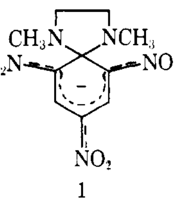
Intermediates in Nucleophilic Aromatic Substitution. XIV.[1] Spiro Meisenheimer Complexes Derived from *N,N'*-Dimethylethylenediamine. Kinetics in Aqueous Dimethyl Sulfoxide

Claude F. Bernasconi*[2a] and François Terrier[2b]

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received May 5, 1975*

Abstract: The rates of the equilibrium formation of the spiro Meisenheimer complexes derived from *N,N'*-dimethyl-*N*-(2,6-dinitro-4-trifluoromethylphenyl)ethylenediamine (**2**) in 70% Me_2SO-30% water and from *N,N'*-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine (**3**) in 70% Me_2SO-30% water and 80% Me_2SO-20% water have been measured. Proton transfer is rate limiting at low buffer concentrations and low pH and partially rate limiting at high buffer concentrations and/or high pH. While protonation of the anionic form of the complex by H_3O^+ is diffusion controlled, the rate of deprotonation of the zwitterionic form of the complex by OH^- is two to three orders of magnitude lower than diffusion controlled, indicating intramolecular hydrogen bonding in the zwitterion. The low values of the proton transfer rates between the buffer components and the complexes lead to the same conclusion. Previous inferences which led to a reconsideration of current notions about the mechanism of base catalysis in nucleophilic aromatic substitutions by amines are reenforced by the present study.



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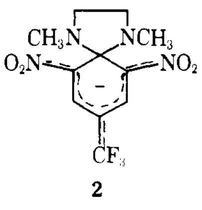

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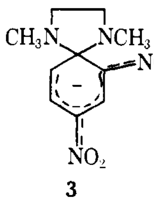

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A recent study[3] of the reversible formation of **1** in aqueous solution has shown that the reaction can be described by Scheme I. The reaction was strongly buffer catalyzed at pH ≤9.5 with a curvilinear dependence on buffer concentration leveling off at high concentration. The interpretation was that below pH 9.5 and at low buffer concentrations, the proton transfer, XH $\rightleftarrows$ X^-, is slow compared with the step AH ← XH; i.e., $k_{-1} > k_3'$, k_{-3}' with

$$k_3' = k_3 + k_3^{OH}[OH^-] + \sum_{i=1}^{n} k_3^{B_i}[B_i] \tag{1}$$

$$k_{-3}' = k_{-3}[H^+] + k_{-3}^{OH} + \sum_{i=1}^{n} k_{-3}^{B_i}[BH_i] \tag{2}$$

where k_3, k_3^{OH}, and $k_3^{B_i}$ refer to the deprotonation of XH by the solvent, by OH^-, and by any general base (buffer, AH, X^-), respectively, and k_{-3}, k_{-3}^{OH}, $k_{-3}^{B_i}$ refer to the protonation of X^- by H_3O^+, by the solvent, and by any general acid (buffer, AH_2^+), respectively.

In this paper, we report a similar study for the two complexes **2** and **3**. The lower stability of these complexes necessitated a change of solvent to 70% Me_2SO-30% water (v/v) and 80% Me_2SO-20% water (v/v). In general our results confirm the conclusions reached with **1**, but they reveal some new features as well. In particular we report, apparently for the first time, rates of proton transfers in aqueous Me_2SO. We also present kinetic evidence of intramolecular hydrogen bonding to the *o*-nitro group in the zwitterionic form (XH). The relevance of our results to the mechanism of base catalysis in nucleophilic aromatic substitutions by amines will be pointed out.

Results

General Features. *N,N'*-Dimethyl-*N*-(2,6-dinitro-4-trifluoromethylphenyl)ethylenediamine and *N,N'*-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine are rapidly converted to the respective complexes **2** and **3** when base is added to their solution in 70% or 80% Me_2SO. This is evident from Figures 1 and 2.

The kinetics of equilibration between the various species of Scheme I was studied over a wide pH range (see Tables I-III). At low pH, buffered solutions were employed while, in strongly basic solutions, tetramethylammonium hydroxide was used; the ionic strength was always kept constant at 0.5 *M* by adding tetramethylammonium chloride as needed.

The kinetic data were all obtained under pseudo-first-order conditions, at 20°. At the lower end of the pH range, the relaxation time (τ) was relatively shortest in the more concentrated buffer solutions and only measurable by the temperature-jump technique.[4] At high pH, the equilibrium favors X^- (and XH) over AH (and AH_2^+) to such an extent that the relaxation amplitude becomes too small for accurate measurements by the temperature-jump method. However, here the relaxation time is longer and within reach of the stopped-flow technique.[5]

Rate Equations. Arguments similar to those presented earlier[3] show that the rate equation developed for **1** in aqueous solution can also be used here. Thus for the reciprocal relaxation time, we have

$$\tau^{-1} = \frac{k_1\left(k_3 + k_3^{OH}[OH^-] + \sum_{i=1}^{n} k_3^{B_i}[B_i]\right)}{k_{-1} + k_3 + k_3^{OH}[OH^-] + \sum_{i=1}^{n} k_3^{B_i}[B_i]} \times \frac{K_A}{K_A + [H^+]} + \frac{k_{-1}\left(k_{-3}[H^+] + k_{-3}^{OH} + \sum_{i=1}^{n} k_{-3}^{B_i}[BH_i]\right)}{k_{-1} + k_3 + k_3^{OH}[OH^-] + \sum_{i=1}^{n} k_3^{B_i}[B_i]} \tag{3}$$

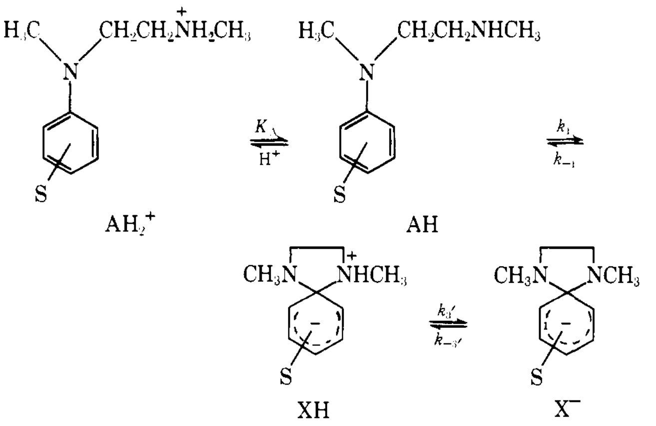
Three special cases are of particular interest.

I. When the concentration of at least one of the B_i's (usually the buffer base) and/or of OH^- is high so that $k_3 + k_3^{OH}[OH^-] + \Sigma k_3^{B_i}[B_i] \gg k_{-1}$, eq 3 becomes

$$\tau_{hi}^{-1} = k_1 \frac{K_A}{K_A + [H^+]} + k_{-1}\frac{[H^+]}{K_X} \tag{4}$$

where K_X is the acid dissociation constant of XH ("hi" in τ_{hi} stands for "high buffer concentration"). Experimentally

Scheme I



this situation manifests itself in the leveling off of a τ^{-1} vs. $[B_i]$ plot.

II. When the concentration of all the B_i's is zero, we have eq 5

$$\tau_{no}^{-1} = \frac{k_1(k_3 + k_3^{OH}[OH^-])}{k_{-1} + k_3 + k_3^{OH}[OH^-]}\frac{K_A}{K_A + [H^+]} + \frac{k_{-1}(k_{-3}[H^+] + k_{-3}^{OH})}{k_{-1} + k_3 + k_3^{OH}[OH^-]} \qquad (5)$$

("no" in τ_{no}^{-1} stands for "no buffer"). This corresponds to the intercepts of plots of τ^{-1} vs. buffer concentration, extrapolated to zero substrate concentration, or of plots of τ^{-1} vs. substrate concentration, extrapolated to zero buffer concentration.

