Intermediates in Nucleophilic Aromatic Substitution. VIII.[1] Temperature-Jump and Equilibrium Study of the Spiro Meisenheimer Complex of *N*-2-Hydroxyethyl-*N*-methyl-2,4-dinitroaniline

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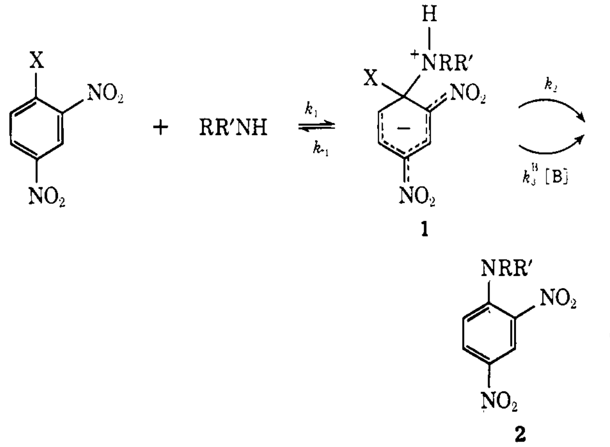
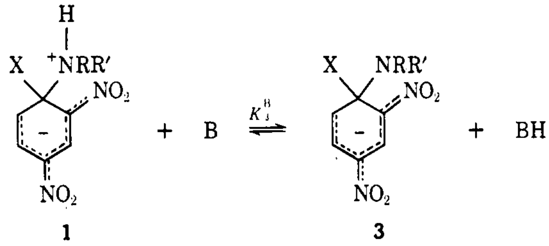
Received October 24, 1972

In the presence of strong base *N*-2-hydroxyethyl-*N*-methyl-2,4-dinitroaniline forms a spiro Meisenheimer complex in aqueous DMSO. In 2% DMSO (v/v) and 1 *M* KOH only 0.5% of the starting material is in the form of the complex but its stability increases in DMSO-rich solvents. In 85% DMSO (v/v) virtually all starting material is in the form of the complex at base concentrations ≥ 0.01 *M*. In solvents containing $\leq 65\%$ DMSO the rate of reversion of the complex to starting material could be measured. In 80 and 85% DMSO (v/v) the rate of its formation and the acid dissociation constant of the alcoholic proton in the starting material could be determined as well. The agreement between kinetic data and spectrophotometric equilibrium measurements was unsatisfactory when KOH was used as base and KCl as compensating electrolyte; it was excellent for the pair $(CH_3)_4NOH/(CH_3)_4NCl$. This suggests the presence of a differential salt effect in the former system and the absence of such an effect in the latter. The complex serves as a model for the anionic intermediate complex in nucleophilic aromatic substitutions by amine nucleophiles. Its rate of breakdown is central to an argument about the mechanism of the direct conversion of the zwitterionic intermediate complex into products.

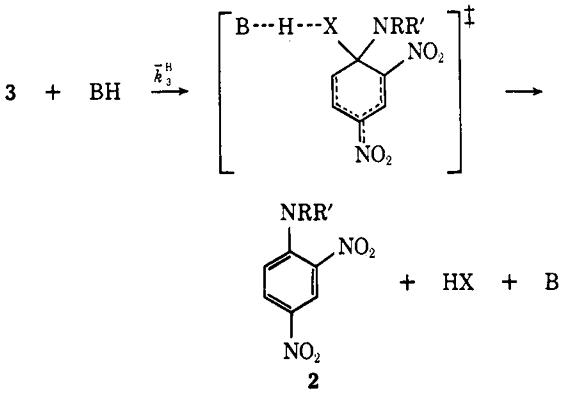
Reactions of primary and secondary amines with activated aromatic substrates have played a central role in firmly establishing Bunnett's[3] intermediate complex mechanism for nucleophilic aromatic substitution reactions.[4] Equation 1 is representative and shows the most frequently studied type of aromatic substrate. Owing to their greater complexity compared to substitutions by anionic nucleophiles, reactions of amines have also raised additional questions regarding the detailed mechanism of the conversion of the intermediate complex 1 into final products. The mechanism of the general base catalyzed step (k_3^{B}) has been controversial for several years,[4a] but that of eq 2 appears now firmly established mainly owing to the work of Orvik and Bunnett.[5] It involves a rapid acid-base equilibrium between the initially formed zwitterionic intermediate 1 and its conjugate base 3 followed by a rate-limiting expulsion of the leaving group with general acid catalysis by BH.[6]



(1)



(2a)



(2b)

Until recently[4a] the mechanism of the direct conversion of the zwitterion 1 into products (k_2) has only received meager attention. It is sometimes referred to as "solvent assisted" or "solvent catalyzed"[4b] with the implication that the labile proton of the zwitterion is transferred to the solvent, presumably

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[1] Part VII: C. F. Bernasconi, *J. Amer. Chem. Soc.*, **93**, 6975 (1971).

[2] Alfred P. Sloan Fellow, 1971–1975.

[3] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 275 (1951).

[4] For recent reviews see (a) C. F. Bernasconi, *MTP Int. Rev. Sci., Org. Chem. Ser. One*, **3**, in press; (b) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969); (c) T. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups," Part I, H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 487; (d) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968; (e) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

[5] J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).

[6] Discussions concerning the mechanism of base catalysis[4a,b,5] might leave one with the impression that all base-catalyzed reactions follow the mechanism of eq 2. This is not the case. When BH is a weaker acid than XH there is no driving force for a general acid catalyzed leaving group expulsion; in such a case the $\bar{k}_3^{H}$ step does not involve general acid catalysis and the overall base catalysis (step k_3^{B} in eq 1) is specific rather than general (Libido rule[7]). Such must be the case with most leaving groups when B is the lyate ion, although it is difficult to prove directly. The absence of piperidine catalysis in the hydroxide ion catalyzed reactions of piperidine with 2,4-dinitrophenyl phenyl sulfide[8] and with 2,4-dinitrophenyl 4-nitrophenyl ether[9] in aqueous dioxane is probably a manifestation of this rule, since the pK_a of thiophenol is 6.52, of 4-nitrophenol 7.14 and of piperidinium ion 11.06. This interpretation of the lack of piperidine catalysis is, however, somewhat uncertain because the catalytic effect of the lyate ion is not very large so that catalysis by the weaker base might have been undetectable.

[7] W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972).

[8] (a) J. F. Bunnett and C. F. Bernasconi, *ibid.*, **87**, 5209 (1965); (b) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).

