Nitrosation of Amines in Nonaqueous Solvents. 1. Evidence of a Stepwise Mechanism

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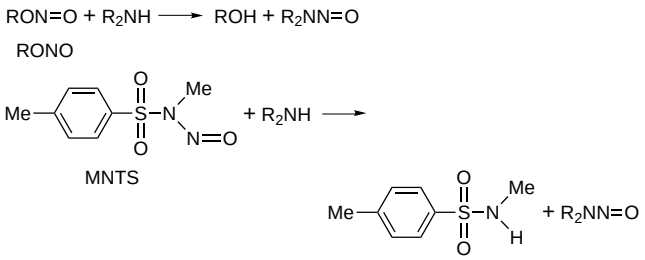
We studied the nitrosation of piperidine, morpholine, pyrrolidine, *N*-methylpiperazine, *N*,*N*′-dimethylethylenediamine and diethylamine by 2-bromoethyl nitrite, 2,2-dichloroethyl nitrite, 2,2,2-trichloroethyl nitrite, or *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in cyclohexane, isooctane, dichloromethane, 1,4-dioxane, or tetrahydrofuran. The dependence of the first-order pseudoconstant k_0 on the amine concentration (always in excess) was sigmoid for nitrosation by alkyl nitrites and linear or quadratic for nitrosation by MNTS. The effects on k_0 of isotopic substitution, temperature, and base catalysis by a less reactive amine were also determined. The experimental data are in keeping with a reaction mechanism involving a zwitterionic tetrahedral intermediate $T^{\pm}$ analogous to intermediates postulated for the aminolysis of carboxylic esters in similar solvents: according to this mechanism, $T^{\pm}$ is formed either directly from the amine and nitrosating agent (in the case of MNTS) or indirectly via a hydrogen-bonded complex between the amine and nitrosating agent (in the case of alkyl nitrites) and decomposes either spontaneously or with the catalytic assistance of a second amine molecule. For alkyl nitrites, the rate-controlling step is the formation of $T^{\pm}$ at high amine concentrations and its decomposition at low amine concentrations; for MNTS, the rate-controlling step is the formation of $T^{\pm}$ in more polar solvents and its decomposition in less polar solvents. An alternative mechanism, involving the formation of $T^{\pm}$ from both monomers and dimers of the amine, is ruled out.

Introduction

Alkyl nitrites form a major group of nitrosating agents able to convert amines to nitrosamines (Scheme 1).[1] Because of the known toxicity,[2] carcinogenicity,[3] mutagenicity,[4] and teratogenicity[5] of nitrosamines, and of the ensuing possibility that both alkyl nitrites[6] and their precursors[1,7,8] are involved in pathogenic processes, the reactions of alkyl nitrites with amines in aqueous solution have been studied extensively.[7,9−13] Oae *et al.*[9] have suggested that these reactions are controlled by interaction between the frontier orbitals of the nucleophile (the amine) and the electrophile (the alkyl nitrite). Traditionally, they have been considered to proceed via a concerted mechanism involving a four-center transition state,[7,9,10] but the recent findings that they exhibit solvent isotope effects close to two and have high negative entropies of activation are more in keeping with a six-center transition state in which a water molecule assists displacement of the alkoxy group.[11] Further support for this latter mechanism comes from evidence of appreciable negative charge on the alkoxy oxygen in the transition state:[13] this charge would account for the observed solvent isotope effects, since the alkoxy group is likely to bind solvating water molecules strongly and so cause the isotopic fractionation factors of the bound water protons to differ appreciably from unity.[14]

Scheme 1



N-Methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) is a nitrosating agent which has a better leaving group than that of the alkyl nitrites and therefore has reactivity similar to that of alkyl nitrites activated by an electron-withdrawing β-substituent, such as in 2-ethoxyethyl nitrite (Scheme 1).[12] Solvent isotope effects close to unity have been observed for reactions between this reagent and nitrogen nucleophiles, and so these reactions are thought to occur via a concerted mechanism which, unlike that for alkyl nitrites, does not involve protonation of the leaving group or its water-assisted expulsion.[13]

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The solvent in which a reaction takes place plays a crucial role in determining its mechanism,[15] for example, by controlling aggregation of the reactants or by altering the lifetimes of any intermediates. To date, the influence of the solvent on nitrosation reactions has not been studied very intensively. Williams *et al.*[16] examined the S-nitrosation of thiourea and thioglycollic acid by alkyl nitrites in acidified isopropyl and *tert*-butyl alcohols and concluded that under these conditions the reactive species is probably the protonated alkyl nitrite. Later these authors also studied the nitrosation of alcohols, thioglycollic acid, and water by alkyl nitrites in acidified acetonitrile, concluding that the rate-controlling step of these reactions was the formation of NO^+ from the protonated nitrite or nitrous acid.[1] More recently, experiments in our laboratory have shown that the mechanism of the nitrosation of ureas in dioxane/water or acetonitrile/water mixtures depends on the composition of the solvent.[17,18]

In spite of similarities between the electronic structures of alkyl nitrites and those of carboxylic esters,[9] whose C═O group is isoelectronic with N═O, there are marked differences between the chemical behaviors of these two families of compounds. Particularly striking is the fact that in aqueous solution alkyl nitrites react with OH^- much more slowly than the corresponding carboxylic esters, in spite of their reactions with other nucleophiles, such as amines, being much faster than those of carboxylic esters. More generally, whereas NO donation by alkyl nitrites is thought to occur via a concerted mechanism (as we have seen above for the nitrosation of amines), the chemistry of carboxylic esters is characterized by the formation of tetrahedral intermediates.

In this work we investigated the nitrosation of secondary amines in several different organic solvents by alkyl nitrites or by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS). The reactions of MNTS with amines in water have rates similar to those of alkyl nitrites activated by electron-withdrawing β-substituents (e.g., 2-ethoxyethyl nitrite[12]), have solvent isotope effects close to unity, and are thought, unlike those of alkyl nitrites, to proceed via a concerted mechanism which does not involve either protonation of the leaving group or its water-assisted expulsion.[13] We found that a reaction mechanism analogous to that proposed for the aminolysis of carboxylic esters[19] is able to account for the effect of the solvent on the kinetics of these reactions.

Experimental Section

Isooctane (nominal purity >99%, from Merck) and cyclohexane and dichloromethane (nominal purities >99.9%, water contents <0.01% and 0.02%, respectively; both from Aldrich) were used as supplied. Published data for the solubility of water in these solvents[20] indicated that no special precautions would be necessary in the kinetic experiments involving them. 1,4-Dioxane and tetrahydrofuran (nominal purities >99%, water contents <0.005% and 0.02%, respectively; both from Aldrich) are miscible with water and were dried over 3 Å molecular sieves prior to use.[21] Deuterated water (99.77% D) was supplied by CIEMAT (Spain). Pyrrolidine (PYR), piperidine (PIPER), diethylamine (DEA), *N*,*N*′-dimethylethylenediamine (DED), *N*-methylpiperazine (MePIP), and morpholine (MOR), all from Aldrich, were of the highest commercially available purity and were distilled under argon shortly before use. All other commercially supplied materials were Merck or Aldrich products of the highest available purity and were used as supplied.

^{1}H NMR spectroscopy was performed on 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 procedure[22] involving reaction of the corresponding alcohol with sodium nitrite in an acid medium and were stored over 3 Å molecular sieves pending use. N-Deuterated pyrrolidine and N-deuterated diethylamine were prepared by repeated fractional distillation of a mixture of the amine with a 10-fold molar excess of D_2O through a 20 cm Vigreux column.[19] After at least three runs, the product was dried over calcium hydride, from which it was later distilled. ^{1}H NMR spectroscopy of the final product confirmed N-deuteration.

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 absorbance (generally at a wavelength in the range 250−270 nm) in Uvikon 930 or Milton Roy 3000 array spectrophotometers. In all cases, absorbance−time data were fitted by integrated first order rate equations, and k_0, the corresponding first-order pseudoconstant, was reproducible to within 3%. Regardless of the experimental conditions, the *N*-nitrosamine was the product detected, and it showed no signs of decomposition. Reaction yields calculated from the absorbance data together with published values of the molar absorption coefficients of the reagents and products[23,24] were always very close to 100% (±5%). In some experiments (dioxane and THF) HPLC separation were carried out and retention times and peak areas were compared with that of pure *N*-nitrosamines. In every case we found quantitative *N*-nitrosamine formation compatible with spectral changes observed in kinetic experiments.

Results

This section summarizes the results of an exhaustive study of the reactions of 2-bromoethyl nitrite, 2,2-dichloroethyl nitrite, 2,2,2-trichloroethyl nitrite, and MNTS with each of several secondary aliphatic amines in cyclohexane, and those obtained in selected experiments using other aprotic solvents (isooctane, dichloromethane, 1,4-dioxane, and THF).

