Rate-Limiting Proton Transfer in the Formation of Meisenheimer Complexes between 1,3,5-Trinitrobenzene and Amines. The Effect of Dimethyl Sulfoxide on Proton-Transfer Rates. Relative Leaving-Group Abilities of Amines and Alkoxide Ions[1]

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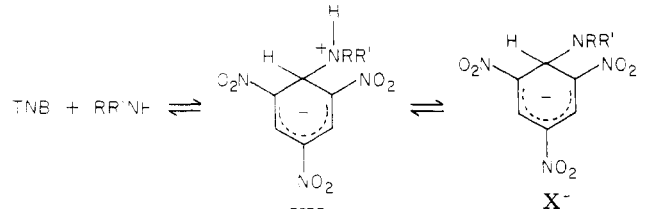
The kinetics of the reversible Meisenheimer complex formation between 1,3,5-trinitrobenzene and methylamine, dimethylamine in 10% dioxane–90% water (v/v), piperidine, pyrrolidine, and *n*-butylamine in 30% Me_2SO–70% water (v/v) has been studied by the temperature-jump method. At low pH and low amine concentration proton transfer between the zwitterionic and the anionic Meisenheimer complex is rate limiting, while at high pH and/or high amine concentration nucleophilic attack by the amine is rate determining. Our results necessitate a reinterpretation of data published in 1970 on the reactions of 1,3,5-trinitrobenzene with piperidine and pyrrolidine in 10% dioxane. Deprotonation of the zwitterionic complex by OH^- is about tenfold slower in 30% Me_2SO compared to 10% dioxane, possibly due to intramolecular hydrogen bonding of the ammonio proton to the *o*-nitro group, or due to *inter*molecular hydrogen bonding to Me_2SO. A comparison of rate constants of expulsion of amines with those of expulsion of alkoxide ions shows that for a given basicity amines and alkoxide ions have comparable leaving-group abilities. This behavior is intermediate between that of tetrahedral addition compounds of the *N,O*-trimethylenephthalimidium ion, where amines are better leaving groups than alkoxide ions of the same p*K* by a factor of about 10^5, and that of tetrahedral addition compounds of formaldehyde, where alkoxide ions appear to be much better leaving groups than amines of the same p*K*.

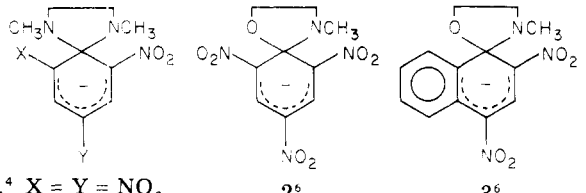
In 1970 we published a kinetic study concerning the reactions of 1,3,5-trinitrobenzene (TNB) with piperidine, pyrrolidine, and *n*-butylamine to form the respective Meisenheimer complexes as shown in eq 1.[2] The data,



(1)

obtained by the temperature-jump method in 10% dioxane–90% water (v/v), were interpreted based on the assumption that the proton-transfer equilibrium between XH and X^- is always rapidly established compared to the reaction TNB + RR'NH ⇌ XH. In the light of commonly held notions at that time this assumption seemed reasonable.[3]

However, recent findings that proton transfer can be rate limiting in the formation of spiro Meisenheimer complexes such as 1–3[4-6] led us to reconsider the TNB–amine systems. We have studied the reactions of methylamine and dimethylamine in 10% dioxane–90% water (v/v) and reinvestigated the reactions of piperidine, pyrrolidine, and *n*-butylamine, but this time in 30% Me_2SO-70% water (v/v). This latter solvent offered the advantage of permitting us to study the reactions over a wider range of concentrations, particularly at low amine concentrations, because of a better solubility of TNB and a somewhat enhanced complex stability which compensate for an unfavorable equilibrium position at low amine concentrations.



1a,[4] X = Y = NO_2
b,[5] X = H; Y = NO_2
c,[5] X = NO_2; Y = CF_3

2[6] **3**[6]

Our new results show that proton transfer is rate limiting under certain conditions; this forces us to reinterpret some of the earlier data.

Results

General Features. In a typical experiment a solution of TNB in an amine–amine hydrochloride buffer was subjected to a temperature jump of 2.5 °C and the ensuing relaxation effect was monitored spectrophotometrically in the range of 450–575 nm, i.e., at or near an absorption maximum of the complex X^-. The relaxation time was determined as a function of amine concentration at constant pH for a number of different pH values. In most runs the amine concentration was in large excess over the TNB concentration, thus assuring pseudo-first-order conditions.

In a few runs at low amine concentration the amine and TNB concentrations were of comparable magnitude making the first step in the forward direction of eq 2 (see below) non-pseudo first order. This was of no consequence, however, because in these runs the relaxation time was virtually completely determined by the rate of the reverse reaction, which always met the requirements of pseudo-first-order conditions.

The ionic strength was kept constant at 0.5 M by the addition of KCl in 30% Me_2SO, and of NaCl in 10% dioxane.

(1) This is part 20 in the series Intermediates in Nucleophilic Aromatic Substitution. Part 19: C. F. Bernasconi and J. R. Gandler, *J. Am. Chem. Soc.*, **100**, 8117 (1978).
(2) C. F. Bernasconi, *J. Am. Chem. Soc.*, **92**, 129 (1970).
(3) (a) C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, 3, 33 (1973); (b) J. A. Orvik and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 2417 (1970); (c) J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, **35**, 70 (1970); (d) J. F. Bunnett and C. F. Bernasconi, *J. Am. Chem. Soc.*, **87**, 5209 (1965); (e) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3217 (1965).
(4) C. F. Bernasconi and C. L. Gehriger, *J. Am. Chem. Soc.*, **96**, 1092 (1974).
(5) C. F. Bernasconi and F. Terrier, *J. Am. Chem. Soc.*, **97**, 7458 (1975).
(6) C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *J. Am. Chem. Soc.*, **98**, 8451 (1976).

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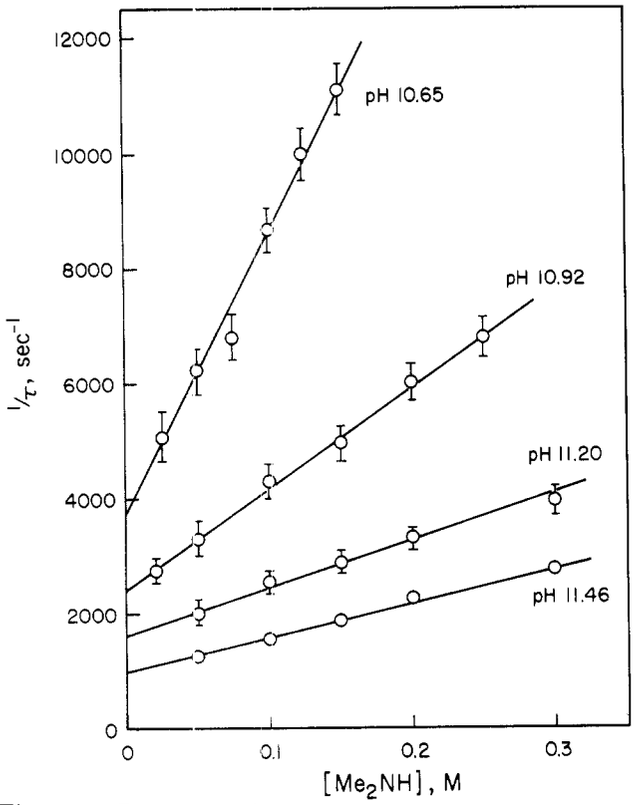


Figure 1. Reaction of dimethylamine with TNB in 10% dioxane–90% water (v/v) at 25 °C, μ = 0.5 M (NaCl).