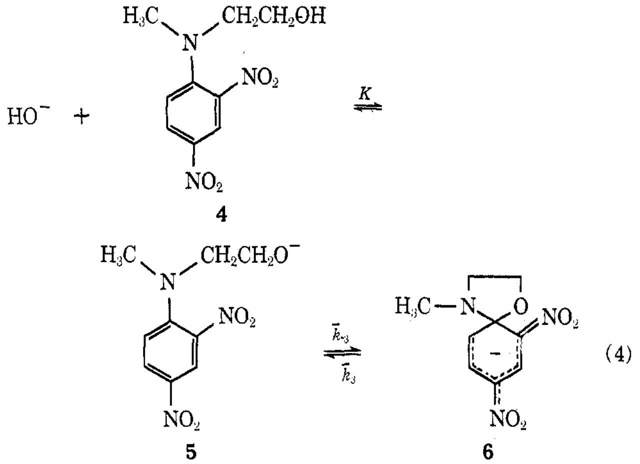
[9] J. F. Bunnett and C. F. Bernasconi, *ibid.*, **35**, 70 (1970).

prior to the rate-determining leaving group expulsion. In keeping with the idea of the mechanism of general base catalysis, Orvik and Bunnett[5] considered the logical possibility that the k_2 mechanism might also consist of two steps including a lyonium ion catalyzed expulsion of X from **3**, *i.e.*, eq 2b, with BH being the lyonium ion.

Recently one of us[4a] presented evidence rendering such a mechanism very unlikely. The principal argument hinged upon an estimate of the rate ($\bar{k}_3$) at which **3** expels the leaving group in a protic solvent. Note that eq 3 is a special case of eq 2b where BH is the solvent;[6] a logical symbol for the rate constant would be $\bar{k}_3{}^L$, where L stands for lyate ion. For simplicity we will use $\bar{k}_3$.

$$\mathbf{3} \xrightarrow{\bar{k}_3} \mathbf{2} + X^- \qquad (3)$$

Thus an attempt to find a system where an intermediate like **3** would be stable enough to allow direct observation and a kinetic study of its decomposition seemed of special interest. We found that in the presence of base *N*-2-hydroxyethyl-*N*-methyl-2,4-dinitroaniline (**4**) is converted to a σ complex as shown in eq 4. We will demonstrate in the Discussion that the rate coefficient for the transformation **6** → **5** can serve as an estimate of the lower limit to be expected for $\bar{k}_3$ in eq 3.



(4)

We now report a kinetic and equilibrium study of system 4 in aqueous DMSO of varying DMSO content. This study goes beyond the mere determination of $\bar{k}_3$, since the system is of interest in its own right.

Results

When base is added to an aqueous DMSO solution of **4** there is immediate formation of a red color which is very faint when the DMSO content is ≤20% (v/v) but intense in DMSO-rich mixtures. Figure 1 shows the characteristic Meisenheimer complex spectrum in 80% DMSO (v/v), λ_{max} 510 nm (ϵ_{510} 22,800). Conversion to the complex **6** is virtually quantitative in 80% DMSO (v/v) with 0.1 *M* $(CH_3)_4NOH$ or in 85% DMSO (v/v) with 0.01 *M* $(CH_3)_4NOH$.[10]

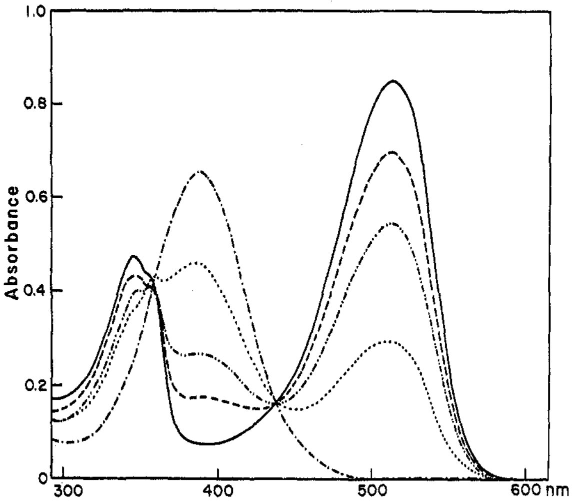
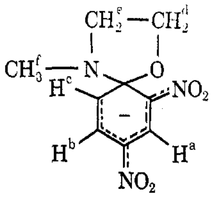


Figure 1.—Uv-visible spectra of **4** at various $(CH_3)_4NOH$ concentrations in 80% DMSO (v/v) (μ = 0.1 *M*; $[4]_0 = 3.79 \times 10^{-5}$ *M*): — · —, without base; · · · ·, 0.95×10^{-3} *M*; — · · —, 3.0×10^{-3} *M*; — —, 5.9×10^{-3} *M*; ——, 9.5×10^{-3} *M*.

The pmr spectrum, with its characteristic AMX pattern for the ring protons and a complex ABCD pattern for the methylene protons, is similar to the spectrum reported for **7**.[11] The following chemical shifts and coupling constants have been recorded in pure DMSO-d_6 in the presence of *t*-BuOK. The numbers in parentheses refer to **7**: τ_a 1.50 d[12] (1.48),[11a] τ_b 3.12 dd[12] (3.10),[11a] τ_c 4.87 d[12] (4.64),[11a] τ_d 6.03 m[12] (5.92),[11b] τ_e 6.92 m,[12] τ_f 7.63 s,[12] J_{ab} = 2.7 (3)[11a] Hz, J_{bc} = 10 (10)[11a] Hz.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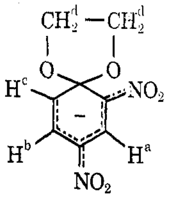
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Kinetics.—Chemical relaxation was studied by the temperature-jump method in DMSO-water mixtures at 25°. In any given solvent the ionic strength was kept constant by adding KCl when KOH was used as base, or $(CH_3)_4NCl$ when $(CH_3)_4NOH$ was used. Reaction system 4 is characterized by two relaxation times. One is associated with the rapid acid-base equilibrium $\mathbf{4} \rightleftharpoons \mathbf{5}$ and is too short for the temperature-jump method. The much longer relaxation time associated with the equilibrium $\mathbf{5} \rightleftharpoons \mathbf{6}$ is in an easily accessible time range. It is governed by eq 5. Equation 5 was derived according to standard procedures;[13] the concentrations refer to their values at equilibrium.

$$\frac{1}{\tau} = \bar{k}_{-3}\,\frac{K([HO^-]_e + [4]_e)}{1 + K([HO^-]_e + [4]_e)} + \bar{k}_3 \qquad (5)$$

2, 20, 50, and 65% DMSO (v/v).—Table I summarizes the data in these solvents. In all the runs the base was in large excess over **4**. For solvents ≤50% in DMSO the relaxation times are independent of base and substrate concentration within experimental error.

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[10] The imperfect isosbestic point at 355–360 nm in Figure 1 is probably due to some hydrolysis of **4** to form the 2,4-dinitrophenolate ion, which has a strong absorption at these wavelengths; not, however, at 438 nm, the location of the other isosbestic point.

[11] (a) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Foreman, *Tetrahedron*, **23**, 227 (1967); (b) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4141 (1968).

[12] s = singlet, d = doublet, m = multiplet, dd = double doublet.

[13] M. Eigen and L. DeMaeyer in A. Weissberger, "Technique of Organic Chemistry," Vol. VIII, Part 2, Wiley-Interscience, New York, N. Y., 1963, p 895.