Influence of Amine Concentration. For nitrosation by RONO, plotting k_0 against [amine] (generally in the range 3×10^{-3} to 1.00 M) gave sigmoid curves: Figures 1 and 2 show those obtained for the reactions between pyrrolidine and 2-bromoethyl nitrite (Figure 1) and between *N*-methylpiperazine and 2,2-dichloroethyl nitrite (Figure 2) in cyclohexane. At an amine concentration that was lower for the more basic amines (pyrrolidine and piperidine) than for the others, k_0 began to level off at a limiting value that likewise depended on the amine (Figure 3). The linear dependence of k_0/[amine] on [amine] at low amine concentration (Figure 4) shows that under these conditions the reaction has both a pathway of first order with respect to amine and one of second order.

No leveling off was observed in the corresponding plots for nitrosation by MNTS. For example, for the nitrosa-

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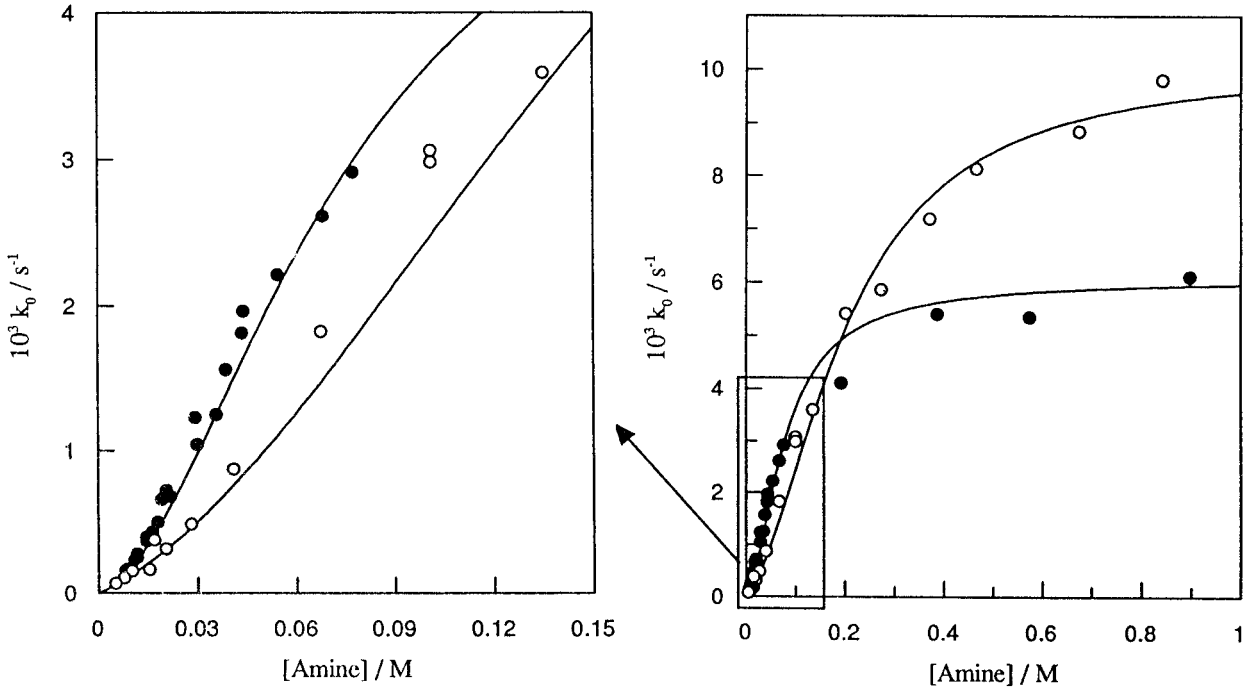

Figure 1. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2-bromoethyl nitrite in cyclohexane at 25 °C (●) and 35 °C (○).

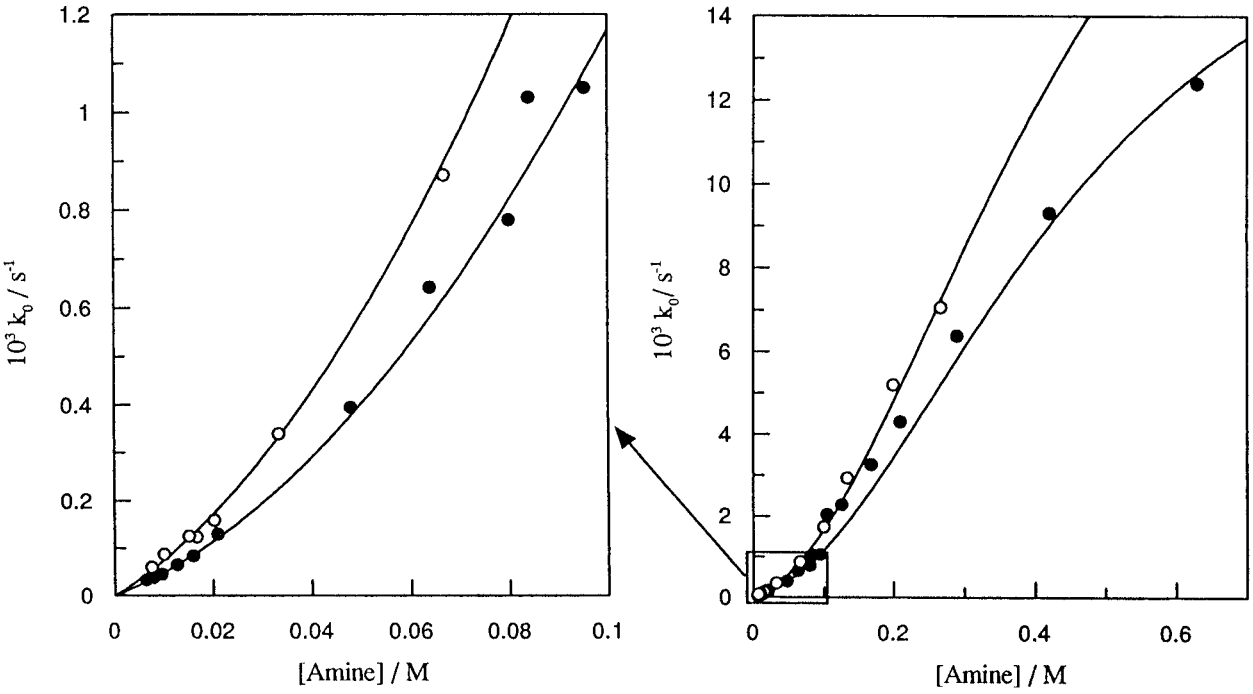

Figure 2. Influence of [MePIP] on the pseudo-first-order rate constant (k_0) for nitrosation of *N*-methylpiperazine by 2,2-dichloroethyl nitrite in cyclohexane at 25 °C (●) and 35 °C (○).

tion of PYR by MNTS, k_0 showed first- and second-order-dependence on amine concentration in isooctane (Figure 5), cyclohexane, and THF (not shown) and linear dependence in dioxane and dichloromethane (Figure 6).

Effects of Adding Isopropylamine. The effects of adding the strongly basic and weakly nucleophilic amine isopropylamine ($iPrNH_2$) to the reaction mixture were evaluated after prior experimental verification that, under the conditions used in this work, nitrosation of this amine did not compete with the nitrosation reactions being studied. Figure 7 shows that for the nitrosation of low concentrations of pyrrolidine by 2,2-dichloroethyl nitrite in cyclohexane, the presence of isopropylamine eliminated the second-order-dependence of k_0 on PYR concentration, leaving a linear plot with a slope that decreased with increasing [$iPrNH_2$]. For the nitrosation of pyrrolidine by 2-bromoethyl nitrite in cyclohexane, Figure 8 shows that the presence of $iPrNH_2$ at the same concentration as PYR lowered both the PYR concentration at which k_0 began to level off and the limiting value of k_0.

For the least basic amines studied (i.e., those less basic than $iPrNH_2$), isopropylamine proved to be inhibitory at high amine concentration (as with the more basic amines) but catalytic at low amine concentration. Figure 9 shows the results obtained for the nitrosation of *N*-methylpip-

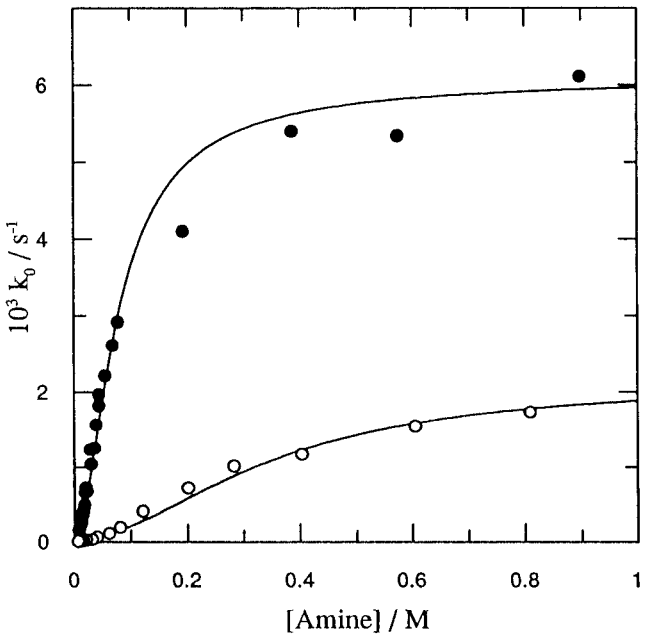

Figure 3. Influence of [amine] on the pseudo-first-order rate constant (k_0) for nitrosation of (●) pyrrolidine and (○) piperidine by 2-bromoethyl nitrite in cyclohexane at 25 °C.

