ = 4), hence the use of the symbols $k_3$ and $k_{-3}$ instead of $Kk_1$ and $k_{-1}$, see text.

$OH^-$ attack on the 3 position of 2,4,6-trinitroanisole (TNA), reaction 6. This is not the case. Kinetic and equilibrium data




(6)

for reaction 6 in $H_2O$ and in $D_2O$, as a function of [NaOH], are summarized in Table IV,[11] whereas the rate and equilibrium constants calculated therefrom are in Table VI. We note that $KK_1$ = 22.6 for **5b** (Table III) is 27-fold larger than $K_3$ = 0.83 (eq 6) for TNA (Table VI), whereas $k_{-1}$ = 0.87 for **5b** (Table III) is about ten times smaller than $k_{-3}$ = 8.90 for TNA (Table VI). Furthermore, the different isotope effects on $k_{-1}$ (**5b**) and $k_{-3}$ (TNA) also indicate that we deal with different reactions; the value of $k_{-3}(H_2O)/k_{-3}(D_2O)$ = 1.72 (Table VI) is similar to the 1.70 for $OH^-$ ($OD^-$) departure from the 4 position of the Meisenheimer complex derived from 1,3,6,8-tetranitronaphthalene,[12] whereas the value $k_{-1}(H_2O)/k_{-1}(D_2O)$ = 1.26 (Table III) is similar to 1.31 for ring opening of the spiro complex derived from **5a**.[3a]

**9** ($n$ = 3), though undoubtedly present at low concentrations as a precursor to picrate ion formation, cannot account for the kinetic and equilibrium parameters of complex formation either. This follows from the rate data on picrate ion formation, summarized in Table VII.[11] The pseudo-first-order rate constant ($k_\psi$) for picrate ion formation depends curvilinearly on [NaOH], as expected when there is an accumulating intermediate. If the data are analyzed by assuming that **9** ($n$ = 3) is this accumulating intermediate, this requires that $OH^-$ leaves **9** 12.4 times faster than $HOCH_2CH_2CH_2O^-$, which is contrary to the known tendency of alkoxide ions to be better leaving groups than $OH^-$.[7,13] Similar arguments exclude **9** ($n$ = 4) and **12** ($n$ = 3 or 4) in the systems described later in this paper and will not be repeated.

Analysis of the hydrolysis data according to

$$k_\psi = \frac{k_H[\text{NaOH}]}{1 + KK_1[\text{NaOH}]} \quad (7)$$

where $k_H$ is the rate constant for hydrolysis of **5b** [equivalent to the rate constant of formation of **9** ($n$ = 3)] leads, by way of an inversion plot ($k_\psi^{-1} = k_H^{-1}[\text{NaOH}]^{-1} + KK_1k_H^{-1}$), to $k_H$ = 1.20 ± 0.12 $M^{-1}$ $s^{-1}$ and $KK_1$ = 17.2 ± 1.7 $M^{-1}$; this latter value is in fairly good agreement with $KK_1$ = 22.6 ± 1.1 (Table III) determined directly.

From the temperature dependence of $Kk_1$, $k_{-1}$ and $KK_1$ (Table III) activation and thermodynamic parameters were calculated; they are summarized in Table VIII. For comparison purposes, analogous data were obtained for the spiro complex derived from **5a**, also included in Table VIII; the raw data for **5a** are in Table IX,[11] the rate and equilibrium constants in Table X,[11] whereas the experimental procedure is described in the Experimental Section.

**Table VIII. Activation and Thermodynamic Parameters for Spiro Complex Formation**

| | 5a[a] | 5b[b] |
|---|---|---|
| $\Delta H^\ddagger(Kk_1)$, kcal/mol | 4.3 ± 0.5 | 9.6 ± 0.5 |
| $\Delta S^\ddagger(Kk_1)$, gibbs/mol | −17.4 ± 1.5 | −20.4 ± 1.5 |
| $\Delta H^\ddagger(k_{-1})$, kcal/mol | 13.8 ± 1.0 | 12.1 ± 0.5 |
| $\Delta S^\ddagger(k_{-1})$, gibbs/mol | −18.4 ± 3.0 | −18.2 ± 1.5 |
| $\Delta H°(KK_1)$, kcal/mol | −9.5 ± 0.5 | −2.5 ± 1.0 |
| $\Delta S°(KK_1)$, gibbs/mol | 1.0 ± 1.5 | −2.2 ± 3.0 |
| $\Delta H^\ddagger(k_1)$,[c] kcal/mol | ≈7.8 | ≈13.1 |
| $\Delta H°(K_1)$,[c] kcal/mol | ≈−6.0 | ≈1.0 |