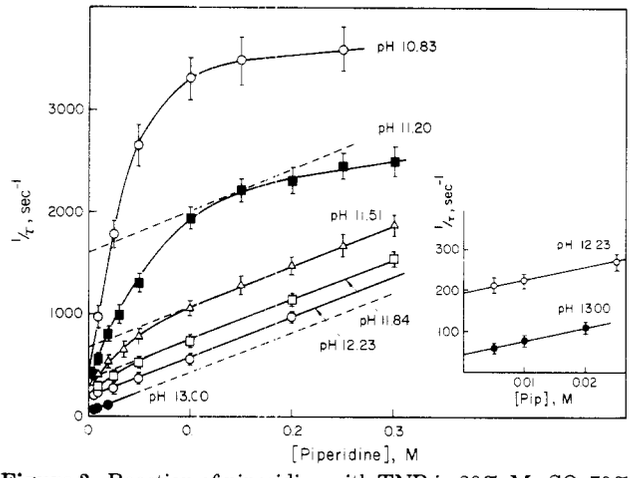


Figure 2. Reaction of piperidine with TNB in 30% Me_2SO–70% water (v/v) at 20 °C, μ = 0.5 M (KCl).

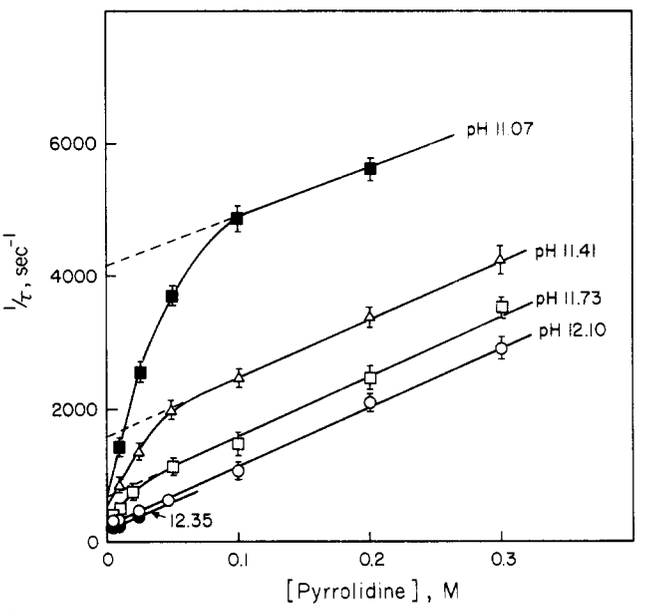


Figure 3. Reaction of pyrrolidine with TNB in 30% Me_2SO–70% water (v/v) at 20 °C, μ = 0.5 M (KCl).

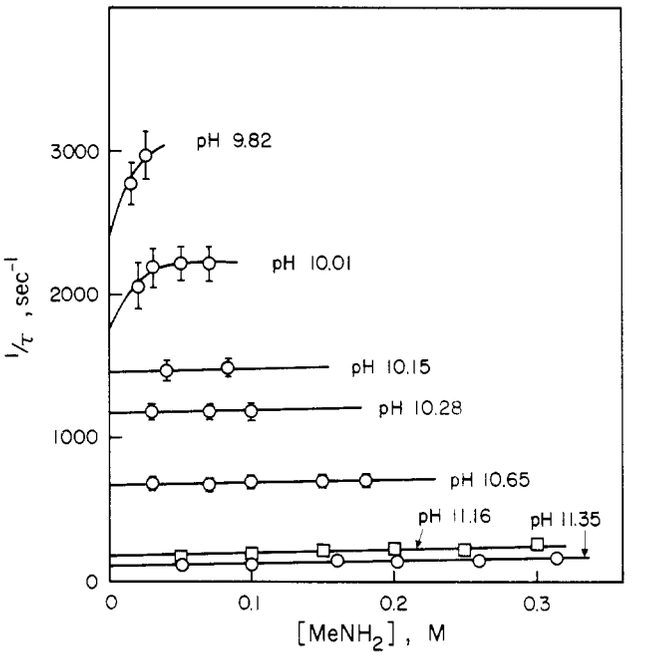


Figure 4. Reaction of methylamine with TNB in 10% dioxane–90% water (v/v) at 25 °C, μ = 0.5 M (NaCl).

Our results are summarized in Figures 1–5. Note that in all figures the horizontal axis refers to the *free* amine concentration. The plots shown fall into three categories. (1) In the first, the plots of $1/\tau$ vs. amine concentration are linear but the slopes increase with decreasing pH, as in the reaction of dimethylamine in 10% dioxane (Figure 1). In retrospect it appears now that the reactions of piperidine and pyrrolidine in 10% dioxane[2] also show this behavior, although the slope only starts to increase at the lowest pH value used (Figure 4 and 5 in ref 2) and, at the time, we assumed that the higher slope was due to a high experimental error.

(2) In the second category, the plots are linear at high pH but become curved at low pH; the curved part has a steep initial slope which becomes steeper the lower the pH. At high amine concentration the plot levels off into a straight line with a slope similar to that of the straight lines at high pH. This behavior is seen for piperidine and pyrrolidine in 30% Me_2SO (Figures 2 and 3). The reaction of methylamine in 10% dioxane appears to follow the same pattern, although here the situation is less clearcut because the curvature only begins to appear at the lowest pH values (Figure 4). At these low pH values the amine–amine hydrochloride ratio becomes very low (~1:20 at pH 9.82), which restricts the measurements to [RR'NH] $\lesssim$0.025 M due to the limitation imposed by the ionic strength of 0.5 M.

(3) In the third category, the plots are linear with a small positive slope at high pH, linear with approximately zero slope at intermediate pH, and approximately linear with negative slopes at low pH. This is the case for *n*-butylamine in 30% Me_2SO and similar to our earlier findings for the same reaction in 10% dioxane.[2]

We shall show in the next section that the increasing slopes and the curved plots at low pH are a consequence of the proton transfer between XH and X^- becoming rate limiting. The negative slopes in the *n*-butylamine reaction

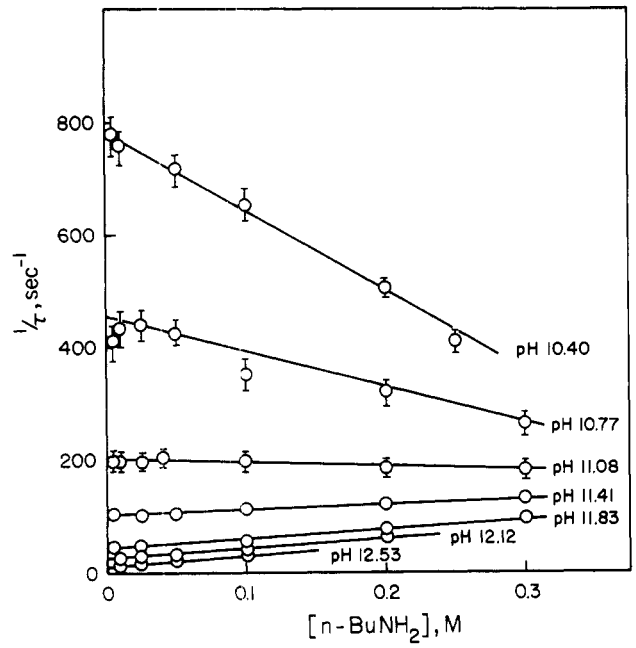


Figure 5. Reaction of *n*-butylamine with TNB in 30% Me_2SO–70% water (v/v) at 20 °C, μ = 0.5 M (KCl).

are best interpreted in terms of a salt or medium effect by the *n*-butylamine hydrochloride, as discussed in more detail below.