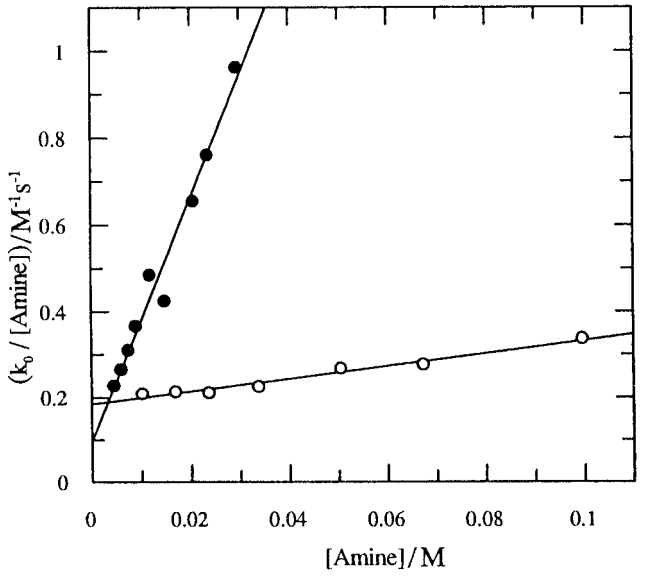

Figure 4. Plot of k_0/[amine] vs [amine] for nitrosation of (●) pyrrolidine by 2,2-dichloroethyl nitrite and (○) piperidine by by 2,2,2-trichloroethyl nitrite in isooctane at 25 C°.

erazine by 2,2-dichloroethyl nitrite in cyclohexane and Table 1 those obtained for the nitrosation of morpholine by 2,2-dichloroethyl nitrite in the same solvent.

Effects of Isotopic Substitution. Figure 10 compares the k_0−[amine] plots for the nitrosation of pyrrolidine and *N*-deuteriopyrrolidine by 2-bromoethyl nitrite in cyclohexane. The kinetic isotope effect increased from near unity at low [PYR] to values close to 2 for the limiting value of k_0. For the nitrosation of the less reactive amine diethylamine (DEA) by 2,2-dichloroethyl nitrite in cyclohexane (Figure 11), kinetic isotope effects close to 2 were obtained regardless of [DEA].

Influence of Temperature. In the nitrosation of pyrrolidine by 2-bromoethyl nitrite in cyclohexane, k_0 increased with temperature for [PYR] < 5×10^{-3} M (indicating positive overall activation energy), decreased with increasing temperature for [PYR] between 5×10^{-3}

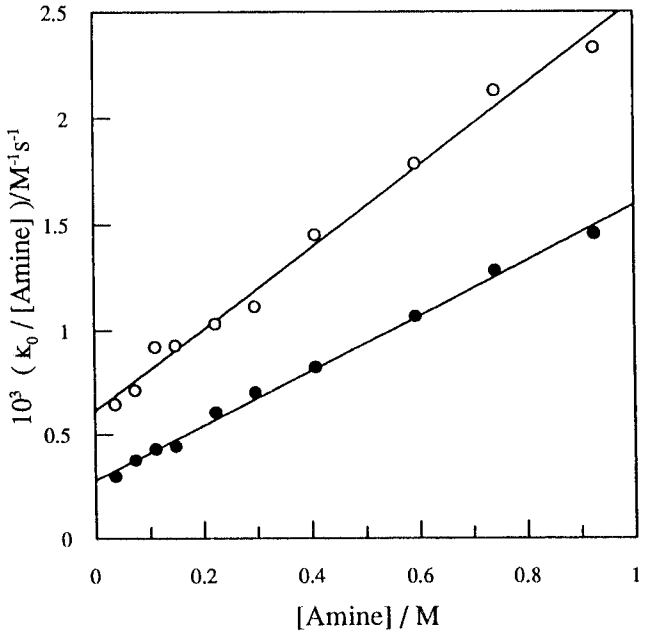

Figure 5. Plot of k_0/[amine] vs [amine] for nitrosation of pyrrolidine by MNTS in isooctane at 25 °C (●) and 35 °C (○).

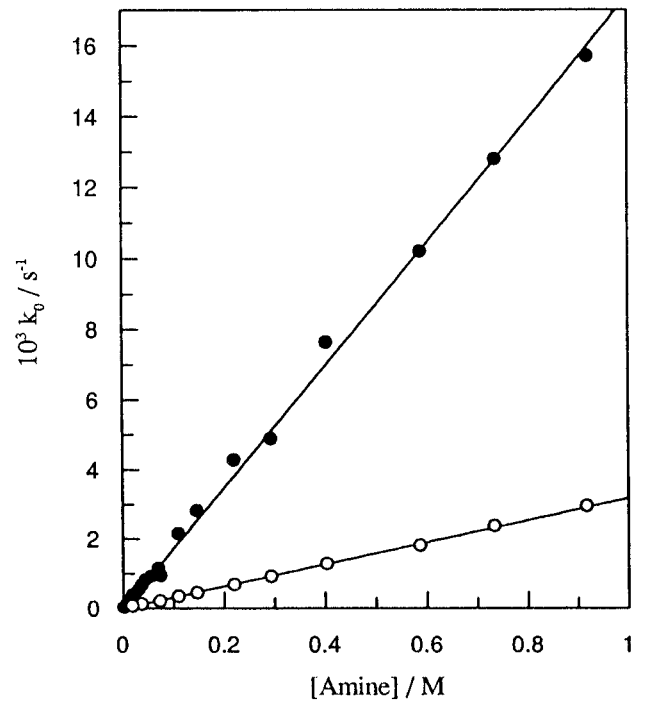

Figure 6. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by MNTS in 1,4-dioxane (○) and in dichloromethane (●) at 25 °C.

and 0.14 M (anti-Arrheniusian behavior), and increased with temperature for [PYR] > 0.14 M (Figure 1). Anti-Arrheniusian behavior was not observed in the nitrosation reactions of other amines (for example, Figures 2 and 5 show that overall activation energies were positive regardless of amine concentration for the nitrosation of MePIP by 2,2-dichloroethyl nitrite in cyclohexane and the nitrosation of PYR by MNTS in isooctane), but a 10 °C rise in temperature increased k_0 only to a rather small extent, which furthermore varied with amine concentration.

Anti-Arrhenius behavior has previously been observed for the aminolysis of carboxylic esters[25] and for nucleophilic aromatic substitution involving amine nucleophiles

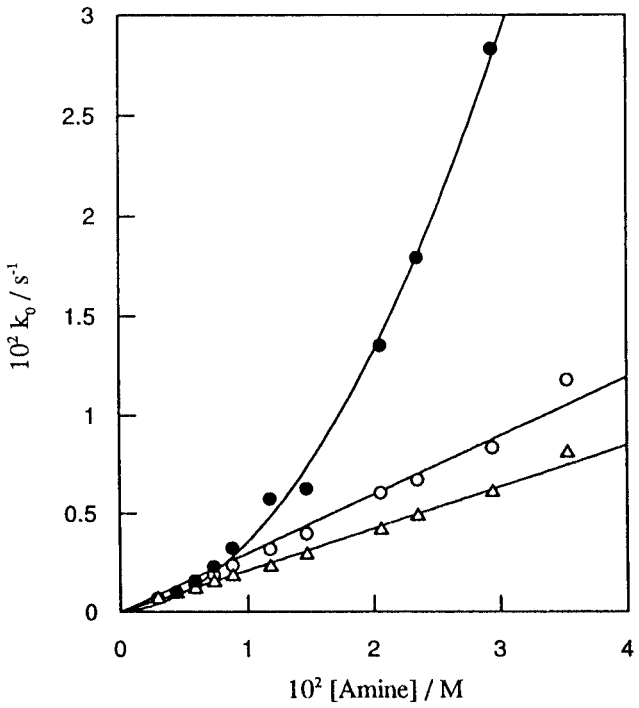

Figure 7. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2,2-dichloroethyl nitrite in cyclohexane (●) and in cyclohexane containing (○) 0.31 M and (Δ) 0.62 M isopropylamine at 25 °C.