[a] $\Delta H^\ddagger(Kk_1)$ and $\Delta H°(KK_1)$ determined from temperature dependence of $Kk_1$ and $KK_1$, respectively; $\Delta H^\ddagger(k_{-1})$ calculated as $\Delta H^\ddagger(Kk_1) - \Delta H°(KK_1)$; same holds true for entropies. [b] $\Delta H^\ddagger(Kk_1)$ and $\Delta H^\ddagger(k_{-1})$ determined from temperature dependence of $Kk_1$ and $k_{-1}$, respectively; $\Delta H°(KK_1)$ calculated as $\Delta H^\ddagger(Kk_1) - \Delta H^\ddagger(k_{-1})$; same holds true for entropies. [c] Estimated by assuming $\Delta H(K) \approx -3.5$ kcal/mol, see J. Murto, in "The Chemistry of the Hydroxyl Group", S. Patai, Ed., Interscience, Part 2, 1971, p 1087.

**1-(4-Hydroxybutoxy)-2,4,6-trinitrobenzene (5c).** The reaction of **5c** with NaOH also gives rise to a short-lived colored complex which is rapidly converted to picrate ion. Kinetic and equilibrium data obtained in the stopped-flow apparatus are summarized in Table V,[11] whereas in Table VI the rate and equilibrium constants are listed. We note that the equilibrium constant for complex formation is 0.64, which is very close to $K_3$ = 0.83 obtained for reaction 6; this suggests that the colored species formed in the reaction of **5c** with $OH^-$ is **8** ($n$ = 4) instead of the spiro complex. This conclusion is supported by the near identity of the reverse rate constant (8.4 $s^{-1}$) with $k_{-3}$ = 8.9 $s^{-1}$ for reaction 6.

The solvent isotope effect on the reverse reaction (1.53) is somewhat in between the one on $k_{-3}$ in reaction 6 (1.72) and the one on $k_{-1}$ for the ring opening of the spiro complexes derived from **5a** (1.31[3a]) and from **5b** (1.26), but closer to the one on $k_{-3}$. A possible interpretation of the intermediate value of the isotope effect is that there is a mixture of spiro complex with **8** ($n$ = 4), but that $k_{-1}$ and $k_{-3}$ are close enough to prevent the detection of two separate kinetic processes.[14] This hypothesis is pure speculation at this point and shall not be discussed further.

**1-(3-Hydroxypropoxy)-2,4-dinitrobenzene (6b).** Due to the much lower reactivity of 2,4-dinitrobenzene derivatives, the reaction of NaOH with **6b** was studied in 52% $Me_2SO$–48% water; $Me_2SO$ is known to favor Meisenheimer complex formation.[15] A visible spectrum, taken in the stopped-flow apparatus (not shown), is very similar to the one of the spiro complex derived from **6a**.[2d]

Kinetic and equilibrium data, obtained by the stopped-flow technique, are summarized in Table XI.[11] $1/\tau$ is independent of [NaOH], indicating that $Kk_1[\text{NaOH}] \ll k_{-1}$ so that eq 5 reduces to $1/\tau = k_{-1}$. Rate and equilibrium constants are summarized in Table XIV.

There is little doubt that the observed reaction is due to spiro complex formation; spiro complex formation is relatively more favored in 2,4-dinitrobenzene compared to 2,4,6-trinitrobenzene derivatives, because of less steric strain (see Discussion). As seen below this makes it even possible to see a spiro complex with **6c**.

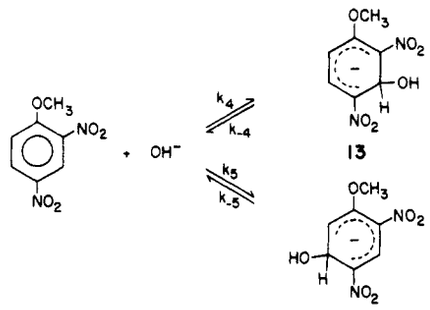
**1-(4-Hydroxybutoxy)-2,4-dinitrobenzene (6c).** In contrast to the cases discussed above, the reaction of **6c** with NaOH, studied in 52% $Me_2SO$–48% water and also in 60% $Me_2SO$–40% water, is characterized by *two* fast kinetic processes, followed by the usual much slower hydrolysis. Both