III. At low buffer concentration, plots of τ^{-1} vs. total buffer concentration, $[B_1]_0$,[6] are linear because the $k_3^{B_1}[B_1]$ term[6] in question is small and negligible compared with the other rate terms in the denominators of eq 3. The initial slope of such plots is given by eq 6 where K_{B_1} is the acid dissociation constant of BH_1.

slope =

$$\frac{k_1k_3^{B_1}\dfrac{K_AK_{B_1}}{(K_A + [H^+])(K_{B_1} + [H^+])} + k_{-1}k_{-3}^{B_1}\dfrac{[H^+]}{K_{B_1} + [H^+]}}{k_{-1} + k_3 + k_3^{OH}[OH^-] + \sum_{i=2}^{n} k_3^{B_i}[B_i]} \qquad (6)$$

From eq 4 through 6 and some simplifications thereof, coupled with some equilibrium measurements, most rate constants characterizing Scheme I can be evaluated, as will be shown below.

Kinetic and Equilibrium Measurements of 2 in 70% Me2SO. A representative plot of τ^{-1} vs. buffer concentration is shown in Figure 3 for the *o*-bromophenol buffer at pH 10.58. At this and at higher pH values, low substrate concentrations ($<10^{-4}$ *M*) could be used rendering substrate catalysis negligible. At pH ≤9.54 substantially higher substrate concentrations (up to 1.7×10^{-3} *M*) were necessary in order to achieve measurable complex concentrations. As a consequence, substrate catalysis became significant, particularly at low buffer concentrations. Two typical plots are shown in Figure 4. From plots such as Figure 4, the contribution of substrate catalysis to τ^{-1} was evaluated for any given run. It amounted typically to about 10% of τ^{-1} or less. "Corrected" τ^{-1} values, representing only buffer and OH^- catalysis, were then calculated for use in plots of τ^{-1} vs. buffer concentration.

As is apparent from Figure 3 and was true at all other pH values investigated, the buffer plots do not quite reach the plateau, in contrast to our findings for 1 in aqueous solution.[3] τ_{hi}^{-1} can nevertheless be obtained from "inversion plots" as follows. From the very strong dependence on buffer concentration, it is obvious that, for moderate and high concentrations, we have

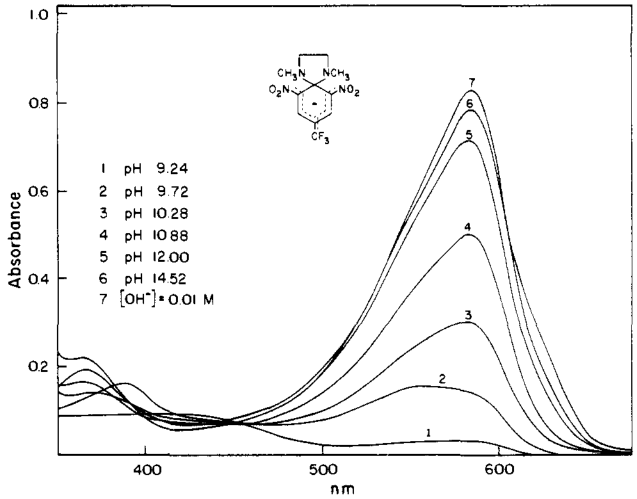


Figure 1. Absorption spectra of *N,N'*-dimethyl-*N*-(2,6-dinitro-4-trifluoromethylphenyl)ethylenediamine hydrochloride at various pH's (buffer solutions) and in strong base, in 70% Me2SO-30% water (v/v); $[AH_2^+]_0 = 3.52 \times 10^{-5}$ *M*. Note that the irregularities below 400 nm are due to some absorption by the buffers.

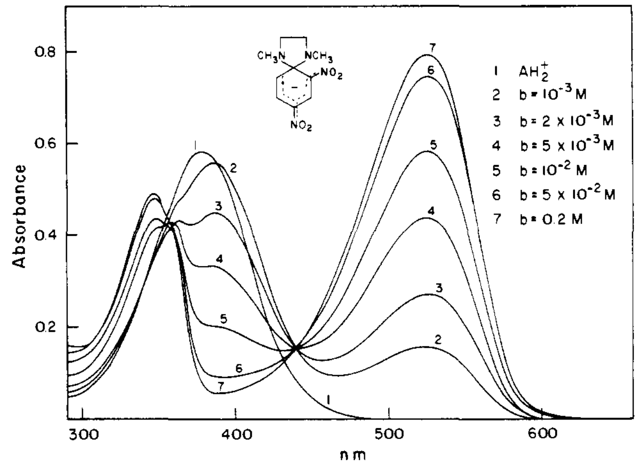


Figure 2. Absorption spectra of *N,N'*-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine hydrochloride at various base (OH^-) concentrations, in 70% Me2SO-30% water (v/v); $[AH_2^+]_0 = 3.78 \times 10^{-5}$ *M*.

$$k_3^{B_1}[B_1] \gg k_3 + k_3^{OH}[OH^-] + \sum_{i=2}^{n} k_3^{B_i}[B_i]$$

and

$$k_{-3}^{B_1}[BH_1] \gg k_{-3}[H^+] + k_{-3}^{OH} + \sum_{i=2}^{n} k_{-3}^{B_i}[BH_i]$$

Thus eq 3 simplifies to

$$\tau^{-1} = \frac{k_1k_3^{B_1}[B_1]}{k_{-1} + k_3^{B_1}[B_1]}\frac{K_A}{K_A + [H^+]} + \frac{k_{-1}k_{-3}^{B_1}[BH_1]}{k_{-1} + k_3^{B_1}[B_1]} \qquad (7)$$

which upon inversion and some arithmetic manipulation affords

$$\tau = \tau_{hi} + \tau_{hi}\frac{k_{-1}(K_{B_1} + [H^+])}{k_3^{B}K_{B_1}[B_1]_0} \qquad (8)$$

Table I. Kinetics of 2 in 70% Me_2SO at 20°

Buffer		pH	τ_{no}^{-1},[a, b] sec^{-1}	10^{-4} × slope,[b, c] M^{-1} sec^{-1}	τ_{hi}^{-1},[d] sec^{-1}	$k_{-1}/k_3^{B_1}$,[e] M
p-Cyanophenol	1:4	8.64	69 ± 5			
	1:3	8.76	55 ± 3			
	1:2	8.94	35.5 ± 2.5	6.69 ± 0.21	40000 ± 6000	0.185
	1:1	9.24	22 ± 3	5.20 ± 0.15	21000 ± 2000	0.210
	2:1	9.54	14 ± 2	3.84 ± 0.12	12500 ± 1000	0.205
o-Bromophenol	1:1	10.58	7 ± 2	1.22 ± 0.03	2860 ± 300	0.106
	2:1	10.88	≈2	1.43 ± 0.04	2380 ± 200	0.106
	4:1	11.18	≈2	1.34 ± 0.04	2000 ± 100	0.104
p-Chlorophenol	1:3	11.06	≈2	0.28 ± 0.01		
	1:1	11.54	≈2	0.52 ± 0.02	1750 ± 80	0.163
Phenol	1:3	12.00	≈2.5	0.25 ± 0.01		
	1:1	12.48	≈2.5	0.52 ± 0.02		
	3:1	12.96	≈2.5	0.82 ± 0.03		
Benzimidazole	1:1	13.01	≈3	0.49 ± 0.02		
	3:1	13.49	≈2.5	0.83 ± 0.03		
Indazole	1:3	14.04	≈2	0.24 ± 0.01		
	1:1	14.52	12 ± 2	0.59 ± 0.02		
$[Me_4N^+OH^-]$	0.0005	14.81	29.0 ± 2.0			
	0.0007	14.96	42.8 ± 1.0			
	0.001	15.11	58.6 ± 1.0			
	0.0015	15.29	95.2 ± 1.0			
	0.002	15.41	117 ± 2			
	0.0025	15.51	139 ± 2			
	0.003	15.59	187 ± 6			
	0.004	15.71	212 ± 5			
	0.005	15.81	245 ± 12			
	0.010	16.11	396 ± 25			

[a] τ_{no}^{-1} equals τ^{-1} extrapolated to zero buffer and zero substrate concentration. [b] From data obtained by the temperature-jump method at pH ≤11.54, from data obtained by the stopped-flow method at pH ≥11.54. [c] Initial slope of τ^{-1} vs. $[B_1]_0$. [d] Reciprocal of intercept of plot according to eq 8, from data obtained by the temperature-jump method. [e] Calculated from eq 9.

