

Nitrosation of Amines in Nonaqueous Solvents. 2. Solvent-Induced Mechanistic Changes

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We studied the nitrosation of amines (pyrrolidine, piperidine, diethylamine, *N*-methylpiperazine, *N,N'*-dimethylethylenediamine, and morpholine) by alkyl nitrites (2-bromoethyl nitrite or 2,2-dichloroethyl nitrite) or by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in the solvents chloroform, acetonitrile, and dimethyl sulfoxide (DMSO). The mechanism of nitrosation by alkyl nitrites depends on the solvent: in chloroform, all the results were in keeping with formation of a hydrogen-bonded complex between the amine and alkyl nitrite being followed by rate-controlling formation of a tetrahedral intermediate T^\pm that rapidly decomposes to afford the final products; in acetonitrile, a situation intermediate between those obtaining in chloroform and cyclohexane results in the [amine] dependence of the first-order pseudoconstant k_0 being qualitatively influenced by temperature and by the identities of both the amine and the alkyl nitrite; in DMSO, the results suggest a mechanism close to the mechanism acting in water. For nitrosation by MNTS, k_0 depended linearly on [amine] in all three solvents. The Grunwald–Winstein coefficients correlating the rate constants k for nitrosation by MNTS in the chloroform, acetonitrile, DMSO, dioxane, dichloromethane, and water were $l = 0.12$ and $m = 0.29$. Correlation with the Kamlet–Abboud–Taft equation confirmed that k depends largely on the dipolarity of the solvent and, to a lesser extent, its capacity for hydrogen bonding.

Introduction

Studies of structure–reactivity relationships and solvent effects have widely popularized the idea that reaction mechanisms can be profoundly altered by changing reactant substituents and/or reaction medium.² In the case of nucleophilic substitution and addition reactions, extensive application of this concept has allowed several new conclusions to be drawn with regard to the role of nucleophile, leaving group, and solvent in reaction mechanism. The classification of a series of solvents can present numerous difficulties.³ With this series of articles on nitroso group transfer, we set out to classify solvents phenomenologically by examining their effects on nitrosation kinetics. In part 1¹ we examined the reactions of several secondary amines with alkyl nitrites (RONO) and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in nonaqueous apolar media (isooctane, cyclohexane, dichloromethane, 1,4-dioxane, and tetrahydrofuran) and found them to differ significantly from the corresponding aqueous phase reactions.⁴

We now report the extension of this study to the more polar nonaqueous solvents chloroform, acetonitrile, and dimethyl sulfoxide (DMSO), which were chosen in view of the results of part 1:¹ acetonitrile and DMSO both have large dielectric constants ($\epsilon = 36$ for acetonitrile, 45 for DMSO); DMSO in particular has a very high capacity

for solvation of ions; and proton donation by chloroform⁵ might affect HBC formation. We did not use alcohols (which would ideally have been desirable because of their structural similarity to water) because they are themselves readily nitrosated,^{6,7} and preliminary experiments in which nitrosation of formamides was detected similarly deterred us from further investigation of the nitrosation of amines in solvents of this family.

As expected, we found that the more polar the solvent, the more strongly was the mechanism deduced for the reaction in cyclohexane distorted toward the mechanism acting in water. Of particular interest, however, was the finding that, for nitrosation by alkyl nitrites, acetonitrile represents a kind of singular point in the continuum of solvent properties, in that the mechanism acting in this solvent depends qualitatively on both the nature of the leaving group of the nitrosating agent and the nature of the amine (whereas in other solvents the identity of the amine generally has only a quantitative influence). This finding underlines the difficulty of classifying solvents or predicting their effects on even a single class of reaction³ and provides an elegant example of how the mechanism of a nucleophilic substitution reaction can depend critically on the nature of nucleophile, leaving group, and solvent.²

Experimental Section

Chloroform (HPLC grade), acetonitrile (anhydrous), and DMSO (spectrophotometric grade) were supplied by Aldrich and had nominal purities >99.9% and water contents <0.01%, <0.005%, and <0.05%, respectively. Solubilization of atmospheric moisture during experiments was to some extent

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Table 1. Influence of Isopropylamine Concentration on the Chemical Shifts of the Central Peaks of the Triplets due to 2-Bromoethyl Nitrite in Chloroform

[iPrNH ₂]/M	δ /ppm	δ /ppm
	3.5775	5.1021
0.39	3.5628	5.0852
0.97	3.5189	5.0403
$\Delta\nu$ /Hz	-17.6	-18.5

countered by drying acetonitrile and DMSO over 3 Å molecular sieves⁸ and by preparing the reaction mixtures for selected experiments carried out in acetonitrile in a glovebox previously purged with Ar (99.999%, <2 vpm H₂O) for 4 h. It was confirmed experimentally that the levels of water remaining in the solvents did not appreciably affect the kinetics of nitrosation. Pyrrolidine (PYR), piperidine (PIPER), diethylamine (DEA), *N,N'*-dimethylethylenediamine (DED), *N*-methylpiperazine (MePIP), and morpholine (MOR) were of the highest commercially available purity (Aldrich) and were distilled under argon shortly before use. All other commercially supplied materials (Aldrich or Merck) were of the highest available purity and were used as supplied.

¹H NMR spectroscopy was performed in a Bruker AMX300 instrument operating at 300.1 MHz. The external reference and lock signal were provided by DMSO-*d*₆ contained in an internal capillary coaxial with the NMR tube.

Alkyl nitrites (RONO) were prepared by a standard procedure⁹ and were stored over 3 Å molecular sieves pending use.

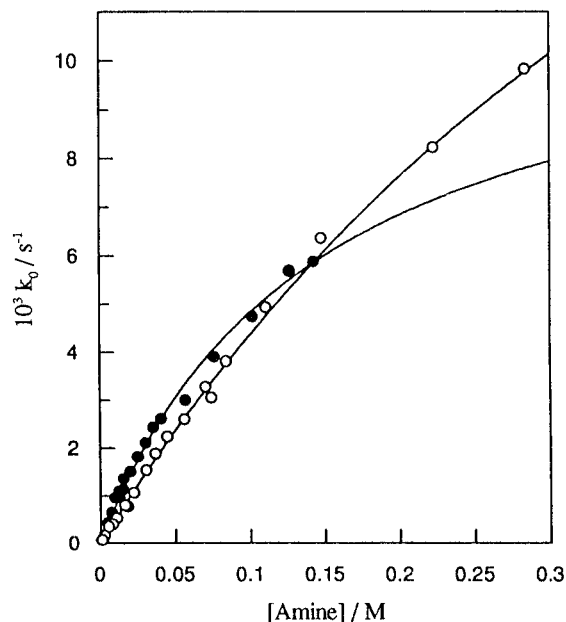
In all the kinetic experiments the nitrosating agent (RONO or MNTS) was in deficit, its concentration generally ranging from 1×10^{-4} to 2×10^{-4} M. Reaction kinetics were studied by monitoring the change in absorbance (generally in the range 250–270 nm) in Uvikon 930 or Milton Roy 3000 array spectrophotometers. In all cases, absorbance–time data were fitted by the integrated first-order rate equation, and k_0 , the corresponding pseudo-first-order rate constant, was reproducible to within 3%. Regardless of the experimental conditions, the *N*-nitrosamine was the only product detected and showed no signs of decomposition. Reaction yields were calculated from the absorbance data and published values of the molar absorption coefficients of the reactants and products.^{10,11} Additionally, the products of the reaction between pyrrolidine and 2-bromoethyl nitrite in acetonitrile were analyzed by reverse-phase HPLC on a Beckman Ultrasphere C₁₈ column of 5 μm particle size, using 1:1 CH₃CN:H₂O as mobile phase (flow rate 0.50 mL/min) and UV detection at 250 nm. Electronic integration of the peak of *N*-nitrosopyrrolidine confirmed the reaction to be quantitative.