Rate Equations. Let us rewrite eq 1 as

$$\mathrm{TNB} + \mathrm{RR'NH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{XH} \underset{k_{-3p}}{\overset{k_{3p}}{\rightleftharpoons}} \mathrm{X^-} \qquad (2)$$

with

$$k_{3p} = k_{3p}^{OH}\, a_{OH^-} + k_{3p}^{A}\,[\mathrm{RR'NH}] \qquad (3)$$

$$k_{-3p} = k_{-3p}^{s} + k_{-3p}^{AH}\,[\mathrm{RR'NH_2^+}] \qquad (4)$$

where k_{3p}^{OH} and k_{3p}^{A} are the rate constants for deprotonation of XH by hydroxide ion and by the amine, respectively, and k_{-3p}^{S} and k_{-3p}^{AH} are the rate constants of protonation of X^- by the solvent (water) and the conjugate acid of the amine, respectively.[7]

Making use of the steady-state approximation with respect to XH,[8] the reciprocal relaxation time which characterizes reaction 2 is, under pseudo-first-order conditions, given by

$$\frac{1}{\tau} = \frac{k_1 k_{3p}[\mathrm{RR'NH}]}{k_{-1} + k_{3p}} + \frac{k_{-1}k_{-3p}}{k_{-1} + k_{3p}} \qquad (5)$$

There are two limiting situations with respect to eq 5 which are of interest in the present context.

A. $k_{3p} \gg k_{-1}$. Proton transfer is rapid and eq 5 simplifies to

$$\frac{1}{\tau} = k_1[\mathrm{RR'NH}] + \frac{k_{-1}a_{H^+}}{K_a^{XH}} \qquad (6)$$

where K_a^{XH} is the acid dissocition constant of XH. Plots of $1/\tau$ vs. [RR'NH] are linear with equal slopes (k_1) and with intercepts which are proportional to a_{H^+}. The condition for eq 6 is met at high pH ($k_{3p}^{OH}a_{OH^-} \gg k_{-1}$) and/or at high amine concentration (k_{3p}^{A} [RR'NH] $\gg k_{-1}$). For example, in the piperidine reaction in 30% Me_2SO (Figure 2) it holds at pH $\gtrsim$ 12.23 for all amine concentrations and at pH $\leq$ 11.84 only for amine concentrations $\geq$0.1 M.

B. $k_{3p} \ll k_{-1}$. In this situation deprotonation of XH is rate limiting in the forward direction (following rapid equilibrium addition of amine to TNB) and protonation of X^- rate determining in the reverse direction. Equation 5 becomes

$$\frac{1}{\tau} = \frac{k_1}{k_{-1}}(k_{3p}^{OH}a_{OH^-} + k_{3p}^{A}\,[\mathrm{RR'NH}])[\mathrm{RR'NH}] + k_{-3p}^{S} + k_{-3p}^{AH}\,[\mathrm{RR'NH_2^+}] \qquad (7)$$

The increase in initial slopes with decreasing pH is seen to arise from the $k_{-3p}^{AH}[\mathrm{RR'NH_2^+}]$ term in eq 7 since for a given free amine concentration the proportion of $\mathrm{RR'NH_2^+}$ increases with decreasing pH. When the amine concentration is increased, the relationship $k_{3p} \ll k_{-1}$ changes into $k_{3p} \sim k_{-1}$ and finally into $k_{3p} \gg k_{-1}$; this causes curvature (eq 5) until the straight line with slope = k_1 (eq 6) is reached.

Rate Retarding Effect of Amine Hydrochloride. Closer inspection of Figure 2 reveals that the curved plots at low pH level off into a straight line whose slope is somewhat smaller than k_1. We attribute this to a rate-retarding salt or medium effect by the amine hydrochloride whose concentration is quite high in these experiments (e.g., in the piperidine reaction at pH 10.83 we have $[\mathrm{RR'NH_2^+}]/[\mathrm{RR'NH}]$ = 2:1). An even more striking manifestation of the same phenomenon are the negative slopes in the *n*-butylamine reaction (Figure 5) as already noted before.

It appears that the effect of the amine hydrochloride is mainly to depress the $k_{-1}a_{H^+}/K_a^{XH}$ term (eq 6). Since in the *n*-butylamine reaction $k_{-1}a_{H^+}/K_a^{XH} \gg k_1[\mathrm{RR'NH}]$ at low pH, the relaxation time is dominated by the $k_{-1}a_{H^+}/K_a^{XH}$ term and the net effect of increasing the amine (and with it the amine hydrochloride) concentration is to decrease $1/\tau$. In the piperidine reaction the $k_1[\mathrm{RR'NH}]$ term contributes significantly to $1/\tau$ (eq 6) even at low pH; here the net effect of increasing the amine concentration is to increase $1/\tau$, but with a smaller slope than at high pH because of a partially compensating decrease in the $k_{-1}a_{H^+}/K_a^{XH}$ term. In the methylamine reaction the $k_1[\mathrm{RR'NH}]$ term is also small as in the *n*-butylamine reaction but we do not see negative slopes at low pH (Figure 4); this is because proton transfer is (partially) rate limiting so that any rate retarding effect is overcompensated by the $k_{-3p}^{AH}[\mathrm{RR'NH_2^+}]$ term (eq 7).

Evaluation of Kinetic Parameters. As described in the Experimental Section, analysis of our data by means of eq 5 and its limiting forms, eq 6 and 7, allows all or some of the parameters k_1, k_{-1}/K_a^{XH}, k_{-3p}^{S}, k_{3p}^{OH}/k_{-1}, and k_{-3p}^{AH} to be determined directly. Furthermore, by estimating a value for k_{3p}^{OH}, values for k_{-1}, K_a^{XH}, and k_{3p}^{A} can also be calculated: k_{-1} is obtained from k_{3p}^{OH}/k_{-1} and k_{3p}^{OH}, K_a^{XH} from k_{-1}/K_a^{XH} and k_{-1}, or from k_{3p}^{OH} and k_{-3p}^{S} ($K_a^{XH} = k_{3p}^{OH}K_w/k_{-3p}^{S}$ with K_w being the ionic product of the solvent), k_{3p}^{A} from k_{-3p}^{AH} and K_a^{XH} ($k_{3p}^{A} = K_a^{XH}k_{-3p}^{AH}/K_a^{AH}$ where K_a^{AH} is the acid dissociation constant of $\mathrm{RR'NH_2^+}$). We have estimated $k_{3p}^{OH} = 5 \times 10^9$ M^{-1} s^{-1} in 10% dioxane and 5×10^8 M^{-1} s^{-1} in 30% Me_2SO; these estimates will be justified in the Discussion. Table I summarizes all kinetic parameters for the five systems of this study as well as those for the previously studied reactions of piperidine, pyrrolidine, and *n*-butylamine in

(7) Deprotonation of XH by the solvent and protonation of X^- by H_3O^+ contributed negligibly in the pH range of this study.

