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Nitroso group transfer from *N*-nitrososulfonamides to thiolate ions. Intrinsic reactivity

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Abstract—The nitroso group transfer from *N*-nitrososulfonamides to thiolate ions was studied. Based on the results, the reaction rate is strongly dependent on the nature of the leaving group $\left(\alpha_{lg} \approx -1.30\right)$, but virtually independent of the basicity of the thiol $(\beta_{nuc} \approx 0.10)$. This dependence is ascribed to the presence of a nucleophile desolvation equilibrium (β_d) that is followed by the attack of the thiolate ion on the nitroso group $\left(\beta'_{nuc}\right)$ via a concerted mechanism. The equilibrium constants for the loss of a nitroso group from a nitrosothiol and an *N*-nitrososulfonamide were used to obtain the equilibrium constants for the different reactions involved. By using rate–equilibrium correlations, the parameters α_{lg}^{norm}, β_d, and $\beta_{nuc}^{\prime norm}$ were obtained.

1. Introduction

The physiological properties of NO,[1,2] particularly those of vasodilation[3] and of the inhibition of platelet aggregation,[4] can explain the enormous interest aroused by the chemistry of *S*-nitrosothiols (RSNO) in the last few years. They have also been identified as bodily fluids, notably as *S*-nitrosoglutathione[5] and *S*-nitrosoalbumins.[6] Indeed, the current belief[7] is that NO is transported around the body as RSNO (mostly as the nitrosoalbumins), from which NO can be released under certain conditions.

S-Nitrosothiols are very readily generated in solution by conventional nitrosation of thiols, and examples have been known for about a 100 years.[8] Nitrosation of thiols has been examined mechanistically and follows the pattern of amine nitrosation, in which both acid- and halide ion-catalysis occur.[9] In contrast with the corresponding nitrosation of alcohols by sodium nitrite in mildly acidic solution, the equilibrium position corresponding to thiol nitrosation lies well over the right, with equilibrium constant[10] of 10^5–$10^6\ M^{-1}$. *S*-Nitrosothiols can also be obtained in a neutral or alkaline medium via transnitrosation, the nitroso group being transferred from an NO group donor to a suitable acceptor. One well-known example is the nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide to cysteine.[11]

Recently, our group[12] calculated the equilibrium constants for the loss of an NO^+ group from a protonated *N*-nitrosamine $(pK_{NO}^{R_2NH^+NO})$ and an *N*-methyl-*N*-nitrosobenzenesulfonamide (pK_{NO}^{X-NO}). The relation $\Delta pK_{NO} = pK_{NO}^{R_2NH^+NO} - pK_{NO}^{X-NO}$ allows one to calculate the equilibrium constant for the transfer of a nitroso group from an *N*-nitrososulfonamide to an amine. In fact, this allowed us to derive a single rate–equilibrium correlation spanning a range of 10 pK_{NO} units and including both thermodynamically favorable and unfavorable reactions. In the light of the Marcus theory, the calculated intrinsic barriers for nitroso group transfer reactions reveal that the presence of electron-withdrawing groups on the aromatic ring of *N*-methyl-*N*-nitrosobenzenesulfonamide does not alter such barriers.

The purpose of this work was to expand a previous treatment of the nitroso group transfer from an N–N=O donor to an acceptor sulfur atom. To this end, we studied the nitroso group transfer from *N*-nitrososulfonamides to thiols (Scheme 1). The *N*-nitrososulfonamides used borne substituents of variable electron-releasing ability on their aromatic rings. The thiols used [viz. methyl thioglycolate (MTG), methylmercaptopropionate (MMP), mercaptoethanol (ME), and ethanothiol (EtSH)] were chosen on the grounds of their basicity.

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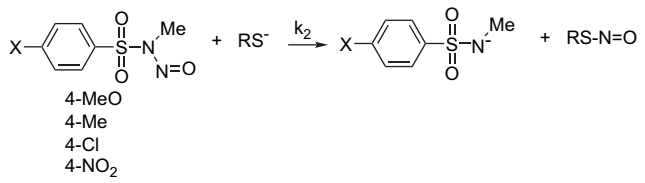


Scheme 1.

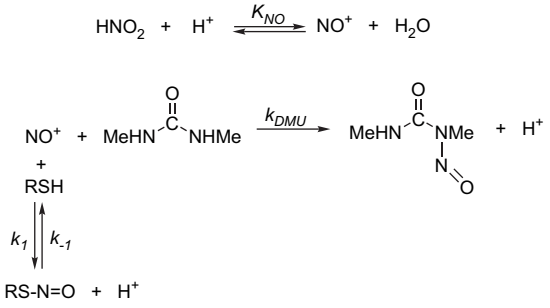
2. Results

Previous studies revealed that the formation of nitrosothiols by nitroso group transfer occurs via the basic form of the thiol.[11] Figure 1 illustrates the good linear relationship between the observed rate constant and the thiolate concentration (reaction showed in Scheme 1) in the nitrosation of mercaptoethanol:

$$k_{obs} = k_2[RS^-] \quad (1)$$

The slopes of the plots of Figure 1 were used to calculate the bimolecular rate constants shown in Table 1. From such rate constants and the pK_a values for the corresponding thiols and sulfonamides, we calculated parameters β_{nuc} and α_{lg}, which are also shown in Table 1. As can be seen, the bimolecular rate constants increased very slightly with increase in nucleophile basicity ($\beta_{nuc} < 0.1$); on the other hand, the nature of the leaving group was much more influential than the corresponding deprotonation equilibria ($|\alpha_{lg}| > 1$). Accurately interpreting these values in quantitative terms requires their normalization with respect to the corresponding equilibrium process.

As noted earlier, the equilibrium constants for the formation of nitrosothiols from the parent thiols and NO^+ were very high (10^5–10^6 M^{-1}) and difficult to quantify owing the instability of the products. In this work, we used an alternative approach based on the nitrosation of 1,3-dimethyl urea in an acid medium containing variable concentrations of the thiol (see Scheme 2).



Scheme 2.

Kinetic experiments were performed at a constant sodium nitrite concentration (1.00×10^{-4} M), [DMU]=5.00×10^{-3} M, [$HClO_4$]=0.50 M and an ionic strength ($NaClO_4$) of 1.00 M. As can be seen in Figure 2, the observed rate constant increased with increasing thiol concentration. The linear increase in k_{obs} was the result of two simultaneous, competitive processes, namely, the nitrosation of DMU[13] and that of the thiol.[14] