Nitroso Group Transfer from Substituted *N*-Methyl-*N*-nitrosobenzenesulfonamides to Amines. Intrinsic and Apparent Reactivity

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We have studied the nitroso group transfer from substituted *N*-methyl-*N*-nitrosobenzenesulfonamides to primary and secondary amines, observing that the rate of the reaction increases as a consequence of the presence of electron withdrawing groups on the aromatic ring of the nitrosating agents. The rate constants determined for the nitroso group transfer, k_{tr}, give good Bronsted-type relationships between log k_{tr} (rate constant for nitroso group transfer) and $pK_a^{R_2NH_2^+}$ and $pK_a^{leaving\ group}$. The study of the nitrosation processes of secondary amines catalyzed by ONSCN and denitrosation catalyzed by SCN^-, in combination with the formation equilibrium of ONSCN, has enabled us to calculate the value of the equilibrium constant for the loss of the NO^+ group from a protonated *N*-nitrosamine ($pK_{NO}^{R_2N^+HNO}$), which can be defined by analogy with $pK_a^{R_2NH_2^+}$. The value of pK_{NO}^{X-NO} for the loss of the NO^+ group from an *N*-methyl-*N*-nitrosobenzenesulfonamide was obtained in a similar way. By using values of $\Delta pK_{NO} = pK_{NO}^{R_2N^+HNO} - pK_{NO}^{X-NO}$, we were able to calculate the equilibrium constant for the nitroso group transfer and characterize the transition state. On the basis of Bronsted-type correlations, we have obtained values of β_{nucl}^{norm} and $\alpha_{lg}^{norm} \cong 0.55$, showing a perfectly balanced transition state. In terms of the Marcus theory, the calculation of the intrinsic barriers for the nitroso group transfer reaction shows that the presence of electron withdrawing groups on the aromatic ring of the *N*-methyl-*N*-nitrosobenzenesulfonamides does not cause these barriers to vary.

Introduction

Increasing attention is being paid to the chemistry of nitrosamines owing to the toxicity[1] and carcinogenic,[2] mutagenic,[3] and teratogenic[4] properties of these compounds. In this sense, transnitrosation from nitrosamines to amines has important repercussions because noncarcinogenic nitrosamines or those with only a weak activity have the potential to generate more powerfully carcinogenic nitrosamines by transnitrosation in vivo, particularly in the acid environment of the stomach, where additional catalysis from naturally occurring nucleophiles might also occur.

The N−N bond of a *N*-nitrosamine ($R_2N-N{=}O$) can undergo heterolytic or homolytic cleavage, producing fragments capable of affecting nitrosation. The alternative possibility is that direct transfer of the NO group can occur without the intermediacy of a free nitrosating agent formed from the above fragments. This is the basis of the so-called *transnitrosation reactions* of nitrosamines where a direct transfer of the nitroso group occurs, by attack of a nucleophile on the N-atom. The best studied nitrosamine that can promote transnitrosation of a great variety of nucleophiles is the *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, MN-4-Me-BS. In the presence of nucleophiles such as OH^- or EtO^- (Scheme 1) which attack the SO_2 group of MN-4-Me-BS, the latter decomposes to afford diazometane.[5] However, unlike nitrosamides and nitrosoureas, MN-4-Me-BS also undergoes nucleophilic attack by amines at its N=O group to give the corresponding nitrosamines,[6] and meanwhile in acid medium, as is common with other *N*-nitrosamines, denitrosation occurs.[7] MN-4-Me-BS (diazald) is also known to transfer its nitroso group, forming nitrosyl complexes.[8]

This paper will examine the nitroso group transfer from substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (Scheme 2) (MN-4-MeO-BS, MN-4-Me-BS, MN-4-Cl-BS, MN-4-NO_2-BS) to primary and secondary amines. The use of different nitrosating agents will allow us to study not just the effect of the nucleophile but also that of the nitrosating agent on the rate of the process. The

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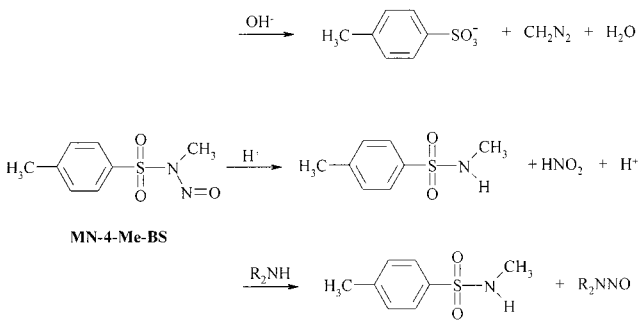
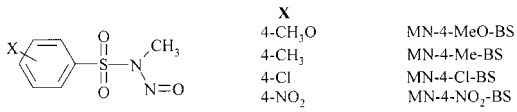
Scheme 1



Scheme 2



results obtained show that for amines with similar steric hindrance their reactivity against the substrate carriers of the nitroso group varies linearly with their basicity.

The study of the nitrosation processes of secondary amines by ONSCN and their corresponding denitrosation catalyzed by SCN^- enables us, in combination with the protonation pK_a of the nitrosamines, to define a scale for the loss of the nitroso group with regard to a protonated nitrosamine, $pK_{NO}^{R_2N^+HNO}$. This scale is similar to the basicity scale for proton-transfer reactions, $pK_a^{R_2NH_2^+}$. The reactivities of the different amines against the different nitrosating agents correlate perfectly with the calculated values of ΔpK_{NO}, a behavior pattern similar to that observed in proton-transfer reactions. The Marcus theory[9] of outer sphere electron-transfer reactions leading to the relationship between kinetic and thermodynamic barriers to chemical reaction has explained the empirical findings concerning a certain number of reaction processes including proton transfer,[10] hydride transfer,[11] or methyl transfer[12,13] reactions. This wide range of applications indicates that the Marcus theory could also be invoked to explain nitroso group transfer reactions.

Experimental Section

N-methylbenzenesulfonamides were synthesized by reaction of the corresponding benzenesulfonyl chlorides with an excess of methylamine in water. The products were extracted with dichloromethane and washed with a solution of sodium hydrogen carbonate and water. *N*-methyl-*p*-toluenesulfonamide and its nitroso derivative, MN-4-Me-BS, were supplied by Ega-chemie and Merck, respectively. *N*-methyl-*N*-nitrososulfonamides were prepared using a biphasic water/dichloromethane mixture. The aqueous phase containing sodium nitrite and the organic phase containing the parent sulfonamide were mixed together, and then concentrated perchloric acid (5 M) was slowly added. The mixture was stirred for 1 h. The organic phase was separated and washed with water, and the *N*-methyl-*N*-nitrososulfonamides were finally recrystallized from dichloromethane/petroleum ether with a final yield of 80%. This method has the advantage of preventing the hydrolysis of the nitrosoderivatives by sequestering the latter in the organic phase as soon as they are formed. The secondary and primary amines (Aldrich), pyrrolidine, piperidine, *N*-methylpiperazine, piperazine, morpholine, glycine ethyl ester, glycyl glycine, methoxyethylamine, glycine, and propylamine, were of the highest available purity and in some cases were distilled under argon and used shortly afterward.