Table 1. Influence of [MOR] on the Pseudo-First-Order Rate Constant (k_0) for Nitrosation of Morpholine by 2,2-Dichloroethyl Nitrite in Cyclohexane and in Cyclohexane Containing 0.19 M Isopropylamine at 25 °C

[iPrNH$_2$] = 0		[iPrNH$_2$] = 0.19 M	
10^2[MOR]/M	$10^5k_0/s^{-1}$	10^2[MOR]/M	$10^5k_0/s^{-1}$
		0.35	3.57
		0.52	5.44
0.69	1.60	0.69	6.53
0.87	1.83	0.87	6.83
1.04	2.25	1.08	7.69
1.39	3.25	1.39	9.20
1.73	4.02	1.73	11.30

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

[iPrNH$_2$]/M	δ/ppm	δ/ppm
	3.2665	4.8232
0.28	3.2873	4.8355
1.05	3.3490	4.8749
$\Delta\nu$/Hz	24.7	15.5

in apolar media.[26,27] Although the precise mechanisms responsible for this behavior are still disputed, various authors have suggested that exothermic preequilibria which contribute to the overall rate coefficient might be involved. If the amount of energy evolved in these preequilibria were sufficiently large, it could exceed the activation energy for the endothermic rate-controlling step and thus produce a negative overall activation energy. The preequilibrium step involved is thought to be the formation of charge-transfer complexes[25] or amine self-association.[28]

Spectroscopic Evidence of Association between Reagents. There is evidence in the literature suggesting that amines and carboxylic esters form charge-transfer complexes,[25] a process that may influence the reactions of these esters with amine nucleophiles. Moreover, the existence of similarities between the electronic structures of alkyl nitrites and carboxylic esters has also been discussed in the literature.[9] The observed effects of temperature on the nitrosation of amines by alkyl nitrites suggest that these compounds might also form complexes. Comparison of the UV spectra of the reagents and their mixtures revealed no evidence of pre-nitrosation association. However, the ^{1}H NMR spectra of mixtures of 2-bromoethyl nitrite and increasing concentrations of the unreactive amine isopropylamine in cyclohexane did show evidence of interaction. Specifically, the chemical shifts of the central peaks of the triplets due to 2-bromoethyl nitrite increased with [iPrNH$_2$] (Table 2), indicating that these groups were being deshielded, presumably due to hydrogen bonding between the alkyl nitrite and the isopropylamine. The shifts for the highest isopropylamine concentration, 15.5 and 24.7 Hz for the upfield and downfield triplets, respectively, are of the same order of magnitude as those reported for similar interactions.[29]

Discussion

Influence of Amine Concentration. 1. Behavior at High Amine Concentration. In this work, plots of k_0 against amine concentration for the reactions of the alkyl nitrites were sigmoid, whereas k_0 exhibits strictly quadratic [amine] dependence in the aminolysis of carboxylic esters in chlorobenzene.[22] Reported sigmoid dependence of k_0 on amine concentration in the aminolysis of [methoxy(phenyl)carbene]pentacarbonylchromium-(0) in aqueous acetonitrile has been attributed to the amine reducing the dielectric constant of the medium at high concentration ($\epsilon_{\text{acetonitrile}} = 36$, $\epsilon_{\text{amine}} \approx 5$, $\epsilon_{\text{chlorobenzene}} = 5.6$).[30] However, a similar explanation for the flattening off of the k_0−[amine] plot at high amine concentrations in this work is ruled out by the dielectric constants of the solvents used being close to those of the amines, ranging from 2 for cyclohexane to 9.8 for dichloromethane. Furthermore, appeal to a medium effect of this kind does not explain why sigmoid [amine] dependence was observed for alkyl nitrites but not for MNTS.

A priori, an alternative explanation for the sigmoid curves shown in Figures 1 and 2 might be the existence of a preequilibrium between the alkyl nitrite and its nitrosoalcohol tautomer,[31] but this too must be rejected: it implies that the limiting value of k_0 should be constant for a given alkyl nitrite regardless of the amine being nitrosated, which contradicts the experimental observations (Figure 3).

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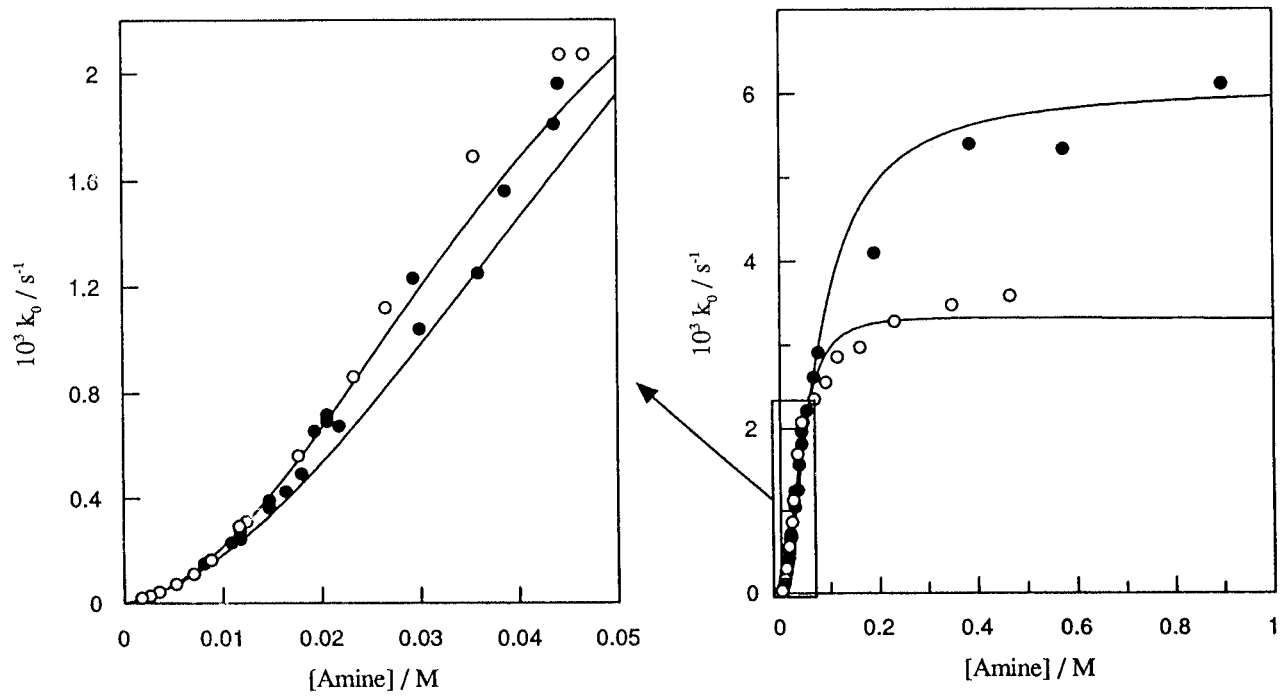


Figure 8. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine by 2-bromoethyl nitrite in cyclohexane (●), and in cyclohexane containing isopropylamine (○) in a constant 1:1 mole ratio with respect to pyrrolidine at 25 °C.

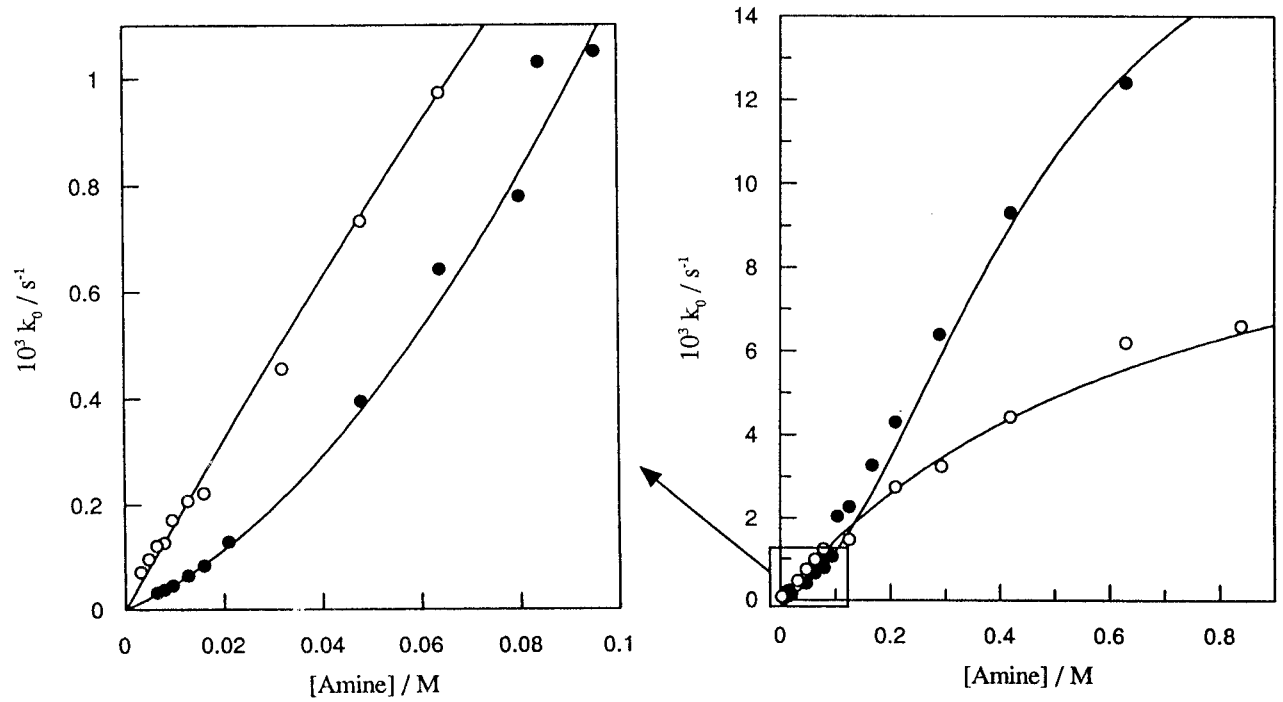


Figure 9. Influence of [MePIP] on the pseudo-first-order rate constant (k_0) for nitrosation of *N*-methylpiperazine by 2,2-dichloroethyl nitrite in cyclohexane (●), and in cyclohexane containing 0.19 M isopropylamine (○) at 25 °C.

