Nitrosation of Amines in Non-Aqueous Solvents − Difference Between N−N=O and O−N=O Nitroso Donors[‡]

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A kinetic study has been carried out on nitroso group transfer from substituted *N*-methyl-*N*-nitroso-benzenesulfonamides to different secondary amines: pyrrolidine, piperidine, *N*-methylpiperazine, and morpholine in cyclohexane. The observed pseudo-first-order rate constant k_{obs} shows a linear and quadratic dependency on the amine concentration with the existence of a primary kinetic isotope effect. Experiments carried out at different temperatures show Arrhenius-type behavior. Addition of isopropylamine (iPrNH$_2$) to the reaction medium produces an increase in k_{obs}. In the presence of a high iPrNH$_2$ concentrations the influence of secondary amine concentration on k_{obs} shows the disappearance of the quadratic dependency of k_{obs} on the secondary amine. These results would be compatible with an addition-elimination mechanism, similar to that observed for the aminolysis of the alkyl nitrites in apolar solvents. The observed behavior in the presence of 18-crown-6 is very different, however. Addition of crown ether catalyses the reaction of aminolysis of alkyl nitrites insofar as it does not alter the rate of the nitroso group transfer from *N*-nitrososulfonamides. This behavior has been interpreted in terms of a concerted reaction mechanism through cyclical transition states, with four or six centers, involving one or two molecules of secondary amine. Addition of iPrNH$_2$ to the reaction medium causes the appearance of a third reaction path, which emerges through a mixed transition state formed by a molecule of a secondary amine and a molecule of isopropylamine.

Introduction

The mechanism by which a reaction occurs can be altered as the reaction medium varies, as has been clearly shown for reactions involving the aminolysis of esters.[1] Nitrosation reactions generally display such behavior, and it has in fact been shown that the mechanism of nitrosation of ureas can be modified by changing the percentage of organic co-solvent in the reaction medium. It is now known that the complete mechanism[2] is in fact as shown in Scheme 1: attack by the nitrosating agent on the carbonyl oxygen atom, followed by a slow proton-transfer step and then by an internal rearrangement in which the NO group is transferred from oxygen to a nitrogen atom to afford the thermodynamically stable *N*-nitroso compound.

In 9:1 (w/w) dioxane/water[3] or THF/water[4] mixtures, however, the rate-determining step is the attack on the substrate by the nitrosating agent. When the reaction medium is 90% acetonitrile,[5] though, it is possible to observe a rate-limiting step consisting of the rearrangement of the nitrosourea, transferring the nitroso group from the more nucleophilic O atom to the N atom. It has also been noted that mechanism changes caused by the solvent occur in the acid hydrolysis reaction of the alkyl nitrites. In an aqueous medium the reaction takes place by a concerted mechanism[6] (Scheme 2), while if the percentage of dioxane in the medium is greater than 70% a stepwise reaction will take place, with prior protonation of the alkyl nitrite.[7]

The mechanism changes are more profound when the operative reaction mechanisms in an aqueous medium and in non-aqueous solvents are compared. Alkyl nitrites (R−O−N=O) form a major group of nitrosating agents able to nitrosate amines.[8] Nitroso group transfer can also take place with an N-nitroso donor, N−N=O, as in the case of the *N*-nitrososulfonamides.[9] In an aqueous medium the mechanism of nitroso group transfer from alkyl nitrites[10] or *N*-nitrososulfonamides[11] to amines takes places in a concerted manner (Scheme 3).

[‡] Nitrosation of Amines in Non-Aqueous Solvents, 4. Part 3: Ref.[12b]

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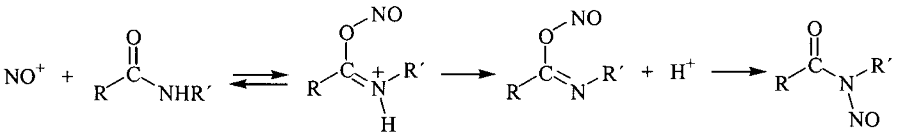
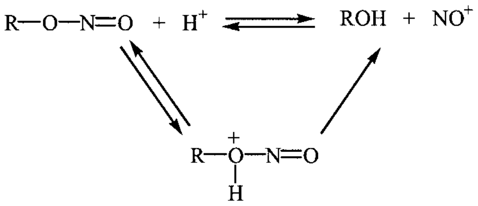


Scheme 1



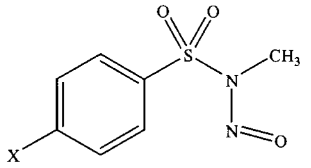
Scheme 2

The nitroso group transfer occurs in the slow step and the protonation of X^- and deprotonation of *N*-nitrosamine occur subsequently. The corresponding reaction mechanism for nitroso group transfer from alkyl nitrites in non-aqueous solvents is different from that found in the aqueous medium.

In non-aqueous solvents the reaction occurs through the formation of a hydrogen bond complex (HBC) between the amine and the alkyl nitrite. Subsequently this HBC evolves to form a reaction intermediate (T^0) that can decompose quite spontaneously or by means of a process involving basic catalysis[12] (Scheme 4).

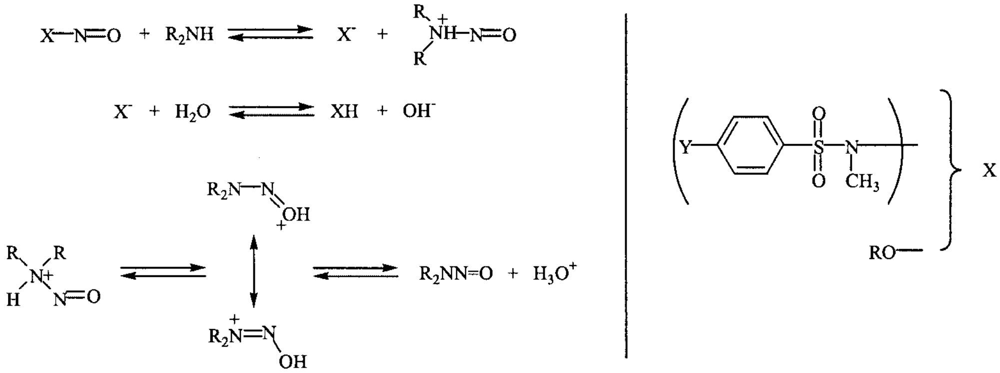
If the polarity of the solvent, or its capacity to act as a proton donor in hydrogen bond formation, are decreased, the concerted mechanism observed in aqueous media is gradually replaced by a stepwise mechanism, apparently because the more difficult solvation of the alkoxide leaving group produces an energy barrier that delays cleavage of the RO−N bond.[13]