All kinetic experiments were performed with a great excess of the nucleophile over *N*-methyl-*N*-nitrososulfonamide. The pH was controlled using buffer solutions of the nucleophile itself, which were made up of amine and perchloric acid. Because of their poor solubility in water, the *N*-methyl-*N*-nitrososulfonamides were dissolved in a small amount of organic solvent (dioxane) prior to the preparation of aqueous solutions. The final concentration of organic solvent in the medium was usually 3.3% (v/v). The reaction kinetics were generally studied by following the change in absorbance (generally in the range 250−270 nm for MN-4-MeO-BS, MN-4-Me-BS, and MN-4-Cl-BS and in the range 290−340 nm for MN-4-NO_2-BS) using an spectrophotometer fitted with thermostated cell holders (all experiments were carried out at 25 °C). The absorbance−time data always fitted the first-order integrated equation, and k_{obs}, the corresponding pseudofirst-order rate constant, could be reproduced to within 3%.

The identity of the reaction products was confirmed from the characteristics of the UV spectra of the reactions on completion and in some cases by HPLC with 1:1 acetonitrile−water as the eluant, where retention times and peak areas were compared with those of pure *N*-nitrosamines. In every case we found quantitative *N*-nitrosamine formation compatible with the spectral changes observed in kinetic experiments.

Results

1. Nitroso Group Transfer from Substituted *N*-Methyl-*N*-nitrosobenzenesulfonamides. Reactions between *N*-methyl-*N*-nitrosobenzenesulfonamides and secondary amines produce *N*-nitrosamines in quantitative yield. Plotting k_{obs} against the pH for constant total amine concentration produced sigmoid curves that could be put in linear form by plotting $1/k_{obs}$ against $[H^+]$. This behavior is in keeping with the assumption that reaction takes place directly with the basic form of the amine, without the involvement of general acid or base catalysis.[6] When k_{obs} was plotted against amine concentration, good straight lines were produced, showing that the reaction was of first order with respect to the amine (see Figure 1). The kinetic law found for the present reactions is given by eq 1

$$k_{obs} = k_{OH}[OH^-] + k_{tr}[R_2NH] \qquad (1)$$

where k_{OH} and k_{tr} (values of k_{tr} can be found in Table 1) are the rate constants for hydrolysis[5b,c] and aminolysis of the substrate. For all the reactions, the value of k_{OH} was negligible compared to the aminolysis term in eq 1. The slopes of Bronsted-type plots (statistically corrected) obtained with the log k_{tr} vs $pK_a^{R_2NH_2^+}$ values are collected in Table 1 (β_{nuc} values). The slope of Bronsted-type plots obtained with the log k_{tr} vs $pK_a^{\text{leaving group}}$ values are also reported in Table 1 (α_{1g} values), where $pK_a^{\text{leaving group}}$ refers to the substrate.

Primary amines react with *N*-methyl-*N*-nitrososulfonamides considerably more slowly than secondary amines

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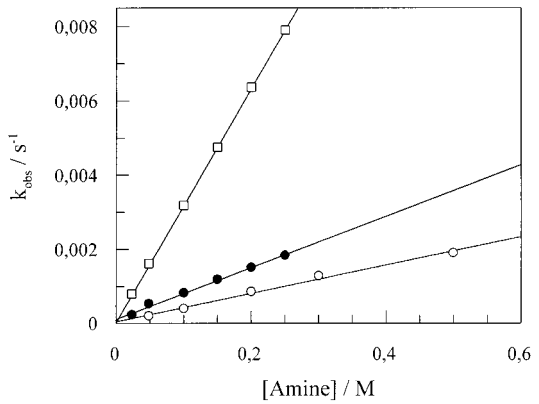

Figure 1. Plot of k_{obs} vs [amine] for nitroso group transfer from MN-4-MeO-BS to several secondary amines at 25 °C: (○) morpholine; (●) *N*-methylpiperazine; and (□) piperazine (first pK_a). [MN-4-MeO-BS] = 1×10^{-5}M, pH = $pK_a^{R_2NH_2^+}$.

of similar basicity. By applying eq 1 (see Figure 2) we can obtain k_{OH} and k_{tr} (see k_{tr} data in Table 2). The slopes of Bronsted-type plots (statistically corrected) obtained with the log k_{tr} vs $pK_a^{RNH_3^+}$ values are collated in Table 2 (β_{nuc} values). The slope of Bronsted-type plots obtained with the log k_{tr} vs $pK_a^{\text{leaving group}}$ values are also collated in Table 2 (α_{lg} values). It can be observed that the primary amines react approximately 40 times more slowly than the secondary amines of a similar basicity. Since in sterically insensitive reactions small secondary aliphatic amines are typically substantially more reactive than primary amines of equal basicity,[14] the above ratio of k_{tr} values which favors the secondary amines indicates a small steric hindrance in the transition state.

2. Nitrosation of Amines by ONSCN. For the purpose of evaluating the equilibrium constant for the nitrosation process of amines, it is necessary to find out their nitrosation and denitrosation rates. In the bibliography, a systematic study of the denitrosation of *N*-nitrosamines catalyzed by SCN^- can be found.[15] If the rate constants of the nitrosation of amines catalyzed by ONSCN can be ascertained then the equilibrium constant for the process can be evaluated.

$$R_2^+NHN{=}O + SCN^- \underset{k_{nit}^{ONSCN}}{\overset{k_{des}^{SCN}}{\rightleftharpoons}} R_2NH + ONSCN \quad (2)$$

The nitrosation of *N*-methylbenzylamine, morpholine, and piperazine has been studied in the presence of SCN^- in conditions where the concentration of $NaNO_2$ was in deficit. The influence of the SCN^- concentration on the rate of nitrosation of *N*-methylbenzylamine, morpholine, and piperazine was studied at [$HClO_4$] = 0.30M, [R_2NH] = 0.10M, and [NaSCN] ranging from 3.3×10^{-3} to 4.00 $\times 10^{-2}$ M. The pseudo-first-order rate constants, k_{obs}, were in all cases found to depend linearly on the concentration of SCN^- (see Figure 3). The following expression for k_{obs} in the amine nitrosation by ONSCN can be derived from Scheme 3.

$$k_{obs} = \frac{(k_{nit}^{NO}K_{NO^+} + k_{nit}^{ONSCN}K_{ONSCN}[SCN^-])K_a^{R_2NH_2^+}[R_2NH]_{tot}[H^+]}{K_a^{HNO_2} + [H^+](1 + K_{NO^+}[H^+] + K_{ONSCN}[H^+][SCN^-])} \quad (3)$$

Under the experimental conditions of this study this equation can be simplified[16]

$$k_{obs} = (k_{nit}^{NO}K_{NO^+} + k_{nit}^{ONSCN}K_{ONSCN}[SCN^-])K_a^{R_2NH_2^+}[R_2NH]_{tot} \quad (4)$$

The intercept at the origin in the plots of k_{obs} vs [SCN^-] (see Figure 3) corresponds with the nitrosation of the corresponding amines by NO^+. On the basis of the slopes of the plots of k_{obs} vs [SCN^-], the rate constant for nitrosation of secondary amines by ONSCN can be calculated using the value given in the bibliography[16] of $K_{ONSCN} = 30\ M^{-2}$. The values of k_{nit}^{ONSCN} obtained for the nitrosation of piperazine ($k_{nit}^{ONSCN} = 1.13 \times 10^7\ M^{-1}s^{-1}$), morpholine ($k_{nit}^{ONSCN} = 1.35 \times 10^7\ M^{-1}s^{-1}$), and *N*-methylbenzylamine ($k_{nit}^{ONSCN} = 1.40 \times 10^7\ M^{-1}s^{-1}$) agree with the value found by Williams and Meyer[16] for the nitrosation of morpholine by ONSCN.