(8) The treatment of XH as a steady-state intermediate requires that $k_{-1} + k_{3p} \gg k_1[\mathrm{RR'NH}] + k_{-3p}$. Spectrophotometric equilibrium determinations discussed in the section "Acid Dissociation Constant of XH" show that $K_1[\mathrm{RR'NH}] \ll 1$ (equivalent to $k_{-1} \gg k_1[\mathrm{RR'NH}]$) and $a_{H^+}/K_a^{XH} \ll 1$ (equivalent to $k_{3p} \gg k_{-3p}$) under all experimental conditions of this study, thus fulfilling the steady-state condition.

Table I. Summary of Rate and Equilibrium Constants

	30% Me_2SO, 20 °C			10% dioxane, 25 °C				
	piperidine	pyrrolidine	*n*-$BuNH_2$	piperidine[a]	pyrrolidine[a]	*n*-$BuNH_2$[a]	dimethylamine	methylamine
k_1, M^{-1} s^{-1}	4.10×10^3	9.00×10^3	2.50×10^2	3.00×10^3	8.10×10^3	1.23×10^2	6.25×10^3	1.60×10^2
k_{-1}/K_a^{XH}, M^{-1} s^{-1}	2.5×10^{14}	3.8×10^{14}	2.5×10^{13}					1.82×10^{13}
k_{-1}, s^{-1}	1.0×10^6	6.2×10^5	1.4×10^{5b}	2.1×10^6	1.5×10^6	1.5×10^{5b}	7.5×10^5	1.5×10^5
$K_1 = k_1/k_{-1}$, M^{-1}	4.0×10^{-3}	1.45×10^{-2}	1.78×10^{-3b}	1.43×10^{-3}	5.80×10^{-3}	8.2×10^{-4b}	8.0×10^{-3}	1.07×10^{-3}
K_a^{XH},[c] M	4.0×10^{-9}	1.6×10^{-9}						8.25×10^{-9}
pK_a^{XH}[c]	8.4	8.8						8.08
K_a^{XH},[d] M	2.4×10^{-9}	1.3×10^{-9}	5.6×10^{-9} [b]	2.0×10^{-9}	1.25×10^{-9}	4.8×10^{-9}	2.3×10^{-9}	5.0×10^{-9}
pK_a^{XH}[d]	8.62	8.9	8.25	8.7	8.9	8.32	8.64	8.3
k_{3p}^{OH}/k_{-1}, M^{-1}	5.0×10^2	8.1×10^2		2.4×10^3	3.4×10^3		6.5×10^3	3.4×10^4
k_{3p}^{OH}, M^{-1} s^{-1}	5×10^{8i}	5×10^{8i}	5×10^{8i}	5×10^{9i}	5×10^{9i}	5×10^{9i}	5×10^{9i}	5×10^{9i}
k_{-3p}^{S}, s^{-1}	3.3×10^2	6.20×10^2	1.43×10^{2b}	1.25×10^4	2.0×10^4	5.2×10^{3b}	1.1×10^4	5.0×10^3
K_W, M^2	1.6×10^{-15e}	1.6×10^{-15e}	1.6×10^{-15e}	5×10^{-15f}	5×10^{-15f}	5×10^{-15f}	5×10^{-15f}	5×10^{-15f}
pK_W	14.8[e]	14.8[e]	14.8[e]	14.3[f]	14.3[f]	14.3[f]	14.3[f]	14.3[f]
k_{-3p}^{AH}, M^{-1} s^{-1}	3.9×10^4	5.1×10^4					1.0×10^5	
k_{3p}^{A}, M^{-1} s^{-1}	1.6×10^7	1.7×10^7					1.2×10^7	
K_a^{AH}, M	6.03×10^{-12g}	3.80×10^{-12g}	1.51×10^{-11g}	7.6×10^{-12h}	5.0×10^{-12h}	2.1×10^{-11h}	1.85×10^{-11h}	2.2×10^{-11h}
pK_a^{AH}	11.22[g]	11.42[g]	10.82[g]	11.12[h]	11.3[h]	10.68[h]	10.73[h]	10.66[h]
K_a^{XH}/K_a^{AH}	4.0×10^2	3.4×10^2	3.7×10^{2b}	2.6×10^2	2.5×10^2	2.3×10^{2b}	1.2×10^2	2.3×10^2
$K_1 K_a^{XH}$	9.85×10^{-12}	1.88×10^{-11}	1.00×10^{-11b}	2.87×10^{-12}	7.25×10^{-12}	3.94×10^{-12}	1.84×10^{-11}	5.35×10^{-12}

[a] Reference 2. [b] Since k_{3p}^{S} and k_{3p}^{OH}/k_{-1} could not be determined experimentally, K_a^{XH} was estimated assuming $K_a^{XH}/K_a^{AH} = 3.7 \times 10^2$ in 30% Me_2SO (average of K_a^{XH}/K_a^{AH} for piperidine and pyrrolidine) and 2.3×10^2 in 10% dioxane (same as for methylamine); k_{-1} was then obtained from K_a^{XH} and k_{-1}/K_a^{AH}, and K_{-3p}^{S} was obtained from k_{3p}^{OH}, K_a^{XH}, and K_W. [c] From k_{-1}/K_a^{XH} and k_{-1}. [d] From k_{3p}^{OH}/k_{-3p}^{S} and K_W. [e] From pH measurements in dilute KOH. [f] Estimated based on H. S. Harned and L. D. Fallon, *J. Am. Chem. Soc.*, 61, 2374 (1939). [g] From pH measurements where [RR'NH] = [RR'NH_2Cl] = 0.05 M. [h] Literature data in water. [i] Assumed values, see Discussion.

10% dioxane;[2] these latter were recalculated in the light of our current interpretation.

Acid Dissociation Constant of XH. There is a spectrophotometric method which, in principle, would permit us to obtain K_a^{XH} (and $K_1 = k_1/k_{-1}$) directly, as reported for certain spiro complexes.[4-6] It is based on

$$\frac{OD}{l[TNB]_0[RR'NH]} = \epsilon_{XH}K_1 + \frac{\epsilon_{X^-}K_1K_a^{XH}}{a_{H^+}} \quad (8)$$

where OD is the optical density, l the pathlength, ϵ_{XH} and ϵ_{X^-} the extinction coefficients of XH and X^-, respectively, $[TNB]_0$ the stoichiometric TNB concentration, and [RR'NH] the free amine concentration. Since ϵ_{X^-} and ϵ_{XH} are likely to be similar, the assumption that $\epsilon_{XH} = \epsilon_{X^-}$ would permit us to plot the right-hand side of eq 8 vs. $1/a_{H^+}$ and obtain K_a^{XH} = slope/intercept and K_1 from the intercept and an estimate of ϵ_{XH}. In practice only a lower limit of K_a^{XH} could be estimated because $\epsilon_{XH}K_1 \ll \epsilon_{X^-}K_1K_a^{XH}/a_{H^+}$ under all conditions where a measurable OD could be obtained.[9] An additional complication is that solutions of TNB in the presence of amines are not very stable over long periods of time, which precludes measurements in a conventional spectrophotometer. Some measurements in a stopped-flow spectrophotometer lead to an estimate of $K_a^{XH} > 10^{-9}$ for the piperidine reaction in 30% Me_2SO; this result is consistent with K_a^{XH} calculated on the basis of k_{3p}^{OH}/k_{-3p}^{S} (2.4×10^{-9}) or on the basis of k_{-1}/K_a^{XH} (4.0×10^{-9}).