The objective of this study was to investigate the mechanism of nitroso group transfer from *N*-nitrososulfonamides to amines of different basicity in cyclohexane. The *N*-nitrososulfonamides used are shown in Scheme 5. By varying the substituents on the aromatic ring it is possible to modulate its reactivity, in such a way that *N*-nitrososulfonamides with electron-attracting groups show reactivities in aqueous

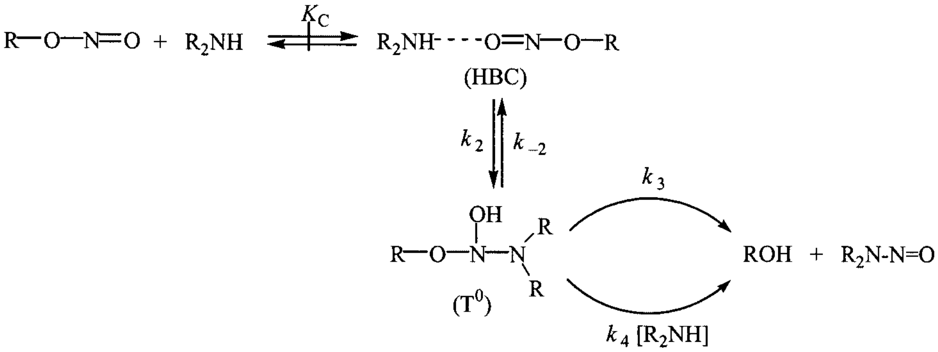


X	
4-CH_3O	MN-4-MeO-BS
4-CH_3	MN-4-Me-BS
4-Cl	MN-4-Cl-BS
4-NO_2	MN-4-NO_2-BS

Scheme 5



Scheme 3



Scheme 4

medium similar to those of the most activated alkyl nitrites.

The main difference between the behavior observed in the nitrosation of amines by alkyl nitrites and by *N*-nitrososulfonamides derives from the effect on the reaction mechanism exerted by crown ethers. 18-Crown-6 is an efficient catalyst in aminolysis reactions of carboxylic esters[14] and also in the nitrosation of amines by alkyl nitrites in cyclohexane. However, addition of 18-crown-6 to the reaction medium does not have any effect on the nitrosation of amines by *N*-nitrososulfonamides. This difference in behavior indicates a difference between the donors $R-N-N=O$ and $R-O-N=O$ in their nitroso group transfer reaction mechanisms in cyclohexane. The experimental results obtained in this study indicate that the transfer of the nitroso group from *N*-nitrososulfonamides to amines in cyclohexane occurs through a concerted mechanism without the formation of addition intermediates.

Results

1. Aminolysis of Alkyl Nitrites Catalyzed by Crown Ethers: The results in Figure 1 show the influence of pyrrolidine on k_{obs} in nitrosation by 2-bromoethyl nitrite. The complex dependency of k_{obs} on amine concentration has been interpreted[12a] in terms of the mechanism shown in Scheme 4. For small amine concentrations the rate-limiting step is the decomposition of the addition intermediate, either spontaneously, or by a process involving basic catalysis by a second amine molecule. This behavior is responsible for the first- and second-order dependency of k_{obs} on the pyrrolidine concentration. As the amine concentration increases, so too does the rate of decomposition of the intermediate, in such a way that the rate-limiting step becomes the formation of the intermediate. Finally, for high amine concentrations, k_{obs} tends to reach a maximum value due to the formation of the hydrogen bond complex between the amine and the alkyl nitrite.

Figure 2 shows the experimental behavior inferred from study of the nitrosation of pyrrolidine by two *N*-nitrososulfonamides: MN-4-Me-BS and MN-4-MeO-BS. In both cases it is possible to observe both first- and second-order dependency of k_{obs} on the amine concentration. In contrast with what occurred in the nitrosation of pyrrolidine by 2-bromoethyl nitrite, the results obtained with MN-4-Me-BS and MN-4-MeO-BS do not suggest any change in the rate-determining step when the amine concentration varies, nor the existence of hydrogen bond complexes between the amine and the *N*-nitrososulfonamide. A simplification of the mechanism shown in Scheme 4 allows us to explain the experimental results shown in Figure 2, which would be compatible with a nitroso group transfer mechanism through the formation of an addition intermediate, where the rate-determining step was the spontaneous or the base-catalyzed decomposition of the intermediate.

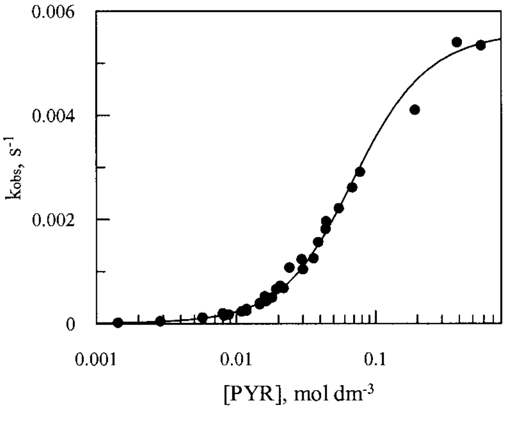


Figure 1. Influence of pyrrolidine concentration on k_{obs} for nitrosation by 2-bromoethyl nitrite at 25 °C in cyclohexane

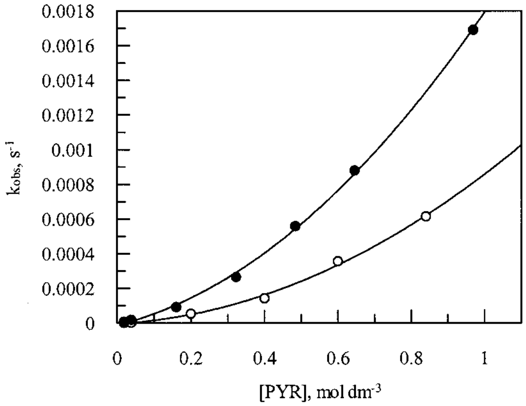


Figure 2. Influence of pyrrolidine concentration on k_{obs} for nitrosation by (·)MN-4-Me-BS and (o)MN-4-MeO-BS at 25 °C in cyclohexane; experimental data are fitted to Equation (1) (parameters in Table 1)

Crown ethers and glymes catalyze the ester aminolysis in aprotic solvents such as chlorobenzene, and the catalytic effect is due to complexation between the crown ether and the zwitterionic adduct. The rate law for butylaminolysis of phenyl acetates in the presence of 18-crown-6 is first order both in butylamine and in 18-crown-6 concentration, which requires the crown to be involved in the rate-limiting step and also in the transition state.[15] The reaction mechanism involves rate-limiting expulsion of phenolate ion from the zwitterionic adduct-crown complex. Earlier studies on the butylaminolysis of phenyl acetate and 4-nitrophenyl acetate in acetonitrile show that the presence of 18-crown-6 catalyses the first reaction but not the second. This difference in behavior has been interpreted in terms of a mechanism involving a common zwitterionic adduct, which presents two decomposition pathways: (i) direct expulsion of the phenolate ion leaving group and (ii) proton transfer prior to phenolate ion expulsion. Formation of the zwitterionic adduct is rate-limiting for path (i) and C−OAr bond fission is rate-limiting for mechanism (ii).[16]

Figure 3 shows the results obtained from examination of the influence of the 18-crown-6 concentration on k_{obs} in the nitrosation of pyrrolidine by 2-bromoethyl nitrite and by MN-4-Me-BS. A study on the influence of the concentration of 18-crown-6 on k_{obs} in nitrosation of pyrrolidine by 2-bromoethyl nitrite was carried out by use of a concentration of pyrrolidine [PYR] of 1.43×10^{-3} mol·dm^{-3}. As shown in Figure 1, this concentration of pyrrolidine corresponds with a situation in which the rate-limiting step of the reaction is the decomposition of the addition intermediate, either spontaneously or by basic catalysis. The results show that the value of k_{obs} increases as the [18-crown-6] does, tending towards a maximum value. This maximum value must correspond with experimental conditions under which the rate-limiting step changes, which will give rise to the formation of the addition intermediate. Moreover, its process will not be catalyzed by the 18-crown-6. Figure 3 also shows that there is no effect on k_{obs} in the nitrosation of pyrrolidine by MN-4-Me-BS derived from the addition of 18-crown-6. This behavior is consistent with a rate-determining step other than the decomposition of an addition intermediate. The obtained results therefore show the difference between the nitroso group transfer mechanism from donors R−O−N=O and R−*N*−N=O in cyclohexane.

2. Influence of the Amine Concentration: Figure 2 shows the experimental results obtained from examination of the influence of the concentration of PYR on k_{obs} in its nitrosation by MN-4-Me-BS and MN-4-MeO-BS. In all cases we can observe the existence of linear and quadratic dependency of k_{obs} on the [PYR] [Equation (1)].

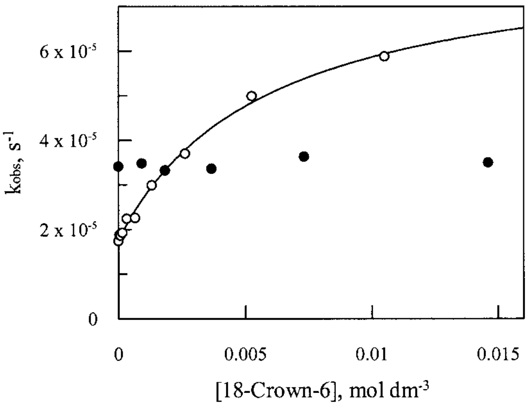


Figure 3. Influence of 18-crown-6 concentration on k_{obs} for nitrosation of pyrrolidine by (o) 2-bromoethyl nitrite, [PYR] = 1.43×10^{-3} mol·dm^{-3}, and (·) MN-4-Me-BS, [PYR] = 8.00×10^{-2} mol·dm^{-3}, at 25 °C in cyclohexane

$$k_{obs} = a[R_2NH] + b[R_2NH]^2 \quad (1)$$

Table 1 shows the values of the parameters *a* and *b* obtained by variation of the nature of the amine and of the nitrosating agent. As can be seen, the values of the parameters *a* and *b* increase together with the electron-attracting substituents on the nitrosating agents, and also when the basicity of the amine increases.

On studying the nitrosation of PYR and other less basic amines by alkyl nitrites, similar experimental behavior was found for small concentrations of amines. As the concentration of the amine increases ([amine]>5×10^{-2} mol·dm^{-3}), however, it can be observed that k_{obs} tends towards a maximum value. This result had been interpreted in terms of the formation of a hydrogen bond complex between the alkyl nitrite and the amine. In the nitrosation of amines by *N*-nitrososulfonamides this tendency cannot be observed even for concentrations of amines higher than 0.50 M.

3. Influence of the Temperature: Figure 4 shows the results obtained from examination of the nitrosation of piperidine by MN-4-Cl-BS at T = 25 and T = 35 °C. As can be observed, the values of k_{obs} increase together with the temperature independently of the concentration of amine used. The experimentally obtained values for k_{obs} were fitted to Equation (1), and the parameters are shown in Table 1. The values of the parameters *a* and *b* increase with the temperature, providing [$a = (7.8\pm0.5) \times 10^{-4}$ and $b = (1.6\pm0.3) \times 10^{-3}$] at T = 25 °C and [$a = (1.6\pm0.3) \times 10^{-3}$ and $b = (3.9\pm0.5) \times 10^{-3}$] at T = 35 °C.

The observed Arrhenius behavior contrasts with the results of previous studies of the nitrosation of amines by alkyl nitrites in cyclohexane.[12a] The existence of a hydrogen bond complex in the nitrosation of amines by alkyl nitrites had been shown kinetically by the existence of anti-Arrhenius behavior when the influence of the temperature

Table 1. Values of the parameters *a* and *b* obtained from Equation (1) for the nitrosation of secondary amines by *N*-nitrososulfonamides under different experimental conditions

Reaction	T/°C	a/M^{-1}s^{-1}	b/M^{-2}s^{-1}
PYR + MN-4-MeO-BS	25	$(4\pm2) \times 10^{-5}$	$(8.6\pm0.5) \times 10^{-4}$
PYR + MN-4-Me-BS	25	$(3.7\pm0.3) \times 10^{-4}$	$(1.46\pm0.06) \times 10^{-3}$
PYR[a] + MN-4-Me-BS	25	$(3.2\pm0.9) \times 10^{-4}$	$(1.0\pm0.2) \times 10^{-3}$
PYR + MN-4-Cl-BS	25	$(1.18\pm0.03) \times 10^{-2}$	$(1.84\pm0.07) \times 10^{-2}$
PYR + MN-4-NO_2-BS	25	0.206 ± 0.006	1.32 ± 0.08
PYR[a] + MN-4-NO_2-BS	25	0.16 ± 0.02	1.1 ± 0.2
PIPER + MN-4-NO_2-BS	25	$(4.3\pm0.3) \times 10^{-2}$	$(7\pm1) \times 10^{-2}$
MePIP + MN-4-NO_2-BS	25	$(6.2\pm0.9) \times 10^{-3}$	$(1.4\pm0.2) \times 10^{-2}$
MOR + MN-4-NO_2-BS	25	$(1.9\pm0.1) \times 10^{-3}$	$(1.8\pm0.2) \times 10^{-3}$
PIPER + MN-4-Cl-BS	25	$(7.8\pm0.5) \times 10^{-4}$	$(1.6\pm0.3) \times 10^{-3}$
PIPER + MN-4-Cl-BS	35	$(1.6\pm0.3) \times 10^{-3}$	$(3.9\pm0.5) \times 10^{-3}$

[a] *N*-Deuterated amine.

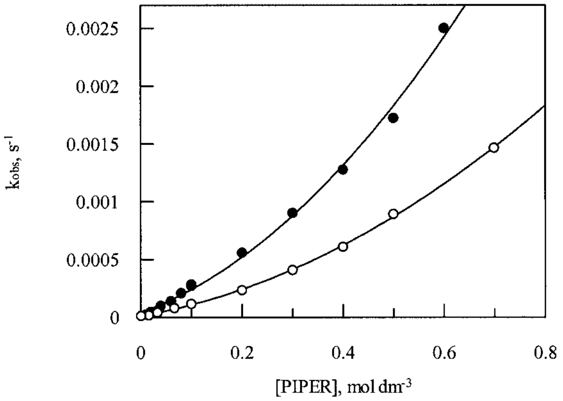


Figure 4. Influence of piperidine concentration on k_{obs} for nitrosation by MN-4-Cl-BS at (·) T = 35 °C and (o) T = 25 °C in cyclohexane; experimental data are fitted to Equation (1) (parameters in Table 1)

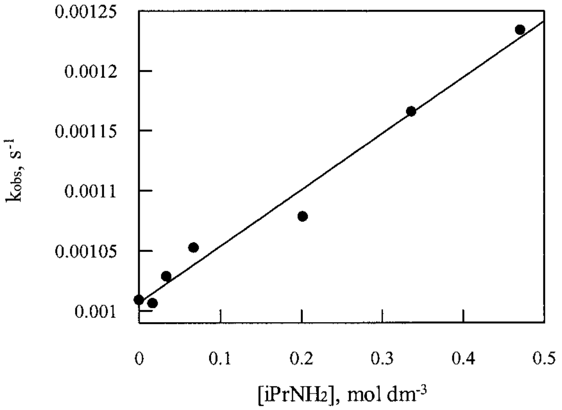


Figure 5. Influence of isopropylamine concentration on k_{obs} for nitrosation of piperidine by MN-4-Cl-BS at 25 °C; [PIPER] = 0.50 mol·dm^{-3}

on the reaction rate is studied. This anti-Arrhenius behavior is compatible with the tendency of k_{obs} on reaching a maximum value for high concentrations of amine. The results obtained from study of the nitrosation of amines by *N*-nitrososulfonamides therefore suggest the absence of hydrogen bond complexes between the *N*-methyl-*N*-nitrosobenzenesulfonamides and the amines.

4. Influence of Isopropylamine Addition: A study on the influence of the addition of a highly basic and only slightly reactive amine, such as isopropylamine (*i*PrNH$_2$), to the reaction medium was carried out. Two types of experiments were carried out: firstly, on the influence of the addition of isopropylamine to the reaction medium, during which the concentration of the secondary amine remained constant, and secondly, on the influence of the concentration of secondary amine in the presence of a high concentration of isopropylamine.

Figure 5 shows the influence of the concentration of *i*PrNH$_2$ on the nitrosation of piperidine by MN-4-Cl-BS, the concentration of piperidine being kept constant ([PIPER] = 0.5 mol·dm^{-3}). We can observe a clear linear dependency of k_{obs} on the concentration of *i*PrNH$_2$ added to the reaction medium [Equation (2)]. On the basis of this linear representation and other analogous plots obtained in the nitrosation of piperidine by MN-4−NO$_2$-BS ([PIPER] = 9.99 × 10^{-2} mol·dm^{-3}) and for the nitrosation of morpholine by MN-4−NO$_2$-BS ([MOR] = 9.92 × 10^{-2} mol·dm^{-3}) we obtain the values shown in Table 2.

$$k_{obs} = \text{Intecept} + \text{Slope}[i\text{Pr}NH_2] \tag{2}$$

Figure 6 shows the influence of the concentration of morpholine on k_{obs} in its nitrosation by MN-4-NO$_2$-BS in the presence ([*i*PrNH$_2$] = 0.20 mol·dm^{-3}) and in the absence of *i*PrNH$_2$. The obtained results show that the quadratic term of Equation (1) disappears. On the basis of the linear dependence we can obtain a slope of 3.05 × 10^{-3} mol^{-2}·dm^{6}·s^{-1}. An analogous result was obtained from investigation of the influence of the concentration of piperidine on k_{obs} in its nitrosation by MN-4-Cl-BS in the presence of [*i*PrNH$_2$] = 1.00 mol·dm^{-3} (not shown). In this case we obtain a linear plot with an slope of 2.23 × 10^{-3} mol^{-2}·dm^{6}·s^{-1}.