Results

Association between the Reactants. In part 1 we demonstrated that associations between the amine and nitrosating agent play a crucial role in determining the nitrosation mechanism. Table 1 lists the ¹H NMR chemical shifts of the triplets due to the methylene groups of 2-bromoethyl nitrite in chloroform at increasing concentrations of added isopropylamine. These signals move upfield with increasing [iPrNH₂]. This behavior is the reverse of the effect observed for isopropylamine/2-bromoethyl nitrite mixtures in cyclohexane.

Because the solvents affected the reaction mechanism differently, the results are discussed separately for each one.

Reactions in Chloroform. 1. Influence of Amine Concentration. The influence of amine concentration on the pseudo-first-order rate constant (k_0) for the nitrosation of pyrrolidine by 2-bromoethyl nitrite is shown

**Figure 1.** Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2-bromoethyl nitrite in chloroform at (●) 25 and (○) 35 °C.**Table 2. Values of the Coefficients e and f in Equation 1 Fitted to the Data for the Variation of the Pseudo-First-Order Rate Constant (k_0) with [Amine] for Nitrosation by the Indicated Alkyl Nitrite (RONO) or MNTS of Several Amines in Chloroform**

amine	R in RONO	$e/M^{-1} s^{-1}$	f/M^{-1}
PYR	BrCH ₂ CH ₂	$(8.2 \pm 0.3) \times 10^{-2}$	7.0 ± 0.6
PYR ^a	BrCH ₂ CH ₂	$(5.1 \pm 0.1) \times 10^{-2}$	1.7 ± 0.1
PIPER	BrCH ₂ CH ₂	$(7.8 \pm 0.1) \times 10^{-3}$	1.08 ± 0.05
PIPER	Cl ₂ CHCH ₂	0.234 ± 0.004	
DEA	Cl ₂ CHCH ₂	$(4.48 \pm 0.05) \times 10^{-2}$	0.11 ± 0.01
MePIP	Cl ₂ CHCH ₂	$(2.24 \pm 0.02) \times 10^{-2}$	0.32 ± 0.02
MePIP ^a	Cl ₂ CHCH ₂	$(3.69 \pm 0.08) \times 10^{-2}$	0.17 ± 0.03
MOR	Cl ₂ CHCH ₂	$(1.56 \pm 0.02) \times 10^{-2}$	0.48 ± 0.02
MOR ^a	Cl ₂ CHCH ₂	$(2.21 \pm 0.03) \times 10^{-2}$	0.57 ± 0.05
PYR	MNTS	$(1.31 \pm 0.01) \times 10^{-2}$	

^a $T = 35$ °C.

in Figure 1. As this concave curve shows, k_0 depends linearly on [PYR] at low concentrations, but approaches a limiting value at high [PYR]; the corresponding curve for this reaction in cyclohexane was sigmoidal.¹ The curve in Figure 1, and also those for nitrosation of piperidine, diethylamine, *N*-methylpiperidine, and morpholine by alkyl nitrites, were fitted by eq 1 which contains no terms in [amine]².

$$k_0 = \frac{e[R_2NH]}{1 + f[R_2NH]} \quad (1)$$

A linear relationship was observed between k_0 for the nitrosation of PYR by MNTS and the corresponding [PYR] (Table 2).

The values of the coefficients e and f for the fits of eq 1 to all these data are given in Table 2 ($f = 0$ for nitrosation by MNTS).

2. Influence of Temperature. Figure 1 compares the influence of [PYR] on k_0 for nitrosation of PYR by 2-bromoethyl nitrite at 25 and 35 °C. These data were fitted by eq 1, for which the corresponding values of coefficients e and f are included in Table 2. The fitted curves cross at a [PYR] of approximately 0.15 M, below

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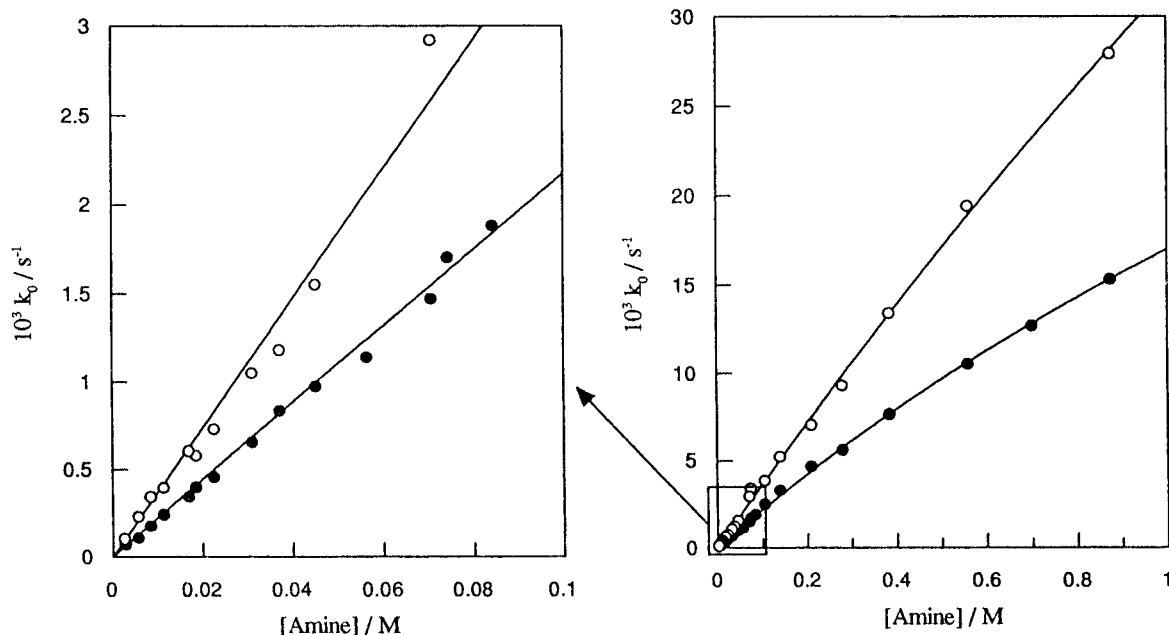


Figure 2. Influence of [MePIP] on the pseudo-first-order rate constant (k_0) for nitrosation of *N*-methylpiperazine by 2,2-dichloroethyl nitrite in chloroform at 25 (●) and 35 °C (○).