Discussion

Rate of Deprotonation of XH. We have assumed that deprotonation of XH by OH^- in 10% dioxane is essentially diffusion controlled,[10] with a $k_{3p}^{OH} \approx 5 \times 10^9$ M^{-1} s^{-1} in all cases; this assumption is based on the analogy with the deprotonation of the conjugate acid of **1a** in aqueous solution for which a $k_{3p}^{OH} = 5 \times 10^9$ M^{-1} s^{-1} was measured.[4] This value contrasts with a previously reported rate constant of 2×10^8 M^{-1} s^{-1} for the reactions of OH^- with XH derived from TNB and piperidine, pyrrolidine, and dimethylamine in 10% dioxane.[11] We consider the new value (5×10^9 M^{-1} s^{-1})[4] to be more reliable because it was obtained under much more favorable experimental conditions.[12]

A rate constant for the deprotonation of XH by the amine (k_{3p}^{A}) in 10% dioxane could only be obtained for the dimethylamine reaction. It is about 500 times smaller than k_{3p}^{OH}. This is about 100-fold lower than expected for a reaction between an NH acid and a N base which is thermodynamically favored by 2 pK units.[10,13] Similar rate reductions have been observed in comparable reactions and have been interpreted in terms of a steric effect.[4,14]

For the reactions in 30% Me_2SO we estimate k_{3p}^{OH} to be about tenfold lower than in 10% dioxane, i.e., $k_{3p}^{OH} \approx 5.0 \times 10^8$ M^{-1} s^{-1}. Our reasoning is as follows. (1) If k_{3p}^{OH} were assumed to be the same as in 10% dioxane, the k_{-1} values in 30% Me_2SO for any given amine, calculated from the measured k_{3p}^{OH}/k_{-1} ratios, would be about fivefold higher than in 10% dioxane (e.g., in the piperidine reaction we have $k_{3p}^{OH}/k_{-1} = 2.4 \times 10^3$ M^{-1} in 10% dioxane and 5.0×10^2 M^{-1} in 30% Me_2SO, thus $k_{-1} = 2.1 \times 10^6$ s^{-1} in 10% dioxane and 1.0×10^7 s^{-1} in 30% Me_2SO if $k_{3p}^{OH} = 5 \times 10^9$ M^{-1} s^{-1} in both solvents). This would lead to K_1 values which would be about three- to fourfold lower in 30% Me_2SO compared to 10% dioxane and would imply that Meisenheimer complex stability is considerably smaller in the Me_2SO containing solvent. This would be in conflict with a large body of evidence which shows that Me_2SO has, without exception, a strong Meisenheimer complex *stabilizing* influence.[5,15] Our estimated value of 5.0×10^8 M^{-1} s^{-1} for k_{3p}^{OH} in 30% Me_2SO makes k_{-1} about half as large as in 10% dioxane; this estimate must be regarded as an upper limit because the reduction of k_{-1} in 30% Me_2SO to half its value in 10% dioxane probably mainly reflects the lower temperature (20 °C in 30% Me_2SO, 25 °C in 10% dioxane); in other words k_{-1} may well be lower still which would imply that k_{3p}^{OH} is even lower than 5×10^8 M^{-1} s^{-1}.

(2) The assumption of equal k_{3p}^{OH} values in both solvents would lead to about 15-fold larger K_a^{XH}/K_a^{AH} ratios in 30% Me_2SO than in 10% dioxane (e.g., in the piperidine reaction $K_a^{XH}/K_a^{AH} = 2.6 \times 10^2$ in 10% dioxane and 4.0×10^3 in 30% Me_2SO) implying a dramatic solvent dependence of the acidifying effect of the picryl moiety. This is unreasonable; furthermore, previous data[5] suggest that if there is a solvent effect at all it should rather be in the direction of *reducing* K_a^{XH}/K_a^{AH} with increasing Me_2SO concentration. This latter conclusion contrasts with Buncel and Eggimann's report of a K_a^{XH}/K_a^{AH} ratio of about 10^4 in the reaction of TNB with aniline in Me_2SO.[16] However, Buncel and Eggimann obtained their K_a^{XH}/K_a^{AH} ratio by assuming that the deprotonation of the aniline–XH by DABCO is essentially diffusion controlled with a $k_{3p}^{A} \approx 10^9$ M^{-1} s^{-1}. As mentioned earlier, the rate constants for the deprotonation of typical XH-type Meisenheimer complexes by amines are usually depressed by a factor of 100 or more[14] due to steric hindrance. Thus a more realistic estimate for k_{3p}^{A} in the aniline reaction would be $\sim 10^7$ M^{-1} s^{-1}, which would make $K_a^{XH}/K_a^{AH} \sim 10^2$ and bring it close to the ratios found in the present study.

The decrease in the value of k_{3p}^{OH} in the presence of Me_2SO as co-solvent is not without precedent;[17a] k_{3p}^{OH} for the deprotonation of the conjugate acid of **1c** was determined to be 4.2×10^7 M^{-1} s^{-1} in 70% Me_2SO–30% water and estimated to be $\sim 4 \times 10^6$ M^{-1} s^{-1} in 80% Me_2SO–20% water.[5,18] In these earlier reports[5,18] we have interpreted the lowering of k_{3p}^{OH} in the presence of large amounts of Me_2SO as being mainly[19] a consequence of intramolecular hydrogen bonding of the acidic ammonio proton to an *o*-nitro group in XH. Inasmuch as this hydrogen bond has to be broken in order for the encounter complex XH...OH^- to be formed, this has a rate-retarding effect on the proton

(9) At low enough pH values to make $\epsilon_{XH}K_1$ comparable to $\epsilon_{X^-}K_1K_a^{XH}/a_{H^+}$ there is only very little free amine and thus only negligible complex concentrations are produced.

(10) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

(11) C. F. Bernasconi, *J. Phys. Chem.*, **75**, 3636 (1971).

(12) The old value (2×10^8 M^{-1} s^{-1})[11] was obtained from temperature-jump relaxation effects with very small relaxation amplitudes and relaxation times near the limit of the capabilities of the temperature-jump method, whereas the new value[4] was obtained from relaxation effects with large amplitudes and relaxation times in the optimal time range of the temperature-jump method.

(13) M.-L. Ahrens and G. Maass, *Angew. Chem., Int. Ed. Engl.*, **7**, 818 (1968).

(14) C. F. Bernasconi, *Acc. Chem. Res.*, **11**, 147 (1978).

(15) For recent reviews, see (a) M. R. Crampton, *Adv. Phys. Org. Chem.*, **3**, 211 (1969); (b) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970); (c) E. Buncel and H. Wilson, *Adv. Phys. Org. Chem.*, **14**, 133 (1977).

(16) E. Buncel and W. Eggimann, *J. Am. Chem. Soc.*, **99**, 5958 (1977).

(17) (a) A high percentage (60%) of dioxane as co-solvent also appears to lower k_{3p}^{OH} under certain conditions.[17b] (b) C. F. Bernasconi, R. H. de Rossi, and P. Schmid, *J. Am. Chem. Soc.*, **99**, 4090 (1977).