A more likely explanation for the flattening off of the k_0−[amine] curves for the reactions with alkyl nitrites, and the one assumed in the rest of this paper, is the formation, prior to formation of the N−NO bond, of a hydrogen-bonded complex (HBC) between the alkyl nitrite and the amine (Scheme 2B). This hypothesis is supported by the results of the NMR experiments (Table 2) and provides a possible explanation for the absence of any flattening off in the reactions of MNTS, since the toluenesulfonamide nitrogen atom is a poorer electron donor than the alkoxide oxygen and so less likely to form an HBC. Hydrogen-bonding between the amine and the nitroso oxygen, as in Scheme 2A (analogous to that between amine nucleophiles and carbonyl compounds[36]), seems not to occur; if it did, both alkyl nitrites and MNTS would form HBCs and have sigmoid kinetics, contrary to the experimental evidence.

2. Second-Order-Dependence. At low and medium amine concentrations in the reactions of the alkyl nitrites, and at all concentrations in those of MNTS in isooctane, cyclohexane, and THF, k_0 depended on both [amine] and

(36) Sandorfy, C.; Buchet, R.; Lussier, L. S.; Menassa, P.; Wilson, L. *Pure Appl. Chem.* **1986**, *58*, 1115

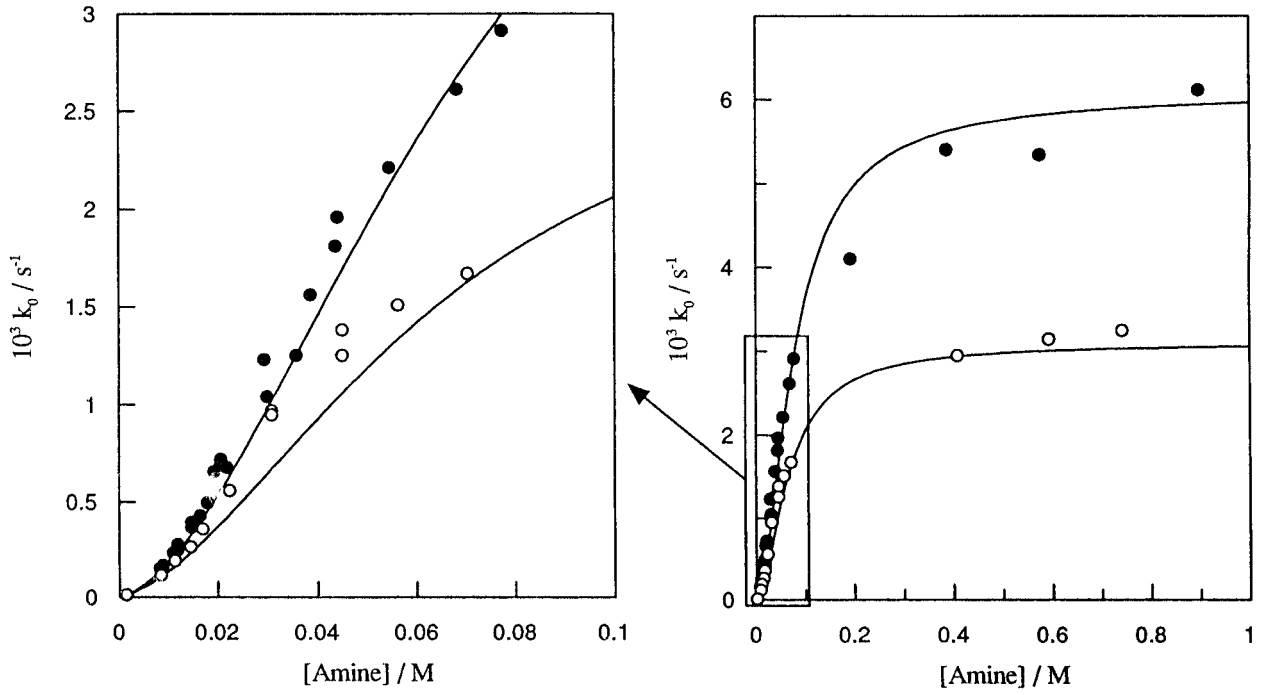


Figure 10. Influence of [PYR] on the pseudo-first-order rate constant (k_0) for nitrosation of pyrrolidine (●) and *N*-deuteriopyrrolidine (○) by 2-bromoethyl nitrite in cyclohexane at 25 °C.

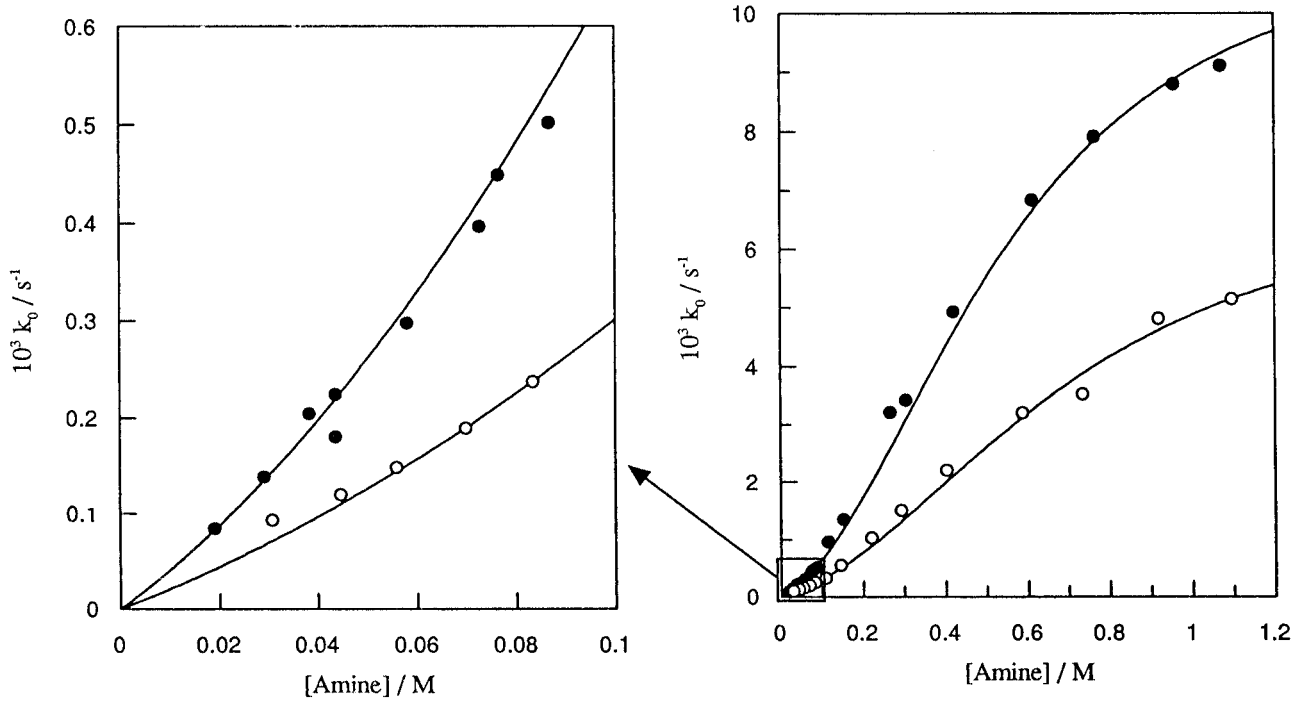


Figure 11. Influence of [DEA] on the pseudo-first-order rate constant (k_0) for nitrosation of diethylamine (●) and *N*-deuteriodiethylamine (○) by 2,2-dichloroethyl nitrite in cyclohexane at 25 °C.

[amine].[2] This implies the existence of a reaction pathway involving a second amine molecule. In the remainder of this section we discuss two possibilities for this involvement: reaction of the nitrosating agent with both monomers and dimers of the amine and the action of the second amine molecule in a catalytic role.