The rate constants determined experimentally, k_{nit}^{ONSCN}, verify the Bronsted relationship (eq 5) on the basis of which the values of k_{nit}^{ONSCN} will be interpolated or extrapolated for each amine studied in the transnitrosation process.

$$\log k_{nit}^{ONSCN} = 6.919 + 2.43 \times 10^{-2}pK_a^{R_2NH_2^+} \qquad (R = 0.992) \quad (5)$$

3. Denitrosation of *N*-Nitrosamines by SCN^-. Singer[15a] studied the denitrosation of different *N*-nitrosamines in the presence of a constant concentration of SCN^-, [SCN^-] = 0.05 M. The denitrosation mechanism of nitrosamines takes place through the initial protonation of the *N*-nitrosamine and subsequent nucleophile attack on the protonated *N*-nitrosamine (slow stage) (see Scheme 4).

Under the experimental conditions the following rate equation can be deduced:

$$k_{obs} = \frac{K_T}{K_a^{R_2N^+HNO}}[H^+](k_{des}^{H_2O} + k_{des}^{SCN}[SCN]) \quad (6)$$

where $1/K_a^{R_2N^+HNO}$ corresponds with the protonation constant of the *N*-nitrosamine. *N*-nitrosamines appear to be 10^{10} less basic than the corresponding amines.[17] Until recently, there has also been considerable doubt about the site of protonation of *N*-nitrosamines, reminiscent of the controversy surrounding the protonation of amides. The best available evidence, however, now suggests that the most stable conjugate acid for *N*-nitrosamines is that which results from O-protonation[18]

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Table 1. Compilation of Rate Constants for Nitroso Group Transfer from Substituted *N*-Methyl-*N*-nitrosobenzenesulfonamides to Secondary Amines: Pyrrolidine (PYR), Piperazine (PIP), *N*-Methylpiperazine (Me-PIP), Morpholine (MOR), and Piperazine Second p$K_a^{R_2NH_2^+}$ (PIP-H$^+$)

		PYR	PIP	Me-PIP	MOR	PIP-H$^+$	
	pK_a	11.27[a]	9.82[a]	8.98[a]	8.36[a]	5.68[a]	
		k_{tr} / $M^{-1}s^{-1}$					β_{nuc}
MN-4-MeO-BS	11.7[b]	(4.79±0.09)x10^{-1}	(3.15±0.01)x10^{-2}	(6.95±0.24)x10^{-3}	(3.82±0.20)x10^{-3}	(3.04±0.12)x10^{-5}	0.70
MN-4-Me-BS	11.6[b]	(5.97±0.06)x10^{-1}	(4.90±0.15)x10^{-2}	(1.20±0.04)x10^{-2}	(8.90±0.30)x10^{-3}	(4.88±0.24)x10^{-5}	0.72
MN-4-Cl-BS	11.1[b]	1.71±0.05	(1.64±0.03)x10^{-1}	(4.99±0.09)x10^{-2}	(2.64±0.02)x10^{-2}	(1.93±0.09)x10^{-4}	0.70
MN-4-NO$_2$-BS	10.7[b]	6.0±0.3	1.09±0.03	(3.33±0.06)x10^{-1}	(1.50±0.04)x10^{-1}	(1.29±0.03)x10^{-3}	0.66
α_{lg}		-1.07	-1.5	-1.6	-1.5	-1.5	

[a] p$K_a^{R_2NH_2^+}$. [b] p$K_a^{RSO_2N(CH_3)H}$.

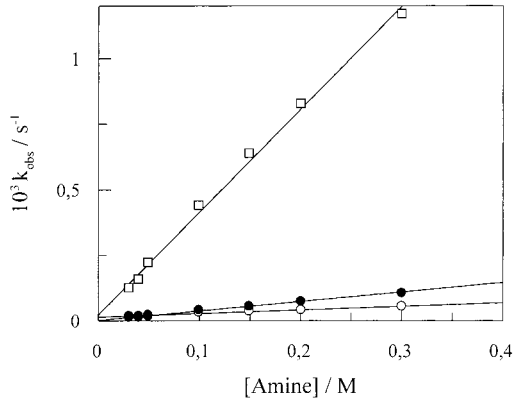

Figure 2. Plot of k_{obs} vs [amine] for nitroso group transfer from MN-4-Cl-BS to several primary amines at 25 °C: (○) glycine ethyl ester; (●) glycil glycine; and (□) methoxyethylamine. [MN-4-Cl-BS] = 1 × 10^{-5}M, pH = p$K_a^{RNH_3^+}$.

where resonance stabilization of the positive charge is feasible (**1**).

1

The alternative conjugate acids (**2**, **3**) cannot undergo

2 **3**

similar resonance stabilization, and they are expected to be of higher energy. This is supported by INDO calculations[19] as well as ^{1}H NMR studies.[20,21] However, since the formation of an N-conjugate acid (**2**) is necessary to explain N−N fission in denitrosation processes, a small amount of this species must be present in acidic media though a tautomeric equilibrium constant, K_T.

In the absence of any added nucleophiles it is believed that in aqueous solution the solvent acts as the nucleophile for the denitrosation reaction. This reaction is necessarily slower than the nucleophile catalyzed reactions. In the experimental conditions used by Singer it is shown that $k_{des}^{H_2O} \ll k_{des}^{SCN}[SCN]$ [22] in such a way that on the basis of the values of k_{obs} the product $K_T k_{des}^{SCN}$ can be obtained. A Bronsted relationship between $K_T k_{des}^{SCN}$ and p$K_a^{R_2NH_2^+}$ can be established.

$$\log(K_T k_{des}^{SCN}) = 9.357 - 1.29 pK_a^{R_2NH_2^+} \qquad (R = 0.996) \tag{7}$$

On the basis of the Bronsted relationship, the values of $K_T k_{des}^{SCN}$ for the amines used in this study can be interpolated. The calculated values for k_{nit}^{ONSCN} and $K_T k_{des}^{SCN}$ allow us to evaluate the equilibrium constant of the nitrosation/denitrosation process by ONSCN. An important question at this point is if K_T depends or not on the nature of the substituents bonded at the amino nitrogen atom. We did not find studies in the bibliography concerning this equilibrium constant for nitrosamines. However, we think that the percentage of N-protonated nitrosamine is independent of the pK_a values for protonation of the nitrosamines because no resonance effects, due to the substituents, are involved in the stabilization of the positive charge at the amine nitrogen atom of the nitrosamines used in this work.