Table II. Kinetics of 3 in 70% Me_2SO at 20°

Buffer		pH	τ_{no}^{-1},[a, b] sec^{-1}	10^{-3} × slope,[b, c] M^{-1} sec^{-1}	τ_{hi}^{-1},[d] sec^{-1}	$k_{-1}/k_3^{B_1}$,[e] M
p-Chlorophenol	2:1	11.84	0 ± 1	10.3 ± 0.3	2550 ± 300	0.158
Phenol	1:3	12.00	0 ± 0.5	2.50 ± 0.07	1850 ± 150	0.137
	1:1	12.48	0.4 ± 0.2	2.08 ± 0.06	600 ± 75	0.138
Benzimidazole	1:1	13.01	0 ± 0.1	0.50 ± 0.02	180 ± 20	0.160
	3:1	13.49	0.4 ± 0.1	0.28 ± 0.01	100 ± 10	0.244
	5:1	13.71	0.28 ± 0.05	0.180 ± 0.006	50 ± 5	0.195
$[Me_4N^+OH^-]$	0.0005	14.81	0.050 ± 0.001			
	0.001	15.11	0.089 ± 0.002			
	0.002	15.41	0.166 ± 0.003			
	0.003	15.59	0.23 ± 0.004			
	0.005	15.81	0.34 ± 0.007			
	0.010	16.11	0.65 ± 0.013			
	0.020	16.41	1.17 ± 0.02			
	0.030	16.59	1.42 ± 0.03			
	0.050	16.81	1.87 ± 0.04			
	0.100	17.11	2.39 ± 0.05			
	0.200	17.41	2.93 ± 0.06			
	0.250	17.51	3.22 ± 0.06			
	0.400	17.71	3.65 ± 0.07			

[a] Same as in Table I. [b] From data obtained by the stopped-flow method. [c–e] Same as in Table 1.

where $[B_1]_0$ is the *total* buffer concentration. Plots of τ vs. $[B_1]_0^{-1}$ are in fact linear as can be seen for a representative example in Figure 3. The intercept yields τ_{hi}, whereas the slope permits one to find $k_{-1}/k_3^{B_1}$ according to

$$\frac{k_{-1}}{k_3^{B_1}} = \frac{\text{slope}}{\tau_{hi}} \frac{K_{B_1}}{K_{B_1} + [H^+]} \tag{9}$$

Table 1 summarizes all τ_{hi}^{-1} (eq 4) and τ_{no}^{-1} (eq 5) values as well as the initial slopes (eq 6) of the buffer plots, and $k_{-1}/k_3^{B_1}$ calculated from eq 9.

The acid dissociation constant of XH, K_X, and the product K_AK_1 could be determined by the same spectrophotometric procedure used before.[3] A plot according to eq 10

$$\frac{OD[H^+]}{l[AH]_0} = \epsilon_{XH}K_AK_1 + \epsilon_{X^-}\frac{K_AK_1K_X}{[H^+]} \tag{10}$$

where OD is the optical density at the λ_{max} (585 nm) of X^-, l the path length, and ϵ_{XH} and ϵ_{X^-} the molar extinction coefficients of XH and X^-, respectively, is shown in Figure 5. Assuming $\epsilon_{XH} = \epsilon_{X^-} = 2.28 \times 10^4$ (ϵ_{X^-} determined at high pH where all substrate is in the form of X^-), we obtain K_X = slope/intercept = 3.25×10^{-8} M and K_AK_1 = intercept/ϵ_{X^-} = 8.95×10^{-12} M.

Calculation of Rate Coefficients for 2 in 70% Me_2SO. The various rate constants, summarized in Table IV, were calculated as follows. (1) A plot of τ_{hi}^{-1} vs. $[H^+]$ is linear,

Table III. Kinetics of 3 in 80% Me_2SO at 20°

Buffer		pH	τ_{no}^{-1},[a, b] sec^{-1}	10^{-3} × slope,[b, c] M^{-1} sec^{-1}	τ_{hi}^{-1},[d] sec^{-1}	$k_{-1}/k_3^{B_1}$,[e] M
o-Bromophenol	3:1	11.91	−2 ± 5	4.30 ± 0.20	1000 ± 200	0.165
p-Chlorophenol	1:1	12.44	2 ± 2	1.55 ± 0.07	330 ± 70	0.091
Phenol	1:3	12.96	0.08 ± 0.10	0.26 ± 0.01	100 ± 20	0.071
Phenol	1:1	13.56	0.12 ± 0.10	0.20 ± 0.01	50 ± 5	0.112
$[Me_4N^+OH^-]$	0.0005	16.59	0.012 ± 0.0002			
	0.001	16.89	0.044 ± 0.0009			
	0.002	17.19	0.107 ± 0.002			
	0.003	17.37	0.168 ± 0.003			
	0.005	17.59	0.291 ± 0.006			
	0.010	17.89	0.613 ± 0.012			
	0.020	18.19	1.08 ± 0.02			
	0.030	18.37	1.50 ± 0.03			
	0.050	18.59	2.12 ± 0.04			
	0.100	18.89	2.88 ± 0.06			
	0.200	19.19	3.80 ± 0.08			
	0.250	19.29	4.15 ± 0.08			

[a–e] Same as in Table II.

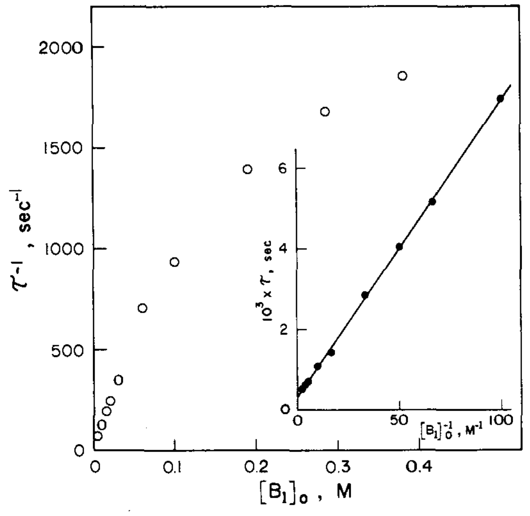


Figure 3. Representative plot of τ^{-1} vs. total buffer concentration for **2** in 70% Me_2SO; o-bromophenol buffer, pH 10.58. (●) Inversion plot according to eq 8.

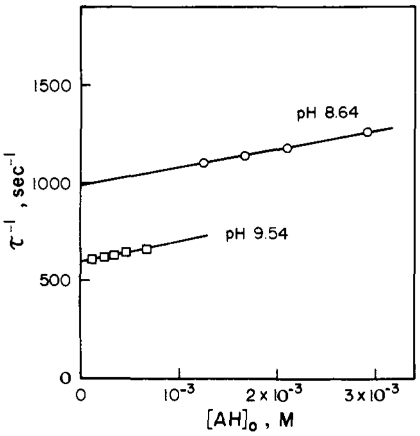


Figure 4. Representative plots of τ^{-1} vs. substrate concentration for **2** in 70% Me_2SO: (○) p-cyanophenol, $[B_1]_0 = 1.2 \times 10^{-2}$ M, pH 8.64; (□) p-cyanophenol, $[B_1]_0 = 1.5 \times 10^{-2}$ M, pH 9.54.

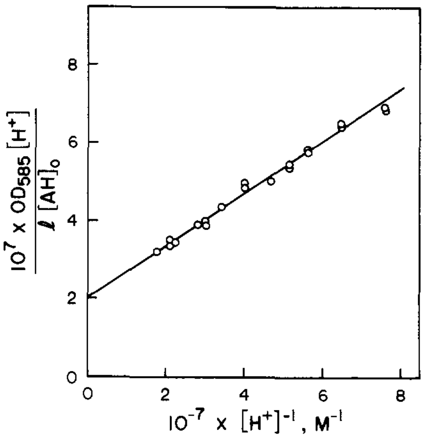


Figure 5. Determination of K_X and K_1K_A for **2** in 70% Me_2SO; plot according to eq 10.

indicating $K_A \gg [H^+]$ (see eq 4). From its intercept, we obtain $k_1 = 1700 \pm 100$ sec^{-1} and from its slope, $k_{-1}/K_X = 3.64 \pm 0.55 \times 10^{13}$ M^{-1} sec^{-1}. In conjunction with K_X determined spectrophotometrically, this yields $k_{-1} = 1.18 \pm 0.30 \times 10^6$ sec^{-1} and $K_1 = k_1/k_{-1} = 1.44 \pm 0.50 \times 10^{-3}$; in combination with K_AK_1 measured spectrophotometrically, we also obtain $K_A = 6.3 \pm 1.5 \times 10^{-9}$ M or $pK_A = 8.20 \pm 0.1$. This value for K_A is consistent with the linearity of the plot of τ_{hi}^{-1} vs. $[H^+]$ since at pH >9.3 $K_A \gg [H^+]$, whereas at pH ≤9.3 the k_1 term in eq 4 is negligible compared with the k_{-1} term.