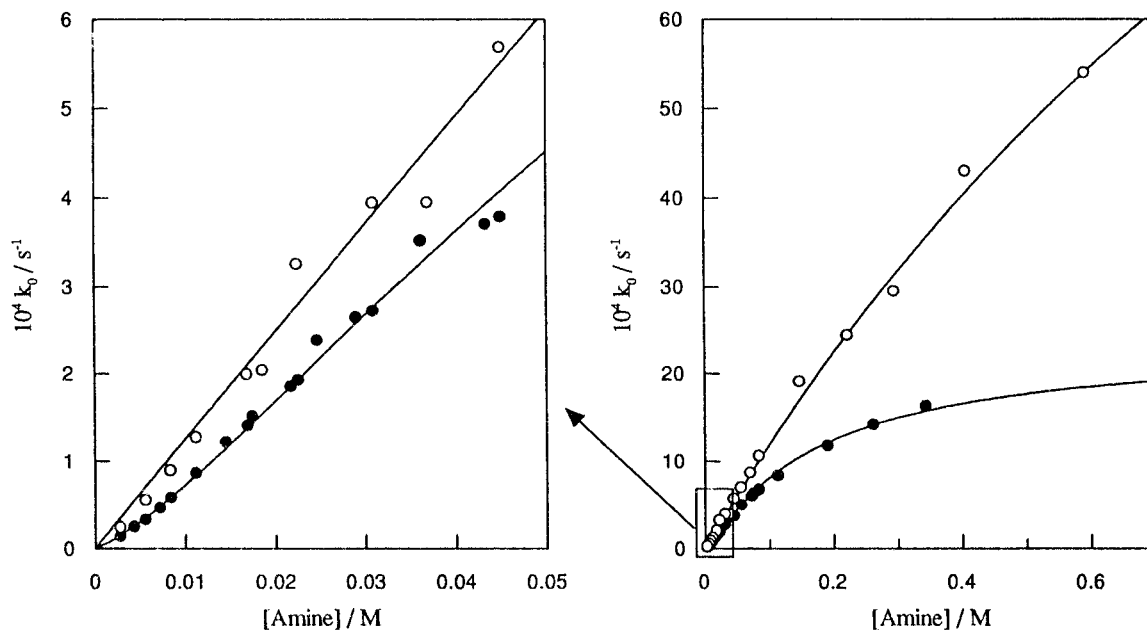


Figure 3. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2-bromoethyl nitrite in acetonitrile at (●) 25 and (○) 35 °C.

which k_0 decreases with increasing temperature, showing anti-Arrhenius behavior. This is in keeping with a preequilibrium involving association of the reactants, since such processes generally have negative enthalpy changes.

Figure 2 shows the corresponding curves for the nitrosation of *N*-methylpiperazine by 2,2-dichloroethyl nitrite at 25 and 35 °C. In this case Arrhenius behavior was observed (parameters e and f of eq 1 are included in Table 2).

Reactions in Acetonitrile. 1. Influence of Amine Concentration. The influence of amine concentration on k_0 for the nitrosation of pyrrolidine by 2-bromoethyl nitrite at 25 °C is shown in Figure 3. This curve closely resembles those obtained for reactions in apolar solvents such as cyclohexane and is described by a similar quadratic equation.

$$k_0 = \frac{a[\text{R}_2\text{NH}] + b[\text{R}_2\text{NH}]^2}{1 + c[\text{R}_2\text{NH}] + d[\text{R}_2\text{NH}]^2} \quad (2)$$

The coefficients a , b , c , and d for the equation of the fitted curve shown in Figure 3, and for similar curves obtained for the reactions of DEA and MOR with 2,2-dichloroethyl nitrite at 25 and 35 °C, are given in Table 3.

Linear k_0 -[amine] plots were obtained for the nitrosation of PYR and PIPER by 2,2-dichloroethyl nitrite (Table 3). These data were fitted to straight lines that passed through the origin. It is therefore apparent that the relative contributions of the first- and second-order terms are dependent on the nature of the alkyl nitrite. The effect of the nature of the alkyl nitrite can be explained by the base-catalyzed mechanism proposed in part 1.¹ In the case of 2,2-dichloroethyl nitrite, k_0 does

Table 3. Values of the Coefficients e and f in Equation 1 and a , b , c , and d in Equation 2, in Both Cases Fitted to the Data for the Variation of the Pseudo-First-Order Rate Constant (k_0) with [Amine] for Nitrosation by the Indicated Alkyl Nitrite or MNTS of Several Amines in Acetonitrile

amine	R in RONO	$e/M^{-1} s^{-1}$	f/M^{-1}
PYR	Cl ₂ CHCH ₂	0.548 ± 0.004	
PYR ^a	BrCH ₂ CH ₂	(1.26 ± 0.01) × 10 ⁻²	0.64 ± 0.02
PYR	MNTS	(5.05 ± 0.01) × 10 ⁻²	
PIPER	Cl ₂ CHCH ₂	(6.33 ± 0.04) × 10 ⁻²	
DEA	MNTS	(1.77 ± 0.02) × 10 ⁻³	
DED	Cl ₂ CHCH ₂	(7.19 ± 0.05) × 10 ⁻²	0.10 ± 0.01
DED ^a	Cl ₂ CHCH ₂	0.116 ± 0.001	0.10 ± 0.02
MePIP	Cl ₂ CHCH ₂	(8.2 ± 0.1) × 10 ⁻³	0.11 ± 0.03
MePIP ^a	Cl ₂ CHCH ₂	(1.30 ± 0.05) × 10 ⁻²	0.12 ± 0.05

amine	$a/M^{-1} s^{-1}$	$b/M^{-2} s^{-1}$	c/M^{-1}	d/M^{-2}
		BrCH ₂ CH ₂ ONO		
PYR	(4.19 ± 0.05) × 10 ⁻³	0.72 ± 0.08	54 ± 9	300 ± 28
		Cl ₂ CHCH ₂ ONO		
DEA	(1.49 ± 0.09) × 10 ⁻²	0.17 ± 0.02	3.8 ± 0.7	7.2 ± 0.6
DEA ^a	(2.6 ± 0.3) × 10 ⁻²	0.25 ± 0.01	5.6 ± 0.3	3 ± 1
MOR	(1.88 ± 0.03) × 10 ⁻³	(2.90 ± 0.08) × 10 ⁻³		0.61 ± 0.02
MOR ^a	(3.5 ± 0.1) × 10 ⁻³	(3.2 ± 0.1) × 10 ⁻³		0.35 ± 0.06

^a $T = 35$ °C.

not depend on [amine]² (base-catalyzed decomposition of the zwitterionic intermediate T[±] by a second amine molecule is not observed) because, by virtue of its greater number of electron-withdrawing β -substituents, the leaving group (2,2-dichloroethoxide ion) is stabilized and so easily expelled spontaneously. Moreover, since this expulsion step is rapid, the rate-controlling step for the reaction becomes evolution of the HBC into T[±]. The fact that the plot for PIPER (not shown) is still highly linear at PIPER concentrations as high as 0.37 M (similar behavior was also observed for this nitrosation reaction of piperidine in chloroform) can also be explained by the electron-withdrawing effect of the β -chloro substituents of the alkyl nitrite: electron withdrawal by these groups will reduce the electron-donating capacity of the alkoxy oxygen and thus the value of the equilibrium constant for formation of the hydrogen-bonded amine-RONO complex.

k_0 -[amine] plots that were fitted by eq 1 for reactions in chloroform were also obtained for the nitrosation of DED and MePIP by 2,2-dichloroethyl nitrite, and, surprisingly, PYR by 2-bromoethyl nitrite at 35 °C (see below), all carried out in acetonitrile. The tendency of the amines to react via a mechanism for which k_0 depends on [amine] and [amine]² or [amine] seems to be dependent on their pK_a values.¹²

The k_0 -[amine] data for nitrosation of PYR and DEA by MNTS were fitted by straight lines (Table 3), indicating behavior similar to that observed for these reactions in chloroform.