**Table XIV. Rate and Equilibrium Constants of the Reactions of NaOH with 6b, 6c, and 2,4-Dinitroanisole (DNA) at 25 °C**

| | $Kk_1$,[a] $M^{-1}s^{-1}$ | $k_{-1}$[b] $s^{-1}$ | $KK_1$,[c] $M^{-1}$ |
|---|---|---|---|
| **6b** (52% $Me_2SO$–48% $H_2O$) | 0.26 ± 0.02 | 10.3 ± 0.3 | 0.025 ± 0.001 |
| **6c** (52% $Me_2SO$–48% $H_2O$) | 0.015 ± 0.0025 ($Kk_1 + k_4$)[d] | 33 ± 3 | 4.5 ± 0.3 × $10^{-4}$ ($KK_1 + K_4$)[d] |
| **6c** (60% $Me_2SO$–40% $H_2O$) | 0.094 ± 0.015 ($Kk_1 + k_4$)[d] | 26 ± 1.3 $\Delta H^{\ddagger}$ = 10.1 ± 0.5 kcal/mol $\Delta S^{\ddagger}$ = −18.0 ± 1.5 gibbs/mol | 3.6 ± 0.36 × $10^{-3}$ ($KK_1 + K_4$)[d] |
| DNA (60% $Me_2SO$–40% $H_2O$) | 0.013 ± 0.003 ($k_4$) | (9.7 ± 1.2) ($k_{-4}$) $\Delta H^{\ddagger}$ = 13.2 kcal/mol $\Delta S^{\ddagger}$ = −9.5 gibbs/mol | 1.3 ± 0.13 × $10^{-3}$ ($K_4$) |

[a] $Kk_1$ obtained as $KK_1 \cdot k_{-1}$. [b] Average of $1/\tau$ values ($Kk_1$[NaOH] ≪ $k_{-1}$). [c] $KK_1$ determined from plot of OD/[parent]$_0$ vs. [NaOH], assuming $\epsilon$ 21 000. [d] Complex formation assumed to be mixture of spiro complex and **10**, see text. [e] Same as ref *c*, but $\epsilon$ 20 000.

Scheme I




rapid processes are associated with an increase in absorption in the range where Meisenheimer complexes typically absorb; this suggests that two different complexes are formed. Only the relaxation time of the fastest process could be evaluated with meaningful precision; the second process has a small amplitude and appears to be about ten times slower. The experimental data are summarized in Table XII;[11] $1/\tau$ is independent of [NaOH],[16] indicating that complex formation is disfavored, as is borne out by the equilibrium measurements. Rate and equilibrium constants are summarized in Table XIV.

A comparison with the interaction of NaOH with 2,4-dinitroanisole (DNA) is helpful for the interpretation of our observation; this interaction also shows two rapid processes, in a similar time range as the reactions of **6c**. According to Hasegawa and Abe,[17] who report a spectral study in 98% $Me_2SO$–2% water, the two processes are best interpreted in terms of Scheme I where **13** is probably the complex which forms faster but where **14** is thermodynamically more stable. Just as for **6c**, kinetic and equilibrium data were only obtained for the faster of the two processes; they are collected in Table XIII,[11,16] whereas rate and equilibrium constants are in Table XIV.

In comparing the reactivity of **6c** with that of 2,4-dinitroanisole in 60% $Me_2SO$–40% water, we note that the rate and equilibrium constants for the two are similar (Table XIV), but the similarity is not as close as that between the reactions of **5c** and 2,4,6-trinitroanisole (Table VI). In particular the rate of complex formation for **6c** is almost sevenfold larger than that for 2,4-dinitroanisole, and the equilibrium constant almost threefold larger. A reasonable interpretation of these findings is that the fast process in the case of **6c** refers to the formation of a mixture of spiro complex and **10** ($n$ = 4). Thus the measured equilibrium constant refers to $KK_1 + K_4$ (defined as in Scheme I) and the rate constant for complex formation to $Kk_1 + k_4$. Ordinarily the formation of two complexes should manifest itself by the observation of two separate relaxation processes. However, if $k_{-4}$ and $k_{-1}$ are very similar and $1/\tau$ is completely determined by the rate of complex dissociation, due to an equilibrium position disfavoring complex formation, the relaxation curves merge into a time function which appears to be one single exponential.[14]

Further support for the assumption that spiro complex formation is in part and perhaps mainly responsible for the observed reaction is that the activation parameters for complex dissociation are quite different for **6c** compared to those of 2,4-dinitroanisole (Table XIV).