(2) At pH ≤9.54, a plot of τ_{no}^{-1} vs. $[H^+]$ is linear. At these pH values, the equilibrium strongly favors AH_2^+ and AH over XH and X^- so that the first term in eq 5 is negligible. Furthermore $k_{-1} \gg k_3^{OH}[OH^-] + k_3$ even if the highest possible values for k_3^{OH} ($\approx 2 \times 10^{10}$ M^{-1} sec^{-1}) and for k_3 ($k_3 = k_{-3}K_X \approx 5 \times 10^{10}K_X \approx 1.6 \times 10^3$) are assumed; hence eq 5 reduces to

$$\tau_{no}^{-1} = k_{-3}[H^+] + k_{-3}^{OH} \tag{11}$$

From the slope, we obtain $k_{-3} = 2.86 \pm 0.50 \times 10^{10}$ M^{-1} sec^{-1}; this also allows calculation of $k_3 = K_Xk_{-3} = 9.3 \pm 2.5 \times 10^2$ sec^{-1}. The intercept (k_{-3}^{OH}) is too small for an accurate evaluation of k_{-3}^{OH}.

(3) In strongly basic solutions (pH ≥14.8), $k_{-3}^{OH} \gg k_{-3}[H^+]$, $k_3^{OH}[OH^-] \gg k_3$, and $K_A \gg [H^+]$; since also $k_{-1} \gg k_3$, eq 5 now reduces to

$$\tau_{no}^{-1} = \frac{k_1k_3^{OH}[OH^-]}{k_{-1} + k_3^{OH}[OH^-]} + \frac{k_{-1}k_{-3}^{OH}}{k_{-1} + k_3^{OH}[OH^-]} \tag{12}$$

As long as $k_{-1} \gg k_3^{OH}[OH^-]$ this further reduces to

$$\tau_{no}^{-1} = \frac{k_1k_3^{OH}}{k_{-1}}[OH^-] + k_{-3}^{OH} \tag{13}$$

Table IV. Rate and Equilibrium Constants Obtained from τ_{hi} and τ_{no}

	1 in H_2O[a]	**2** in 70% Me_2SO[b]	**3** in 70% Me_2SO[b]	**3** in 80% Me_2SO[b]
k_{-1}/K_X, M^{-1} sec^{-1}		$3.64 \pm 0.55 \times 10^{13}$	$1.8 \pm 0.2 \times 10^{15}$	$8.5 \pm 1.5 \times 10^{14}$
k_1, sec^{-1}	1.20×10^{3}	$1.7 \pm 0.2 \times 10^{3}$	4.0 ± 0.5	6.25 ± 0.40
k_{-1}, sec^{-1}	1.93×10^{5}	$1.18 \pm 0.30 \times 10^{6}$	$2.4 \pm 0.2 \times 10^{6}$[c]	$4.3 \pm 0.6 \times 10^{5}$[d] (4.3×10^{6})[c]
$K_1 = k_1/k_{-1}$	6.21×10^{-3}	$1.44 \pm 0.50 \times 10^{-3}$	$1.7 \pm 0.4 \times 10^{-6}$[c]	$1.47 \pm 0.35 \times 10^{-5}$[d] (1.47×10^{-6})[c]
K_X, M[e]	2.29×10^{-7}	$3.25 \pm 0.30 \times 10^{-8}$[f]	$1.33 \pm 0.30 \times 10^{-9}$[c,g]	$5 \pm 2 \times 10^{-10}$[d,g] (5×10^{-9})[c,g]
pK_X[e]	6.64	7.49 ± 0.04[f]	8.87 ± 0.05[c,g]	9.3 ± 0.2[d,g] (8.3)[c,g]
k_3^{OH}, M^{-1} sec^{-1}	5.2×10^{9}	$4.2 \pm 1.5 \times 10^{7}$	4.2×10^{7}[c]	4.2×10^{6}[d] (4.2×10^{7})[c]
k_{-3}^{OH}, sec^{-1}	4.45×10^{2}	$1.0 \pm 0.4 \times 10^{-3}$	$2.5 \pm 0.8 \times 10^{-2}$[c,h]	$1.04 \pm 0.30 \times 10^{-4}$[c,h]
k_3, sec^{-1}[e]	1.35×10^{4}	$9.3 \pm 2.5 \times 10^{2}$	38[i]	14.3[d,i] (143)[c,i]
k_{-3}, M^{-1} sec^{-1}	5.9×10^{10}	$2.86 \pm 0.50 \times 10^{10}$	2.86×10^{10}[i]	2.86×10^{10}[i]
K_A, M	2.23×10^{-9}	$6.30 \pm 1.50 \times 10^{-9}$		
pK_A	8.65	8.20 ± 0.10		
K_S	1.96×10^{-14}	7.85×10^{-19}[j]	7.85×10^{-19}[j]	1.29×10^{-20}[j]

[a] At 25°, $\mu = 0.5$ M maintained by NaCl (ref 3). [b] At 20°, $\mu = 0.5$ M maintained by Me_4NCl (this work). [c] Assuming $k_3^{OH} = 4 \times 10^7$ as for **2**; see text. [d] Assuming $k_3^{OH} = 4.2 \times 10^6$, reduced tenfold from 70% Me_2SO due to hydrogen bonding; see text. [e] Not statistically corrected. [f] Determined spectrophotometrically. [g] Determined from k_{-1}/K_X. [h] Calculated as $k_{-3}^{OH} = k_3^{OH}K_S/K_X$. [i] Assuming $k_{-3} = 2.86 \times 10^{10}$ as for **2**; see text. [j] See Experimental Section.

In the range of $[OH^-] = 5 \times 10^{-4}$ to 2.5×10^{-3} M, a plot of τ_{no}^{-1} vs. $[OH^-]$ is in fact linear; the slope provides $k_1k_3^{OH}/k_{-1} = 5.7 \pm 0.3 \times 10^4$ M^{-1} sec^{-1}. The intercept, k_{-3}^{OH}, is again too small and uncertain.

At $[OH^-] \geq 2.5 \times 10^{-3}$ M, a plot of τ_{no}^{-1} vs. $[OH^-]$ becomes curved. An "inversion plot" according to eq 14

$$\tau_{no} = \frac{1}{k_1} + \frac{k_{-1}}{k_1k_3^{OH}[OH^-]} \tag{14}$$

(note that the second term of eq 12 has been omitted in taking the inverse because it becomes negligible at these base concentrations) is linear. The reciprocal of its intercept provides $k_1 = 1670 \pm 300$ sec^{-1}, in excellent agreement with the value of 1700 obtained from τ_{hi}^{-1}. The reciprocal slope provides $k_1k_3^{OH}/k_{-1} = 6.2 \pm 0.2 \times 10^4$ M^{-1} sec^{-1} which compares well with the same quantity ($5.7 \pm 0.3 \times 10^4$) obtained via eq 13.

In conjunction with k_{-1} and k_1, we now find $k_3^{OH} = 4.2 \pm 1.5 \times 10^7$ M^{-1} sec^{-1} and $k_{-3}^{OH} = k_3^{OH}$ $K_S/K_X = 1.0 \pm 0.4 \times 10^{-3}$ sec^{-1}, where K_S is the self-ionization constant of the solvent.

(4) If the values summarized in Table IV are substituted into eq 5 for the pH range 11 to 14, the only significant term is

$$\tau_{no}^{-1} = k_1k_3/k_{-1} \tag{15}$$

With k_1, k_3, and k_{-1} from Table IV, eq 15 predicts $\tau_{no}^{-1} = 1.34 \pm 0.70$ sec^{-1}. This is consistent with our observation that τ_{no}^{-1} is in fact constant in this range, with an approximate value of 2.5 sec^{-1}. In view of the difficulty in determining τ_{no}^{-1} accurately (small intercepts of buffer plots), the agreement between the two numbers is very good indeed.