2. Effect of Addition of Isopropylamine. The effects of adding the strongly basic and weakly nucleophilic amine, isopropylamine, to the reaction mixture were evaluated. The results for the nitrosation of PYR (at concentrations 1.45×10^{-2} and 7.63×10^{-2} M) by 2-bromoethyl nitrite are listed in Table 4. The isopropylamine had only a small effect on k_0 , but one which was clearly inhibitory and parallel to the effect observed for the corresponding reaction in cyclohexane. As in those experiments, this inhibition can be accounted for by the formation of unreactive hydrogen-bonded complexes (HBCs) between the isopropylamine and the alkyl nitrite.

Table 4. Influence of Isopropylamine Concentration on the Pseudo-First-Order Rate Constant (k_0) for Nitrosation of Pyrrolidine by 2-Bromoethyl Nitrite in Acetonitrile at 25 °C

[PYR]/M	[iPrNH ₂]/M	k_0/s^{-1}
7.63×10^{-2}	1.56×10^{-2}	5.58×10^{-4}
7.63×10^{-2}	3.11×10^{-2}	5.53×10^{-4}
7.63×10^{-2}	6.23×10^{-2}	5.68×10^{-4}
7.63×10^{-2}	0.124	5.43×10^{-4}
7.63×10^{-2}	0.249	5.04×10^{-4}
1.45×10^{-2}	1.56×10^{-2}	1.29×10^{-4}
1.45×10^{-2}	3.11×10^{-2}	1.30×10^{-4}
1.45×10^{-2}	6.23×10^{-2}	1.28×10^{-4}
1.45×10^{-2}	0.124	1.22×10^{-4}
1.45×10^{-2}	0.249	1.03×10^{-4}
1.45×10^{-2}	0.498	9.61×10^{-5}

Table 5. Influence of Isopropylamine Concentration on the Pseudo-First-Order Rate Constant (k_0) for Nitrosation of Diethylamine by 2,2-Dichloroethyl Nitrite in Acetonitrile at 25 °C

[DEA]/M	k_0/s^{-1}	
	[iPrNH ₂] = 0	[iPrNH ₂] = 0.156 M
0.15	3.35×10^{-3}	2.40×10^{-3}
0.11	2.47×10^{-3}	1.88×10^{-3}
7.33×10^{-2}	1.59×10^{-3}	1.25×10^{-3}
5.57×10^{-2}	1.07×10^{-3}	1.20×10^{-3}
4.46×10^{-2}	8.14×10^{-4}	9.17×10^{-4}
3.67×10^{-2}	5.37×10^{-4}	6.05×10^{-4}
3.06×10^{-2}	5.30×10^{-4}	5.73×10^{-4}
2.23×10^{-2}	3.65×10^{-4}	4.28×10^{-4}
1.67×10^{-2}	2.75×10^{-4}	3.10×10^{-4}
1.11×10^{-2}	1.72×10^{-4}	2.09×10^{-4}
8.36×10^{-3}	1.28×10^{-4}	1.64×10^{-4}
5.57×10^{-3}	8.42×10^{-5}	1.07×10^{-4}
2.79×10^{-3}	3.66×10^{-5}	5.60×10^{-5}
1.39×10^{-3}	2.06×10^{-5}	2.64×10^{-5}

Table 5 lists the results of similar experiments examining the effects of adding iPrNH₂ to the reaction between DEA and 2,2-dichloroethyl nitrite. In these experiments, iPrNH₂ had a slight catalytic effect at low DEA concentrations, which is attributable to there being an alternative route for decomposition of T[±] involving catalysis by iPrNH₂ (this must have a pK_a only slightly lower than that of DEA,¹² since even at relatively high [iPrNH₂] k_0 does not increase by more than ca. 50%). At high [DEA] the value of k_0 was slightly lower than that in the absence of isopropylamine, again in keeping with the formation of unreactive HBCs between the iPrNH₂ and the alkyl nitrite.

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Table 6. Influence of Water Concentration on the Slope of the Plot of Pseudo-First-Order Rate Constant (k_0) against [PYR] for Nitrosation of Pyrrolidine by 2,2-Dichloroethyl Nitrite in Acetonitrile at 25 °C

H ₂ O _{add} /% vol	slope/M ⁻¹ s ⁻¹
	0.548 ± 0.004
0.07	0.571 ± 0.003
0.13	0.599 ± 0.003
0.20	0.615 ± 0.002
0.40	0.692 ± 0.004
0.80	0.817 ± 0.005

Table 7. Comparison of the Pseudo-First-Order Rate Constants (k_0) for the Nitrosation of Pyrrolidine by 2-Bromoethyl Nitrite in Anhydrous Acetonitrile at 25 °C (A) for Reaction Mixtures Prepared in the Open Air (Calculated Using Equation 2 and the Parameters in Table 3) and (B) for the Corresponding Mixtures Prepared under Dry Argon

[PYR]/M	k_0^a/s^{-1}	k_0^b/s^{-1}
2.39×10^{-2}	2.22×10^{-4}	1.69×10^{-4}
1.59×10^{-2}	1.51×10^{-4}	1.08×10^{-4}
1.19×10^{-2}	1.15×10^{-4}	8.01×10^{-5}
7.97×10^{-3}	7.77×10^{-5}	4.85×10^{-5}
3.98×10^{-3}	3.92×10^{-5}	2.15×10^{-5}

^a Calculated using parameters in Table 3. ^b Working under argon.

3. Effects of Addition of Water. The effects of adding water to the reaction between pyrrolidine and 2,2-dichloroethyl nitrite were evaluated. For reaction mixtures prepared in anhydrous acetonitrile (<0.005% water) in the open air, Table 6 lists the slopes of the k_0 -[PYR] plots (which were linear in all cases) for several concentrations of added water. Increasing the water concentration caused this slope to increase, probably because the reaction is sensitive to the polarity of the medium,⁴ which would increase concomitantly.

Variations in the water content of the reaction medium may be partially responsible for the differences observed among the k_0 -[amine] plots for the amines and nitrosating agents studied. Moreover, the 0.8% (v/v) of water added in the above experiments could potentially be insignificant in comparison to the water already dissolved in the solvent. However, a comparison of (a) pseudo-first-order constants calculated (using eq 2 and the parameters in Table 3) for reactions between mixtures of pyrrolidine and 2-bromoethyl nitrite in anhydrous acetonitrile that were prepared in the open air with (b) those for the reactions of the corresponding mixtures prepared under dry argon showed only small differences (Table 7). These results confirm that absorption of atmospheric moisture by the acetonitrile is not contributing significantly to the observed variations in k_0 .