5. Influence of Isotopic Substitution: The results obtained from study of the influence of the concentration of *i*PrNH$_2$ suggest that the rate-limiting step is susceptible to basic catalysis. To confirm this hypothesis we studied the effect of isotopic substitution on k_{obs}. Figure 7 shows the influence of the concentration of pyrrolidine. The experimentally obtained results were fitted to Equation (1), giving the values of the parameters *a* and *b* shown in Table 1. The results show the existence of a primary isotopic effect on the terms *a* and *b* as much in the nitrosation of PYR by MN-4-Me-BS (a_H/a_D = 1.16 and b_H/b_D =1.4) as in the nitrosation of PYR by MN-4-NO$_2$-BS (a_H/a_D = 1.29 and b_H/b_D = 1.2). These results are consistent with the existence of proton transfer in the rate-limiting step.

Table 2. Values of the slopes obtained from Equation (2) from study of the influence of the isopropylamine concentration on the nitrosation of piperidine and morpholine by MN-4-Cl-BS and MN-4-NO$_2$-BS at T = 25 °C under different experimental conditions

		Slope, mol^{-1}·dm^{3}·s^{-1}
MN-4-Cl-BS	[PIPER] = 0.50 mol·dm^{-3}	(4.7±0.3) × 10^{-4}
MN-4-NO$_2$-BS	[PIPER] = 9.99 × 10^{-2} mol·dm^{-3}	(3.2±0.3) × 10^{-3}
MN-4-NO$_2$-BS	[MOR] = 9.92 × 10^{-2} mol·dm^{-3}	(6.4±0.3) × 10^{-4}

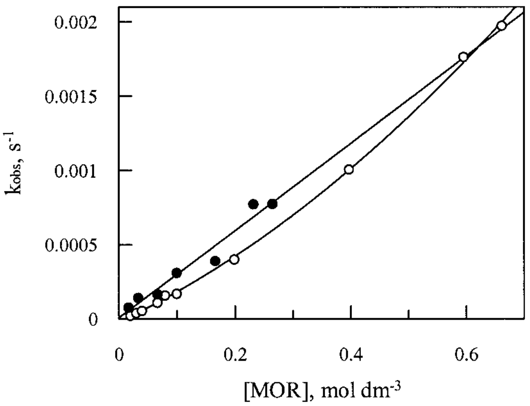


Figure 6. Influence of morpholine concentration on k_{obs} for nitrosation of morpholine by MN-4-NO$_2$-BS at 25 °C; (·) [*i*PrNH$_2$] = 1.00 mol·dm^{-3} and (o) [*i*PrNH$_2$] = 0 mol·dm^{-3} in cyclohexane

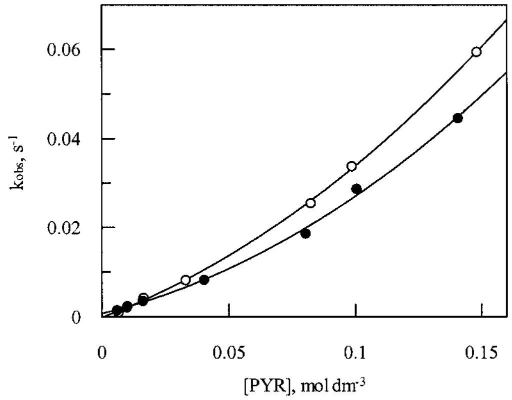


Figure 7. Influence of pyrrolidine concentration on k_{obs} for nitrosation of pyrrolidine by MN-4-NO$_2$-BS at 25 °C; (·) *N*-deuterated pyrrolidine and (o) non-deuterated pyrrolidine in cyclohexane

Discussion

The reaction mechanism proposed for the nitroso group transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides to amines in cyclohexane must be compatible with the experimentally obtained results and with the reaction mechanisms obtained for this reaction in water and for the nitrosation by alkyl nitrites in water and in non-aqueous solvents.

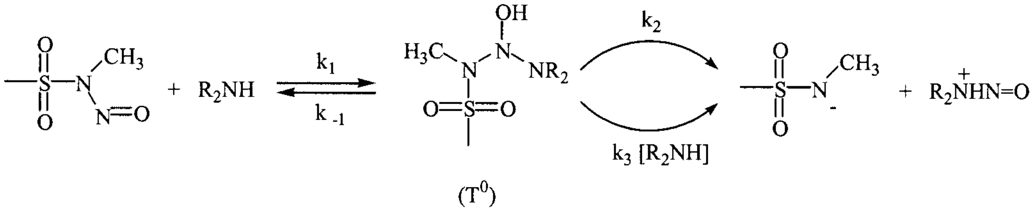
1. Addition-Elimination Mechanism: The experimentally obtained results might suggest the existence of an addition-elimination mechanism, such as that presented by alkyl nitrites in cyclohexane. This mechanism can be simplified (Scheme 6), since no evidence has been found of the formation of a hydrogen bond complex between the amines and the *N*-nitrososulfonamides.

The reaction mechanism may take place through an addition intermediate (T^0), the decomposition of which, either by a spontaneous pathway (k_2) or by a base-catalyzed process (k_3), may be rate-limiting. However, the results shown in Figure 3 indicate that there is no catalysis by 18-crown-6, in contrast with what is found for the nitrosation of pyrrolidine by 2-bromoethyl nitrite.