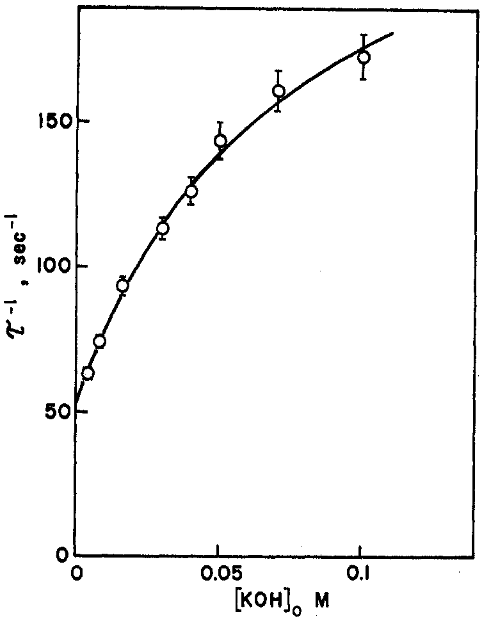

Figure 2.—Reaction in 80% DMSO (v/v), base KOH, μ = 0.1 M, τ^{-1} as a function of $[\mathrm{KOH}]_0$, $[\mathbf{4}]_0 = 4\text{–}8 \times 10^{-5}\,M$.

Table I

Relaxation Times in 2, 20, 50, and 65% DMSO (v/v) at 25°

% DMSO (v/v)	$[\mathbf{4}]_0$, M	$[\mathrm{KOH}]_0$, M	μ,[a] M	τ^{-1}, sec^{-1}
2	$\sim 3 \times 10^{-3}$ [b]	0.50	1.0	892 ± 90
2	$\sim 3 \times 10^{-3}$ [b]	1.00	1.0	966 ± 50
20	2.0×10^{-3}	0.24	1.0	675 ± 40
20	2.0×10^{-3}	0.50	1.0	612 ± 30
20	2.0×10^{-3}	1.00	1.0	665 ± 30
20	2.0×10^{-3}	0.50	0.5	701 ± 35
50	2.0×10^{-3}	0.08	0.5	353 ± 20
50	2.0×10^{-3}	0.24	0.5	310 ± 20
50	2.0×10^{-3}	0.50	0.5	341 ± 20
50	2.0×10^{-4}	0.50	0.5	323 ± 15
65	3.1×10^{-4}	0.20	0.5	166 ± 7
65	2.0×10^{-4}	0.50	0.5	188 ± 8

[a] Compensating electrolyte KCl. [b] Saturated solution.

Independence of base concentration indicates that the first term in eq 5 is negligible and thus eq 6 holds. In

$$\frac{1}{\tau} = \bar{k}_3 \tag{6}$$

other words, little complex **6** is present in equilibrium with **4** and **5** under these conditions; in fact, in the most aqueous solvents a high concentration of **4** is required in order to produce enough complex for spectral detection and monitoring chemical relaxation. Independence of substrate concentration excludes catalytic effects by **4**, **5**, or **6**; since such catalytic effects have been observed in related systems,[14] this is not a trivial point, particularly in view of the high substrate concentrations used.

Data in 20% DMSO (v/v) suggest a slight reduction in $\bar{k}_3$ with increasing ionic strength from 0.5 to 1.0 M.

In 65% DMSO (v/v) there is a slight dependence of τ^{-1} on base concentration which is just outside the experimental error.

80 and 85% DMSO (v/v).—In these solvents a significant fraction of the starting material is in the form of the complex and the concentration dependence of the relaxation time is strong. In 80% DMSO experiments with KOH as well as with $(\mathrm{CH_3})_4\mathrm{NOH}$ were carried out. The latter base is more effective in converting **4** to **6**. In 85% DMSO only $(\mathrm{CH_3})_4\mathrm{NOH}$ could be used for reasons of solubility.

Table II

Relaxation Times in 80% DMSO with $(\mathrm{CH_3})_4\mathrm{NOH}/(\mathrm{CH_3})_4\mathrm{NCl}$ at 25°

$10^4[\mathbf{4}]_0$, M	$10^4[\mathrm{HO^-}]_0$, M	τ^{-1},[a] sec^{-1}
2.30	1.92	28.5 ± 1.0
2.00	19.0	57.9 ± 1.8
0.80	47.0	71.1 ± 2.0
0.80	98.8	146 ± 5
0.80	190	246 ± 7
0.80	240	266 ± 8
0.80	330	341 ± 13
0.80	380	353 ± 14[b]
0.80	476	424 ± 16[b]
2.20	570	481 ± 20[b]
2.20	761	520 ± 25[b]
2.20	1000	597 ± 30[b]

[a] Determined at 510 or 530 nm. [b] Determined at 390 nm.

Table III

Relaxation Times in 85% DMSO with $(\mathrm{CH_3})_4\mathrm{NOH}/(\mathrm{CH_3})_4\mathrm{NCl}$ at 25°

$10^4[\mathbf{4}]_0$, M	$10^4[\mathbf{4}]_e$,[a] M	$10^4[\mathrm{HO^-}]_0$, M	$10^4[\mathrm{HO^-}]_e$,[a] M	τ^{-1},[b] sec^{-1}
0.21	0.09	1.18	1.06	17.3 ± 0.6
0.33	0.12	1.57	1.36	18.5 ± 0.7
0.33	0.11	1.97	1.74	24.1 ± 0.8
0.21	0.05	2.99	2.83	25.0 ± 0.8
0.50	0.09	3.94	3.54	36.2 ± 1.0
0.66	0.07	7.85	7.26	63.5 ± 2.0
0.66	0.03	15.8	15.2	120 ± 4
0.66	0.01	39.4	38.8	295 ± 12
0.66	0.01	78.8	78.1	507 ± 25
4.64	0.02	192	187	940 ± 60[c]
9.28	0.05	192	183	976 ± 60[c]
6.60	0.03	285	278	1080 ± 70[c]

[a] Equilibrium concentrations; see text. [b] Determined at 510 or 525 nm. [c] Determined at 390 nm.

In 80% DMSO with KOH a large excess of base was used throughout, assuring pseudo-first-order conditions. Equation 5 simplifies to eq 7 where the con-

$$\frac{1}{\tau} = \bar{k}_{-3}\frac{K[\mathrm{HO}]_0}{1 + K[\mathrm{HO}]_0} + \bar{k}_3 \tag{7}$$

centrations are stoichiometric. Figure 2 shows a plot of τ^{-1} *vs.* $[\mathrm{KOH}]_0$. From the intercept in Figure 2 one obtains $\bar{k}_3$. For the determination of $\bar{k}_{-3}$ and K eq 7 is rearranged and inverted to give eq 8. By

$$\frac{1}{\tau^{-1} - \bar{k}_3} = \frac{1}{\bar{k}_{-3}} + \frac{1}{\bar{k}_{-3}K[\mathrm{HO^-}]_0} \tag{8}$$

plotting the left-hand side of eq 8 *vs.* $[\mathrm{HO^-}]_0^{-1}$ ("inversion plot," not shown) one obtains a straight line with intercept $(\bar{k}_{-3})^{-1}$ and slope $(\bar{k}_{-3}K)^{-1}$; $\bar{k}_{-3}$ and K are in Table IV.