(5) The proton transfer rate constants $k_3^{B_1}$ and $k_{-3}^{B_1}$ for the buffers were calculated from eq 16

$$k_3^{B_1} = \frac{\text{slope}(k_{-1})}{k_1\dfrac{K_A}{K_A + [H^+]} + k_{-1}\dfrac{[H^+]}{K_X}} \frac{K_{B_1} + [H^+]}{K_{B_1}} \tag{16}$$

which is obtained from eq 6 after replacing $k_{-3}^{B_1}$ with $k_3^{B_1}K_{B_1}/K_X$ and neglecting

$$k_3 + k_3^{OH}[OH^-] + \sum_{i=2}^{n} k_3^{B_i}[B_i]$$

which is small compared with k_{-1}. Average values from different pH solutions are summarized in Table V. In some cases, $k_3^{B_1}$ could also be calculated from the $k_{-1}/k_3^{B_1}$ values (eq 9); they are included in Table V. The agreement between the numbers obtained from the two methods is excellent.

Kinetics of 3 in 70% and 80% Me_2SO. Plots of τ^{-1} vs. buffer and vs. substrate concentration, respectively, and of τ^{-1} vs. $[OH^-]$ at high pH are qualitatively very similar to those for **2**. Tables II and III summarize our results which were obtained by the same procedures as for **2**. Due to a lower complex stability, no data below pH 11.84 could be obtained with reasonable accuracy; this also precluded a spectrophotometric determination of K_X.

The rate and equilibrium constants summarized in Tables IV and V were calculated in the same manner as for **2** except for the following variations.

(1) The intercepts (k_1) of the plots of τ_{hi}^{-1} vs. $[H^+]$ are very small and thus give only approximate values, $k_1 \approx 10 \pm 5$ sec^{-1} in 70% Me_2SO, $k_1 \approx 12 \pm 5$ sec^{-1} in 80% Me_2SO; k_1 could, however, be obtained more accurately from inversion plots according to eq 14 at high pH, and it is these values which are reported in Table IV.

(2) It was difficult to get accurate data on τ_{no}^{-1} in the buffered solutions because of very strong buffer dependence which leads to small intercepts. Hence plots of τ_{no}^{-1} vs. $[H^+]$ according to eq 11 are merely scatter diagrams, and k_{-3} cannot be determined at all. We assume that k_{-3} is the same as for **2**; this is doubtless a very good assumption in 70% Me_2SO and probably also in 80% Me_2SO (see Discussion).

(3) Because K_X cannot be determined directly, neither can k_{-1} nor k_3^{OH}; the values given in Table IV were calculated based on the hypothesis that, in 70% Me_2SO, k_3^{OH} is the same as for **2**, in 80% Me_2SO tenfold smaller than in 70% Me_2SO. With these assumptions, to be analyzed in the Discussion, k_{-1} is calculated from the slope of the plot of τ_{no}^{-1} vs. $[OH^-]$, eq 13 (or τ_{no} vs. $[OH^-]^{-1}$, eq 14). This, in turn, allows calculation of K_X from k_{-1}/K_X which is the slope of τ_{hi}^{-1} vs. $[H^+]$. Note that an over- or underestimation of k_3^{OH} leads to a proportional over- or underestimation in k_{-1}, in K_X as well as in $k_3^{B_1}$, but leaves k_{-3}^{OH} and $k_{-3}^{BH_1}$ unaffected.

Discussion

Reliability of Data Analysis. Ion pairing of buffer base or OH^- with the tetramethylammonium ion and association of the type $BH_1 + B_1^- \rightleftarrows BH_1 \ldots B_1^-$ are possible features which in principle could lead to a distortion of our data. For example, the curvature in the buffer plots (Figure 3) could arise from such phenomena rather than from a change in the rate-limiting step of the mechanism. By working at constant ionic strength, ion pairing, if significant at all, should,

Table V. Proton Transfer Rates for $XH + B_1 \rightleftarrows X^- + BH_1$

BH_1	pK_{B_1}	pK_X	$\Delta pK = pK_{B_1} - pK_X$	$10^{-6} \times k_3^{B_1}$,[a] M^{-1} sec^{-1}	$k_{-3}^{B_1}$,[b] M^{-1} sec^{-1}
			A. **2** in 70% Me_2SO		
p-Cyanophenol	9.24	7.49	1.75	5.7[c] (5.9)[q]	1.0×10^5
o-Bromophenol	10.58	7.49	3.09	10.2[d] (11.2)[q]	8.3×10^3
p-Chlorophenol	11.54	7.49	4.05	6.9[e] (7.2)[q]	6.1×10^2
Phenol	12.48	7.49	4.99	7.3[f]	7.4×10^1
Benzimidazole	13.01	7.49	5.52	7.2[g]	2.2×10^1
Indazole	14.52	7.49	7.03	7.5[h]	7.0×10^{-1}
			B. **3** in 70% Me_2SO		
p-Chlorophenol	11.54	8.87[i]	2.67[i]	14.9[i,j] (15.2)[q]	3.2×10^4
Phenol	12.48	8.87[i]	3.61[i]	14.9[i,k] (17.5)[q]	3.7×10^3
Benzimidazole	13.01	8.87[i]	4.14[i]	11.0[i,l] (11.9)[q]	1.1×10^3
			C. **3** in 80% Me_2SO		
o-Bromophenol	11.43	9.3[m]	2.1[m]	2.44[m,o] (2.61)[m,q]	1.8×10^4
		(8.3)[n]	(3.1)[n]	[24.4][n]	[1.8×10^4]
p-Chlorophenol	12.44	9.3[m]	3.1[m]	4.00[m,o] (4.73)[m,q]	2.9×10^3
		(8.3)[n]	(4.1)[n]	[40.0][n]	[2.9×10^3]
Phenol	13.56	9.3[m]	4.3[m]	4.45[m,p] (4.73)[m,q]	2.5×10^2
		(8.3)[n]	(5.3)[n]	[44.5][n]	[2.5×10^2]

[a] From eq 16. [b] $k_{-3}^{B_1} = k_3^{B_1} K_B / K_X$. [c] Average from three slopes: 5.91×10^6 (pH 8.94), 5.82×10^6 (pH 9.24), 5.44×10^6 (pH 9.54). [d] Average from three slopes: 1.01×10^7 (pH 10.58), 1.06×10^7 (pH 10.88), 0.99×10^7 (pH 11.18). [e] Average from two slopes: 6.6×10^6 (pH 11.06), 6.8×10^6 (pH 11.54). [f] Average from three slopes: 6.95×10^6 (pH 12.00), 7.32×10^6 (pH 12.48), 7.60×10^6 (pH 12.96). [g] Average from two slopes: 6.8×10^6 (pH 13.01), 7.7×10^6 (pH 13.49). [h] Average from two slopes: 6.7×10^6 (pH 14.04), 8.2×10^6 (pH 14.52). [i] K_X and k_{-1} obtained by assuming $k_3^{OH} = 4.2 \times 10^7$ as for **2**. [j] From one slope only. [k] Average from two slopes: 1.32×10^7 (pH 12.00), 1.66×10^7 (pH 12.48). [l] Average from three slopes: 1.34×10^7 (pH 13.01), 0.9×10^7 (pH 13.49), 1.05×10^7 (pH 13.71). [m] K_X and k_{-1} obtained by assuming $k_3^{OH} = 4.2 \times 10^6$, reduced tenfold from 70% Me_2SO due to hydrogen bonding; see text. [n] K_X and k_{-1} obtained by assuming $k_3^{OH} = 4.2 \times 10^7$ as for **2** in 70% Me_2SO. [o] From one slope only. [p] Average from two slopes: 5.5×10^6 (pH 12.96), 3.41×10^6 (pH 13.56). [q] From $k_{-1}/k_3^{B_1}$.

however, be independent of buffer concentration and hence should not affect the curvature of these plots.

That association between buffer base and buffer acid[7] is not significant, at least in 70% Me_2SO, can be inferred from a number of observations.

(1) The pH values of solutions made up of buffers in the $[B_1]$:$[BH_1]$ ratios 1:3, 1:1, and 3:1 differ by the theoretical amount of 0.48 unit up to the highest concentrations used in this study.