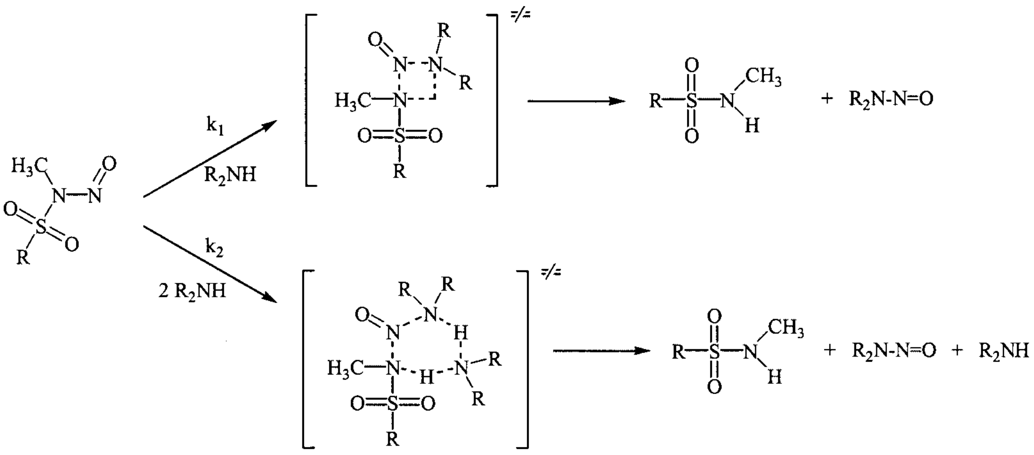
The absence of catalysis by 18-crown-6 in the aminolysis of carboxylic esters was interpreted by Williams[16] as a consequence of the existence of a reaction mechanism in which the rate-limiting step is the formation of a reaction intermediate. This change in the rate-limiting step would be compatible with an addition-elimination mechanism for the amine nitrosation by *N*-nitrososulfonamide. If this is the case it would be necessary that the formation of the intermediate should show first- and second-order dependency on the amine concentration. This behavior contrasts with that observed in the nitrosation of pyrrolidine by 2-bromoethyl nitrite, in which the formation of the addition intermediate only shows first-order dependency on the amine concentration.

These results lead us to propose a concerted reaction mechanism, similar to that operating in an aqueous medium, in which the amine attack on the nitroso group and the expulsion of the sulfonamide take place simultaneously.

2. Concerted Mechanism: In the nitrosation of amines by alkyl nitrites in cyclohexane we can observe a change in the rate-limiting step as the amine concentration is varied (Figure 1).[17] For small amine concentrations, the rate-limiting step is the decomposition of the addition intermediate T^0. As the concentration of the amine increases, the rate-limiting step is the formation of T^0. The anions of sulfonamides are much better leaving groups that the alkoxides, given that the pK_a values of the alcohols are 2−3 units greater than those of the sulfonamides.[18] This weaker capacity to act as a leaving group should be reflected in greater difficulty in the decomposition of the reaction intermediate. The balance between the processes of formation and decomposition of T^0 is responsible for a change in the rate-limiting step. In aqueous medium the transition states for amine nitrosation by alkyl nitrites and *N*-nitrososulfonamides are analogous, the extension of the bond formation (O···N and N···N) and the bond breaking (O···N=O and N···N=O) being similar in the two cases. However, the



Scheme 6



Scheme 7

2-ethoxyethyl nitrite and the MN-4-Me-BS present similar reactivities. The difference in the pK_a values of the leaving groups is approximately three units larger for the alcohol. From this we can conclude that the nitroso group of the alkyl nitrites must be more electrophilic that than of the *N*-nitrososulfonamides. The inversion in the rate-limiting step for the nitrosation of amines by alkyl nitrites in cyclohexane should therefore also be observable for the nitrosation of amines by *N*-nitrososulfonamides.

The greater capacity of the anion of the sulfonamide to act as a leaving group leads us to propose a concerted mechanism for this reaction. According to Scheme 7, the nucleophilic attack on the nitroso group will occur concertedly with the protonation of the leaving group, through the formation of a four-center, cyclical transition state, which is responsible for the linear dependency of k_{obs} on the amine concentration, or by means of a six-center transition state, responsible for the quadratic dependency of k_{obs} on the amine concentration.

From the proposed mechanism we can obtain the rate Equation (3).

$$k_{obsd} = k_1[R_2NH] + k_2[R_2NH]^2 \quad (3)$$

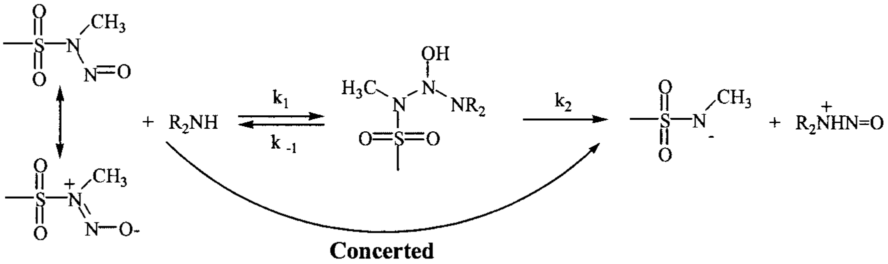
The existence of two transition states with one or two amine molecules provides a satisfactory explanation for the linear and quadratic dependency of k_{obs} on the amine concentration. The terms *a* and *b* in Equation (1) and Table 1 correspond to the rate constants: $a = k_1$ and $b = k_2$. The relationship k_1/k_2 is always less than 1, which shows that the six-membered transition state is more favorable that that with four.

From the data in Table 1 we can obtain the Brønsted slopes for the rate constants k_1 and k_2 with varying nature of the amine. The values corresponding to the nitrosation of piperidine are not included in this correlation, since, as also occurs in the aqueous medium, this amine presents a reactivity very much lower than that which would be expected in view of its pK_a.[10] The obtained values, $\beta_{nucl.} = (0.69\pm0.03)$ and $\beta_{nucl.} = (0.9\pm0.1)$, for k_1 and k_2, respectively, are in the vicinity of the obtained value in aqueous medium, $\beta_{nucl.} = (0.55\pm0.01)$.

The rate constants k_1 and k_2 show a high sensitivity to the nature of the leaving group. From the pK_a values of the sulfonamides obtained in an aqueous medium we can obtain the corresponding Brønsted slopes: $\alpha_{1g} = (-3.5\pm0.4)$ and $\alpha_{1g} = (-3.1\pm0.5)$ for $k_1$and k_2 respectively. These values show a greater sensitivity to the nature of the leaving group than the values obtained in an aqueous medium, $\alpha_{1g} \cong -1.5$. The difference may be due to the low capacity of the cyclohexane to solvate charges, and therefore a modification of the pK_a values of the sulfonamides. The great sensitivity of the rate constants k_1 and k_2 to the electron-withdrawing substituents is additional evidence in favor of a concerted mechanism, and against a stepwise mechanism. Obtained values of α_{1g}, $\alpha_{1g} < -1$ are interpreted on the basis of a concerted nitroso group transfer. Such large values for Brønsted slopes are easy to explain by considering that the transnitrosation reaction involves a change in charge of close to two units at the sulfonamide nitrogen, from partial positive in the nitroso compound $[Ar-SO_2-N(CH_3)^+=N-O^-]$ to partial negative in the transition state $[Ar-SO_2-N(CH_3)^-]$. With a change of charge of close to two units in the reaction, in contrast with only one in the reference reaction (the acid dissociation), these values become reasonable. This change of charge of close to two units is only compatible with a concerted mechanism for nitroso group transfer, so the stepwise mechanism shown in Scheme 8 can be ruled out.