Data with $(\mathrm{CH_3})_4\mathrm{NOH}$ as base are summarized in Table II and III. Note that at base concentrations ≥0.038 M in 80% DMSO and ≥0.0192 M in 85% DMSO relaxation was monitored at the wavelength of substrate absorption (~390 nm) with a concomitant use of a higher substrate concentration. This is because the equilibrium favors the complex to such an

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(14) Unpublished results.

TABLE IV

KINETIC AND EQUILIBRIUM PARAMETERS IN VARIOUS SOLVENT MIXTURES AT 25°

% DMSO (v/v)	$\bar{k}_3$, sec^{-1}	$\bar{k}_{-3}$, sec^{-1}	$\bar{K}_{-3}$ (kinetic)	$\bar{K}_{-3}$ (spec)	K (kinetic), M^{-1}	K (spec), M^{-1}	KK_{-3}, (kinetic), M^{-1}	$K\bar{K}_{-3}$ (spec), M^{-1}
2	929 ± 40[a,b]							$4.92 \pm 0.15 \times 10^{-3}$[b]
20	650 ± 20[b,c] (701 ± 30)[d]							$7.60 \pm 0.22 \times 10^{-3}$[b]
50	332 ± 15[d,e]							$5.98 \pm 0.18 \times 10^{-2}$
65	166 ± 8[d]			2.86 ± 0.15[d]		0.305 ± 0.015[d]		0.94 ± 0.05[d] (0.92 ± 0.05)[d,f]
80	53 ± 2[g]	238 ± 20[g]	4.5 ± 0.6[g]		12.7 ± 1.0[g]		57 ± 6[g]	295 ± 15[g]
80	26 ± 1[h]	1050 ± 50[h]	40.4 ± 4.0[h]		13.5 ± 1.0[h]		545 ± 70[h]	530 ± 25[h]
85	9 ± 1[h]	2000 ± 100[h]	222 ± 33[h]		43 ± 2[h]		9550 ± 1800[h]	

[a] Average of two runs at different [KOH]. [b] $\mu = 1\ M$, KOH/KCl. [c] Average of three runs with varying [KOH]. [d] $\mu = 0.5\ M$, KOH/KCl. [e] Average of four runs. [f] From initial slope in Figure 4. [g] $\mu = 0.1\ M$, KOH/KCl. [h] $\mu = 0.1\ M$, $(CH_3)_4NOH/(CH_3)_4NCl$.

extent as to render the relaxation amplitude very small at the wavelengths where the complex absorbs.[15]

In 80% DMSO pseudo-first-order conditions could be used at all but the two lowest base concentrations. At these lowest concentrations $[HO^-]_e$ and $[\mathbf{4}]_e$ are unknown. However, here the equilibrium position strongly favors **4** over **6** and **5** and no significant error is introduced by setting $[HO^-]_e + [\mathbf{4}] = [HO^-]_0 + [\mathbf{4}]_0$.[17] A plot of τ^{-1} *vs.* $[HO^-]_0 + [\mathbf{4}]_0$ (not shown) is similar to the one in Figure 2; from its intercept and from an inversion plot (not shown), including data points at base concentrations $\geq 0.019\ M$,[18] one obtains $\bar{k}_3$, $\bar{k}_{-3}$, and K as listed in Table IV.

In 85% DMSO the equilibrium favors **6** over **4** and **5**, even at relatively low base concentrations. This made it difficult to work under truly pseudo-first-order conditions; as can be seen in Table III, the excess of base over **4** is often less than tenfold. Therefore plotting τ^{-1} *vs.* $([HO^-]_e + [\mathbf{4}]_e)$ according to eq 5 would be preferable to plotting τ^{-1} *vs.* $[HO^-]_0$ (eq 7). The equilibrium concentrations not being known, a plot of τ^{-1} *vs.* $[HO^-]_0$ was first made which yields a set of approximate values for $\bar{k}_3$, $\bar{k}_{-3}$, and K in the manner described for 80% DMSO. From these one can calculate "equilibrium concentrations" and use these in a new plot of τ^{-1}. In principle the procedure has to be repeated until convergence occurs. Since $[HO^-]_0$ is not much different from $[HO]_e + [\mathbf{4}]_e$, the first plot is already a good approximation so that only one iteration was needed to obtain convergence. The first plot yields $\bar{k}_3 = 7 \pm 1$ sec^{-1}, $\bar{k}_{-3} = 2000 \pm 100$ sec^{-1}, $K = 42.7 \pm 2\ M^{-1}$. The equilibrium concentrations based on these values are listed in Table III. From the new plot one obtains an intercept $\bar{k}_3 = 9 \pm 1$ sec^{-1}; from an inversion plot—note that $([HO^-]_e + [\mathbf{4}]_e)$ replaces $[HO^-]_0$ in eq 8—including data at $[HO^-]_0 \geq 3.94 \times 10^{-4}$ M[18] (not shown) $\bar{k}_{-3} = 2000 \pm 100$ sec^{-1} and $K = 42.7 \pm 2\ M^{-1}$ are obtained. Thus only $\bar{k}_3$ changes slightly by the iteration procedure.

Equilibrium Measurements.—Except for the solvents containing 80 and 85% DMSO, kinetic measurements provide only the rate coefficient $\bar{k}_3$. Spectrophotometric evaluation of the fraction of **4** converted to **6** gives access to some equilibrium parameters and thus complements the kinetic study. In 80% DMSO, equilibrium measurements are redundant with the equilibrium data derived from kinetics and thus provide a check for internal consistency. This is highly desirable in view of possible differential salt effects arising from the varying proportion of base and compensating electrolyte.

Light absorption was measured in solutions of **4** containing variable amounts of base, which was always present in large excess; the same ionic strength as for the kinetic runs was used throughout. Because of the mentioned slow hydrolysis, absorbance was determined as a function of time and extrapolated to time zero. Typically the extent of decomposition amounted to about 5% or less within 5 min after mixing, so that a linear extrapolation procedure could be used.