Discussion

1. Evidence of a Concerted Mechanism. As we have seen, the denitrosation process of an *N*-nitrosamine takes place through its protonation. Next, a nucleophile attack on the N-protonated form of the nitrosamine takes place in the rate limiting step. By applying the principle of microscopic reversibility, we can conclude that the slow

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Table 2. Compilation of Rate Constants for Nitroso Group Transfer from Substituted *N*-Methyl-*N*-nitrosobenzenesulfonamides to Primary Amines: Glycine Ethyl Ester (gee), Glycyl Glycine (ggl), Methoxyethylamine ($MeOEtNH_2$), Glycine (glc), and Propylamine ($PrNH_2$)

		gee	ggl	$MeOEtNH_2$	glc	$PrNH_2$	
	pK_a	7.75[a]	8.25[a]	9.43[a]	9.78[a]	10.6[a]	
		k_{tr} / $M^{-1}s^{-1}$					β_{nuc}
MN-4-MeO-BS	11.7[b]	(2.79±0.23)x10^{-5}	(5.33±0.27)x10^{-5}	(7.25±0.13)x10^{-4}	(8.62±0.26)x10^{-4}	(4.27±0.07)x10^{-3}	0.78
MN-4-Me-BS	11.6[b]	------	5.30x10^{-5}	-----	8.94x10^{-4}	9.16x10^{-3}	0.93
MN-4-Cl-BS	11.1[b]	(1.37±0.05)x10^{-4}	(3.60±0.07)x10^{-4}	(3.9±0.1)x10^{-3}	(3.44±0.16)x10^{-3}	(1.92±0.03)x10^{-2}	0.74
MN-4-NO_2-BS	10.7[b]	(3.4±0.3)x10^{-3}	(6.95±0.28)x10^{-3}	(2.24±0.05)x10^{-2}	(3.36±0.09)x10^{-2}	(1.00±0.01)x10^{-1}	0.50
α_{lg}		-2.0±0.6	-2.1±0.3	-1.5±0.2	-1.6±0.3	-1.2±0.2	

[a] $pK_a^{RNH_3^+}$. [b] $pK_a^{RSO_2N(CH_3)H}$.

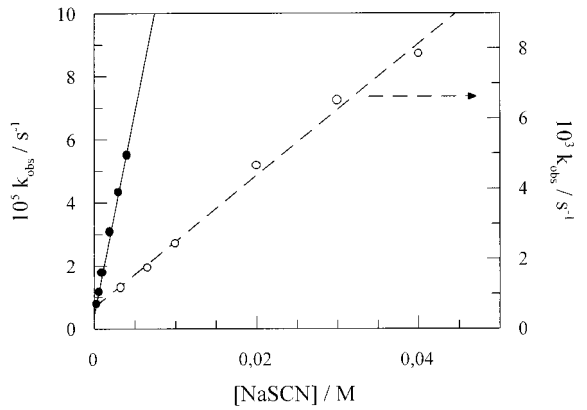
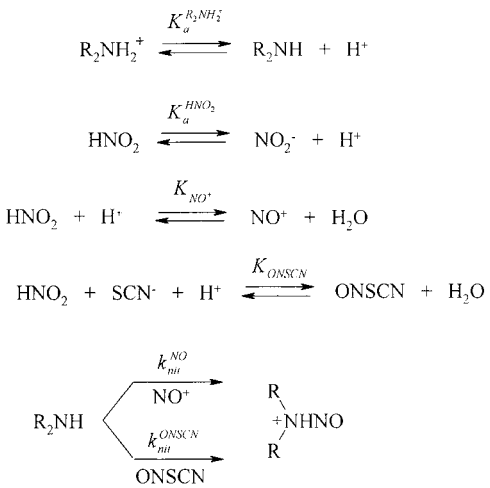


Figure 3. Plot of k_{obs} vs [NaSCN] for nitrosation of (○) morpholine and (●) *N*-methylbencylamine at 25 °C and ionic strength 0.50 M ($NaClO_4$). [Amine] = 0.10 M, [$HClO_4$] = 0.30M.

Scheme 3



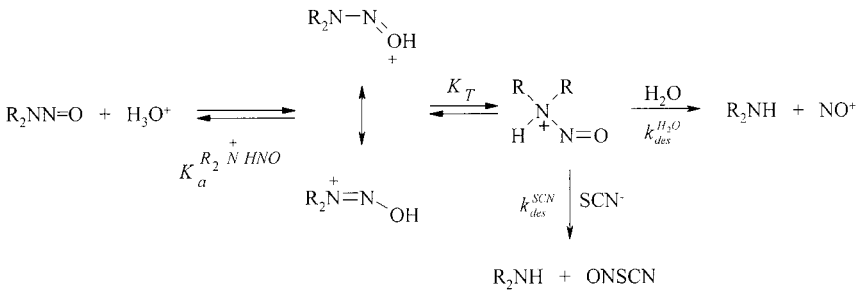
stage involved in the nitroso group transfer from substituted *N*-methyl-*N*-nitrososulfonamides to amines must be the reverse of the denitrosation of *N*-nitrosamines. This behavior is evidenced by the fact that the direct nitrosation of nucleophiles by nitrosamines (denitrosation) is clearly established[15] but is limited to fairly powerful nucleophiles and also to nonbasic nucleophiles because of the fairly strong acid concentrations required.[22]

We can propose the following mechanistic scheme (Scheme 5) for the nitroso group transfer from *N*-methyl-*N*-nitrososulfonamides to amines. The first step is the rate limiting one. In this step, the nitroso group transfer from *N*-methyl-*N*-nitrososulfonamide to the amine takes place. Subsequently in fast stages the protonation of the anion of the sulfonamide will take place (depending on the experimental pH value) and the deprotonation of the *N*-nitrosamine. These processes should not be included in the rate-determining step, since the inverse nitroso group transfer process from the *N*-nitrosamine to any nucleophile must occur through the protonated form of the *N*-nitrosamine. In addition, in a previous study[6] we investigated the kinetic solvent isotope effect on the nitroso group transfer from MN-4-Me-BS to different primary, secondary, and tertiary amines. We can assume that nitroso group transfer from *N*-methyl-*N*-nitrososulfonamides involves a mechanism in which the leaving group is not aided by any kind of proton transfer. This assumption is supported by the isotope effects close to unity for primary, secondary, and tertiary amines and for the azide ion and rules out proton transfer from either the amine or the solvent in the rate-controlling step.