## Discussion

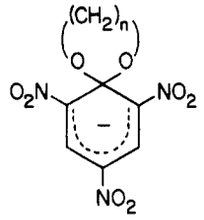
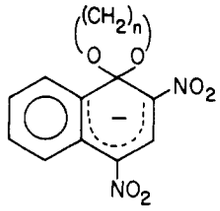
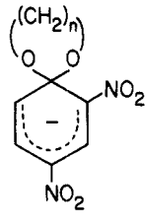
**Spiro Complex Formation vs. $OH^-$ Attack.** For $n$ = 3 we observe spiro complex formation for the 2,4,6-trinitrobenzene (**5b**) and 2,4-dinitrobenzene derivatives (**6b**), in agreement with Crampton and Willison's[3b] findings in the 2,4-dinitronaphthalene derivative (**7b**). Crampton and Willison[3b] also reported that spiro complex formation is the main interaction of **7c** with NaOH and that competition with $OH^-$ attack on the aromatic ring is insignificant. This contrasts with our own conclusions in the 2,4,6-trinitrobenzene series where the main interaction of **5c** with NaOH is the formation of **8** ($n$ = 4) and where there is no clear evidence that a spiro complex forms in detectable concentrations, and in the 2,4-dinitrobenzene series where our data suggest that **6c** forms a mixture of spiro complex with **10** ($n$ = 4) and **11** ($n$ = 4).

Absence of competing $OH^-$ attack on the 3 position of **7c** is not surprising in view of the scarcity of reports about nucleophilic attack at the 3 position of 1-alkoxy-2,4-dinitronaphthalenes.[18] This is probably due to the absence of a nitro group para to the reaction site; nitro groups are known to have their greatest stabilizing influence on Meisenheimer complexes when in the para position.[15,19]

**Effect of Ring Size on Spiro Complex Formation.** Table XV summarizes kinetic and equilibrium parameters on the various spiro complexes. We note that in all three systems the effect of increasing ring size is to strongly decrease $KK_1$ and $Kk_1$, whereas $k_{-1}$ is relatively little affected.[20] We agree with Crampton and Willison[3b] that the main effect on $Kk_1$ must be on the rate of the cyclization step ($k_1$), whereas $K$ depends little on $n$.

In discussing the effect of ring size on rates of cyclizations it is usually recognized that there is an interplay of two main factors.[8,9,21] First, the formation of a ring results in the loss of rotational freedom and hence is accompanied by a decrease in entropy. With increasing chain length the loss in rotational freedom increases, which leads to increasingly more negative activation entropies. This is, for example, borne out by Illuminati's[20a] recent studies. The second factor is ring strain, which in cycloalkanes is known to decrease from three- to six-membered rings and then to increase with increasing ring size up to nine-membered rings.[22a,b] Recent data by Dale[22c] show that this is also true for oxygen containing rings; for

Table XV. Summary of Kinetic and Equilibrium Parameters on Spiro Complex Formation at 25 °C

| | | $Kk_1$, $M^{-1}$ $s^{-1}$ | $\frac{Kk_1(n=2)}{Kk_1(n=3)}$ | $k_{-1}$, $s^{-1}$ | $\frac{k_{-1}(n=2)}{k_{-1}(n=3)}$ | $KK_1$, $M^{-1}$ | Solvent |
|---|---|---|---|---|---|---|---|
|  | $n = 2$[f] | $7.25 \times 10^5$[a] | $3.68 \times 10^4$ | 0.045[a] | 0.052 | $1.6 \times 10^7$[a] | $H_2O$ |
| | $n = 3$[b] | $1.97 \times 10^1$ | | 0.87 | | $2.26 \times 10^1$ | $H_2O$ |
| | $n = 4$[b,g] | $\ll 10$ | | | | $\ll 1$ | $H_2O$ |
|  | $n = 2$[c] | $9 \times 10^4$ | $5.30 \times 10^4$ | 2.3 | 2.70 | $3 \times 10^4$ | $H_2O$ |
| | $n = 3$[d] | 1.7 | | 0.85 | | 1.7 | $H_2O$ |
| | $n = 4$[d] | 0.6 | | 0.64 | | 0.7 | $H_2O$ |
|  | $n = 2$[e] | $4.0 \times 10^3$ | $1.54 \times 10^4$ | 62 | 6.02 | $6.42 \times 10^1$ | 50% $Me_2SO$–50% $H_2O$ |
| | $n = 3$[b,h] | $2.6 \times 10^{-1}$ | | 10.3 | | $2.5 \times 10^{-2}$ | 52% $Me_2SO$–48% $H_2O$ |
| | $n = 4$[b,i] | $\leqslant 1.5 \times 10^{-2}$ | | ~33 | | $\leqslant 4.5 \times 10^{-4}$ | 52% $Me_2SO$–48% $H_2O$ |

[a] This work, at ionic strength 1.0 M; ref 3a reports $Kk_1 = 1.6 \times 10^6$ $M^{-1}$ $s^{-1}$, $k_{-1} = 0.095$ $s^{-1}$, $KK_1 = 1.8 \times 10^7$ $M^{-1}$. [b] This work. [c] Reference 3a. [d] Reference 3b. [e] Reference 2d. [f] Registry no., 63058-85-5. [g] Registry no., 63018-33-7. [h] Registry no., 63018-34-8. [i] Registry no., 63018-35-9.