According to Beer's Law the absorption in cuvettes of 1-cm path length is given by eq 9. The measurements were carried out at 510 nm, which is the absorption maximum of **6** (ϵ_6 22,800 in 85% DMSO; see below). At this wavelength ϵ_4 and ϵ_5 are very small (ϵ_4 81 in 20% DMSO, ϵ_5 presumably very similar), which allows some simplifications in the use of eq 9.

$$A = \epsilon_4[\mathbf{4}] + \epsilon_5[\mathbf{5}] + \epsilon_6[\mathbf{6}] \tag{9}$$

The equilibrium concentration of **6** is given by eq 10. With regard to the system under investigation,

$$[\mathbf{6}]_e = \frac{K\bar{K}_{-3}[HO^-]_0}{1 + (K + K\bar{K}_{-3})[HO^-]_0}[\mathbf{4}]_0 \tag{10}$$

$$\bar{K}_{-3} = \frac{\bar{k}_{-3}}{\bar{k}_3} \tag{11}$$

two limiting situations are of interest. In the first the equilibrium positions strongly favors **4** over **5** and **6**, *i.e.*, $(K + K\bar{K}_{-3})$ $[HO]_0 \ll 1$ and also $K[HO^-]_0 \ll 1$ so that eq 10 simplifies to eq 12. At the same time

$$[\mathbf{6}]_e = K\bar{K}_{-3}[HO^-]_0[\mathbf{4}]_0 \tag{12}$$

the relations $[\mathbf{4}]_e \cong [\mathbf{4}]_0$ and $[\mathbf{5}]_e \ll [\mathbf{4}]_0$ hold so that eq 9 becomes eq 13. Note that despite the much

$$\frac{A}{[\mathbf{4}]_0} = \epsilon_4 + \epsilon_6 K\bar{K}_{-3}[HO]_0 \tag{13}$$

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[15] Everything else being equal, the relaxation amplitude is always largest at the absorption wavelength of the disfavored species.[16]

[16] Reference 13, p 935.

[17] In fact, at the very lowest base concentration a more significant uncertainty arises from the possible presence of acidic impurities in the solvent, which may slightly reduce the base concentration in an uncontrolled way, as indicated by our equilibrium measurements described below.

[18] When points at lower base concentrations are included in the inversion plot, deviations from a straight line occur which may be due to uncertainties in the base concentrations[17] and to an increasing error in $\tau^{-1} - \bar{k}_3$ (difference between two large numbers). The possibility of a differential salt effect will be analyzed in the Discussion.

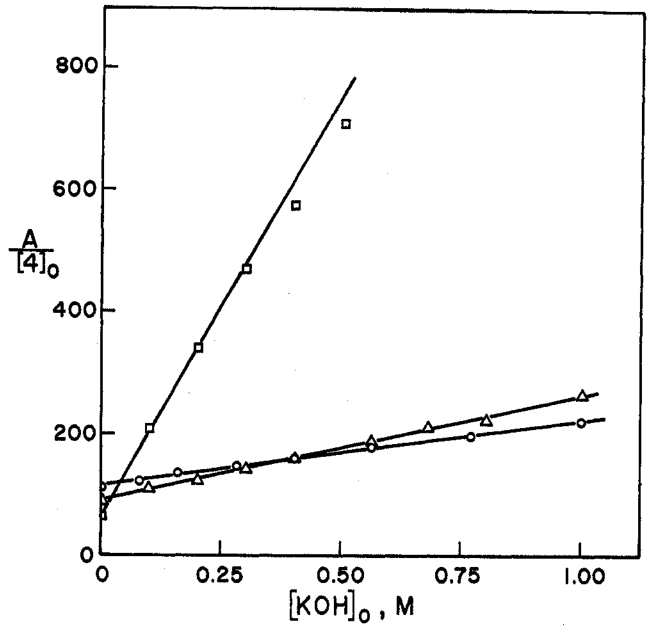

Figure 3.—$A/[4]_0$ (λ 510 nm) as a function of $[\mathrm{KOH}]_0$ according to eq 13: ○, 2% DMSO (v/v), $[4]_0 = 1.87 \times 10^{-3}$ *M*; △, 20% DMSO (v/v), $[4]_0 = 8.6\text{–}9.1 \times 10^{-4}$ *M*; □, 50% DMSO (v/v), $[4]_0 = 9.1 \times 10^{-4}$ *M*.

smaller value of ϵ_4 compared to ϵ_6 the first term in eq 13 may not be negligible since $K\bar{K}_{-3}$ $[\mathrm{HO}^-]_0$ may be quite small.

In the second limiting situation complex **6** is present at equilibrium concentrations comparable to that of **4** so that the last term in eq 9 becomes predominant. Equation 9 then takes the form of eq 14.

$$A = \epsilon_6 \frac{K\bar{K}_{-3}[\mathrm{HO}^-]_0}{1 + (K + K\bar{K}_{-3})[\mathrm{HO}^-]_0}[4]_0 \qquad (14)$$

2, 20, and 50% DMSO (v/v).—The measurements in the three most aqueous solvents are summarized in Figure 3. In 2 and 20% DMSO the plot of $A/[4]_0$ *vs.* base concentration is linear up to the highest concentration used and conforms strictly to eq 13. Thus it is evident, in harmony with the kinetic results, that in these two solvents complex formation is strongly disfavored. In fact substrate concentrations in the order of 10^{-3} *M* had to be used in order to obtain workable absorptions. The possibility that Beer's Law might not hold at such high concentrations was a real one. However, it turned out that absorbance was linear with substrate concentration both in the presence and the absence of base throughout the range used in this study. This finding also excludes the presence of significant amounts of a Meisenheimer complex formed by a possible nucleophilic attack of **5** on **4**.

From the slopes in Figure 3 we calculated $K\bar{K}_{-3}$ as listed in Table IV. Since ϵ_6 cannot be determined in these solvents, the value in 85% DMSO was used instead. Inasmuch as ϵ_6 might be somewhat solvent dependent, $K\bar{K}^{-}{}_{3}$ may be affected by a small systematic error.[19]

In 50% DMSO (v/v) the plot of $A/[4]_0$ *vs.* $[\mathrm{HO}^-]_0$ is linear up to about 0.3 *M* with an indication of a slight downward curvature at higher concentrations. $K\bar{K}_{-3}$ was determined from the slope at $[\mathrm{HO}^-]_0 \leq 0.3$ *M*.

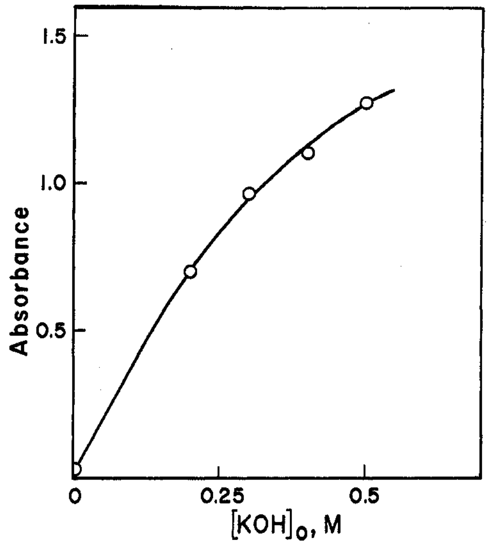

Figure 4.—Absorbance (λ 510 nm) as a function of $[\mathrm{KOH}]_0$ in 65% DMSO (v/v), $[4]_0 = 1.97 \times 10^{-4}$ *M*. Intercept = 0.016 arising from residual absorption of **4**.