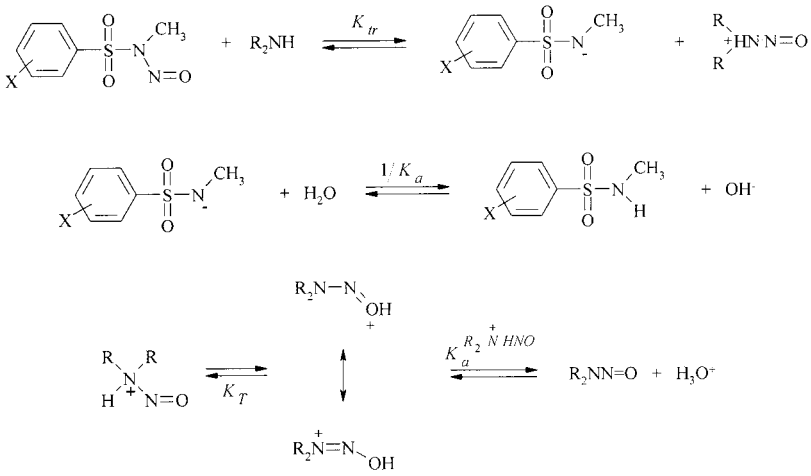
There exist at least two possible mechanisms for the nitroso group transfer. One is a mechanism of the addition−elimination type and another involves a direct (concerted) displacement of the N═O group as in the case of the basic hydrolysis of alkyl nitrites.[23] Williams[24] and Jencks[25] have applied a methodology considering that if it can be predicted that a change in the rate-limiting step for a putative stepwise mechanism (Scheme 6) will occur with a given range of substituents, then the absence of a break at the predicted point in a linear free energy relationship is evidence of a single-step mechanism. Plots of log k_{tr} *vs* $\Delta pK_a = pK_a^{Nucleophile} - pK_a^{lg}$ obey an excellent Bronsted rate law (not shown). There were no cases of breaks in the correlation at the point of $\Delta pK_a = 0$.

(23) Oae, S.; Asai, N.; Fujimori, K. *J. Chem. Soc., Perkin Trans. 2* **1978**, 571.
(24) (a) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387. (b) Williams, A. *Adv. Phys. Org. Chem.* **1992**, *27*, 1.
(25) Jencks, W. P. *Bull. Soc. Chim. Fr.* **1988**, 218.

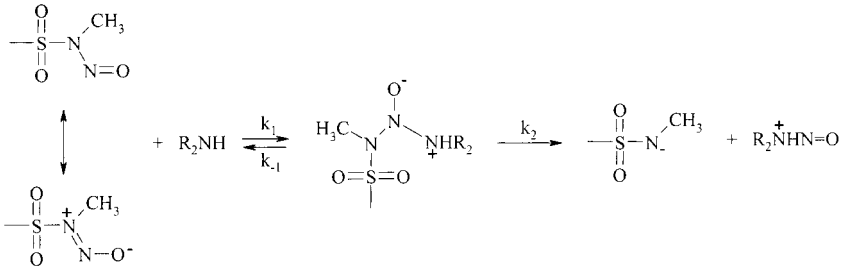
Scheme 4



Scheme 5



Scheme 6



However, the leaving groups from the hypothetical intermediate in the reverse direction (nucleophile) are structurally not the same as those in the forward direction. So application of this methodology is inconclusive in our study.

Bronsted slopes reported in Tables 1 and 2 are dramatically large. A possible explanation is that the denitrosation reaction involves a two unit change in charge at the sulfonamide nitrogen, from positive in the nitroso compound ($Ar-SO_2-N(CH_3)^{+}=N-O^{-}$) to negative in the product ($Ar-SO_2-N(CH_3)^{-}$). With a change of charge of two units in the reaction vs only one in the reference reaction (the acid dissociation), these values become reasonable. This change of charge of two units is only compatible with a concerted mechanism for nitroso group transfer, so the stepwise mechanism shown in Scheme 6 can be ruled out. The existence of a concerted mechanism for the nitroso group transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides to amines agrees with the results obtained for the nitrosation of amines by alkyl nitrites in an aqueous medium[6] and for the basic hydrolysis of alkyl nitrites.[23] The fact that nitrogen is more electronegative than carbon and has a lone pair probably explains the significant differences between the chemistry of alkyl nitrites or *N*-methyl-*N*-nitrosobenzenesulfonamides and the chemistry of carboxylic esters: carboxyl chemistry is dominated by the formation of tetrahedral intermediates, whereas it is assumed that nitroso compounds transfer the N=O group intact in water.

2. Evaluation of Equilibrium Constants. The attack of primary and secondary amines on substituted *N*-methyl-*N*-nitrosobenzenesulfonamides has a simple Bronsted type dependence on the pK_a of the corresponding amine (β_{nuc} values can be obtained from Tables 1 and 2). To carry out a rigorous interpretation of the Bronsted exponents with the aim of characterizing the structure of the transition state, it is necessary to normalize β_{nuc} and α_{lg} through the values of β_{eq}. In the nitroso group transfer reactions under investigation here, the equilibrium is displaced toward the formation of the *N*-nitrosamine to such an extent that it is not possible to determine it experimentally. However, the equilibrium constant of the transfer process can be evaluated indirectly through the equilibrium constants for the nitrosation/denitrosation of the corresponding *N*-nitrosamines and *N*-methyl-*N*-nitrosobenzenesulfonamides.

Scheme 7

$$R_2\overset{+}{N}HN{=}O + SCN^- \underset{k_{nit}^{ONSCN}}{\overset{k_{des}^{SCN}}{\rightleftharpoons}} R_2NH + ONSCN \quad K_2$$

$$HNO_2 + H^+ + SCN^- \rightleftharpoons ONSCN \quad K_{ONSCN}$$

$$HNO_2 + H^+ \rightleftharpoons NO^+ \quad K_{NO^+}$$

Hypothetical liberation equilibrium of the nitroso group on the basis of a protonated *N*-nitrosamine can be written as

$$R_2{}^+NHN{=}O \overset{K_{NO}^{R_2N^+HNO}}{\rightleftharpoons} R_2NH + NO^+ \qquad (8)$$

on the basis of which and by analogy with proton-transfer equilibria, we can write $pK_{NO}^{R_2N^+HNO} = -\log K_{NO}^{R_2N^+HNO}$.

The difficulty in estimating the value of the tautomerization constant between nitrosamine O-protonated and N-protonated, K_T, means that on the basis of the Brønsted correlations, eq 5 and eq 7, we obtain a value for the equilibrium constant, $K_2^{exp} = K_T k_{des}^{SCN}/k_{nit}^{ONSCN}$, which corresponds with the quotient $K_2^{exp} = K_T K_2$ ($K_2 = k_{des}^{SCN}/k_{nit}^{ONSCN}$). The combination of the following equilibria (Scheme 7) gives us an expression for $K_{NO}^{R_2N^+HNO}$:

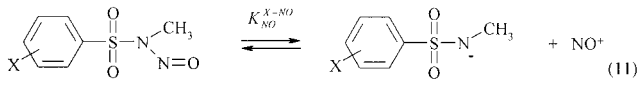
$$K_{NO}^{R_2N^+HNO} = \frac{K_2 K_{NO^+}}{K_{ONSCN}} \qquad (9)$$

from which we obtain

$$K_T K_{NO}^{R_2N^+HNO} = \frac{K_2^{exp} K_{NO^+}}{K_{ONSCN}} \qquad (10)$$

When the values given in the bibliography[16,22] for K_{NO^+}, $K_{NO^+} = 3.5 \times 10^{-7}M^{-1}$ and K_{ONSCN}, $K_{ONSCN} = 30M^{-2}$ are used, the values of $K_T K_{NO}^{R_2N^+HNO}$ presented in Table 3 can be calculated.