The values of the isotopic effects ($k_1^H/k_1^D = 1.29$ and $k_1^H/k_1^D = 1.16$ for the nitrosation of pyrrolidine by MN-4-NO$_2$-BS and MN-4-Me-BS and $k_2^H/k_2^D = 1.2$ and $k_2^H/k_2^D = 1.4$ for the same reactions) indicate that there is a proton transfer involved in the rate-limiting step of the reaction.

From study of the nitrosation of piperidine by MN-4-Cl-BS at 25 °C and 35 °C, we can estimate the values of the activation parameters for the reaction. The obtained results: $[\Delta H^{\#} = 52.3\ \text{kJ·mol}^{-1}$ and $\Delta S^{\#} = -129\ \text{J·mol}^{-1}\text{·K}^{-1}]$ for the formation of the transition state in which only one am-



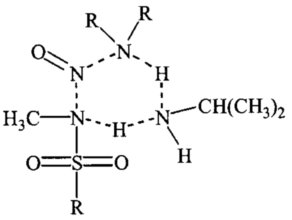
Scheme 8

ine molecule intervenes, k_1, and [$\Delta H^{\#} = 65.4$ kJ·mol^{-1} and $\Delta S^{\#} = -79$ J·mol^{-1}·K^{-1}] for the transition state in which two amine molecules intervene, k_2, are compatible with the existence of highly ordered transition states.[19]

The proposed concerted mechanism is perfectly compatible with the results obtained from investigation of the influence of the concentration of *i*PrNH$_2$. As we have seen previously, the formation of a six-centered transition state is more common than that with four members. In this way, the effect of the addition of *i*PrNH$_2$ can be explained through the formation of a cyclical transition state of six members, as shown below.

It is therefore appropriate to adapt the mechanism proposed in Scheme 7 by inclusion of a third path in which a mixed transition state forms, such as that shown in Scheme 9. The rate Equation (4) can be written thus:

$$k_{\mathrm{obsd}} = k_1[R_2NH] + k_2[R_2NH]^2 + k_3[R_2NH][i\mathrm{Pr}NH_2] \quad (4)$$



Scheme 9

The experimentally obtained results clearly confirm this behavior and from the values in Table 2 we can calculate k_3. The obtained results – $k_3 = 3.2 \times 10^{-2}$ mol^{-2}·dm^6·s^{-1} ($k_2 = 7.1 \times 10^{-2}$ mol^{-1}·dm^3·s^{-1}) and $k_3 = 9.4 \times 10^{-4}$ mol^{-2}·dm^6·s^{-1} ($k_2 = 1.6 \times 10^{-3}$ mol^{-1}·dm^3·s^{-1}) for the nitrosation of piperidine by MN-4-NO$_2$-BS and MN-4-Cl-BS, respectively, and $k_3 = 6.45 \times 10^{-3}$ mol^{-2}·dm^6·s^{-1} ($k_2 = 1.8 \times 10^{-3}$ mol^{-1}·dm^3·s^{-1}) for the nitrosation of morpholine by MN-4-NO$_2$-BS – show that $k_3 > k_2$ for the nitrosation of morpholine and $k_3 < k_2$ for the nitrosation of piperidine. Similarly, the difference in reactivity between MN-4-NO$_2$-BS and MN-4-Cl-BS can also be translated to the term catalyzed by *i*PrNH$_2$. The reason for the difference in reactivity between k_2 and k_3 in the nitrosation of piperidine and morpholine should be interpreted by taking into account the fact that the isopropylamine is a more basic amine than the morpholine, so path k_3 will be more favorable than k_2. However, the *i*PrNH$_2$ is less basic than piperidine, which causes the reaction path k_2 to be more favorable than k_3.

The results in Figure 6 and the analogous results obtained for the nitrosation of morpholine by MN-4-NO$_2$-BS allow us to calculate the rate constant k_3 thus: k_3 = (Slope – k_1)/[*i*Pr*NH*$_2$]. The obtained values – $k_3 = 1.45 \times 10^{-3}$ mol^{-2}·dm^6·s^{-1} and $k_3 = 5.75 \times 10^{-3}$ mol^{-2}·dm^6·s^{-1} – are compatible with those obtained previously for the nitrosation of piperidine and morpholine by MN-4-Cl-BS and MN-4-NO$_2$-BS respectively.

Conclusions

Nitroso group transfer from *N*-nitrososulfonamides to amines in cyclohexane is not catalyzed by 18-crown-6, unlike what is observed when alkyl nitrites are used as nitrosating agents. This behavior has been interpreted in terms of a concerted reaction mechanism. This change in behavior from an addition-elimination reaction (alkyl nitrites) to a concerted mechanism (*N*-nitrososulfonamides) must be a consequence of the greater stability presented by the sulfonamides as leaving groups.

The concerted mechanism occurs through two parallel paths, with the formation of two cyclical transition states of four and of six centers, in which one and two molecules of the secondary amine are involved. In all cases the six-centered transition state has greater stability than that with four centers. The reaction rate accelerates as the basicity of the amine is increased, with a Brønsted slope similar to those obtained in an aqueous medium. At the same time the reaction rate shows a much greater degree of sensitivity to the nature of the leaving group than that observed in an aqueous medium, which has been attributed to a variation of two units of charge on the nitrogen atom of the sulfonamide during the course of the reaction.

The addition of isopropylamine to the reaction medium causes the appearance of a third reaction path through a mixed transition state formed by a secondary amine molecule and an *i*PrNH$_2$ molecule. The experimental results show that the evolution through this six-centered transition state is either more or less favorable than that occurring through a transition state with two secondary amine molecules, depending on the relative basicities of the $i\text{PrNH}_2$ and of the secondary amine.