65, 80, and 85% DMSO (v/v).—As can be seen from Figures 4–6, the plots of *A vs.* $[\mathrm{HO}^-]_0$ in 65 and 80% DMSO are distinctly curved, indicating that the term $(K + K\bar{K}_{-3})[\mathrm{HO}]_0$ in the denominator of eq 14 becomes appreciable and eventually predominant at higher concentrations. This effect is most pronounced in 80% DMSO with $(\mathrm{CH_3})_4\mathrm{NOH}$.

For evaluation we invert and rearrange eq 14 and obtain eq 15. A plot of the left-hand side of eq 15

$$\frac{\epsilon_6\,[4]_0}{A} = 1 + \frac{1}{\bar{K}_{-3}} + \frac{1}{K\bar{K}_{-3}[\mathrm{HO}^-]_0} \qquad (15)$$

vs. $[\mathrm{HO}^-]_0^{-1}$ (inversion plot) should yield a straight line with an intercept $(1 + 1/\bar{K}_{-3})^{-1}$. Unless $\bar{K}_{-3} \gg 1$, making the intercept indistinguishable from 1, both $\bar{K}_{-3}$ and *K* may be determined; otherwise only $K\bar{K}_{-3}$ can be obtained.

In 65% DMSO only points at $[\mathrm{KOH}]_0 \geq 0.2$ *M* could be obtained because of precipitation of KCl. An inversion plot (not shown) allows the separate determination of $\bar{K}_{-3} = 2.86$ and $K = 0.305\ M^{-1}$. $K\bar{K}_{-3} = 0.92\ M^{-1}$ determined from the initial slope in Figure 4 compares well with $K\bar{K}_{-3} = 0.94\ M^{-1}$ from the slope in the inversion plot and shows consistency of the data.

In 80% DMSO (v/v) the intercepts of both inversion plots (not shown) are indistinguishable from 1, which indicates $\bar{K}_{-3} \gg 1$; with KOH $K\bar{K}_{-3} = 295\ M^{-1}$, with $(\mathrm{CH_3})_4\mathrm{NOH}$ $K\bar{K}_{-3} = 530\ M^{-1}$. A check for consistency with the initial slopes in Figures 5 and 6 is impractical because the lowest base concentrations are somewhat uncertain owing to minute acidic impurities in the solvent. Evidence for this is that *A* increases slightly more than linearly with $[\mathrm{HO}^-]_0$ at the very lowest base concentrations.

In 85% DMSO (v/v) $K\bar{K}_{-3}$ is so large that a plot of *A vs.* $[\mathrm{HO}^-]_0$ levels off at such low base concentrations that their determination is inaccurate owing to the mentioned acidic impurities. Therefore no attempt has been made to determine $K\bar{K}_{-3}$ spectrophotometrically in this solvent. The parameters ϵ_6 22,800 at $\lambda_{\max}$ 510 nm could conveniently be determined in this solvent.

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[19] There is some indication from related systems[14] that ϵ_6 in aqueous solution might be about 20% lower than in a solvent high in DMSO.

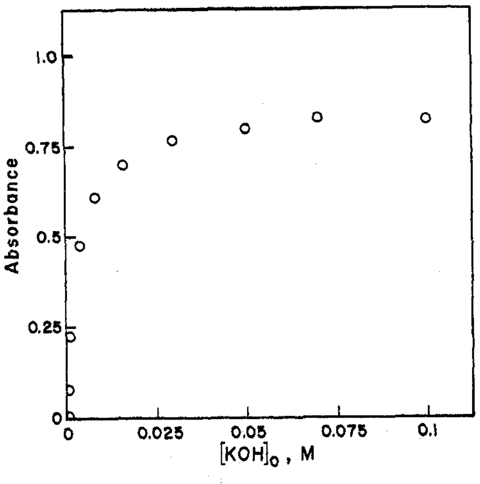

Figure 5.—Absorbance (λ 510 nm) as a function of $[KOH]_0$ in 80% DMSO (v/v), $[4]_0 = 3.79 \times 10^{-5}\ M$.

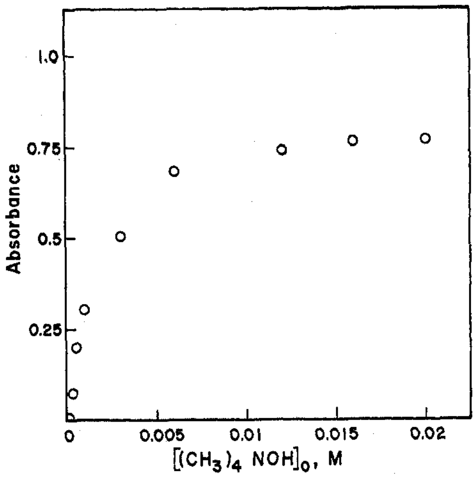

Figure 6.—Absorbance (λ 510 nm) as a function of $[(CH_3)_4NOH]_0$ in 80% DMSO (v/v), $[4]_0 = 3.79 \times 10^{-5}\ M$.

Discussion

Solvent Effects.—Table IV summarizes all kinetic and equilibrium parameters. The stability of **6** relative to **4** depends on both the acidity of the 2-substituted 2-aminoethanol (K) and the complex formation constant ($\bar{K}_{-3}$) proper. Enriching the solvent with DMSO increases the product $K\bar{K}_{-3}$ about 10^5 fold from 2 to 80% DMSO and about 2×10^6 fold from 2 to 85% DMSO. Note that these comparisons are somewhat crude, since the conditions (ionic strength, base) in the various solvents are not all identical.

In media containing ≥65% DMSO (v/v) K and $\bar{K}_{-3}$ could be determined separately by kinetics and/or spectrophotometrically. Both constants increase with DMSO content from 65 to 85%. Based on numerous findings in related Meisenheimer complexes,[20] it is safe to conclude that K_{-3} increases with DMSO content over the entire solvent range. From the kinetic data it is apparent that both an increase in $\bar{K}_{-3}$ as well as a decrease in $\bar{k}_3$ is responsible for augmenting $\bar{K}_{-3}$, again as expected.[20] An increase in the nucleophilic reactivity of the oxy anion by desolvation in conjunction with a stabilization of the polarizable complex and of the transition state by the polarizable DMSO are commonly invoked to rationalize these effects.[20-22] It is noteworthy that a plot (not shown) of log $\bar{k}_3$ as a function of the mole fraction of DMSO is linear in solvents containing ≤65% DMSO. Although there may not be any theoretical significance, it can be useful for predictive purposes.

In interpreting the solvent dependence of K we have to consider two main factors. First, adding DMSO to an aqueous solution decreases the water activity both by dilution and *via* the ability of DMSO to form strong hydrogen bonds with water.[23] This effect, which becomes more pronounced at higher DMSO levels, is expected to increase K.

Second, the activity of both the hydroxide ion and of **5** increases as DMSO replaces water in the solvent.[21] If the activity of the former increases more than that of the latter, K is further augmented, whereas a stronger increase in the activity of **5** would have the opposite effect. A prediction seems rather difficult; all we can say is that between 65 and 85% DMSO the combined result of both effects is to increase K.