4. Influence of Temperature. Figure 3 shows that k_0 for nitrosation of PYR by 2-bromoethyl nitrite increases with temperature over the range of PYR concentrations studied. For this reaction in cyclohexane and in chloroform, the corresponding curves showed regions of anti-Arrhenius behavior (negative overall activation energy) that were attributable to association of the reactants in preequilibria which, being exothermic, had smaller equilibrium constants at higher temperatures. Similarly here, as Figure 3 shows, upon increasing the reaction temperature from 25 to 35 °C, the second-order [amine] term in the rate expression effectively disappeared.

Similar experiments examining nitrosation of DEA (see Figure 4) and MOR at 25 and 35 °C gave plots that indicated dependence of k_0 on both [amine] and [amine]².

There were no regions of negative activation energy in these plots; however, the increase in k_0 upon increasing the reaction temperature varied over the range of amine concentrations studied. Similarly, no regions of negative activation energies were observed in k_0 -[amine] plots for experiments examining nitrosation of *N,N'*-dimethylethylenediamine (DED; see Figure 5) and MePIP at 25 and 35 °C. However, the curvature of these plots decreased markedly as [amine] increased, such that they were roughly linear over the range of amine concentrations studied.

Reactions in DMSO. The influence of amine concentration on k_0 for the nitrosation of PYR by 2-bromoethyl nitrite in DMSO is shown in Figure 6 for the reactions at 25 and 35 °C. Similar plots were obtained for the nitrosation of PYR by MNTS in this solvent and for the nitrosation by alkyl nitrites of a selection of the other amines studied. For these latter experiments, Table 8 lists the slopes and *y*-intercepts of the k_0 -[amine] plots; the non-zero *y*-intercept for the reactions of MOR with 2-bromoethyl nitrite in fact correspond quantitatively to the rates of decomposition of the alkyl nitrite in DMSO.

The solvating power of DMSO is much greater than those of the other solvents studied, so there will be little association of reactants in this solvent. The similarity between the nitrosation mechanism in DMSO and that in water was confirmed by experiments in which addition of *i*PrNH₂ or water to the DMSO solution had no appreciable effects on k_0 (Table 9).

Discussion

The reaction mechanism should account for the results obtained in this work and also for those obtained with apolar solvents in part 1. The base-catalyzed mechanism proposed in part 1 could account for the tendency of k_0 to depend either on [amine] or [amine] and [amine]² according to the natures of the nitrosating agent, the amine nucleophile, and the solvent. In this mechanism (Scheme 1-A) a hydrogen-bonded complex (HBC) composed of the monomeric amine and the alkyl nitrite evolves into a zwitterionic nitrosamine intermediate (T[±]), which then decomposes either spontaneously or via a pathway involving catalysis by a second amine molecule. At high amine concentrations the rate-controlling step is formation of the intermediate T[±], while at low amine concentrations it is decomposition of this intermediate, either spontaneously or via the base-catalyzed pathway. According to this mechanism, the pseudo-first-order rate constant (k_0) is given by the following equation, which is analogous to eq 2.

$$k_0 = \frac{\frac{k_2 k_4 K_C}{k_{-2} + k_4} [R_2NH] + \frac{k_3 k_2 K_C}{k_{-2} + k_4} [R_2NH]^2}{1 + \frac{k_3 + k_{-2} K_C + k_4 K_C}{k_{-2} + k_4} [R_2NH] + \frac{k_3 K_C}{k_{-2} + k_4} [R_2NH]^2} \quad (3)$$

This mechanism must now account for the effects observed upon increasing the polarity of the reaction medium.

Our study comparing the reactivities of a series of amines with alkyl nitrites and MNTS suggests that, between reaction in nonpolar solvents such as cyclohexane and reaction in aqueous media, there is a continuous

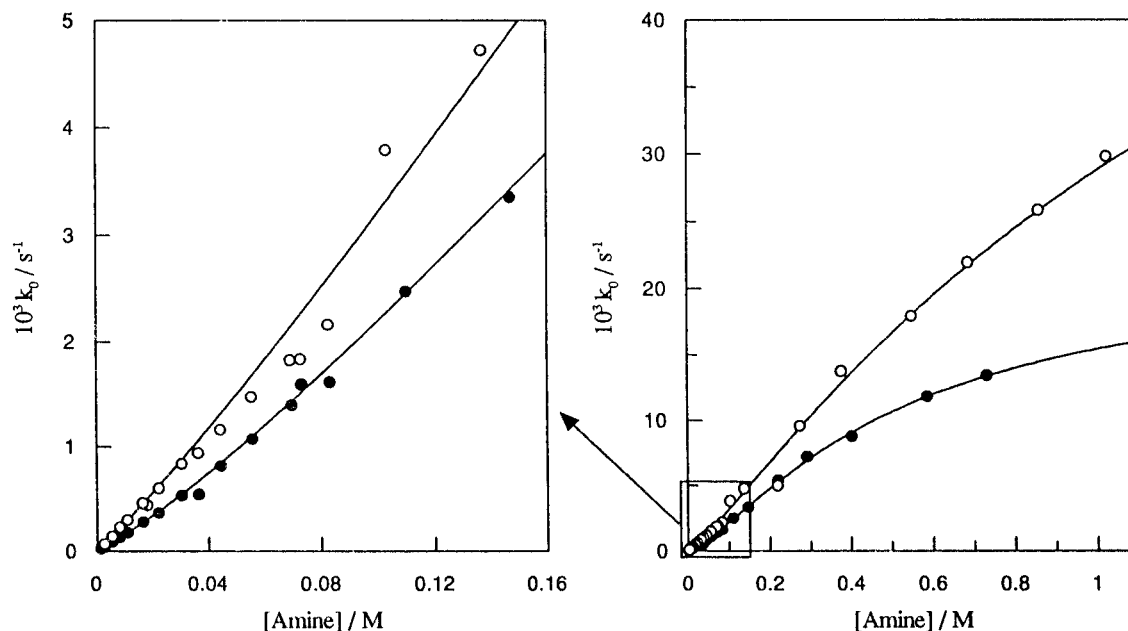


Figure 4. Influence of [DEA] on the pseudo-first-order rate constant (k_0) for nitrosation of diethylamine by 2,2-dichloroethyl nitrite in acetonitrile at (●) 25 and (○) 35 °C.