By analogy we can define the equilibrium constant for the loss of the nitroso group from an *N*-methyl-*N*-nitrosobenzenesulfonamide with formation of its anion, K_{NO}^{X-NO}.



(11)

This equilibrium constant can easily be calculated from the values of the equilibrium constant for the nitrosation/denitrosation of the sulfonamides,[7b] K_3, and the acidity constant of the *N*-methylbenzenesulfonamides,[5c] K_a (Scheme 8).

$$K_{NO}^{X-NO} = K_3 K_a \qquad (12)$$

Table 3 shows the calculated values of pK_{NO}^{X-NO} for the substituted *N*-methyl-*N*-nitrosobenzenesulfonamides.

The results show that the most basic amines (or sulfonamides) produce the most stable *N*-nitrosocompounds. The stability of the *N*-nitrosamines according to the basicity of the corresponding amines had already been made clear by studying the nitroso group transfer in acid medium from an *N*-nitrosamine to another amine.[15a,b,26] The structure and stereochemistry of *N*-nitrosamines should reflect extensive delocalization of the amino nitrogen lone-pair electrons into the π-system of the N=O group. Electron diffraction studies[27] show that N−N and N−O bond orders are ca. 1.5, implying a structure intermediate between the following valence structures **4**.

4

Independent evidence for considerable charge development in the ground state comes from dipole moments for aliphatic *N*-nitrosamines.[28] As the basicity of the amine increases, there will also be an increase in the stability of the resonant form with a positive charge on the nitrogen atom and consequently the stability of the *N*-nitrosamine will increase.[29]

The use of the values of $pK_{NO}^{R_2N^+HNO}$ and pK_{NO}^{X-NO} enables us to evaluate the equilibrium constant,[30] $K_{tr}K_T$, for the rate-limiting step of the nitroso group transfer (Scheme 5) as $\log(K_{tr}K_T) = pK_{NO}^{R_2N^+HNO} - K_{NO}^{X-NO} = \Delta pK_{NO}$ (values in Table 3).

As we can observe in Table 3, the equilibrium constant corresponding with the nitroso group transfer process depends on the value of the tautomerization constant K_T. This constant has not been determined experimentally but its value is considered to be $K_T < 5\%$.[17] If we assume an arbitrary value of $K_T = 0.01$, then the values of the equilibrium constant K_{tr} would be 2 logarithmic units bigger than those shown in Table 3.[31] Even with these values of K_{tr}, we would observe that the nitroso group transfer process would not be thermodynamically favorable and should lead to a mixture of equilibrium between the *N*-nitrosamine and the *N*-nitrososulfonamide. However, in stages after the slow step, the deprotonation of the protonated *N*-nitrosamine should occur, and this process should take place at a rate controlled by diffusion of the reagents, as is usual for proton transfers between nitrogen and oxygen atoms. Once the *N*-nitrosamine is formed, it will not revert to products reacting with sulfonamide. A simple evaluation of the $pK_{NO}^{R_2NNO}$ corresponding to the unprotonated *N*-nitrosamine shows that the latter should be approximately 35 units greater than the corresponding ($pK_{NO}^{R_2N^+HNO} - \log K_T$).[33]

(26) Meyer, T. A.; Williams, D. L. H.; Bonnett, R.; Ooi, S. L. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1383.

(27) Rademacher, P.; Stolevik, R. *Acta Chem. Scand.* **1969**, *23*, 660.

(28) (a) Cowley, E.; Partington, J. *J. Chem. Soc.* **1933**, 1255. (b) George, M.; Wright, G. *J. Am. Chem. Soc.* **1958**, *80*, 1200. (c) Hall, P. G.; Horsfall, G. S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1280.

(29) If K_T is strongly dependent on the protonation pK_a of the nitrosamines, then calculated values of $pK_{NO}^{R_2N^+HNO} - \log K_T$ (Table 3) should yield $pK_{NO}^{R_2N^+HNO}$ values that are independent of the basicity of the parent amine. These values should be incompatible with experimental studies of nitroso group transfer in acid medium from an *N*-nitrosamine to another amine.

(30) K_{tr} is the equilibrium constant for the rate limiting step. The problem is that as a consequence of the equilibrium constant of tautomerization between the O-protonated and N-protonated nitrosamine, only $K_{tr}K_T$ is available from the analysis.

(31) A reviewer suggested to use a K_T value of $K_T = 10^{-7}$ by analogy with Fersht's result for simple carboxamides (see ref 32). Using $K_T = 10^{-7}$ yields a diffusion control value of k_{des}^{SCN} for *N*-nitroso-*O*,*N*-dimethylhydroxylamine ($pK_a^{R_2NH_2^+} = 4.72$ in water from ref 15b) (see eq 7) that is not in agreement with the experimental evidence, suggesting that K_T should be smaller that 10^{-7}.

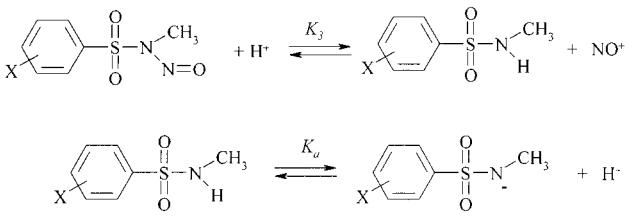
(32) Fersht, A. R. *J. Am. Chem. Soc.* **1971**, *93*, 3504.

Table 3. Compilation of Equilibrium Constants for Nitroso Group Transfer from *N*-Methyl-*N*-nitrosobenzenesulfonamides to Secondary Amines

		PIRR	PIP	MePIP	MOR	PIP-H$^+$	
	pK_{NO}	20.31[a]	18.40[a]	17.30[a]	16.48[a]	12.96[a]	
		$\Delta pK_{NO} = \log K_{tr} + \log K_T$					β_{nucl}^{norm}
MN-4-MeO-BS	20.12	0.19	-1.72	-2.82	-3.64	-7.16	0.56±0.02
MN-4-Me-BS	19.83	0.48	-1.43	-2.53	-3.35	-6.87	0.55±0.03
MN-4-Cl-BS	18.83	1.48	-0.43	-1.53	-2.35	-5.87	0.53±0.02
MN-4-NO$_2$-BS	17.55	2.76	0.85	-0.25	-1.07	-4.59	0.50±0.03
α_{lg}^{norm}		0.43±0.01	0.59±0.02	0.64±0.01	0.59±0.05	0.63±0.01	

[a] For *N*-nitrosamines we obtain $pK_{NO}^{R_2N^+HNO} - \log K_T$.