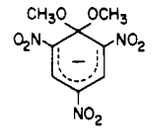
example, **15** is more strained than **16.** The strain factor is expected to be reflected in $\Delta H^{\ddagger}$.

**15**

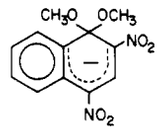
**16**

When comparing cyclizations of five- and six-membered rings, the latter are usually substantially slower,[8,9] just as in our cases, indicating that the smaller ring strain in the six-membered ring is over compensated by the more negative entropy. However, although $\Delta S^{\ddagger}$ for $KK_1$ is slightly more negative for the six-membered ring, **5a,** the difference between the two numbers is small and hardly distinguishable from experimental error. More significantly, however, $\Delta H^{\ddagger}$ for $Kk_1$ is about 5 kcal/mol more positive for the six-membered spiro complex, which suggests that ring strain is substantially *larger* in the *six*-membered rather than the five-membered ring. This probably arises from an unfavorable interaction of the spiro ring with the ortho nitro groups (steric compression) which, according to space filling molecular models, becomes worse as the ring size increases from five to six to seven (puckering of the ring). The consequence is to either increase steric strain directly, or to reduce resonance stabilization by the ortho nitro groups as they are moved out of the plane of the aromatic ring (indirect effect) or both. This is similar to Pietra's interpretation for the sulfur analogue spiro complexes.[23]

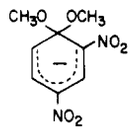
**Intra- ($k_{-1}$) vs. Intermolecular ($k_{-2}$) Leaving Group Departure.** Ring opening ($k_{-1}$) of the spiro complex from **5a** is about 82 times faster than methoxide ion departure from **17** ($k_{-2} = 5.51 \times 10^{-4}$ $s^{-1}$ in water[24]), $k_{-1}$ in the case of **7a** is about 580 times faster than methoxide ion departure from **18** ($k_{-2} = 3.95 \times 10^{-3}$ $s^{-1}$ in methanol[25,26]), whereas $k_{-1}$ for **6a** ($k_{-1} = 725$ $s^{-1}$ in 2% $Me_2SO$–98% water[2d]) is about 17 times faster than methoxide ion departure from **19** ($k_{-2} = 42$ $s^{-1}$ [26,27]). In their first attempt to rationalize these results,



**17**



**18**



**19**

Crampton and Willison[3a] attributed the high rates of spiro complex ring opening to relief of steric strain. Later, based on their observation that in the 2,4-dinitronaphthalene series changing ring size mainly affects $Kk_1$ whereas $k_{-1}$ hardly changes at all (Table XV), they concluded that the transition state for cyclization must already contain most of the strain present in the complex, so that an explanation of the high $k_{-1}$ values in terms of strain relief no longer seemed justified.[3b] They offered an alternative explanation in terms of conformational differences about the C–O bonds in the spiro compared to 1,1-dimethoxy complexes. It was assumed that there is considerably more conformational freedom about the C–O bonds in the 1,1-dimethoxy complexes compared to the spiro complexes. In as much as this freedom is lost on passage to the transition state for C–O bond breaking, this would explain the lower rates.

It is difficult to assess the validity of this argument. If everything else were equal one would expect that this conformational effect should be reflected in more negative $\Delta S^{\ddagger}$ values for the 1,1-dimethoxy complexes. This is not borne out by the experimental data; in fact $\Delta S^{\ddagger}$ for methoxide ion departure from **17** is slightly *less* negative (−14.9 gibbs/mol in water[24]) than $\Delta S^{\ddagger}$ for spiro complex opening (−18.4 gibbs/mol for **5a,** −18.2 gibbs/mol for **5b,** Table VIII). Whether Crampton and Willison's conformational effect is perhaps masked by other effects, such as different solvation requirements in the transition state of spiro complex ring opening compared to 1,1-dimethoxy complex dissociation, or restriction in the rotation of the breaking C–O bond in the transition

state of spiro complex ring opening, cannot be decided on the basis of the data at hand.