Salt Effects.—In order to minimize complications due to salt effects, all our data were collected at constant ionic strength. This does not, however, guarantee the absence of possible special salt effects at the relatively high salt and base concentrations used in this study. This may become a problem for data collected over an extended base concentration range when base and compensating salt exert different salt effects. Our data in 80% DMSO illustrate this point. With the pair KOH/KCl there is a more than fivefold discrepancy between $K\bar{K}_{-3}$ determined spectrophotometrically and from kinetics. Neither set of data taken separately would suggest any problem such as a nonlinear inversion plot except for the normal deviations at very low base concentrations. Nevertheless the discrepancy suggests the operation of a differential salt effect between KOH and KCl. The rationalization is as follows. A differential salt effect is likely to affect $\bar{k}_3$ and $\bar{k}_{-3}$ in opposite ways. The kinetic equilibrium constants are based on data treated according to eq 5, whereas the spectrophotometric constants are calculated from data *via* eq 10. Since these two equations are of quite different form, τ^{-1} and A are expected to respond differently to a differential salt effect and $K\bar{K}_{-3}$ determined by the two methods should be different.

On the other hand, the close agreement between the kinetic and spectrophotometric $K\bar{K}_{-3}$ for the pair $(CH_3)_4NOH/(CH_3)_4NCl$ can probably be taken as evidence that here the differential salt effect is negligible.

In 85% DMSO no such check is possible because spectrophotometric equilibrium determination is impractical. With the pair $(CH_3)_4NOH/(CH_3)_4NCl$ no significant differential salt effect is anticipated.

$\bar{k}_3$ and the Mechanism of Breakdown of the Intermediate Complex 1.—The value of $\bar{k}_3$, particularly in aqueous solution, is pertinent with regard to excluding the proposition[5] of a lyonium ion catalyzed leaving group departure from **3** as part of the mechanism of the nonbase-catalyzed conversion of **1** to **2** (k_2 step

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[20] (a) M. R. Crampton, *Advan. Phys. Org. Chem.*, **3**, 211 (1969); (b) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

[21] (a) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163 (1962); (b) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

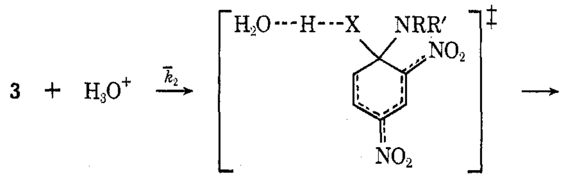
[22] J. W. Larsen, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, **93**, 2910 (1971).

[23] C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 256.

in eq 1). The argument has been briefly developed in a recent review;[4a] it is based upon an analysis of k_3^B/k_2 ratios and particularly k_3^{HO}/k_2 ratios in hydroxylic solvents. These ratios have been determined for a large number of reactions of the general type of eq 1 and have been recently summarized.[4a]

The mechanism suggested by Orvik and Bunnett[5] as a possibility for the k_2 step is represented in eq 16

$$\mathbf{1} + HO^- \overset{K_3^{HO}}{\rightleftharpoons} \mathbf{3} + H_2O \qquad (16a)^{24}$$



$$\mathbf{2} + HX + H_2O \qquad (16b)$$

for the specific case of an aqueous solution. The mechanism of the k_3^B step represented in eq 2 can be recast for catalysis by HO^- (k_3^{HO})[6] as follows.

$$\mathbf{1} + HO^- \overset{K_3^{HO}}{\rightleftharpoons} \mathbf{3} + H_2O \qquad (16a)^{24}$$

$$\mathbf{3} \xrightarrow{\bar{k}_3} \mathbf{2} + X^- \qquad (3)$$

In terms of these two mechanisms both k_3^{HO} and k_2 are composite quantities; they can be written as eq 17 and 18.

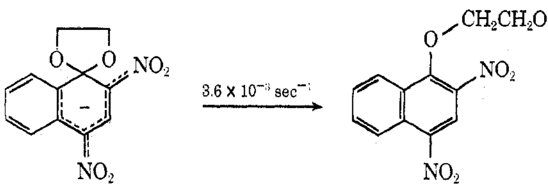
$$k_2 = \bar{k}_2K_3^{HO}[HO^-][H_3O^+] = \bar{k}_2K_3^{HO}K_w = 10^{-14}\bar{k}_2K_3^{HO} \qquad (17)$$

$$k_3^{HO} = \bar{k}_3K_3^{HO} \qquad (18)$$

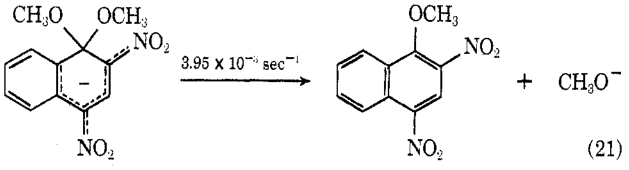
Combining eq 17 and 18 affords eq 19.

$$\frac{k_3^{HO}}{k_2} = 10^{14}\frac{\bar{k}_3}{\bar{k}_2} \qquad (19)$$

We can now estimate a lower limit for the ratio k_3^{HO}/k_2 to be expected on the basis of the mechanism of eq 16. For a leaving group with oxygen as first atom whose pK_a is equal to that of **4** (estimated at 14–15) we assume a $\bar{k}_3$ in the same order of magnitude as the one determined for **6** in 2% DMSO, *i.e.*, 10^3 sec^{-1}. A possible criticism of this assumption is that $\bar{k}_3$ of **6** might be significantly affected by the spiro configuration and thus be a poor model for the $\bar{k}_3$ step of **3**. A comparison between the rates of the two reactions 20[11b] and 21[25] in methanol at 25° shows in fact the leaving group expulsion to be slowed down compared to the noncyclic complex. The difference in rates is larger than the numbers suggest, since the pK_a of 2,4-dinitronaphthyl glycol ether may be 1 to 2 units lower than that of methanol.



(20)



(21)

In conclusion we can assume conservatively that the value of 10^3 sec^{-1} from **6** is a lower limit to be expected for the rate of leaving group departure from **3** in aqueous solution.

For $\bar{k}_2$ we assume the highest possible value, *i.e.*, $\sim 10^{10}$ M^{-1} sec^{-1}, for a diffusion controlled process. Thus we obtain eq 22. Note this is a conservative

$$\frac{k_3^{HO}}{k_2} \geq 10^{14}\frac{10^3}{10^{10}} = 10^7 \qquad (22)$$

estimate, since $\bar{k}_2$ is likely to be considerably slower than diffusion controlled. Furthermore $\bar{k}_3$ is certainly higher than 10^3 for less basic leaving groups. Thus the conclusion $k_3^{HO}/k_2 \gg 10^7$ is more realistic.