3. Formation of Dimers. Experimental evidence of the self-association of amines in nonaqueous solvents is provided by ^{1}H NMR spectra,[32] liquid−vapor equilibrium data,[33] and IR spectra,[34,35] and it has been suggested that in nonaqueous solution amine oligomers may play an important role in certain amine reactions such as nucleophilic aromatic substitution.[28] The involvement of both monomers and dimers in nucleophilic attack by amines on alkyl nitrites and MNTS would explain not only the mixed first- and second-order [amine] dependence of k_0 observed in this work but also, upon superficial analysis, the effects of varying the temperature and of adding isopropylamine to the reaction mixture. It might plausibly be hypothesized that the effect of raising the temperature is the overall result of its reducing the equilibrium constants for both amine dimerization and HBC formation and that the influence of isopropylamine is due to the formation of mixed dimers between isopropylamine and the reactive amine (in a mixed dimer, the nucleophilicity of an amine less basic than isopropy-

Scheme 2

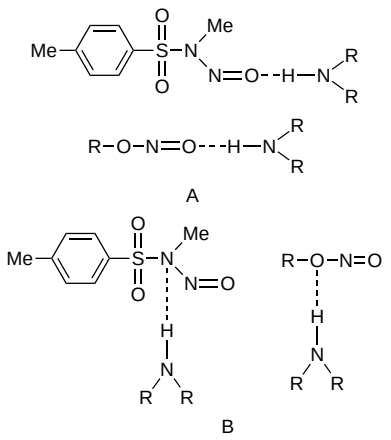


Table 3. Values of the Coefficients *a* and *b* for Equation 1 Fitted to the Data for the Variation of the Pseudo-First-Order Rate Constant (k_0) with [PYR] for Nitrosation of Pyrrolidine by 2,2-Dichloroethyl Nitrite in Dioxane Containing the Indicated Amount of Water at 25 °C

% vol $(H_2O)_{add}$	$a/M^{-1}\,s^{-1}$	$b/M^{-2}\,s^{-1}$
	0.171 ± 0.005	1.3 ± 0.2
0.07	0.158 ± 0.003	1.1 ± 0.1
0.13	0.168 ± 0.005	1.3 ± 0.2
0.27	0.179 ± 0.009	1.9 ± 0.4
0.53	0.203 ± 0.004	2.6 ± 0.2
1.07	0.255 ± 0.007	2.5 ± 0.3

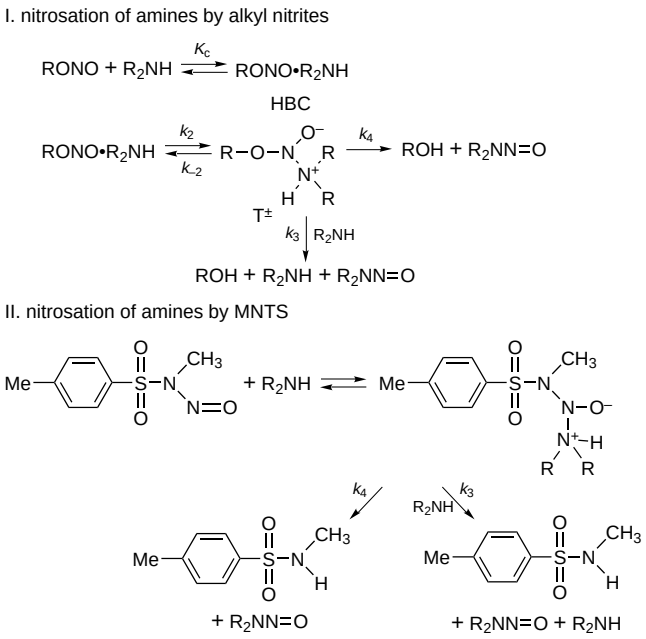
lamine, such as *N*-methylpiperazine, would be enhanced, and its reaction with nitrosating agents promoted, while that of a more basic amine such as pyrrolidine would be reduced and its reaction with nitrosating agents inhibited; indeed, the total conversion of pyrrolidine to mixed dimer form would explain the disappearance of [amine]^2 dependence and the lower limiting value of k_0 observed at high isopropylamine concentrations). However, closer scrutiny throws doubt on both these arguments. Since amine dimerization would affect both reactions with alkyl nitrites and reactions with MNTS, it seems unlikely to cause the former to have negative overall activation energy (Figure 1) but not the latter (Figure 5); while the argument concerning isopropylamine requires a mixed dimerization equilibrium constant of the order of $K_D \cong 10$, some 100 times the values usually reported for the formation of symmetrical amine dimers.[28,32,35,37]

Positive evidence against the formation of amine dimers in our experiments comes from the results obtained upon reacting pyrrolidine with 2,2-dichloroethyl nitrite in dioxane containing varying amounts of water. As a polar cosolvent, the water will have disrupted any amine dimers[39] and would therefore have eliminated any second-order-dependence due to reaction by dimers; but in fact, no such elimination of second-order-dependence occurred (see Table 3, in which the constants *a* and *b*, reflecting respectively first- and second-order-dependence of k_0 on [amine]). Indeed, both first- and second-order-dependence increased with water concentration, probably due to the increased polarity of the reaction medium.

Finally, evidence against amine dimerization is also provided by the values of k_0 obtained for the nitrosation

(37) Abello, L.; Kern, M.; Caseres, C.; Pennetier, G. *Bull. Soc. Chim. Fr.* **1970**, 94.
(38) Druzian, J.; Zucco, C.; Rezende, M. C.; Nome, F. *J. Org. Chem.* **1989**, *54*, 4767.
(39) Palleros, D. R.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 479.

Scheme 3



of pyrrolidine in solvents of different polarity and donicity. Dimerization might be expected to be favored in cyclohexane and isooctane (which have near-zero donicities) and hindered in dioxane ($D_n = 14.8$ kcal/mol[15]), THF ($D_n = 20$ kcal/mol[15]), and dichloromethane (in which amine−amine association might be prevented by amine−CH_2Cl_2 association[36]). Hence second-order-dependence of k_0 on [PYR], if due to dimerization, would be more likely for reactions in isooctane and cyclohexane than for reactions in dioxane, dichloromethane, or THF. However, this expected pattern is not complied with by the reaction of PYR with MNTS in THF, which exhibits second-order-dependence even though the same reaction exhibits only first-order dependence in dioxane and dichloromethane, or by the reactions of the same amine with alkyl nitrites in THF, dichloromethane, and dioxane, for all of which k_0 likewise exhibits second-order-dependence on [PYR]. In conclusion, the hypothesis that the observed second-order kinetics were due to dimerization of the amine must be rejected.

Base Catalysis by the Amine. The alternative explanation for the second-order kinetics observed in our experiments is that the second amine molecule acts catalytically. If we assume, by analogy with proposed mechanisms for the aminolysis of carboxylic esters in similar solvents,[19] that the reaction involves a zwitterionic tetrahedral intermediate $T^{\pm}$ (which in view of the foregoing discussion of behavior at high amine concentration will be formed via a hydrogen-bonded complex in the reactions of alkyl nitrites but not in those of MNTS), then catalytic intervention by the amine presumably affects the decomposition of $T^{\pm}$. We are thus led to the mechanistic hypotheses shown in Schemes 3-I and 3-II for the reactions of alkyl nitrites and MNTS, respectively. If the steady state approximation is applied to $T^{\pm}$ and it is assumed that total alkyl nitrite concentration is the sum of those of the free and complexed species, then these reaction schemes imply eq 1.

In this mechanism, the rate-controlling step is the catalyzed or uncatalyzed decomposition of $T^{\pm}$ at low amine concentrations and the formation of the intermediate $T^{\pm}$ at high amine concentrations.

In support of the hypothesized mechanism, the k_0−[amine] data were fitted well (see Figures 1−3 and 6−11)

$$k_0 = \frac{\frac{k_2k_4K_C}{k_{-2}+k_4}[R_2NH] + \frac{k_3k_2K_C}{k_{-2}+k_4}[R_2NH]^2}{1 + \frac{k_3 + k_{-2}K_C + k_4K_C}{k_{-2}+k_4}[R_2NH] + \frac{k_3K_C}{k_{-2}+k_4}[R_2NH]^2} \quad (1)$$

by eq 1. For the reactions of alkyl nitrites

$$k_0 = \frac{a[R_2NH] + b[R_2NH]^2}{1 + c[R_2NH] + d[R_2NH]^2} \quad (2)$$

(when the optimized value of c was very small or negative, the reduced equation

$$k_0 = \frac{a[R_2NH] + b[R_2NH]^2}{1 + d[R_2NH]^2} \quad (3)$$

was fitted); and for MNTS,

$$k_0 = a[R_2NH] + b[R_2NH]^2 \quad (4)$$

The values of the fitted constants in eqs 2, 3, and 4 are listed in Table 4.

Influence of the Solvent. We now acknowledge explicitly the hitherto implicit working hypothesis that the same mechanism holds in all the solvents discussed in this paper and that the observed kinetic influence of the solvents is limited to facilitation of one or another of the steps of this mechanism. A priori it is conceivable that the solvent might determine a kinetically occult radical change in mechanism (for example, the dimerization mechanism ruled out above also leads to rate equations of the form of eqs 2 and 3), but the assumption that only a single mechanism is involved is supported by the precedent of ester aminolysis reactions, for which the same mechanism holds in a range of solvents similar to those discussed in this paper.[40] Accordingly, in the remainder of this section, the observed effects of the solvents on the kinetics of the reactions studied are discussed in terms of the mechanism of Scheme 3.

In aqueous solution, the differences between the mechanisms of nitrosation by MNTS and RONO were manifest as solvent isotope effects:[13] these were appreciably greater than unity for RONO and close to unity for MNTS, which was therefore considered to be better at stabilizing the negative charge forming on the leaving group.