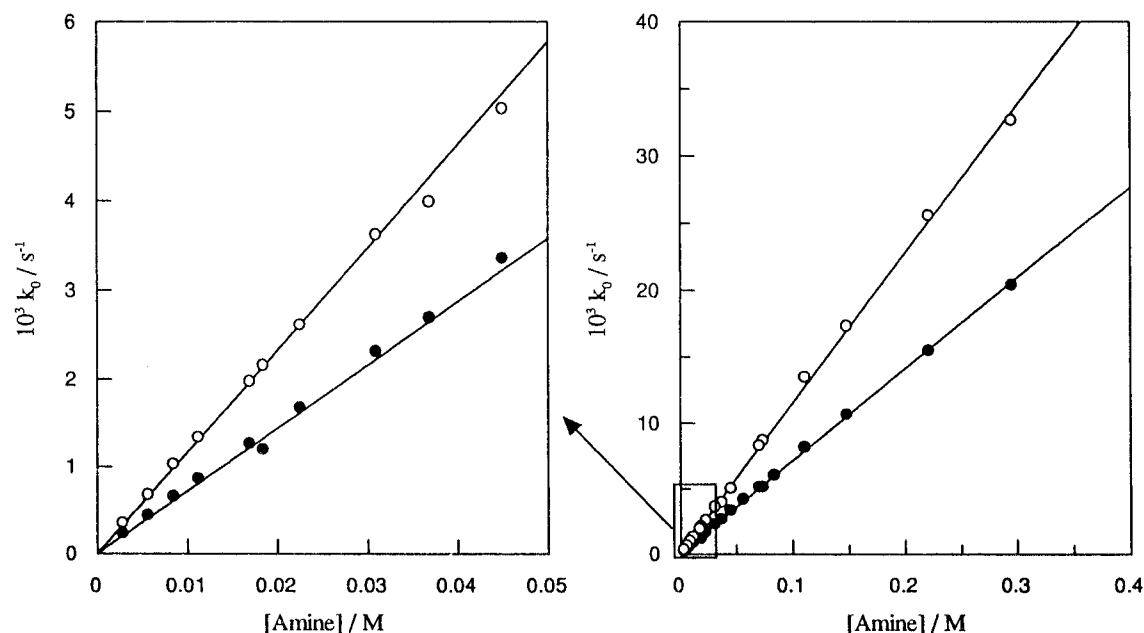


Figure 5. Influence of [DED] on the pseudo-first-order rate constant (k_0) for nitrosation of *N,N'*-dimethylethylenediamine by 2,2-dichloroethyl nitrite in acetonitrile at (●) 25 and (○) 35 °C.

change in the reaction mechanism. In nonpolar solvents with no capacity for hydrogen bond formation, the alkyl nitrite and amine form a hydrogen-bonded complex (HBC), which evolves into a tetrahedral intermediate (T^\pm) in which the amine is attached to the nitroso group. According to the reaction conditions, the spontaneous or base-catalyzed decomposition of this intermediate will be the rate-limiting step of the nitrosation reaction. As the polarity of the medium is increased, the rate of decomposition of T^\pm also increases due to greater solvation of the ionic decomposition products. Such increases in the rates of base-catalyzed processes have also been observed in dimethyl sulfoxide/water and dioxane/water mixtures; and the rate of proton transfer in DMSO/water mixtures has been observed to decrease with increasing DMSO

concentration, which was attributed to hydrogen bonding between the proton donor and the DMSO (a much more protophilic solvent than water¹⁴) and the consequent need to break this hydrogen bond prior to proton transfer.¹⁵

In this way, the observed kinetics of amine nitrosation in polar solvents can be explained by considering that evolution of the HBC into T^\pm (k_2) is the rate-controlling step, while decomposition of the intermediate T^\pm derived from this HBC is a rapid process. The corresponding pseudo-first-order rate constant is given by,

$$k_0 = \frac{K_C k_2 [R_2NH]}{1 + K_C [R_2NH]} \quad (4)$$

which is analogous to eq 1.

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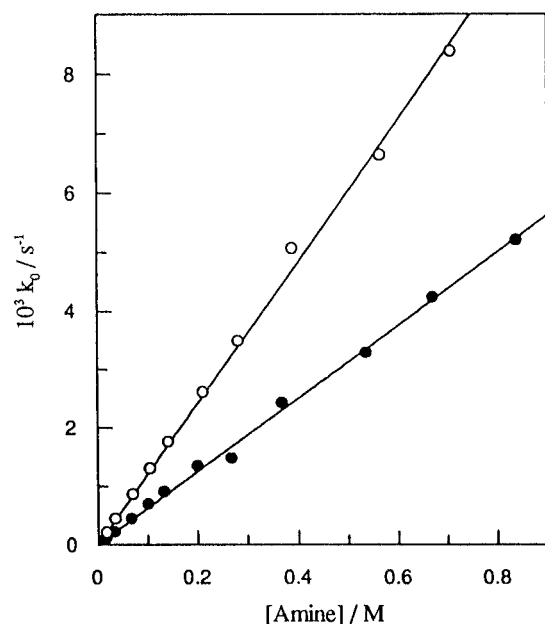


Figure 6. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2-bromoethyl nitrite in DMSO at (●) 25 and (○) 35 °C.

Table 8. Values of the Slopes and y -Intercepts of Plots of the Pseudo-First-Order Rate Constant (k_0) against [Amine] for Nitrosation of Several Amines by 2-Bromoethyl Nitrite, 2,2-Dichloroethyl Nitrite, and MNTS in DMSO at 25 and 35 °C

amine	$T/^\circ\text{C}$	y -intercept/ s^{-1}	slope/ $\text{M}^{-1} \text{s}^{-1}$
PYR ^a	25		$(6.24 \pm 0.07) \times 10^{-3}$
PYR ^a	35		$(1.19 \pm 0.02) \times 10^{-2}$
PYR ^c	25		$(4.61 \pm 0.02) \times 10^{-2}$
PIPER ^b	25		$(4.98 \pm 0.05) \times 10^{-2}$
DEA ^b	25		$(1.26 \pm 0.01) \times 10^{-2}$
MOR ^b	25	$(3.9 \pm 0.2) \times 10^{-4}$	$(2.02 \pm 0.05) \times 10^{-3}$
MOR ^b	35	$(7.9 \pm 0.8) \times 10^{-4}$	$(5.0 \pm 0.1) \times 10^{-3}$

^a 2-Bromoethyl nitrite. ^b 2,2-Dichloroethyl nitrite. ^c MNTS.

The linear k_0 -[amine] plots obtained for reactions in DMSO can be explained by a mechanism in which the reactants, which will be highly solvated, react without formation of the hydrogen-bonded complex. In this work, as the polarity of the medium increases and the rate of decomposition of T^\pm becomes faster, this intermediate should effectively cease to form, and so its decomposition will no longer be the rate-limiting step. The results do indeed suggest that the energy barrier to decomposition of T^\pm decreases as the solvent polarity increases until, in polar solvents such as H_2O , nitrosation proceeds via a concerted mechanism.

The results of experiments examining the nitrosation of the amines by MNTS in Cl_3CH , CH_3CN , and DMSO are not in keeping with a mechanism involving amine-MNTS association or base catalysis. These results can therefore be considered consistent with a mechanism that is unaffected by the nature of the solvent and which involves nucleophilic attack of the nitroso group to form an intermediate, T^\pm , which rapidly decomposes.