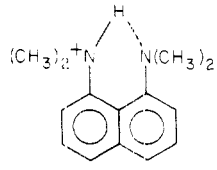
(18) C. F. Bernasconi and F. Terrier in "Chemical and Biological Applications of Relaxation Spectrometry", E. Wyn-Jones, Ed., D. Reidel, Dordrecht, Holland, 1975, p 379.

(19) The higher viscosity of Me_2SO–water mixtures[20] may account for part of the reduction.

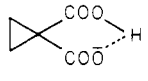
(20) G. J. Janz and R. P. T. Tomkins, "Nonaqueous Electrolyte Handbook", Vol. 1, Academic Press, New York, N.Y., 1972, p 86.

transfer which otherwise would be diffusion controlled.[10,21] This hydrogen bonding which is insignificant in aqueous solution was assumed to become increasingly more important in Me_2SO richer solvents.[5]

Our present findings which show that k_{3p}^{OH} is significantly reduced in the presence of as little as 30% Me_2SO raises the question whether *intra*molecular hydrogen bonding is the best interpretation or whether we are witnessing a more specific effect by Me_2SO. A comparison with the effect of adding small amounts of Me_2SO on the deprotonation rate by hydroxide ion in other systems, which have strong intramolecular hydrogen bonds even in water, is interesting in the present context. In the case of **4** the rate is slightly enhanced[22] ($k = 1.9 \times 10^5$ in H_2O



4



5

at 25 °C, 2.9×10^5 in 20% Me_2SO at 25 °C, and 6.2×10^5 in 30% Me_2SO at 30 °C) while in the case of **5** it is significantly retarded[23] ($k = 4.29 \times 10^7$ in H_2O, 1.32×10^7 in 20% Me_2SO, and 0.43×10^7 in 33% Me_2SO, all at 25 °C).

A possible explanation for the different behavior of **4** and **5** would be that, as Me_2SO is added, the hydrogen bond in **5** becomes stronger because the acceptor is an oxyanion whose basicity increases while this is not the case for **4**.

Inasmuch as the hydrogen-bond acceptor in our zwitterionic Meisenheimer complex XH is also an oxyanion one might expect a similar effect of Me_2SO on k_{3p}^{OH}. However, due to the strong delocalization of the negative charge in XH this effect should be much smaller than for **5**, whereas in fact we observe a rate reduction which is of comparable size as that found for **5**. Thus an alternative (or possibly complementary) interpretation of our reduced k_{3p}^{OH} values seems to be called for.

Since Me_2SO is a much better hydrogen-bond acceptor than water,[24] the rate reduction could be due to an *inter*molecular hydrogen bond to the oxygen of Me_2SO: just as in *intra*molecular hydrogen bonding, the hydrogen bond to Me_2SO would have to be broken prior to the $XH...OH^-$ encounter complex formation.

This interpretation might also provide a framework for explaining why k_{3p}^{A} (deprotonation of XH by amine) is *not* reduced by Me_2SO ($k_{3p}^{A} = 1.2 \times 10^7$ for dimethylamine in 10% dioxane; $k_{3p}^{A} = 1.6 \times 10^7$ and 1.7×10^7 for piperidine and pyrrolidine, respectively, in 30% Me_2SO). The low k_{3p}^{A} value implies that the reaction is activation rather than encounter controlled. Thus, if the energy of breaking the hydrogen bond of XH to Me_2SO is essentially compensated for by the formation of a new hydrogen bond of the incipient $RR'NH_2^+$ to Me_2SO in the activated complex, k_{3p}^{A} would in fact remain unchanged. Alternatively, the effect which compensates for the hydrogen bonding of XH may be of the same origin as the one invoked in explaining why the deprotonation of carbon acids by anionic oxygen bases is much faster in Me_2SO than in methanol.[25]

Based on the above considerations one is tempted to draw the following tentative general conclusions. The change from a hydroxilic solvent to Me_2SO (1) decreases the rate of encounter-controlled deprotonation of acids capable of strong hydrogen bonding to Me_2SO (e.g., ammonium ions), (2) increases the rate of activation-controlled deprotonation of acids *in*capable of hydrogen bonding (carbon acids), and (3) has a relatively small effect on an activation-controlled deprotonation of strong hydrogen bond donors, due to the opposing nature of the rate affecting factors.

It should be noted that there exists other reports of strongly retarded proton transfers involving amines in Me_2SO, but these refer to an anhydrous solvent;[26] since a Me_2SO–water mixture which contains a significant fraction of water is still mainly a protic solvent with very different properties from pure Me_2SO these rate-retarding effects have probably quite different origins. For example, protonation of amines by the solvated proton is strongly retarded in Me_2SO;[26a,b] on the other hand, in 70% Me_2SO–30% water, where *de*protonation of the conjugate acid of **1c** is reduced 100-fold, protonation of **1c** by the solvated proton proceeds at the normal diffusion-controlled rate.[5a] Or, the addition of small quantities of water (<1 M) to Me_2SO has a dramatic rate increasing effect on proton transfer.[26b]

Effect of Structure on Rates and Equilibria. It should be noted at the outset that inasmuch as K_a^{XH}, k_{-1}, k_{3p}^{A}, and parameters derived from these constants (K_a^{XH}/K_a^{AH}, K_1) depend on our estimates for k_{3p}^{OH}, their values are somewhat uncertain, perhaps by as much as a factor of 2–3. Furthermore, some difficulty in obtaining very accurate intercepts of the curved plots of $1/\tau$ vs. amine concentration at low pH in the piperidine and pyrrolidine reactions is probably responsible for some additional uncertainties as is evident from a comparison of pK_a^{XH} determined from k_{-1}/K_a^{XH} with that determined from k_{3p}^{OH}, k_{-3p}^{S}, and K_w; the two values differ by 0.1–0.2 units. However, the effects to be discussed in the following are larger than the uncertainties in our parameters and thus our main conclusions will not be affected by them.

The following points are noteworthy. (1) The rate constants for nucleophilic attack (k_1) follow the familiar pattern for S_NAr reactions, i.e., pyrrolidine > piperidine ≫ *n*-butylamine or dimethylamine ≫ methylamine.[3a]

(2) The rate constants for amine expulsion (k_{-1}) are considerably higher with secondary amines than with primary amines. This is again consistent with many previous observations[3a,17b] and probably due to greater steric strain in XH with secondary amines.[27] It is interesting to note that for the secondary amines the k_{-1} values are only slightly higher than those for the ring opening of the protonated spiro complexes **1a** (1.93×10^5 s^{-1})[4] and **2** (1.2×10^5 s^{-1});[6] this contrasts with the situation for alkoxide ion nucleophiles where, e.g., methoxide ion expulsion from the TNB Meisenheimer complex[28] is about

(21) For recent reviews, see (a) A. J. Kresge, *Acc. Chem. Res.*, 8, 354 (1975); (b) P. Schuster, P. Wolschann, and K. Tortschanoff in "Chemical Relaxation in Molecular Biology", I. Pecht and R. Rigler, Eds., Springer Verlag, New York, N.Y., 1977, p 107; (c) F. Hibbert and A. Awwal, *J. Chem. Soc., Chem. Commun.*, 995 (1976).

(22) A. Awwal and F. Hibbert, *J. Chem. Soc., Perkin Trans. 2*, 1589 (1977).

(23) C. D. Slater, personal communication.