Experimental Section

N-Methyl-*N*-nitrosobenzenesulfonamides were synthesized as described previously.[11] *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide was supplied by Merck. Cyclohexane (nominal purity > 99.9% from Aldrich) was used as supplied. Secondary amines: pyrrolidine (PYR), piperidine (PIPER), *N*-methylpiperazine (MePIP) and morpholine (MOR), all from Aldrich, were of the highest available purity and were distilled under argon and used shortly afterwards. *N*-Deuterated pyrrolidine was prepared by repeated fractional distillation of a mixture of the amine with a tenfold molar excess of D_2O through a 20 cm Vigreux column.[1a] After at least three runs, the product was dried with calcium hydride, from which it was later distilled. The ^{1}H NMR spectra of the final product confirmed *N*-deuteration. 2-Bromoethyl nitrite was prepared by treatment of the parent alcohol with sodium nitrite in acid medium. 2-Bromoethyl nitrite was stored over molecular sieves to prevent its hydrolysis.

In all the kinetic experiments the nitrosating agent concentration was in deficit, generally ranging from $(1-2) \times 10^{-4}\text{mol}\cdot\text{dm}^{-3}$. Reaction kinetics were monitored by following changes in absorbance (generally in the 250−270 nm range for MN-4-MeO-BS, MN-4-Me-BS, MN-4-Cl-BS, and 2-bromoethyl nitrite and in the 290−340 nm range for MN-4−NO_2-BS) by use of a Varian Cary 500 spectrophotometer equipped with thermostatted cell holders. The absorbance-time data always show first-order behavior, and k_{obs}, the corresponding pseudo-first-order rate constant, could be reproduced within 3%. Identification of reaction products was confirmed from UV spectra of the reactions on completion and in some cases by HPLC with acetonitrile/water (1:1) as the eluent, retention times and peak areas being compared with those of the pure N-nitrosamines. In every case we found quantitative N-nitrosamine formation compatible with the spectral changes observed in kinetic experiments.

Acknowledgments

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[1] [1a] F. M. Menger, J. H. Smith, *J. Am. Chem. Soc.* **1972**, *94*, 3824. [1b] C. W. Su, J. W. Watson, *J. Am. Chem. Soc.* **1974**, *96*, 1854.

[2] [2a] A. Castro, E. Iglesias, J. R. Leis, M. E. Peña, J. Vázquez Tato, *J. Chem. Soc., Perkin Trans. 2* **1986**, 1725. [2b] J. Casado, A. Castro, F. Meijide, M. Mosquera, J. Vázquez Tato, *J. Chem. Soc., Perkin Trans. 2* **1987**, 1759.

[3] C. Bravo, P. Hervés, E. Iglesias, J. R. Leis, M. E. Peña, *J. Chem. Soc., Perkin Trans. 2* **1990**, 1969.

[4] P. Hervés, J. R. Leis, *J. Chem. Soc., Perkin Trans. 2* **1995**, 2035.

[5] C. Bravo, P. Hervés, J. R. Leis, M. E. Peña, *J. Chem. Soc., Perkin Trans. 2* **1991**, 2091.

[6] E. Iglesias, L. García-Río, J. R. Leis, M. E. Peña, D. Williams, H. Lyn, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1673.

[7] [7a] A. D. Allen, *J. Chem. Soc.* **1954**, 1968. [7b] G. Bhattacharjee, *Ind. J. Chem. Sect. B.* **1981**, *20*, 526.

[8] D. L. H. Williams, *Nitrosation*; Cambridge University Press: Cambridge, **1988**.

[9] L. García-Río, J. R. Leis, J. A. Moreira, F. Norberto, *J. Phys. Org. Chem.* **1998**, *11*, 756.

[10] L. García-Río, E. Iglesias, J. R. Leis, M. E. Peña, A. Rios, *J. Chem. Soc., Perkin Trans. 2* **1993**, *11*, 756.

[11] L. García-Río, J. R. Leis, J. A. Moreira, F. Norberto, *J. Org. Chem.* **2001**, *66*, 381.

[12] [12a] L. García-Río, J. R. Leis, E. Iglesias, *J. Org. Chem.* **1997**, *62*, 4701. [12b] J. C. Boni, L. García-Río, J. R. Leis, J. A. Moreira, *J. Org. Chem.* **1999**, *64*, 8887.

[13] L. García-Río, J. R. Leis, E. Iglesias, *J. Org. Chem.* **1997**, *62*, 4712.

[14] [14a] R. D. Gandour, D. A. Walker, A. Nayak, G. R. Newkome, *J. Am. Chem. Soc.* **1978**, *100*, 3608. [14b] J. C. Hogan, R. D. Gandour, *J. Am. Chem. Soc.* **1980**, *102*, 2865. [14c] J. C. Hogan, R. D. Gandour, *J. Org. Chem.* **1992**, *57*, 55. [14d] J. C. Hogan, R. D. Gandour, *J. Org. Chem.* **1991**, *56*, 2821.

[15] A. B. Maude, A. Williams, *J. Chem. Soc., Perkin Trans. 2* **1995**, 691.

[16] A. B. Maude, A. Williams, *J. Chem. Soc., Perkin Trans. 2* **1997**, 179.

[17] In the nitrosation of pyrrolidine by 2-bromoethyl nitrite, for which the reactivity in water is similar to that of MN-4-Cl-BS, we observe a change in the rate-determining step of the reaction for amine concentrations lower than $0.05\ \text{mol}\cdot\text{dm}^{-3}$.

[18] G. Dauphin, A. Kergomard, *Bull. Soc. Chim. Fr.* **1961**, *5*, 486.

[19] As mentioned by one of the reviewers, the activation parameters obtained from just two temperatures (25 and 35 °C) are not generally accurate mainly for the activation entropy. In fact, a value of $\Delta S^{\#}$-129 $\text{J}\cdot\text{mol}^{-1}\text{K}^{-1}$ is obtained for the four-membered transition state whereas a value of $\Delta S^{\#} = -79$ $\text{J}\cdot\text{mol}^{-1}\text{K}^{-1}$ is obtained for the six-membered transition state. We think that the temperature study showing Arrhenius behavior − in contrast with that observed in the amine nitrosation by alkyl nitrites − is important.

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