(2) The same value for k_1 is obtained from data points collected at high buffer concentrations (k_1 = intercept of plot of τ_{hi}^{-1} vs. $[H^+]$) and those collected in the absence of any buffer (eq 14). We also note that $k_1 k_3^{OH}/k_{-1}$ determined at low $[OH^-]$ (eq 13) is about the same as that determined at high $[OH^-]$ (eq 14), showing the reliability of our data treatment in basic solutions as well.

(3) Where such a comparison is possible, the $k_{-1}/k_3^{B_1}$ values (Tables I-III), for any given buffer system, are independent of the buffer ratio within the experimental error;[8] this is significant because $k_{-1}/k_3^{B_1}$ was obtained at *high* buffer concentrations where association would be most pronounced. Furthermore, $k_3^{B_1}$ values calculated from initial slopes, i.e., from data at *low* buffer concentrations, are in excellent agreement with those calculated from $k_{-1}/k_3^{B_1}$ (data at high buffer concentrations), again demonstrating the consistency of our analysis.

In 80% Me_2SO, the situation is a little less clear cut. The pH intervals for various buffer ratios are slightly dependent on buffer concentration, indicating some association. On the other hand, the close agreement between the $k_3^{B_1}$ values obtained at low and at high buffer concentrations again indicates that our analysis is basically sound; association thus seems to have a negligible effect on our results even in 80% Me_2SO.

Effects of Structure and Solvent on k_1, k_{-1}, and K_1. Based on numerous analogies,[9,10] one expects, for a given solvent, k_1 and K_1 to decrease in the order **1** > **2** > **3** and k_{-1} to increase in the order **1** < **2** < **3**. For example, in the case of methoxide ion attack on the respective anisoles to form the 1,1 complex in methanol, one has $k_1 = 4.0\ M^{-1}$ sec^{-1}, $k_{-1} = 5 \times 10^{-4}$ sec^{-1}, and $K_1 = 7700\ M^{-1}$ for 2,4,6-trinitroanisole,[11] $k_1 \approx 0.4\ M^{-1}$ sec^{-1}, $k_{-1} \approx 5.3$ sec^{-1} and $K_1 \approx 0.07$ for 2,6-dinitro-4-trifluoromethylanisole,[12] and $k_1 = 2.12 \times 10^{-3}\ M^{-1}$ sec^{-1}, $k_{-1} = 42$ sec^{-1}, and $K_1 = 5.06 \times 10^{-5}$ for 2,4-dinitroanisole.[14,15]

On the other hand, adding Me_2SO to a protic solvent has the effect of increasing k_1 and K_1, and of decreasing k_{-1}.[9]

The qualitative picture emerging from Table IV is entirely consistent with these expectations. Thus, despite the lower temperature, the change from water to 70% Me_2SO apparently slightly overcompensates the expected decrease in k_1 caused by substituting a 4-nitro group with a 4-trifluoromethyl group. On the other hand, k_{-1} is about sixfold larger for **2** compared with that for **1**; i.e., the change in solvent does not fully compensate for the change in structure. The above effects are not unexpected on the basis of the anisole-MeO^- reactions since there the replacement of the 4-nitro group with a 4-trifluoromethyl group lowers the k_1 only about tenfold but increases k_{-1} about 10^4-fold. In fact, based on this comparison, one might have expected that k_{-1} for **2** in 70% Me_2SO is more than sixfold larger than for **1** in water. Intramolecular hydrogen bonding to the *o*-nitro group, for which evidence is presented below, may be responsible for the low value of k_{-1} since the activation energy of the k_{-1} process would have to include the energy required to break this hydrogen bond.

In comparing **2** and **3** in 70% Me_2SO, we note that k_1 for **3** is 425-fold smaller than for **2**, while k_{-1} for **3** is 2-fold larger than for **2**. This compares rather closely with the anisoles where MeO^- attack on 2,4-dinitroanisole is about 200 times slower but dissociation about 8 times faster than for 2,6-dinitro-4-trifluoromethylanisole. It should be noted that, in the case of **3**, k_{-1} was calculated based on the *assumed* value $k_3^{OH} = 4.7 \times 10^7\ M^{-1}$ sec^{-1}. Below it will be shown that it would not be unreasonable to assume a slightly higher value for k_3^{OH}. As a consequence, k_{-1} for **3** in 70% Me_2SO would also become larger, by the same relative amount as k_3^{OH}

The effect of changing the solvent from 70 to 80% Me_2SO on k_1 also appears "reasonable", though a slightly greater increase might have been anticipated;[9,13] for a discussion of k_{-1}, see below.

Rates of Proton Transfer. H_3O^+ and OH^-. The high rate constant, $k_{-3} = 2.86 \times 10^{10}\ M^{-1}\ sec^{-1}$, for the protonation of **2** by H_3O^+ makes it evident that this reaction is diffusion controlled,[16] just as the analogous reaction of **1** in aqueous solution.[17] It is the first report of such a proton transfer rate in this solvent system; in view of Delpuech's[19] recent findings on proton transfers in pure Me_2SO, our result is not surprising.

Although we could not determine k_{-3} for the reaction of **3** with H_3O^+ in the same solvent, there can be little doubt that it must be about the same as for **2**. In our analysis, we assumed that this is also true in 80% Me_2SO.

A most interesting finding is that k_3^{OH} for **2** in 70% Me_2SO is about 100-fold lower than that for **1** in water. Since the increased viscosity can at best explain a rate decrease by a factor of 3 to 4, two other possible interpretations come to mind: (1) ion pairing between OH^- and $(CH_3)_4N^+$; (2) intramolecular hydrogen bonding to the *o*-nitro group in XH.[16]

In view of the rather high dielectric constant ($D \approx 69.5$ in 70% Me_2SO, $D \approx 64.7$ in 80% Me_2SO[18]), ion pairing is not expected to be very significant; based on comparisons with known systems,[20,21] the ion association constant is expected to be smaller than 10, possibly very much smaller. Even with an association constant of 10, there would still be 20% free ions; even if only the free ions were reactive, this could still not account for more than a fivefold reduction in k_3^{OH}. It is clear that intramolecular hydrogen bonding must be an important (additional) factor. One would in fact expect such hydrogen bonding to become increasingly important when changing the solvent from water to 70% Me_2SO. In a related system, weak intramolecular hydrogen bonding was invoked even in a 10% dioxane-90% water solution in order to explain a value of $2 \times 10^8\ M^{-1}\ sec^{-1}$ for k_3^{OH}.[22]

For **3**, k_3^{OH} could not be measured; in 70% Me_2SO, we have simply assumed k_3^{OH} to be the same as that for **2**. This implies that the strength of the intramolecular hydrogen bond is the same in both complexes. It is conceivable that the negative charge density on the *o*-nitro group of **3** is slightly different from the one on the two *o*-nitro groups of **2**; this would probably affect the hydrogen bond strength. Let us assume that, in **3**, the *p*-nitro group bears a substantially larger fraction of the charge than the *o*-nitro group, as suggested by the numerous observations that the *p*-nitro group is more effective in stabilizing σ-complexes.[10b,23,24] If we further assume that, in **2**, most of the negative charge resides on the nitro groups so that any one carries a larger fraction than does the *o*-nitro group in **3**, the hydrogen bond in **3** would presumably be weaker than that in **2**, and thus k_3^{OH} for **3** should be assumed $>4.2 \times 10^7\ M^{-1}\ sec^{-1}$. As mentioned above, k_{-1} would become larger too, thus increasing the difference in k_{-1} between **2** and **3** in the direction of that found in the reaction of methoxide ion with anisoles. On the other hand, the inverse assumption, viz., that it is **3** which has a stronger hydrogen bond, would bring k_{-1} for **3** closer to or even below that of **2** which would be difficult to rationalize. Based on these considerations, we tentatively conclude that any difference in the hydrogen bonding strength between **2** and **3**, if significant at all, is more likely to be in the direction **2** > **3**.

In going from 70 to 80% Me_2SO, an even stronger hydrogen bond is expected. We have assumed that this lowers k_3^{OH} by another factor of 10; with this assumption, one obtains a "reasonable" k_{-1} value as well as "reasonable" $k_3^{B_i}$ values (see below). The factor could, however, well be only 3 to 5; the alternative assumption that there is no further strengthening of the hydrogen bond in the less polar solvent would, however, lead to k_{-1} and $k_3^{B_i}$ values which are larger in 80 than 70% Me_2SO, an unrealistic result.