Influence of the Nature of the Amine. The reaction mechanism should also explain the influence of the nature of the amine on the rate of reaction. The proposed mechanism for amine nitrosation by alkyl nitrites in chloroform involves formation of an HBC, composed of the amine and alkyl nitrite, that evolves into the T^\pm intermediate which rapidly decomposes. Values of the rate constant for this reaction (k_2) can be obtained from

eq 4 ($k_2 = e/f$). Comparison of these rate constants for diethylamine, *N*-methylpiperazine, and morpholine reveals that these amines have reactivities in the ratio 12.5:2.1:1 in chloroform. Similar relative reactivities (11.7:1.6:1, respectively) were obtained for the nitrosation of these amines by MNTS in water (under which conditions, MNTS behaves similarly to alkyl nitrites).⁴

A similar comparison of the reactivities of the amines in acetonitrile was complicated by the fact that the behavior observed was similar to that in cyclohexane for some amines and experimental conditions and similar to that in chloroform for others. The differing behavior observed for the nitrosation of PYR by 2-bromoethyl nitrite (sigmoidal k_0 -[amine] plot) is attributable to differences between the basicities of the alkoxide leaving groups. A similar effect is seen for the hydration of carbonyl compounds:¹⁶ for compounds with poor leaving groups, the rate-controlling step is expulsion of that leaving group; for compounds with very good leaving groups (as in the hydrolysis of phenyl or alkyl esters), hydration of the carbonyl group is rate limiting.

The sensitivity of the reaction to the nature of the leaving group will to some extent depend on the attacking nucleophile: for reactive nucleophiles, the transition state will be early and therefore less affected by the nature of the nucleophile. For the amine nucleophiles studied, basicity decreases in the order $\text{PYR} > \text{PIPER} > \text{DEA} > \text{DED} > \text{MePIP} > \text{MOR}$, and the sensitivity of the nitrosation reaction to the nature of the leaving group increases in the same order. Thus, for the least basic amine (MOR), the rate-controlling step can be either the formation or the decomposition of T^\pm . The anomalous behavior of DEA, which also reacts with MNTS in water at a rate three times lower than that expected on the basis of its $\text{p}K_a$, is attributable to the steric bulk of this amine impeding nucleophilic attack by it.

For the reactions of the amines in DMSO the behavior observed was consistently similar to that in water, and the relative reactivities of piperidine, diethylamine, and morpholine with 2,2-dichloroethyl nitrite were evaluated as 24.6:6.2:1, which compare very well with those for nitrosation of these amines by MNTS in water (32:11.7:1, respectively).⁴

Influence of Temperature. For the nitrosation of MOR and MePIP by 2,2-dichloroethyl nitrite in chloroform, the rate constants increased between 25 and 35 °C. However, for the corresponding reaction between PYR and 2-bromoethyl nitrite, the rate constant exhibited complex behavior that was indicative of regions of both positive and negative overall activation energy depending on the concentration of the amine. These results must be interpreted using true rate and equilibrium constants. From the data in Table 2, the effects of temperature on k_2 (the rate of conversion of the HBC into products) and K_C (the equilibrium constant for formation of the HBC) in eq 4 were evaluated: for the 10° rise in temperature, the k_2 for nitrosation of PYR by 2-bromoethyl nitrite and for nitrosation of MePIP by 2,2-dichloroethyl nitrite increased by factors of 2.5 and 3.1, respectively (the results for nitrosation of MOR by 2,2-dichloroethyl nitrite were not considered indicative, since the corresponding plots of k_0 against [amine] barely deviated from linearity), while K_C decreased for all three amines, most notably in the case of PYR. The existence of regions of overall negative activation energy was therefore attributed to the decrease in K_C being greater than the increase in k_2

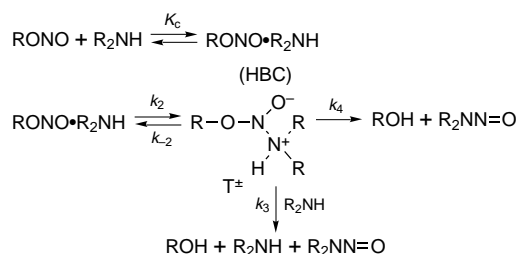
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Table 9. Influence of Pyrrolidine and Isopropylamine or Water Concentration on the Pseudo-First-Order Rate Constant (k_0) for Nitrosation of PYR by 2-Bromoethyl Nitrite in DMSO at 25 °C

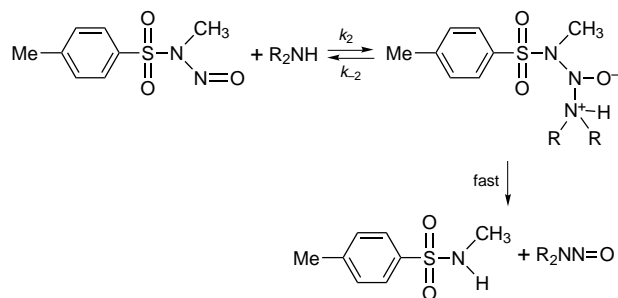
[PYR]/M	[iPrNH ₂]/M	k_0/s^{-1}	[PYR]/M	H ₂ O/% vol	k_0/s^{-1}
3.7×10^{-2}	0.16	2.21×10^{-4}	7.01×10^{-2}		4.56×10^{-4}
7.33×10^{-2}	0.16	5.75×10^{-4}	7.01×10^{-2}	6.67×10^{-2}	4.61×10^{-4}
0.15	0.16	1.08×10^{-3}	7.01×10^{-2}	0.13	4.63×10^{-4}
0.30	0.16	2.09×10^{-3}	7.01×10^{-2}	0.27	4.65×10^{-4}
0.41	0.16	2.81×10^{-3}	7.01×10^{-2}	0.53	4.57×10^{-4}
0.59	0.16	3.93×10^{-3}	7.01×10^{-2}	1.07	4.76×10^{-4}
0.74	0.16	4.72×10^{-3}	7.01×10^{-2}	2.13	4.96×10^{-4}
0.31	2.33×10^{-2}	2.02×10^{-3}	7.01×10^{-2}	3.53	5.90×10^{-4}
0.31	4.67×10^{-2}	2.03×10^{-3}			
0.31	9.34×10^{-2}	1.98×10^{-3}			
0.31	0.19	2.01×10^{-3}			
0.31	0.37	1.99×10^{-3}			
0.31	0.75	2.05×10^{-3}			
0.31	0.93	2.00×10^{-3}			

Scheme 1

A. nitrosation of amines by alkyl nitrites



B. nitrosation of amines by MNTS



for certain amine concentrations. Consistent with this interpretation are the effects of the temperature increase on k_2 and the ratio k_4/k_3 (the ratio of the rate of spontaneous to base-catalyzed decomposition) for the nitrosation of DEA and MOR by 2,2-dichloroethyl nitrite in acetonitrile, which were evaluated from Table 3 and eq 3 as b/d and a/b , respectively. Specifically, k_2 increases with temperature for both reactions (i.e., Arrhenius behavior) and so does the ratio k_4/k_3 , thus indicating that spontaneous decomposition is favored at the higher temperature.