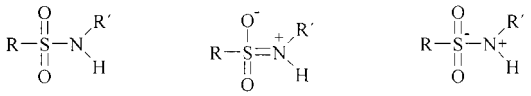
Scheme 8



3. Characterization of the Transition State. The values of the equilibrium constant for the rate-limiting step in the nitroso group transfer, K_TK_{tr}, enable us to represent the log k_{tr} vs $\log(K_{tr}K_T) = \Delta pK_{NO}$ for the nitrosation of an amine by the different *N*-methyl-*N*-nitrosobenzenesulfonamides. From these plots we can obtain the values of α_{lg}^{norm}, which can be considered a measurement of the charge development on the nitrogen atom of the nitrososulfonamide. An equivalent representation of log k_{tr} vs $\log(K_{tr}K_T) = \Delta pK_{NO}$ for the nitrosation of the different amines for each *N*-nitrososulfonamide enables us to obtain β_{nucl}^{norm}. Table 3 shows the values of β_{nucl}^{norm} and α_{lg}^{norm}. It can be seen that both values remain virtually constant despite variation in both the amine and the nature of the nitrosating agent.[34]

The transition state of the majority of chemical reactions has the potential for being imbalanced. In fact, whenever there is more than one process involved in a reaction, there will be an imbalance if these processes have developed nonsynchronously at the transition state.[35] The results obtained for the nitroso group transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides to amines show that $\beta_{nucl}^{norm} - \alpha_{lg}^{norm} \cong 0$. This result indicates that the transition state is closely balanced. It implies that the amount of charge lost by the amine (β_{nucl}^{norm}) is the same amount of charge received by the sulfonamide (α_{lg}^{norm}). Usually, the size of the transition-state imbalance measured by $\alpha_{CH} - \beta_B$ is considered to correlate with the degree of charge stabilization by resonance. Therefore, the balanced nature of the transition state has significant repercussions on the stabilization of the negative charge of the anionic form of the sulfonamide.

4. Stabilization of the Nitrogen Negative Charge by the α-Sulfonyl Group. The mechanism by which carbanion stabilization by sulfur occurs has generated great interest;[36] in particular, α-sulfonyl carbanions have long been a widely debated subject.[37] The sulfonamides are apparently similar to the amides, but the sulfonyl group, unlike the carbonyl group, does not seem to have a capacity for delocalizing the electron pair of the nitrogen. Various studies carried out involving sulfonamides[38,39,40] point out that the **6** structure has an



5 **6** **7**

insignificant contribution in its stabilization. The absence of any significant stabilization by resonance is probably due to the fact that the d orbitals of the sulfur act like a "plug" for the p−π electrons donated by the nitrogen. The effect of the sulfonyl group must be fundamentally inductive. In any case, we cannot discard any influence of the resonant form **7**, resulting from the delocalization of the negative charge in the 3d orbitals of the sulfur (not involved in the sulfur−oxygen bond[39,41,42]).

(33) $pK_{NO}^{R_2NNO}$ values can be obtained as $pK_{NO}^{R_2NNO} = pK_{NO}^{R_2N^+HNO} + p K_a^{R_2NH} - pK_a^{R_2N^+HNO}$, where typical values of $pK_a^{R_2NH}$ and $pK_a^{R_2^+HNO}$ are 35 and 0, respectively. So, typical $pK_{NO}^{R_2NNO}$ values should be approximately 35 units larger than ($pK_{NO}^{R_2N^+HNO} - \log K_T$) (values in Table 3).

(34) α_{lg}^{norm} and β_{nucl}^{norm} values in Table 3 are not compatible with K_T being very dependent on protonation pK_a of the nitrosamines.

(35) (a) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9. (c) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301.

(36) Bernasconi, C. F.; Kittredge, K. W. *J. Org. Chem.* **1998**, *63*, 1944.

(37) Terrier, F.; Kizilian, E.; Goumont, R.; Faucher, N.; Wakselman, C. *J. Am. Chem. Soc.* **1998**, *120*, 9496 and references therein.

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(42) Hovius, K.; Zuidema, G.; Engberts, J. B. F. N. *Recl. Trav. Chim.* **1971**, *90*, 633.

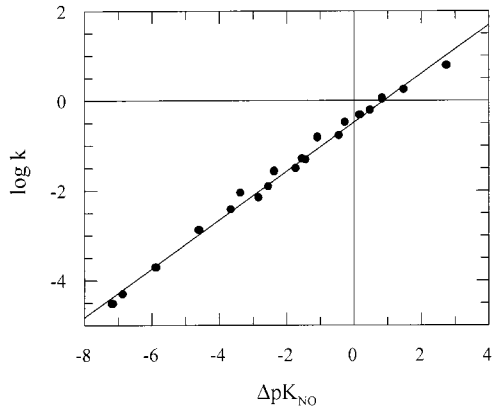

Figure 4. Plot of log k_{tr} vs ΔpK_{NO} for nitroso group transfer from substituted *N*-methyl-*N*-nitrosobencenesulfonamides to secondary amines. See text for ΔpK_{NO} evaluation.

Recently Bernasconi and Kittredge[36] have researched the stabilization of carbanions in α to sulfur atoms by using an approach that combines kinetic and thermodynamic data. It is based on the assumption that the kind of factors that potentially stabilize the transition state of the deprotonation of a carbon acid are the same as those that potentially stabilize the carbanion, i.e., polarizability, d−p π-bonding, negative hyperconjugation, and possibly others. It makes use of the fact that typically the relative importance of these factors in stabilizing the transition state is not the same as in stabilizing the carbanion. As has been amply demonstrated,[35] the transition state of the deprotonation of carbon acids activated by π-acceptors is imbalanced, in the sense that $sp^3 \rightarrow sp^2$ rehybridization of the α-carbon and charge delocalization into the π-acceptor group lag behind proton transfer. In short, the reason for this lag is that the degree of charge delocalization into the π-acceptor group (Y) is coupled with the degree of C−Y bond formation which in turn depends on the fraction of charge that has been transferred from the base to the carbon acid. Since neither C−Y π-bond formation nor charge transfer are complete at the transition state, the charge delocalized into the Y group is just a fraction of a fraction and is therefore quite small.[35,43]

The stabilization by resonance of the negative charge in α at the sulfonyl group would give rise to an imbalanced transition state during the nitroso group transfer process. The results given previously show that $\beta_{nucl}^{norm} - \alpha_{lg}^{norm} \cong 0$, suggesting that the charge development on the nitrogen atom in α at the sulfonyl group is similar to that which exists on the aminic nitrogen. This result is contrary to what would be expected if the transition state was stabilized by a resonance effect, and it appears clearly that stabilization of a negative charge by the electron-withdrawing SO_2 group must be the result of polarization effects rather than of conjugative dπ−pπ bonding or negative hyperconjugation.

5. Rate−Equilibrium Relationships for Nitroso Group Transfer. Logarithmic plots of the statistically corrected rate constants for proton transfer reactions against the statistically corrected ionization constants of the acids are the most usual type of representation, enabling us to obtain information about these processes. Figure 4, drawn up using the data from Tables 1 and 3, shows an Eigen type plot of the statistically corrected rate constants for nitroso group transfer between secondary amines and *N*-methyl-*N*-nitrososulfonamides, $\log(k_{tr}/p)$, against $\Delta pK_{NO} = \log K_{tr} + \log K_T$. The good linear correlation is maintained with a slope of 0.54 ± 0.01. Therefore, approximately 55% of the substituent effect on the equilibrium constant (K_{tr}) for formation of the *N*-nitrosamine is expressed in the rate constant for its formation (k_{tr}). The results shown in Figure 4 do not show any type of deviation from the linearity. The linearity of this empirical rate−equilibrium correlation, which spanned a range of 10 pK_{NO} units and included both thermodynamically favorable and unfavorable reactions, stands in sharp contrast with the reports of changes in Bronsted exponents for a wide range of proton-transfer reactions from carbon acids.[44,45,46]

There are a great many examples of rate−equilibrium relationships where no curvature can be detected. Recently Amyes and Richard have measured rates of proton abstraction by hydroxide from ethyl acetate[47] and ethyl thiolacetate.[48] In combination with previously measured rates of proton abstraction from simple aldehydes and ketones;[49] these results lead to a linear Bronsted plot extending over 14 log units in equilibrium and 5 log units in rate. This extended linearity is not consistent with a constant Marcus intrinsic barrier but could be interpreted in terms of varying intrinsic barriers. Recently Page et al.[50] have extended a rate−equilibrium correlation for proton transfer to a hydroxide ion from carbon acids activated by a mono carbonyl group. The linearity of this Bronsted relationship now spans 19 pK_a units and covers proton transfers in both thermodynamically favorable and unfavorable directions.