Be it as it may, the faster rate with the spiro complex is an enthalpy effect ($\Delta H^{\ddagger}$ = 17.5 kcal/mol for **17**,[24] $\Delta H^{\ddagger}$ = 12.8 and 12.1 kcal/mol for **5a** and **5b**, respectively, Table VIII). We believe there are three factors which may all contribute to this effect. One of them is the lower $pK_a$ of the OH group in **5a**, **6a**, and **7a** ($pK_a \leq 14.8$ based on $pK_a$ of $CH_3OCH_2CH_2OH$[28]) compared to that of methanol ($pK_a \sim 15.5$ in water[28]). In view of our recent findings that the rate of alkoxide ion departure from 1,1-dialkoxy-2,4,6-trinitrohexadienate ions is roughly proportional to the acidity constant of the respective alcohols,[29] the above $pK_a$ difference of $15.5 - \leq 14.8 = \geq 0.7$ could account for a factor of $\geq 5$ in the accelerated spiro complex ring opening.

The second factor is relief of ring strain even though this was recently discounted by Crampton and Willison[3b] on the basis that the effect of ring size on $k_{-1}$ is minimal in the 2,4-dinitronaphthalene series. This factor reveals itself when the effect of ring size on $k_{-1}$ is compared among the three aromatic systems: $k_{-1}(n = 2)/k_{-1}(n = 3) = 0.052$ in the 2,4,6-trinitrobenzene system, 2.70 in the 2,4-dinitronaphthalene system, and 6.02 in the 2,4-dinitrobenzene system. This trend suggests that there are two opposing effects which influence these $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios. One of these effects could be the basicity of the leaving oxyanion, which might be expected to be somewhat higher when $n = 3$ than when $n = 2$, due to the attenuation of inductive effects. This would make the oxyanion for $n = 3$ a poorer leaving group and could account for $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios greater than one. The other effect is relief of strain (mainly with $n = 3$) which tends to make these ratios smaller than one and which is expected to be most pronounced in the most crowded 2,4,6-trinitrobenzene series.

A third factor, more speculative in nature, is that the most stable conformation about the C–O bonds in the 1,1-dimethoxy complexes is one where the lone pairs on the oxygen of the nonleaving methoxy group are *not* optimally aligned for p–$\pi$ overlap in the transition state, whereas such alignment exists in the spiro complexes. This is similar to Crampton and Willison's suggestion at the end of their paper.[3b]

**Structure of the Transition State.** As pointed out before, the reduction in $KK_1$ with increasing ring size of the spiro complexes is mainly due to a large reduction in $Kk_1$ while $k_{-1}$ changes relatively little with $n$ (Table XV). As noted by Crampton and Willison[3b] this suggests a complex-like transition state.

On the other hand, a *reactant*-like transition state is suggested by a comparison of the effect of increasing bulkiness of the aromatic system on the $Kk_1(n = 2)/Kk_1(n = 3)$ and the $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios: the former change little when comparing the 2,4,6-trinitrobenzene, 2,4-dinitronaphthalene, and 2,4-dinitrobenzene series, the latter span a range of more than 100-fold (Table XV).

This kind of contradiction where different criteria suggest different transition state structures can often be resolved by assuming that different processes have made different progress in the transition state; i.e., it depends on one's definition of the reaction coordinate whether a transition state appears to be "early" or "late". An example somewhat similar to ours is the hydroxide ion addition to substituted benzaldehydes: changes in the equilibrium constants (by varying the substituents) are almost entirely reflected in changes of the forward rate constants (suggesting a product-like transition state), but the reactions are exothermic (suggesting a reactant-like transition state). This was interpreted by assuming that in the forward direction solvent reorganization lags behind C–O bond formation.[30] Other examples include Hupe and Jencks[31a] suggestion that desolvation of alkoxide ions has made more progress than C–O bond formation in the transition state of the reaction of alkoxide ions with esters, Sayer and Jencks[31b] suggestion that double bond formation and change of hybridization of carbon and nitrogen lag behind C–O bond cleavage and proton transfer in imine-forming elimination reactions, and the ionization of nitroalkanes in which rehybridization of carbon appears to lag behind proton removal and electron delocalization into the nitro substituent.[32]

In our own case the *o*-nitro group(s) is(are) probably turned out of the plane of the aromatic ring upon complex formation and it is conceivable that this process lags behind C–O bond formation. The difference in the bulkiness of the different aromatic systems would then be mainly felt when C–O bond formation has already made considerable progress, i.e., between the transition state and the complex. This would explain why the ratios $k_{-1}(n = 2)/k_{-1}(n = 3)$ but not $Kk_1(n = 2)/Kk_1(n = 3)$ are sensitive to the changes in bulkiness. In the absence of more evidence this interpretation is to be regarded as somewhat speculative.