The 10^7 value is several orders of magnitude larger than experimental k_3^{HO}/k_2 ratios; these are typically in the range between 200 and 10^4 [4a] with the highest being $\sim 2 \times 10^5$ for the methoxy leaving group.[4a] We conclude that mechanism of eq 16 is untenable as a general proposition. A similar conclusion was reached previously[4a] based on a different model reaction; an alternative mechanism which involves intramolecular acid catalysis of leaving group departure by the ammonium proton in **1** was proposed.[4a]

Experimental Section

Materials.—*N*-2-Hydroxyethyl-*N*-methyl-2,4-dinitrophenylamine was prepared[26] by adding 7.56 g of *N*-methyl-2-aminoethanol to a solution of 10 g of 2,4-dinitrochlorobenzene in 150 ml of ethanol and refluxing for 2 hr. Afer distilling off the ethanol the remaining orange oil was extracted with four portions of 500 ml of ether, dried over $MgSO_4$, and filtered. After evaporation of the ether 11 g (92% yield) of pure oily product remained. Several attempts to induce crystallization failed.

Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.8; H, 4.61; N, 17.45. Found: C, 44.68; H, 4.51; N, 17.52.

DMSO (Baker Analyzed Reagent Grade) and KCl (Mallinckrodt) were used without further purification. KOH solutions were prepared from Titrisol (Merck). $(CH_3)_4NOH$ and $(CH_3)_4NCl$ (Aldrich) were recrystallized from ethanol. Reaction solutions in solvents containing ≤65% DMSO (v/v) were prepared by dispensing the appropriate amount of DMSO into a volumetric flask, then adding an aqueous solution of the other ingredients, and finally filling to the mark with water. The procedure was reversed for solutions containing 80 and 85% DMSO, *i.e.*, DMSO was added last to fill to the mark.

Rate and Equilibrium Measurements.—Kinetic determinations were made on a temperature-jump transient spectrophotometer of Messanlagen Studiengesellschaft Göttingen, Germany. The solutions equilibrated at 21° were subjected to temperature jumps of 4°. Relaxation was usually monitored between 510 and 530 nm, sometimes at 390 nm depending on the amplitude. Each relaxation time reported represents an average of 3 to 4 relaxation curves. Owing to hydrolysis, sometimes several solutions had to be prepared in order to collect all the data. Spectrophotometric equilibrium measurements were carried out in a thermostated Beckman DU spectrophotometer; the spectra in Figure 1 were taken on a Cary 14 spectrophotometer.

Registry No.—**4**, 37580-86-2; **6**, 37541-32-5; DMSO, 67-68-5.

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[24] Note that depending on the pH, on the presence of other bases, and on the concentration and pK_a of the nucleophile, base catalysis of the proton abstraction from **1** to form **3** by these other bases may contribute or even be more important than hydroxide ion catalysis. Since this is a rapid equilibrium step this is of no consequence to the rate of the complete sequence 16a and 16b.

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[26] We are indebted to Mr. T. E. Glass, who prepared this compound.

Acknowledgment.—We thank the National Science Foundation and the Alfred P. Sloan Foundation for their financial support. A Frederick Gardner Cottrell equipment grant is also gratefully acknowledged. We wish to thank Professor J. F. Bunnett for criticism of the manuscript.

Alkali Metal Reduction of Aromatic Nitro Compounds

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Received May 10, 1972

The reaction of nitrobenzene with lithium in tetrahydrofuran gave a mixture of products consisting of azobenzene, 2-anilinoazobenzene, 2,2′- and 2,4′-dianilinoazobenzenes, anilinodibenzopyridazine, and unidentified polymeric azo compounds. Similar products were obtained from the reaction of nitrosobenzene with lithium, whereas the reaction of azoxybenzene gave exclusively azobenzene. It has been suggested that radical anion intermediates are involved in these reactions. Substituted nitro compounds react in a manner analogous to that of nitrobenzene, whereas nitroanilines are unchanged under similar conditions. Compounds such as 4-bromoazoxybenzene and 2-chloronitrobenzene undergo both deoxygenation and dehalogenation reactions on treatment with lithium in THF. 2,2′-Dinitrobiphenyl, on the other hand, gave dibenzopyridazine and a trace of carbazole on treatment with lithium in ether solvents. Under similar conditions, however, 2,2′-dinitrodiphenyl ether did not give any cyclized product.

Aromatic nitro compounds, in general, are reduced in basic medium to the corresponding azoxy, azo, and hydrazo derivatives, whereas they are converted to the corresponding amines under strongly acidic conditions or under catalytic hydrogenation.[2]

The deoxygenation of nitro and nitroso compounds have been brought about by several reagents to give a variety of products depending on the reaction conditions and the nature of the reagents.[3] Aryl nitro compounds, for example, have been reduced to the corresponding azo derivatives in fairly good yields by metal hydrides[4-6] and thallium.[7]

The reaction of nitrobenzene with sodium in liquid ammonia is very complex and may warrant further investigation.[8] However, sodium amalgam has been reported to reduce aromatic nitro compounds to the corresponding azoxy and azo compounds.[2] Lukashevich[9] had observed the formation of mono- and disodium adducts of nitrobenzene, as well as nitrosobenzene in ether solvents. Addition of alkali metals to nitro compounds in aprotic solvents has been reported to give rise to radical anion intermediates and several groups of workers have examined the esr spectra of some of these intermediates.[10] We previously examined the electronic spectra of the radical anions of a few nitrobenzene derivatives and some of the intermediates formed on treatment with alkali metals.[11,12]

The radical anion of nitrobenzene has been reported to undergo oxidation to nitrobenzene in air[13] or disproportionation to nitrobenzene and phenylhydroxylamine in aqueous solution.[14] The chemistry of nitrobenzene radical anion and the products formed in these reactions, however, have not been investigated in detail. This article describes investigations of the reactions of some aromatic nitro compounds with alkali metals in ether solvents.

Results and Discussion

Reaction of Nitrobenzene with Lithium in Tetrahydrofuran.—Treatment of nitrobenzene with lithium in THF under nitrogen atmosphere gave a mixture of products consisting of azobenzene (**2**) (34%), 2-anilinoazobenzene (**3**) (12%), 2,2′-dianilinoazobenzene (**4**) (0.5%), 2,4′-dianilinoazobenzene (**5**) (0.5%), and a trace of anilinodibenzopyridazine (**6**) (Scheme I). In addition, an unidentified mixture of polymeric azo compounds was also isolated from this reaction. The identities of products **2**–**6** have been established on the basis of analytical results and independent syntheses, whereever possible.

The assignment of structure **3** was accomplished on the basis of its elemental analysis ($C_{18}H_{15}N_3$), mass spectrum (mol wt 273), and ir spectrum, which indicated a weak N–H band at 3340 cm^{-1} which was unaffected by dilution (intramolecular hydrogen bonding).[15] The assignment of **3** was confirmed by an independent synthesis from 2-aminodiphenylamine and nitrosobenzene.[16]

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(1) To whom inquiries should be addressed.

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