(24) (a) M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377 (1976); (b) H. H. Szmant in "Dimethyl Sulfoxide", Vol. 1, S. W. Jacob, E. E. Rosenbaum, and D. C. Wood, Eds., Marcel Dekker, New York, N.Y., 1971, p 1.

(25) (a) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **90**, 3415 (1968); (b) J. R. Keeffe, J. Morey, C. A. Palmer, and J. C. Lee, *ibid.*, **101**, 1295 (1979).

(26) (a) M. M. Kreevoy and Y. Wang, *J. Phys. Chem.*, **81**, 1924 (1977); (b) J.-J. Delpuech and B. Bianchin, *J. Am. Chem. Soc.*, **101**, 383 (1979); (c) S. F. Nelsen, P. J. Kinlen, and D. H. Evans, *ibid.*, **101**, 1875 (1979).

(27) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3875 (1965).

(28) C. F. Bernasconi and R. G. Bergstrom, *J. Org. Chem.*, **36**, 1325 (1971).

5000 times faster than ring opening of the spiro complex derived from 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene.[29]

We also note that k_{-1} for the primary amines methylamine (1.5×10^5 in 10% dioxane) and *n*-butylamine (1.4×10^5 in 30% Me_2SO) are similar to *our* estimate (see above) of $k_{-1} \approx 10^5$ for the aniline reaction in Me_2SO.[16] Thus the lower basicity of aniline which makes it a better leaving group is compensated for by the effect of Me_2SO.

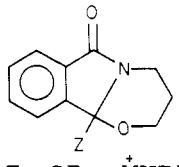
(3) The lower k_{-1} values for primary amines partly compensate for their lower k_1 values so that the stabilities (K_1) of the zwitterionic XH differ much less than the rates of nucleophilic attack. The stabilities ($K_1K_a^{XH}$) of the anionic complex X^- are even more similar to each other because the lower K_1 value for primary amines is partly or completely compensated by a higher K_a^{XH}. For example a comparison between piperidine and *n*-butylamine in 30% Me_2SO shows $k_1(Pip)/k_1(n\text{-}BuNH_2) = 16.4$, $K_1(Pip)/K_1(n\text{-}BuNH_2) = 2.30$, and $K_1K_a^{XH}(Pip)/K_1K_a^{XH}(n\text{-}BuNH_2) = 0.985$. This means that for a given amine concentration and pH approximately the same fraction of TNB is converted into X^- regardless of the nature of the amine. This is borne out by our observations that the OD of such solutions are all about the same for a given TNB concentration.

A similar point was made by Buncel and Eggimann[16] in rationalizing why even a nucleophile as weak as aniline easily forms a complex when a strong base such as DABCO is present to drive the $B + XH \rightleftharpoons X^- + BH^+$ equilibrium to the right.

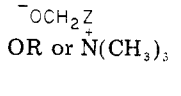
(4) Regardless of the amine, XH is about 100 to 400 times more acidic then the parent $RR'NH_2^+$, showing that the picryl moiety is strongly electron withdrawing even when carrying a negative charge. This is in agreement with the findings by Crampton,[30] by Buncel and Webb,[31] and with theoretical calculations by Caveng et al.[32] Note that the conjugate acids of **1a**,[4] **2**,[6] and **3**[6] are more acidic still, by another factor of about 100, due to the additional electron withdrawing effect of the extra $N\text{-}CH_3$ group or the oxygen atom, respectively.

Relative Leaving-Group Abilities of Amines and Alkoxide Ions. It is well known that amines are usually better nucleofugic leaving groups than alkoxide ions but the question arises whether this is mainly due to the lower basicity of the amines or whether they are intrinsically better leaving groups. To shed more light on this question it is useful to compare our k_{-1} values for the departure of (protonated) amines with the corresponding rate constants for alkoxide ion departure from TNB–alkoxide Meisenheimer complexes. For MeO^- $k_{-1} = 254$ s^{-1} in 22.5% methanol–77.5% water[28] while for EtO^- $k_{-1} = 32$ s^{-1} in 19% ethanol–81% water.[28] If we assume a $\beta_{lg} \approx -1.0$ as found for alkoxide ion departure from 1,1-dialkoxy-2,4,6-trinitrocyclohexadienates[1] one can use the above rate constants to estimate a rate constant of $2\text{–}5 \times 10^6$ s^{-1} for the departure of a hypothetical alkoxide ion of the same basicity as piperidine in 30% Me_2SO, or $6\text{–}15 \times 10^6$ s^{-1} for a hypothetical alkoxide ion of the same basicity as dimethylamine in 10% dioxane.[33] These values are comparable to or even slightly higher than the k_{-1} values for the secondary amines. They show that, for TNB Meisenheimer complexes, amines are not intrinsically better leaving groups than alkoxide ions.

Comparison with other electrophiles is interesting. Gravitz and Jencks[34] report that the expulsion of (protonated) secondary amines from addition complexes of *N,O*-trimethylenephthalimidium ion (**6**) is about 10^5 times



6, Z = OR or $\overset{+}{N}HRR'$



7, Z = OR or $\overset{+}{N}(CH_3)_3$

faster than the expulsion of alkoxide ions of the same basicity. On the other hand, expulsion of trimethylamine from **7** is only slightly faster than expulsion of methoxide ion,[35] which leads to the conclusion that an alkoxide ion of the same basicity as trimethylamine would be a much better leaving group.[36] The difference in the relative leaving-group abilities in **6** and **7** was explained in terms of an electrostatic effect:[36] expulsion of the amine from **7** destroys the electrostatic stabilization due to the opposite charges in the zwitterion, making amine expulsion more difficult than alkoxide ion expulsion. In **6** there are no such charge effects and thus the enhanced leaving-group ability of amines observed in this system shows the intrinsic behavior.

Based on this theory, the TNB Meisenheimer complexes show intermediate behavior because the electrostatic stabilization of the zwitterion is reduced due to the strong delocalization of the negative charge.

Experimental Section

Materials. 1,3,5-Trinitrobenzene, piperidine, pyrrolidine, *n*-butylamine, and dioxane were purified as described previously.[2] Methylamine and dimethylamine were prepared by adding a concentrated aqueous solution of the amine hydrochloride to solid NaOH and absorbing the liberated gaseous amine in water. The amine hydrochlorides were first purified by washing them twice with chloroform and recrystallizing them three times from ethanol: mp 170 °C for methylamine hydrochloride, 231.5 °C for dimethylamine hydrochloride.

Reaction Solutions and pH Measurements. Reaction solutions were prepared as described.[2] The pH value of each solution was determined by a Corning Model 110 pH meter. For a given amine–amine hydrochloride buffer ratio the pH was somewhat dependent on the total amine concentration, particularly for ratios $\ll 1$ or $\gg 1$. In such cases the pH was adjusted by the addition of a few drops of concentrated HCl or KOH so that the pH value would be the same for all solutions of a given buffer ratio. For the measurements in 10% dioxane, the pH meter was calibrated with standard aqueous buffer at 25 °C and the pH value, determined at 25 °C in 10% dioxane at an ionic strength of 0.5 M, was equated with $-\log a_{H^+}$. For the measurements in 30% Me_2SO, the pH meter was calibrated with a phenol–phenolate (1:1) buffer and a 0.01 M NaOH solution in 30% Me_2SO at 20 °C; the pH values of these solutions are known from the work of Hallé et al.[37] The pH of the reaction solutions, determined at 20 °C and at an ionic strength of 0.5 M, are again equated with $-\log a_{H^+}$.