The change in the rate-controlling step of PYR nitrosation by 2-bromoethyl nitrite in acetonitrile upon increasing the reaction temperature was rather surprising. For reaction at 25 °C and amine concentrations <0.01 M, k_0 showed a slight but nonetheless statistically significant dependence on both [PYR] and [PYR]² (described by eq 2), indicating that decomposition of T[±] was the rate-controlling step. For reaction at 35 °C using the same range of PYR concentrations, k_0 showed an approximately linear dependence on [PYR] (described by eq 1) that indicated that the rate-controlling step was now evolution of the HBC into the intermediate T[±]. The effects of increasing the temperature to 35 °C on the rate-controlling step can be estimated by assuming that the coefficients a , b , c , and d of eq 2 for the reaction at 25 °C (Table 3) undergo changes similar to those observed in the corresponding coefficients for this reaction in cyclo-

hexane¹ (this is reasonable given that these solvents have similar hydrogen bond donor acidity). Substitution of the calculated parameters ($a = 5.76 \times 10^{-3}$, $b = 0.14$, $c = 15.4$, and $d = 34.6$) into eq 2 gives an equation which, for [PYR] < 0.01 M, formally reduces to eq 1.

The effects of temperature on the nitrosation of PYR by 2-bromoethyl nitrite and the nitrosation of MOR by 2,2-dichloroethyl nitrite, in both cases in DMSO, are summarized in Table 8. These results indicate that k_0 exhibits Arrhenius behavior, as is also found for these nitrosation reactions in water.⁴

Solvent Effects. In this section we consider the results reported above and in part 1¹ in relation to various systems for characterization of solvents and prediction of their effects on reaction kinetics.

For the nitrosation of pyrrolidine by MNTS, the Kirkwood equation¹⁷ yields a good correlation of the rate constants with dielectric permittivity for dioxane, chloroform, dichloromethane, acetonitrile, and DMSO (i.e., all the solvents used in this work in which the pseudoconstant k_0 varied linearly with [amine]), but the correlation is unsatisfactory when the data for the reaction in water are included, showing that the effect of water is not due solely to electrostatic interaction. For the same reaction the Bentley equation^{18,19} yields a reasonable correlation (using values of N and Y obtained by Peterson²⁰ by conversion of Swain parameters²¹) afforded the values $l = 0.12$ and $m = 0.29$ ($r = 0.98$); the low value of m suggests an early transition state. Better correlation appeared to have been prevented largely by the low rate of the reaction in dioxane, possibly because of dissimilarity between tosylate and the methyl toluenesulfonamide anion (Y values depend on the nature of the leaving group¹⁹).

Using the more sophisticated Kamlet–Abbott–Taft equation²² for the same reaction, a correlation of the rate constants in dioxane, dichloromethane, chloroform, acetonitrile, DMSO, and water by means of this equation afforded the values $s = 2.7 \pm 1.0$, $a = 0.8 \pm 0.5$, and $b = 0.07 \pm 0.70$ ($r = 0.993$) (Figure 7). Although the small number of data points and the large uncertainties in the

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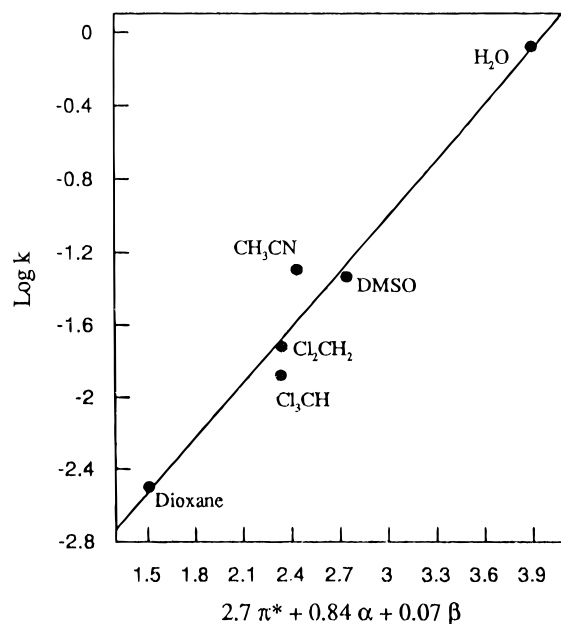


Figure 7. Plot of $\log k$ against Taft's function for the nitrosation of pyrrolidine by *N*-methyl-*N*-nitroso-*p*-toluene-sulfonamide in several solvents.

values of a and b prevent sure interpretation of this correlation, it would appear that the effect of the solvent on this reaction is due to its dipolarity and, to a lesser extent, its ability to form hydrogen bonds through its own protons.

The solvent properties identified by Taft's function as relevant to the kinetics of the nitrosation of secondary amines by MNTS are the same as those applied to explain the effects of the solvents on nitrosation by alkyl nitrites. That the energy barrier to the decomposition of T^\pm is high enough to be rate controlling in cyclohexane but is nonexistent in water is attributable to the greater dipolarity/polarizability of the latter, while the differences between the behaviors observed in dichloromethane and chloroform are attributable to the greater capacity of chloroform to form hydrogen bonds through its hydrogen atom. The singular behavior observed in acetonitrile may be regarded as arising because, although acetonitrile has greater dipolarity/polarizability than either dichloromethane or chloroform, it has virtually no capacity to form hydrogen bonds through its methyl protons.

Conclusions

The mechanism of nitroso group transfer from MNTS or alkyl nitrites to secondary amines is strongly dependent on the reaction medium. Upon increasing the polar-

ity of the solvent, or its capacity to act as a proton donor in hydrogen bond formation, there is a gradual change from a stepwise to a concerted mechanism, the latter mechanism being active in aqueous media. On the basis of the results obtained here, the participation of both amine monomers and dimers in these reactions is ruled out. Instead, the observed behavior is explained by a two-step mechanism in which a hydrogen-bonded complex between the amine and the alkyl nitrite evolves into a tetrahedral intermediate T^\pm , which then decomposes to afford the products. Depending on the reaction conditions, either formation or decomposition of T^\pm will be the rate-controlling step, in keeping with previous reports of reactions in which the rate-controlling step changes according to the concentration of the catalyst. Such a change in rate-controlling step requires that an intermediate be formed in the reaction pathway and that the sensitivity to catalysis of the formation and decomposition reactions of that intermediate be different.

This stepwise mechanism for the nitrosation of amines by alkyl nitrites in relatively apolar media is similar to that for aminolysis of carboxylic esters (which are electronically similar to alkyl nitrites). The fact that the nitrosation mechanism apparently becomes concerted as the polarity and capacity for hydrogen bonding of the medium are increased is attributed to the effective disappearance of the energetic barrier to intermediate decomposition due to increased solvation of the alkoxide leaving group.

The nitrosation of amines by alkyl nitrites without the formation of tetrahedral intermediates has previously²³ been attributed to there being electrostatic repulsion between the nitrogen and oxygen lone pairs of the amine and alkyl nitrite, respectively, a situation that does not apparently arise in the aminolysis of carboxylic esters. Our results suggest that, rather than electronic repulsion between the reactants, the concerted mechanism is due to the effective disappearance of the energy barrier to decomposition of the tetrahedral intermediate except in solvents with poor solvating power, in which its decomposition is the rate-controlling step. For nitrosation in aqueous media, a concerted mechanism is observed because the high energy (high acidity) of the intermediate T^\pm precludes its formation.

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