For nitrosation in cyclohexane, isooctane, and THF, the differences between the results for RONO and MNTS have so far allowed us to rule out a preequilibrium involving association of MNTS and the amine substrate. The results for nitrosation by MNTS in these solvents can be also explained by a similar mechanism in which the rate-controlling step is decomposition of the tetrahedral intermediate $T^{\pm}$ (Scheme 3-II).

If the base-catalyzed step is fast, k_0 will depend linearly on the amine concentration, as is observed for nitrosation of pyrrolidine by MNTS in the most polar solvents studied (dichloromethane and dioxane), and nucleophilic attack by amines on the nitroso group will be the rate-controlling step. The results for the experiments carried out in dichloromethane and dioxane, however, do not indicate that base catalysis is occurring in these solvents. It is therefore likely that expulsion of the anionic MNTS moiety is thus favored in these polar solvents, while it is apparently disfavored in apolar solvents such as cyclohexane.

For nitrosation by alkyl nitrites, the ratio k_4/k_3 (eq 1) corresponds to the ratio a/b (eq 2; see Table 4). This ratio defines the efficiency of the base-catalyzed decomposition of the intermediate $T^{\pm}$ compared to spontaneous decomposition of this intermediate. For the nitrosation of pyrrolidine by 2-bromoethyl nitrite, the ratio a/b (6.67×10^{-3} in cyclohexane, 1×10^{-2} in dioxane, 1.12×10^{-2} in THF, and 2.63×10^{-2} in dichloromethane) increases with the solvents ability to form hydrogen bonds, indicating that spontaneous decomposition is favored by polar solvents.

The forward rate coefficient for formation of the tetrahedral intermetiate ($T^{\pm}$) from the hydrogen-bonded complex (Scheme 3) corresponds to the ratio b/d, which for the nitrosation of pyrrolidine by 2-bromoethyl nitrite was 6.12×10^{-3} in cyclohexane, 2.13×10^{-3} in dioxane, 2.04×10^{-3} in THF, and 0.14 in dichloromethane. There is no apparent trend, but the rate is clearly much faster in CH_2Cl_2, probably because of its greater polarity and ability to act as a proton donor in hydrogen bonds.

Influence of the Nature of the Amine. The ratio b/d (k_2) can be related to the nucleophilicity of the amine forming the HBC in its evolution to the intermediate $T^{\pm}$. From the data in Table 1 for nitrosation by 2,2-dichloroethyl nitrite in cyclohexane (the value of d for this reaction of PYR was assumed to be equal to that for nitrosation by 2-bromoethyl nitrite), the order of amine reactivity obtained was pyrrolidine > piperidine > *N*,*N*′-dimethylethylenediamine > *N*-methylpiperazine > diethylamine > morpholine (relative ratios of k_2 = 17:3.3:3.3:2.2:1.4:1). In aqueous media, the nucleophilicity of secondary amines toward the nitroso group increases parallel to pK_a.[13] The relative reactivities for this sequence follow almost the same order, except that diethylamine is more reactive and the differences between the reactivities of adjacent amines are about ten times larger (167:32:28:1.6:11.7:1 for the order of reactivity above). In spite of the very different media and the possibility of different transition states, the difference in relative reactivities for nucleophilic attack of the amine on the nitroso group does not seem unreasonable.

There are two possible mechanisms which can account for the observed influence of the amine's nature on base-catalyzed nitrosation by RONO. One mechanism involves an equilibrium between $T^{\pm}$ and its conjugate base T^- ($K_a^{\pm}$ being the corresponding acidity constant of $T^{\pm}$), followed by rate-controlling acid-catalyzed expulsion of the leaving group (Scheme 4).

In this case, k_3, the rate coefficient for decomposition of $T^{\pm}$ can be expressed in terms of k'_3 and the acidity constant of the respective amine $R_2NH_2^+$ (K_a^{HA}) as follows:

$$k_3 = k_3' \frac{K_a^{\pm}}{K_a^{HA}} \quad (5)$$

Alternatively, a mechanism in which the rate-controlling step is deprotonation of $T^{\pm}$ to form T^- is also in keeping with the observed results (Scheme 5).

In Scheme 5, k''_3 is equal to k_3 in Scheme 3-II.

Mechanisms involving rate-controlling deprotonation of a zwitterionic intermediate (as in Scheme 5) have been proposed for many nucleophilic aromatic substitutions reactions (in which this intermediate is the Meisenheimer

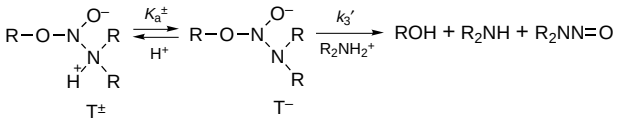
(40) Gandour, R. D.; Walker, D. A.; Nayak, A.; Newkome, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3608.

Table 4. Values of the Coefficients *a*, *b*, *c*, and *d* for Equation 1 Fitted to the Experimental Data for the Variation of the Pseudo-First-Order Rate Constant (k_0) with [Amine] for Nitrosation of Several Amines by the Indicated Alkyl Nitrites (RONO) or *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in the Solvents Studied

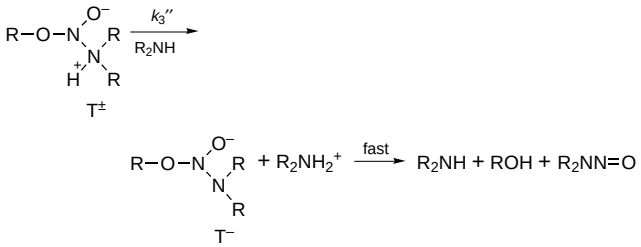
amine	R in RONO	*T*/°C	a/M^{-1} s^{-1}	b/M^{-2} s^{-1}	c/M^{-1}	d/M^{-2}
			Cyclohexane			
PIPER	Cl_3CCH_2	25	0.181 ± 0.006	2.0 ± 0.1		
DED	Cl_3CCH_2	25	0.246 ± 0.001	0.59 ± 0.04		
MOR	Cl_3CCH_2	25	(1.62 ± 0.06) × 10^{-2}	0.19 ± 0.01		3.6 ± 0.2
PYR	Cl_2CHCH_2	25	0.11 ± 0.02	27 ± 2		
PYR	Cl_2CHCH_2	35	0.198 ± 0.005	8.3 ± 0.3		
PYR[a]	Cl_2CHCH_2	25	0.12 ± 0.02	28 ± 3		
PIPER	Cl_2CHCH_2	25	(2.03 ± 0.07) × 10^{-2}	0.19 ± 0.02	0.9 ± 0.3	7.1 ± 0.4
DED	Cl_2CHCH_2	25	(1.54 ± 0.01) × 10^{-2}	(7.8 ± 0.4) × 10^{-2}		2.88 ± 0.07
DEA	Cl_2CHCH_2	25	(3.8 ± 0.1) × 10^{-3}	(2.9 ± 0.2) × 10^{-2}		2.62 ± 0.04
DEA[a]	Cl_2CHCH_2	25	(2.0 ± 0.1) × 10^{-3}	(1.06 ± 0.09) × 10^{-2}		1.58 ± 0.04
MePIP	Cl_2CHCH_2	25	(4.1 ± 0.1) × 10^{-3}	(8.1 ± 0.5) × 10^{-2}		4.4 ± 0.1
MePIP	Cl_2CHCH_2	35	(6.4 ± 0.4) × 10^{-3}	0.11 ± 0.01		4.4 ± 0.4
MOR	Cl_2CHCH_2	25	(1.96 ± 0.07) × 10^{-3}	(1.6 ± 0.1) × 10^{-2}		1.96 ± 0.02
MOR	Cl_2CHCH_2	35	(2.9 ± 0.1) × 10^{-3}	(2.9 ± 0.1) × 10^{-2}		1.72 ± 0.06
PYR	$BrCH_2CH_2$	25	(8 ± 1) × 10^{-3}	1.2 ± 0.1	5.6 ± 0.9	196 ± 3
PYR	$BrCH_2CH_2$	35	(1.1 ± 0.1) × 10^{-2}	0.23 ± 0.05	1.6 ± 0.4	22.6 ± 0.8
PYR[a]	$BrCH_2CH_2$	25	(7.4 ± 0.2) × 10^{-3}	0.76 ± 0.02	6 ± 1	244 ± 6
PIPER	$BrCH_2CH_2$	25	(6.4 ± 0.4) × 10^{-4}	(1.8 ± 0.1) × 10^{-2}	0.6 ± 0.3	8.3 ± 0.3
PYR	MNTS	25	(3.1 ± 0.1) × 10^{-4}	(1.43 ± 0.05) × 10^{-3}		
			Isooctane			
PIPER	Cl_3CCH_2	25	0.185 ± 0.005	1.4 ± 0.1		
PYR	Cl_2CHCH_2	25	0.21 ± 0.01	15 ± 0.8		
PIPER	Cl_2CHCH_2	25	(1.3 ± 0.1) × 10^{-2}	0.8 ± 0.1	9 ± 2	19 ± 2
DED	Cl_2CHCH_2	25	(1.04 ± 0.07) × 10^{-2}	(7.8 ± 0.3) × 10^{-2}		4.8 ± 0.3
DEA	Cl_2CHCH_2	25	(3.3 ± 0.3) × 10^{-3}	(2.6 ± 0.1) × 10^{-2}		2.7 ± 0.1
DEA	Cl_2CHCH_2	35	(3.5 ± 0.2) × 10^{-3}	(2.87 ± 0.07) × 10^{-2}		2.06 ± 0.07
MOR	Cl_2CHCH_2	25	(3.4 ± 0.1) × 10^{-3}	(3.2 ± 0.4) × 10^{-2}		5.8 ± 0.9
PYR	MNTS	25	(2.2 ± 0.3) × 10^{-4}	(1.4 ± 0.1) × 10^{-3}		
PYR	MNTS	35	(5.7 ± 0.2) × 10^{-4}	(2.0 ± 0.1) × 10^{-3}		
			Cl_2CH_2			
PYR	Cl_2CHCH_2	25	1.8 ± 0.3	0.2 ± 0.1		
PYR	Cl_2CHCH_2	35	2.2 ± 0.1	0.11 ± 0.06		
PYR	$BrCH_2CH_2$	25	(2.9 ± 0.4) × 10^{-2}	1.1 ± 0.6	17 ± 11	8 ± 3
PYR[1]	$BrCH_2CH_2$	35	(4.0 ± 0.3) × 10^{-2}	2 ± 1	10.0 ± 0.8	6 ± 0.3
PYR	MNTS	25	(1.85 ± 0.04) × 10^{-2}			
			1,4-Dioxane			
PYR	$BrCH_2CH_2$	25	(5 ± 1) × 10^{-3}	0.5 ± 0.2	17 ± 16	235 ± 100
PYR	Cl_2CHCH_2	25	0.171 ± 0.005	1.3 ± 0.2		
PYR	MNTS	25	(3.17 ± 0.02) × 10^{-3}			
DEA	Cl_2CHCH_2	25	(4.4 ± 0.1) × 10^{-3}	(1.42 ± 0.07) × 10^{-2}		4.6 ± 0.3
			THF			
PYR	$BrCH_2CH_2$	25	(4.5 ± 0.6) × 10^{-3}	0.4 ± 0.1	32 ± 16	196 ± 71
PYR	Cl_2CHCH_2	25	0.146 ± 0.007	2.7 ± 0.1		
PYR	MNTS	25	(2.01 ± 0.03) × 10^{-3}	(5.6 ± 0.8) × 10^{-4}		