**Acid-Catalyzed Leaving Group Departure.** It is interesting to compare the rate of the $H^+$-catalyzed ring opening of the spiro complex derived from **5a** ($k_{-1}^{H^+} = 2.2 \times 10^3\ M^{-1}\ s^{-1}$ [3a]) with that of $H^+$-catalyzed methoxide ion departure from **17** ($k_{-2}^{H^+} = 3.5 \times 10^3\ M^{-1}\ s^{-1}$ [29]). One obtains the ratio $k_{-1}^{H^+}/k_{-2}^{H^+} = 0.63$ which is in contrast to $k_{-1}/k_{-2} = 82$ for the *non*catalyzed reactions. This drastic change means that the factors which are responsible for the relatively much faster noncatalyzed spiro complex ring opening must be ineffective in the acid-catalyzed reaction or that a new, compensating factor plays a role in the acid-catalyzed leaving group departures, or both.

One (though probably minor) factor which was invoked as contributing to the large $k_{-1}/k_{-2}$ ratio in the noncatalyzed reactions was the higher $pK_a$ of methanol compared to the OH group in **5a**. This factor not only becomes ineffective in the acid-catalyzed reactions, but has even the opposite effect in that it slightly favors the departure of the more basic methoxide ion. This conclusion is based on our recent findings that the rate of $H^+$-catalyzed alkoxide ion departure from 1,1-dialkoxy-2,4,6-trinitrocyclohexadienates increases with increasing basicity of the alkoxide.[29]

The higher basicity of the methoxide ion could probably account entirely for the value of 0.63 in the $k_{-1}^{H^+}/k_{-2}^{H^+}$ ratio if protonation of the complex were the rate-determining step. On the other hand, if the mechanism of acid catalysis involved rapid equilibrium protonation followed by rate-limiting departure of the protonated leaving group, or, most likely,[3a,29] if the reaction is concerted, the basicity factor could only account for part of the change from $k_{-1}/k_{-2} = 82$ to $k_{-1}^{H^+}/k_{-2}^{H^+} = 0.63$.

Thus one is compelled to conclude that the other two factors believed to be partly responsible for the high $k_{-1}/k_{-2}$ ratios in the noncatalyzed reaction, viz, relief of strain and alignment of the lone pairs for p–$\pi$ overlap, are less effective in the acid-catalyzed reaction. This would imply that C–O bond breaking has made less progress in the transition state of the acid-catalyzed compared to the noncatalyzed reaction.

## Experimental Section

**Materials.** 1-(3-Hydroxypropoxy)-2,4,6-trinitrobenzene (**5b**) was prepared by adding 9 mL of a 2.1 M sodium 3-hydroxypropoxide solution in 1,3-propanediol to 4 g of picryl chloride in 50 mL of 1,3-propanediol. The solution which immediately turned dark red was allowed to stand for 2 h and was then extracted with chloroform to remove unreacted picryl chloride. The reaction solution was then added to ice water and acidified to pH ~4. A yellow oil appeared which crystallized in the refrigerator, mp 50–52 °C,[33] $^1H$ NMR see Table I.

1-(4-Hydroxybutoxy)-2,4,6-trinitrobenzene (**5c**) was prepared by

a similar procedure, except that 1,3-propanediol was replaced by 1,4-butanediol, the picryl chloride was dissolved in a 1:1 mixture of 1,4-butanediol and *p*-dioxane, and the chloroform extraction was omitted. Mp 51–52 °C, $^1$H NMR ($Me_2SO$-$d_6$) δ 8.99 (s, 2, ring protons), 4.16 (t, 2, α-$CH_2$), 1.70 (m, 4, β- and γ-$CH_2$), 3.37 (t, 2, δ-$CH_2$), 3.82 (s, 1, OH). **5c** decomposes over the time of about 2 weeks when stored in a desiccator.

1-(3-Hydroxypropoxy)-2,4-dinitrobenzene (**6b**) was prepared by adding 15 mL of a 2.6 M sodium 3-hydroxypropoxide solution in 1,3-propanediol to 7 g of 1-chloro-2,4-dinitrobenzene in 60 mL of 1,3-propanediol. After heating on a steam bath for 1 h the solution was poured onto 1 L of ice water and acidified. A yellow oil appeared which slowly crystallized; it was twice recrystallized from water: mp 55–56.5 °C; $^1$H NMR ($CDCl_3$) δ 8.82 (d, 1, aromatic 3 position), 8.43 and 8.60 (dd, 1, aromatic 5 position), 7.37 (d, 1, aromatic 6 position), 4.48 (t, 2, α-$CH_2$), 2.17 (q, 2, β-$CH_2$), 3.93 (t, 2, γ-$CH_2$), ~2 (broad, OH).