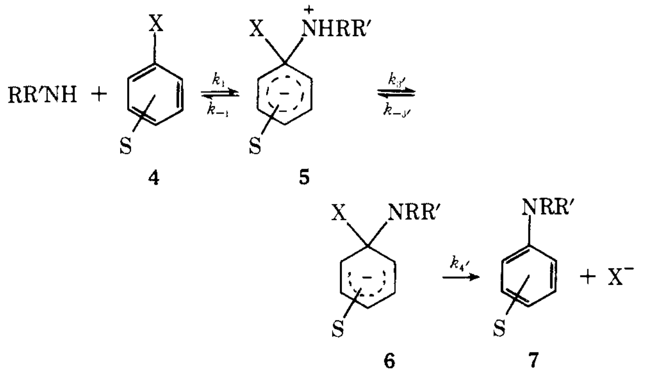
Rates of Proton Transfer. Buffers. The rate constants of the reactions $XH + B_i^- \rightleftarrows X^- + BH_i$ are summarized in Table V. The data for **2** in 70% Me_2SO are again the most reliable since they do not depend on any assumptions as to the value of k_3^{OH}. The reaction from left to right is thermodynamically favored ($\Delta pK > 0$) for all buffers, and thus no great dependence of $k_3^{B_i}$ on pK_{B_i} is expected.[16] Indeed the $k_3^{B_i}$ values differ very little; they are about four to eight times lower than k_3^{OH} which is comparable to other proton transfer reactions in aqueous solution.[16,25] It is nevertheless somewhat surprising that, even for B_i = *p*-cyanophenolate ion, for which ΔpK is less than 2, $k_3^{B_i}$ is not significantly lower than those for the buffers with much larger ΔpK values. The possible significance of these findings with respect to the mechanism of deprotonation of intramolecularly hydrogen bonded species has been discussed elsewhere.[26]

The $k_3^{B_i}$ values for **3** in 70% Me_2SO are all slightly higher than for **2** despite smaller ΔpK values. This could be an artifact because the $k_3^{B_i}$'s depend on which value is assumed for k_3^{OH}. However, lowering the $k_3^{B_i}$'s is only possible by assuming a lower k_3^{OH}, implying a stronger hydrogen bond in **3** compared with **2**, contrary to our earlier conclusions. A more satisfactory explanation of the higher $k_3^{B_i}$ values is therefore in terms of a reduced steric hindrance (one instead of two *o*-nitro groups) to the attack by B_i.

In 80% Me_2SO, the $k_3^{B_i}$ values obtained under the assumption that k_3^{OH} is lowered tenfold compared with 70% Me_2SO are about three to four times lower than that for **3** in 70% Me_2SO. This is consistent with stronger hydrogen bonding in the less aqueous solvent and was one of the criteria in assuming a tenfold decrease in k_3^{OH}.

Implications with Respect to the Mechanism of Base Catalysis in Nucleophilic Aromatic Substitution. The most widely accepted mechanism of base catalysis in nucleophilic aromatic substitutions by amines[27] is shown in Scheme II.

Scheme II



It was originally proposed by Bunnett;[28] k_3' and k_{-3}' are defined by eq 1 and 2, respectively, whereas k_4' is defined by eq 17

$$k_4' = k_4[H^+] + k_4^{OH} + \sum_{i=1}^{n} k_4^{B_i}[BH_i] \qquad (17)$$

where k_4 and $k_4^{B_i}$ refer to hydronium ion and general acid catalyzed leaving group expulsion, respectively, and k_4^{OH} to a nonassisted or solvent assisted pathway. In basic solutions, the $k_4[H^+]$ term is expected to be very small and thus is usually not included.

The second-order rate constant for the over-all reaction of Scheme II, derived by treating both **5** and **6** as steady states, is given by

$$k_A = \frac{k_1 k_3' k_4'}{k_{-1}k_{-3}' + k_{-1}k_4' + k_3'k_4'} \qquad (18)$$

In all discussions of this mechanism, it has been assumed that the equilibrium between **5** and **6** is rapidly established and that the k_4' step is rate limiting (SB-GA mechanism[27]). In fact, assuming $k_{-3}' \gg k_4'$ leads to the following simplification of eq 18

$$k_A = \frac{k_1 k_3' k_4'}{k_{-1}k_{-3}' + k_3'k_4'} = \frac{k_1 K_3' k_4'}{k_{-1} + K_3'k_4'} \qquad (19)^{29}$$

with

$$K_3' = \frac{k_3'}{k_{-3}'} = \frac{k_3}{k_{-3}[\text{H}^+]} = \frac{K_X}{[\text{H}^+]} = \frac{k_3^{\text{OH}}[\text{OH}^-]}{k_{-3}^{\text{OH}}} =$$
$$K_3^{\text{OH}}[\text{OH}^-] = \frac{k_3^{\text{B}_i}[\text{B}_i]}{k_{-3}^{\text{B}_i}[\text{BH}_i]} = K_3^{\text{B}_i}\frac{[\text{B}_i]}{[\text{BH}_i]} \qquad (20)^{29}$$

According to this view, base catalysis is observable as long as k_{-1} is larger than or similar to $K_3'k_4'$; when $K_3'k_4' \gg k_{-1}$ we have $k_A = k_1$.

If on the contrary one assumes $k_{-3}' \ll k_4'$, eq 18 reduces to

$$k_A = (k_1 k_3')/(k_{-1} + k_3') \qquad (21)$$

If this situation prevails, base catalysis is observable as long as k_{-1} is larger than or similar to k_3' and is a consequence of rate-limiting deprotonation of **5**. This interpretation of base catalysis in nucleophilic aromatic substitutions was the first to be proposed[30] but later rejected[27,28] on grounds that proton transfers are generally very fast.[16] We shall show now that the results of this study suggest that this second mechanism makes more sense in some cases, in particular when dealing with a substrate carrying a not too sluggish leaving group and a weakly basic amine nucleophile, and the reaction is conducted in a strongly basic solution.

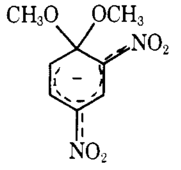
The reaction of 2,4-dinitrofluorobenzene with *N*-methylaniline in 60% dioxane–40% water[30] is a case in point. The reaction is strongly catalyzed by NaOH; treating the data according to eq 19 suggests $K_3^{\text{OH}}k_4^{\text{OH}}/k_{-1} = 50$, while treating them according to eq 21 leads to $k_3^{\text{OH}}/k_{-1} = 50$. Let us estmate k_3', k_{-3}', k_4', and k_{-1} under a typical set of reaction conditions, viz., [RR'NH] = 0.2 *M* and [NaOH] = 0.01 *M*. Since the $k_3^{\text{OH}}[\text{OH}^-]$ term is likely to be the main contributor to k_3', we shall equate k_3' with $k_3^{\text{OH}}[\text{OH}^-]$; this and subsequent simplifying assumptions are not critical to the argument because we shall only deal with orders of magnitude. Based on the results obtained with the spiro complexes, k_3^{OH} is assumed to be 5×10^9 M^{-1} sec^{-1} in water but is probably somewhat lower in 60% dioxane due to intramolecular hydrogen bonding as found in 70% or 80% Me$_2$SO; an additional rate-reducing factor may be ion pairing. Thus in a 0.01 *M* NaOH solution, $k_3' \leq 5 \times 10^7$ sec^{-1}.

With this result, we can estimate k_{-3}' by means of eq 22

$$k_{-3}' = \frac{k_3'}{K_3'} = \frac{k_3'}{K_X}[\text{H}^+] \qquad (22)$$

Let us assume that the pK_X of **5** in water is about 1 unit lower than the p*K* of *N*-methylanilinium ion, a rather conservative estimate in view of the 2 units difference between pK_X and pK_A for **1** (Table IV). This leads to $k_{-3}' \leq 0.5$ sec^{-1}. In 60% dioxane, K_X may go down somewhat as suggested by the data on the spiro complexes in aqueous Me$_2$SO, but this will be overcompensated for by a strong decrease in the self ionization constant of the solvent (pK_S estimated to be close to 17[31]) which reduces [H$^+$] in eq 22 by more than two orders of magnitude. On top of that comes the likely reduction of k_3' due to intramolecular hydrogen bonding and/or ion pairing. Thus in 60% dioxane, $k_{-3}' \ll 0.5$ sec^{-1}, probably $<10^{-2}$ sec^{-1}; this is very slow indeed and suggests that $k_4' \gg k_{-3}'$.