Measurement of Relaxation Times. The relaxation times were measured with a temperature-jump transient spectrophotometer from Messanlangen Studiengesellschaft, Göttingen, Germany. The procedures were essentially the same as those described in our earlier paper.[2]

(29) (a) M. R. Crampton and M. J. Willison, *J. Chem. Soc., Perkin Trans. 2*, 1681 (1974); (b) C. F. Bernasconi and J. R. Gandler, *J. Org. Chem.*, **42**, 3387 (1977).
(30) M. R. Crampton, *J. Chem. Soc. B*, 2112 (1971).
(31) E. Buncel and J. G. K. Webb, *Can. J. Chem.*, **52**, 630 (1974).
(32) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).
(33) pK_a of methanol and ethanol assumed to be 15.5 and 16.0, respectively: P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).
(34) (a) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 499 (1974); (b) N. Gravitz and W. P. Jencks, *ibid.*, **96**, 507 (1974).
(35) J. Hine and F. C. Kokesh, *J. Am. Chem. Soc.*, **92**, 4383 (1970).
(36) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 6970 (1977).
(37) J.-C. Hallé, R. Gaboriaud, and R. Schaal, *Bull. Soc. Chim. Fr.*, 2047 (1970).

Evaluation of Kinetic Parameters. k_1 is equal to the slopes of the plots of $1/\tau$ vs. [RR'NH], under the conditions where eq 6 holds. Extrapolation of the lines of slope k_1 (dashed lines in Figures 2 and 3) to zero amine concentration provides $k_{-1}a_{H^+}/K_a^{XH}$; thus k_{-1}/K_a^{XH} is obtained as the slope of a plot of $k_{-1}a_{H^+}/K_a^{XH}$ vs. a_{H^+}.

The "true" intercepts (extrapolation of actual data points to zero amine concentration) obey eq 9 which is a special case of eq 5 where [RR'NH] = 0.

$$\text{intercept} = \frac{k_{-1}k_{-3p}^{S}}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{9}$$

Inversion of eq 9 affords eq 10

$$(\text{intercept})^{-1} = \frac{1}{k_{-3p}^{S}} + \frac{k_{3p}^{OH}}{k_{-3p}^{S}k_{-1}}a_{OH^-} \tag{10}$$

which describes a straight line with intercept = $1/k_{-3p}$ and slope = $k_{3p}^{OH}/k_{-3p}^{S}k_{-1}$. Thus k_{-3p}^{S} and k_{3p}^{OH}/k_{-1} could be obtained from plots according to eq 10 in all cases except for the *n*-butylamine reaction where $1/k_{-3p}^{S}$ was indistinguishable from zero.

For the determination of k_{-3p}^{AH} we proceeded as follows. At very low amine concentrations and low pH the second term on the right-hand side of eq 5 is dominant because the equilibrium position favors TNB over X^-. For example in the piperidine reaction the ratio $[X^-]/[TNB]$, which is equal to $K_1K_a^{HX}$·$[RR'NH]/a_{H^+}$, is 1.32×10^{-2} at pH 10.83 and an amine concentration of 0.02 M, or 3.09×10^{-2} at pH 11.20 for the same amine concentration. Since at low amine concentrations we also have $k_{3p}^{A}[RR'NH] \ll k_{-1}$, eq 5 simplifies to eq 11[39]

$$\frac{1}{\tau} = \frac{k_{-1}(k_{-3p}^{S} + k_{-3p}^{AH}[RR'NH]a_{H^+}/K_a^{AH})}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{11}$$

Thus the initial slopes at low pH are given by

$$\text{slope} = \frac{k_{-1}k_{-3p}^{AH}a_{H^+}/K_a^{AH}}{k_{-1} + k_{3p}^{OH}a_{OH^-}} \tag{12}$$

from which k_{-3p}^{AH} can be calculated.

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Registry No. 1,3,5-Trinitrobenzene, 99-35-4; dimethyl sulfoxide, 67-68-5; piperidine, 110-89-4; pyrrolidine, 123-75-1; *n*-$BuNH_2$, 109-73-9; dimethylamine, 124-40-3; methylamine, 74-89-5.

(38) $K_1K_a^{XH}[RR'NH]/a_{H^+}$ is equivalent to the ratio of the first over the second term in eq 5.

(39) $[RR'NH]a_{H^+}/K_a^{AH}$ is equivalent to $[RR'NH_2^+]$.

Solvolytic Reactivity of 6-(Chloromethyl)benzo[*a*]pyrene and Selectivity of Trapping of the Arylmethyl Cation by Added Nucleophiles

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The rate of solvolysis of the chemical carcinogen 6-(chloromethyl)benzo[*a*]pyrene in aqueous organic solvents is first order and independent of the presence of added nucleophiles, as expected for a carbonium ion reaction. The solvolytic reactivity of this arylmethyl chloride is comparable to that of compounds, such a *p,p'*-dimethylbenzhydryl chloride, which are known to form relatively stable carbonium ions. Evidence for the formation of a relatively stable carbonium ion in the solvolysis of 6-(chloromethyl)benzo[*a*]pyrene was obtained from the activation parameters ($\Delta S^{\ddagger} = -4.6$ eu) and from the presence of a marked common-ion effect when the solvolysis proceeded in the presence of LiCl. The nucleophilicities of a number of nucleophiles were measured kinetically in the presence of LiCl by their abilities to inhibit the common-ion effect in the solvolysis reaction. The selectivity of trapping of the arylmethyl cation shows the following order: aniline > N_3^- > Cl^- > *N*-acetylcysteine ≃ pyridine > *n*-propylamine > hydroxide > diethylamine > water. This set of nucleophiles ranges in nucleophilic strength (k_{Nu}/k_{H_2O}) from 3 for diethylamine to 1.7×10^3 for aniline. The products of trapping from the solvolysis of 6-(chloromethyl)benzo[*a*]pyrene enriched in carbon-13 at the methyl carbon were analyzed by ^{13}C NMR. There is a good correlation of chemical shifts of carbon in 6-(substituted-methyl)benzo[*a*]pyrenes and 1-substituted alkanes.

Although exact details of the mechanisms whereby chemicals cause cell transformation are not known for any chemical carcinogen, a number of generalizations have emerged from the studies of many investigators. It is now thought that most chemical carcinogens are strong electrophiles either as encountered in the environment or after metabolic activation within the target organism. This concept, developed primarily by Miller and Miller,[3] helps explain the carcinogenic properties of a large number of chemicals which have seemingly unrelated structures. In addition, it is widely believed that a critical event in the process leading to cell transformation is the covalent modification of cellular DNA by the carcinogenic electrophiles.[4] However, there does not appear to be a direct correlation between carcinogenicity and extent of covalent modification, suggesting that specificity of attack of nucleophilic sites by the carcinogenic electrophiles may be critical. The properties of known carcinogenic electrophiles

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(2) Abbreviations: 6-CMBP, 6-(chloromethyl)benzo[*a*]pyrene; 9-CMA, 9-(chloromethyl)anthracene.

(3) E. C. Miller and J. A. Miller, *Annu. Rev. Biochem.*, **28**, 291 (1959); J. A. Miller, *Cancer Res.*, **30**, 559 (1970).

(4) P. Brookes, *Life Sci.*, **16**, 331 (1974).

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