The Marcus theory[9,10] basically predicts nonlinear free energy relationships because of its quadratic form.

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + \frac{\Delta G^0}{2} + \frac{\Delta G^{0^2}}{16\Delta G_0^{\ddagger}} \qquad (13)$$

where $\Delta G^{\ddagger}$ is the free energy of activation for reaction of a given ΔG^0, the free energy change for the process, and $\Delta G_0^{\ddagger}$ is the "intrinsic barrier" corresponding to the free energy of activation when ΔG^0 is zero. In the case of proton transfer, ΔG^0 is given by the difference in pK_a between the proton donor and acceptor. The same formalism can be applied for nitroso group transfer reactions. In our case, ΔG^0 is given by the difference in pK_{NO} between the nitroso group donor and acceptor. From the previous equations, we can also obtain a value of α for the transition state.

$$\alpha = \frac{\partial \Delta G^{\ddagger}}{\partial \Delta G^0} = \frac{1}{2}\left(1 + \frac{\Delta G^0}{4\Delta G_0^{\ddagger}}\right) \qquad (14)$$

From this equation we can see that when the thermodynamics of the system, ΔG^0, are roughly in balance

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(46) Argile, A.; Carey, A. R. E.; Fukata, G.; Harcourt, M.; More-O'Ferrall, R. A.; Murphy, M. G. *Isr. J. Chem.* **1985**, 26, 303.
(47) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129.
(48) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 10297.
(49) Keefe, J. R.; Kresge, A. J. Kinetics and mechanism of enolization and ketonization. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; pp 399−480.
(50) Heathcote, D. M.; Atherton, J. H.; De Boos, G. A.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 541.

Table 4. Values of log k_0 − slope log K_T for Nitroso Group Transfer from *N*-Methyl-*N*-nitrosobenzenesulfonamides to Secondary Amines

substrate	log k_0 − slope log K_T	σ
MN-4-MeO-BS	−0.47 ± 0.07	−0.27
MN-4-Me-BS	−0.46 ± 0.1	−0.17
MN-4-Cl-BS	−0.50 ± 0.02	0.23
MN-4-NO_2-BS	−0.44 ± 0.07	0.78

compared to the kinetic barrier $\Delta G_0^{\ddagger}$, then the transition state is symmetrical, with α approximately equal to $^1/_2$. On the other hand, if the thermodynamics are favorable to the reaction, $\Delta G^0 < 0$, then α will be less than $^1/_2$ and the transition state will be reactant like. Conversely, if the reaction is thermodynamically uphill, then α is greater than $^1/_2$ and the transition state is product like. When a linear free energy relationship gives a constant Bronsted exponent, i.e., it is not curved over a range of free energies for the reaction, then the simplest interpretation is that the transition state structure is "constant". Within the context of the Marcus theory, linearity can be attributed to either a large intrinsic barrier or to a variable intrinsic barrier which changes with ΔG^0.[51]

For an elementary reaction, the intrinsic barrier is generally defined as $\Delta G_0^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ when $\Delta G^0 = 0$ and the intrinsic rate constant as $k_0 = k_1 = k_{-1}$ when $K_1 = k_1/k_{-1} = 1$. The concept of the "intrinsic barrier" was introduced by Marcus[9,10] and is currently considered to be a parameter with more physical meaning than the "current" reaction barrier because it is a purely kinetic parameter of a reaction and is independent of its thermodynamic driving force. In other words, it is, at least in principle, a parameter that describes the reactivity of a group of series of reactions independently of the thermodynamics of a particular member of the series.

Table 4 shows the intrinsic rate constants (log k_0) for the nitroso group transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides to secondary amines. The sum[52] log k_0 − *slope* log K_T is obtained because of the tautomerization constant between the O-protonated and the N-protonated nitrosamine. The values of log k_0 − *slope* log K_T were interpolated or extrapolated from the plots of log k_{tr} vs ΔpK_{NO} for $\Delta pK_{NO} = 0$. As we can see, the values of the intrinsic rate constants for the nitroso group transfer from substituted *N*-methyl-*N*-nitrosobenzenesulfonamides to secondary amines do not vary with the substituents of the aromatic ring of the sulfonamide, and a mean value of log k_0 − *slope* log $K_T = -0.48 \pm 0.04$ can be assumed.

The concept of intrinsic barriers has become a cornerstone in the epistemology of physical organic chemistry, as may be witnessed by the recent important applications of this concept for a variety of chemical reactions. Intrinsic barriers are used mainly as means of understanding reactivity trends in nonidentity reactions. In the framework of the valence bond configuration mixing model (VBCM),[53] the intrinsic barrier in S_N2 reactions is determined by the vertical electron-transfer energy and by the "extra delocalization" properties of the charge transfer states. The constancy of the values of log k_0 − *slope* log K_T when the substituents vary on the aromatic ring is consistent with a balanced transition state and suggests that the electron density on the nitrogen atom of the sulfonamide remains practically constant.

Conclusions

On the basis of this study the following results are particularly worthy of note: (1.) The results obtained have shown that the nitroso group transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides to amines takes place directly via a concerted mechanism. The calculation of the equilibrium constants for these processes has enabled us to quantify the charge development on the nucleophile and leaving group in the transition state of the reaction. The results obtained show that the transition state is perfectly synchronic, which by applying the methodology recently developed by Bernasconi and Kittredge[36] enables us to show that the sulfonyl group does not participate in the establishment by resonance of the negative charge situated on the nitrogen atom in position α. (2.) The establishment of a rate−equilibrium relationship for nitroso group transfer has enabled us to carry out a quantitive explanation of the reactivity observed in a similar way to the proton-transfer reactions. The absence of curvature in the rate−equilibrium correlation has been interpreted in terms of the Marcus theory of electron transfer applied to nitroso group transfer reactions. (3.) The study of the nitroso group transfer from substituted *N*-methyl-*N*-nitroso-benzenesulfonamides to amines shows that the rate of the process is accelerated by the presence of substituents which withdraw charge. This result is chiefly due to the greater thermodynamic conductive force of the reaction. Hence, the intrinsic reactivities of the nitrososulfonamides remain practically constant.

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(52) *Slope* refers to the line in Figure 4, with a numerical value of 0.54 ± 0.01.

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