1-(4-Hydroxybutoxy)-2,4-dinitrobenzene (**6c**) was prepared from 1,4-butanediol by an analogous procedure as for **6b**, mp 41–42 °C, $^1$H NMR ($CDCl_3$) δ 8.80 (d, 1, aromatic 3 position), 8.42 and 8.58 (dd, 1, aromatic 5 position), 7.30 (d, 1, aromatic 6 position), 4.35 (t, 2, α-$CH_2$), 2.0 (m, 4, β- and γ-$CH_2$), 3.78 (t, 2, δ-$CH_2$), ~2 (broad, OH).

2,4,6-Trinitroanisole and 2,4-dinitroanisole were available from previous studies.[27,35] $Me_2SO$ (Baker Analyzed Reagent Grade) was used without further purification. $D_2O$ (Mallinckrodt) was 99.8% pure.

**Spectra.** $^1$H NMR spectra were taken at 60 MHz on a JEOL "Minimar" spectrometer. Visible spectra were obtained in a Durrum stopped-flow spectrophotometer or Cary 14 spectrophotometer (for **5a**).

**Kinetic and Equilibrium Measurement.** Except for the kinetics of picrate formation from **5b**, which was monitored on a Gilford 2000 kinetic spectrophotometer at λ 500 nm, all kinetic measurements were made on a Durrum stopped-flow spectrophotometer, at λ around 500 nm. In the case of **5a, 5b, 5c, 6b,** and 2,4,6-trinitroanisole good first-order plots were obtained and $1/\tau$ was easily evaluated; in the case of **6c** and 2,4-dinitroanisole the first part of the biphasic plots could still be evaluated relatively easily by known procedures,[14] since the time separation between the two processes was about a factor of 10.

In determining the $[OH^-]$ dependence of $1/\tau$ and of OD for **5a**, the $OH^-$ concentration was calculated by solving eq 8 for $[OH^-]$:

$$K_w = \frac{\gamma_{H^+}\gamma_{OH^-}}{a_{H_2O}}[H^+][OH^-] = \frac{\gamma_{H^+}\gamma_{OH^-}}{a_{H_2O}}\frac{a_{H^+}}{\gamma_{H^+}}[OH^-] \qquad (8)$$

where $a_{H^+}$ was measured by a Corning digital pH meter, $\gamma_{H^+}$,[36a] $\gamma_{H^+}\gamma_{OH^-}/a_{H_2O}$,[36b] and $K_w$[37] are known at the employed temperatures and ionic strength.

**Acknowledgment.** Support of this work by Grant MPS 74-08379-A01 from the National Science Foundation is gratefully acknowledged.

**Supplementary Material Available:** Tables II, IV, V, VII, IX–XIII (10 pages). Ordering information is given on any current masthead page.

**Registry No.**—**5a,** 6478-31-5; **5c,** 63018-29-1; **6b,** 63018-30-4; **6c,** 63018-31-5; 2,4,6-trinitroanisole, 606-35-9; 2,4-dinitroanisole, 119-27-7; picryl chloride, 88-88-0; 1,3-propanediol, 504-63-2; 1,4-butanediol, 110-63-4; 1-chloro-2,4-dinitrobenzene, 97-00-7.

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(4) Based on Crampton and Willison's results[3a] and assuming that the equilibrium constants for the deprotonation of 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene by $OH^-$ is 0.3 $M^{-1}$.
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(6) The equilibrium and rate constants given are not strictly comparable for two reasons: (a) $K_2$ and $k_2$ were determined in methanol; in water they are expected to be at least threefold lower.[7] (b) More seriously, since the units of $K_1$ and $K_2$ and of $k_1$ and $k_2$ are not the same they cannot be directly compared. This problem can be avoided by defining the concentration in terms of mole fractions,[8] which necessitates a multiplication of $K_2$ and $k_2$ by the molarity of the solvent (55.5 for water). With these two corrections one obtains $k_2 \approx 320$ (still $\ll k_1$) and $K_2 \approx 3.15 \times 10^5$ (still $\ll K_1$).
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(10) Since the spiro complex is not formed quantitatively, the extinction coefficients were calculated on the basis of the kinetically determined equilibrium constant of complex formation. Whether ε is, in fact, about 25% lower than in the case of **5a** as shown in Figure 1 or whether this reflects an experimental error in the equilibrium constant is difficult to decide.
(11) See paragraph concerning supplementary material at the end of this paper.
(12) J. H. Fendler, E. J. Fendler, and L. M. Casilio, *J. Org. Chem.*, **36,** 1749 (1971).
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