[a] Amine *N*-deuterated.

Scheme 4



Scheme 5



complex)[41] and also for the aminolysis of certain acyl esters.[42] A mechanism similar to that of the latter aminolysis reactions has been proposed for the reaction of Fischer carbene complexes with nucleophiles,[30] the major difference being that for esters the rate-controlling step is general base catalyzed proton transfer, while for Fischer carbene complexes it is general acid catalyzed expulsion of the leaving group. An explanation for this difference could be that the negative charge on the zwitterionic and anionic tetrahedral intermediates is better stabilized by the $Cr(CO)_5$ group than by the carbonyl oxygen. So in $T^{\pm}$ derived from the carbene complex the negative charge is likely to be significantly delocalized into the $(CO)_5Cr$ moiety. It is reasonable to assume that the intermediates $T^{\pm}$ and T^- (Schemes 4 and 5) will have stabilities closer to those of carboxylic esters than those of [methoxy(phenyl)carbene]pentacarbonylchromium(0). Considering the microscopic reversibility principle, the kind of catalysis involved in the decomposition of the tetrahedral intermediate is important to stablish the mechanism of the reverse reaction. The decomposition of $T^{\pm}$ with general basic catalysis should

(41) (a) Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.

(42) (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (c) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580. (d) Yang, C. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 2972.

imply that the reverse reaction would involve general acid catalysis, as was observed for the *N*-nitrosamine decomposition.[1] So the base-catalyzed mechanism shown in Scheme 5 is therefore the more likely one.

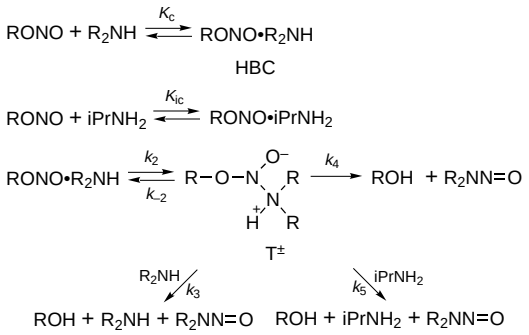
The rate constant (k''_3) for the base-catalyzed deprotonation step should be independent of the nature of the amine, since any increase in the acidity of the $R_2NH_2^+$ will be accompanied by a similar change in the pK_a of $T^{\pm}$; hence the pK_a difference between $T^{\pm}$ and the respective $R_2NH_2^+$ is expected to be constant. Notwithstanding, p$K_a^{\pm}$ must be lower than pK_a^{HA},[30] thus making proton transfer from $T^{\pm}$ to R_2NH thermodynamically favorable. The reaction rate will be close to the diffusion controlled limit.[43]

As the basicity of R_2NH increases and the acidity of $T^{\pm}$ decreases, the rate of spontaneous decomposition of $T^{\pm}$ (k_4) will also decrease. However, as stated above, k_3 ($= k''_3$) will be effectively constant, and so the quotient a/b ($= k_3/k_4$) should also decrease with increasing amine basicity. Examination of the data in Table 4 confirms this to be the case, with the exception that for the least basic amines *N*-methylpiperazine and morpholine, a/b was slightly higher than expected, probably due to the presence of a second heteroatom in the amine structure.

Effects of Isotopic Substitution. The evolution of the HBC into $T^{\pm}$ (Scheme 3-A), involving concomitant rupture of the $R_2NH-RONO$ hydrogen bond and nucleophilic attack by the amine on the alkyl nitrite, will be affected by isotopic substitution. Thus the kinetic isotopic effect will be reflected in the value of the rate coefficient k_2 ($= b/d$, Table 4), and so it can be assumed that k_2^H/k_2^D are 1.97 and 1.65 for the nitrosation of PYR and DEA by 2-bromoethyl nitrite and 2,2-dichloroethyl nitrite, respectively, in cyclohexane (Table 4; Figures 10 and 11). The observation that, for dilute solutions, k_2^H/k_2^D stays close to 2 for DEA but is effectively unity for PYR may be due the greater importance of base-catalyzed over spontaneous decomposition of $T^{\pm}$ for pyrrolidine.

Influence of Temperature. The effects on k_2 ($= b/d$) and k_4/k_3 ($= a/b$) of the temperature of the nitrosation reactions carried out in cyclohexane, isooctane, and dichloromethane can be evaluated from Table 4. The rate coefficient k_2, which describes the rate of evolution of the HBC into $T^{\pm}$, shows Arrhenius type behavior, approximately doubling between 25 and 35 °C. The ratio k_4/k_3 of the rates of spontaneous and base-catalyzed decomposition of $T^{\pm}$ is effectively the same at 25 and 35 °C for the nitrosation reactions of the weakly basic amines MOR and MePIP by 2,2-dichloroethyl nitrite in cyclohexane, while for the same reaction of PYR this ratio increases aproximately 6-fold between 25 and 35 °C. This indicates that base-catalyzed decomposition (k_4) becomes less important as temperature increases, as would be expected if the rate of this process were diffusion controlled.

Scheme 6



Effects of Adding Isopropylamine. The observed effects of isopropylamine addition on reaction rate were somewhat surprising. Our experimental results proved that, like the amine substrates, the added $iPrNH_2$ can form a hydrogen-bonded complex (HBC) with RONO. The experimental results could be explained by considering the mechanism proposed in Scheme 6.

The effect of isopropylamine addition on the nitrosation reactions of pyrrolidine and *N*-methylpiperazine is due to two opposing processes: inhibition due to competition between R_2NH and $iPrNH_2$ to form the HBC with RONO, the complex with $iPrNH_2$ being unreactive, and acceleration due to decomposition of the reactive HBC via a new $iPrNH_2$-catalyzed reaction.

Conclusions

In this work we found that the kinetics of the nitrosation of secondary amines by alkyl nitrites and MNTS in cyclohexane, isooctane, dichloromethane, 1,4-dioxane, and tetrahydrofuran are explicable in terms of a reaction mechanism analogous to the generally accepted mechanism for aminolysis of carboxylic esters. Formation of a tetrahedral intermediate $T^{\pm}$, either directly from the amine and nitrosating agent (in the case of MNTS) or indirectly via a hydrogen-bonded complex between the amine and nitrosating agent (in the case of alkyl nitrites), is followed by its decomposing either spontaneously or with the catalytic assistance of a second amine molecule. For alkyl nitrites, the rate-controlling step is the formation of $T^{\pm}$ at high amine concentrations, and its decomposition at low amine concentrations; for MNTS, the rate-controlling step is the formation of $T^{\pm}$ in more polar solvents and its decomposition in less polar solvents. An alternative mechanism involving the formation of $T^{\pm}$ from both monomers and dimers of the amine may be ruled out.

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