In fact, a rough guide of what to expect for k_4' can be obtained from the rate ($k = 42$ sec^{-1} [15]) of methoxide ion expulsion from **8** in methanol. Based on the reactions, in methanol, of piperidine with 2,4-dinitroanisole[32] and with 2,4-dinitrofluorobenzene,[33] respectively, fluoride ion is a much better leaving group than methoxide ion. Hence k_{-4}' must indeed be several orders of magnitude greater than k_{-3}', and we conclude that base catalysis is a consequence of rate-limiting deprotonation of **5**.



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Having established the mechanism, we can now estimate k_{-1} from the above mentioned ratio $k_3^{\text{OH}}/k_{-1} = 50$: $k_{-1} \leq 10^8$ sec^{-1}, probably $\ll 10^8$ sec^{-1}. This is entirely reasonable in view of the high k_{-1} values for the spiro complexes. In fact, the value of 2×10^5 sec^{-1} in the case of **1**, which is more strongly activated and which involves an appreciably less basic nucleophile than the reaction of *N*-methylaniline with 2,4-dinitrofluorobenzene is surprisingly high; the same is true for $k_{-1} = 2.4 \times 10^6$ sec^{-1} in the case of **3** in the strongly complex-stabilizing solvent 70% Me$_2$SO. Release of steric strain may be responsible for the unusually high ring opening rates in spiro complexes, as has been suggested previously by Crampton.[34]

Generalizations. Rate-limiting proton transfer is likely to prevail in reactions of relatively weak basic amines with 1-substituted 2,4-dinitrobenzenes, if the leaving group is not too sluggish and the reaction is conducted in basic solution. This is because k_{-3}' is small (eq 22), and there is a good chance that $k_4' \gg k_{-3}'$. With substrates activated by, for example, one nitro group only, k_4' is much higher still so that this mechanism should prevail even with more basic amines.

An interesting question is whether the reaction of 2,4-dinitrofluorobenzene with *N*-methylaniline in *ethanol* solution,[30] which is strongly catalyzed by acetate ion in an acetic acid-acetate buffer (ratio 1:1), also proceeds by this mechanism. Here k_{-3}' is much higher than in basic solution, and it is conceivable that here $k_{-3}' \gg k_4'$. This would imply the SB-GA mechanism. However, in view of Jencks' rule,[35] this is unlikely.[36]

Experimental Section

Materials. *N,N'*-Dimethyl-*N*-(2,6-dinitro-4-trifluoromethylphenyl)ethylenediamine hydrochloride and *N,N'*-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine hydrochloride (AH$_2^+$) were prepared by adding a solution of 5 g (40 mmol) of *N,N'*-dimethylethylenediamine monohydrochloride in 20 ml of ethanol (prepared in situ from *N,N'*-dimethylethylenediamine and HCl) dropwise to a solution of 5.4 g (20 mmol) of 4-trifluoromethyl-2,6-dinitrochlorobenzene (Pierce) or 4.05 g (20 mmol) of 2,4-dinitrochlorobenzene (Aldrich) in 40 ml of ethanol. The monohydrochloride of *N,N'*-dimethylethylenediamine rather than the free base was used in order to prevent nucleophilic attack on two aromatic substrates to form "dimers", e.g., *N,N'*-dimethyl-*N,N'*-bis(2,4-dinitrophenyl)ethylenediamine. Nevertheless, small amounts of yellow precipitates were formed, presumably the dimers, which were filtered off. The filtrates were concentrated to about 20 ml which led to precipitation of the products. These were redissolved in slightly acidic water at room temperature. After filtration, the aqueous solutions were concentrated, whereupon the pure products separated as orange or yellow crystals. Trifluoromethyl derivative, orange crystals, had: mp 208°; yield 30%. *Anal.* Calcd for $C_{11}H_{14}N_4O_4ClF_3$: C, 36.83; H, 3.93; N, 15.62. Found: C, 36.78; H, 3.83; N, 15.84. 2,4-Dinitro derivative, yellow crystals, had: mp 198°; yield 53%. Anal. Calcd for $C_{10}H_{15}N_4O_4Cl$: C, 41.31; H, 5.20; N, 19.27. Found: C, 41.44; H, 5.18; N, 19.39.

The corresponding Meisenheimer complexes **2** and **3** (X^-) show a maximum absorption at 585 nm (ϵ 22800) and 525 (21000), respectively, and were characterized by ^1H NMR spectroscopy by adding 1 drop of 5 *N* sodium hydroxide to a solution of the parent hydrochlorides AH_2^+ in Me_2SO-d_6. Whereas a clear spectrum was obtained for **3**, for **2** the spectrum was complicated, apparently representing a mixture of **2** and the complex formed from OH^- attack at the 3-position of **2**. For **2**: Δ 8.48 (q, ring), 3.03 (s, CH_2N), 2.63 (s, CH_3N). For **3**: Δ 8.62 (d, 1, ring), 6.88 (q, 1, ring), 4.99 (d, 1, ring), 3.03 (m, 4, CH_2N), 2.14 (s, 6, CH_3N).

The buffers (Aldrich) were used without further purification except for *p*-cyanophenol, benzimidazole, and indazole which were recrystallized from ethanol. HCl solutions were made from Titrisol, tetramethylammonium hydroxide solutions from commercial (Eastman) 25% aqueous solutions.

Rate Measurements. The temperature-jump experiments were carried out on a temperature-jump transient spectrophotometer of Messanlagen Studiengesellschaft, Göttingen, Germany. The solutions, equilibrated at 17° (2,6-dinitro-4-trifluoromethyl derivative) or 15° (2,4-dinitro derivative), were subjected to temperature-jumps of 3 or 5°, respectively (end temperature 20°). Relaxation was monitored at 585 or 525 nm. Each relaxation time reported represents the average of at least three oscilloscope pictures.

Stopped-flow determinations were performed at 20° on a Durrum stopped-flow spectrophotometer. The relaxation times so obtained also represent average values of at least three independent measurements.

pH Measurements. Since no pH measurements have been made in water-Me_2SO mixtures containing 0.5 *M* $NMe_4^+Cl^-$, we had to build an acidity scale in the two mixtures used. We followed the procedure of Hallé et al.[7a] which has already proved adequate for many solvent mixtures and used the following cell at 20°.

$$\underbrace{\begin{array}{c}\text{calomel, saturated}\\ \text{aqueous KCl}\end{array}\left|\begin{array}{l}\text{saturated KCl in}\\ \text{water—Me}_2\text{SO}\\ \text{(30—70 or 20—80)}\end{array}\right.}_{\text{Reference (S)}}\left|\begin{array}{l}\text{test solution}\\ \text{ in water—Me}_2\text{SO, H}_2\text{ (g, 1 atm), Pt}\\ \text{ (30—70 or 20—80)}\\ \text{ionic strength}\\ \text{ 0.5 }M\text{ (acidic,}\\ \text{ basic or buffer}\\ \text{ solution)}\end{array}\right.$$

The potential of the hydrogen electrode is measured relative to an internal reference in the solvent mixture S. The pH values so obtained and listed in the various tables are relative to the standard state in each solvent H_2O-Me_2SO-0.5 *M* $NMe_4^+Cl^-$. Details of all the experiments and results, including the determination of K_S, will be reported in a separate paper.

By means of the pH scales so determined, we could standardize a glass electrode, the response of which was perfectly linear with a slope close to 58 mV per pH unit in the pH ranges studied (8.64-13.49 in 70% Me_2SO; 11.91-13.56 in 80% Me_2SO). The pH measurements were made with a Corning Model 110 pH meter.

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$$k_A = \frac{k_1(K_3^{OH}k_4^{OH}[OH^-] + \Sigma K_3^{B_i}k_4^{B_i}[B_i])}{k_{-1} + K_3^{OH}k_4^{OH}[OH^-] + \Sigma K_3^{B_i}k_4^{B_i}[B_i]}$$

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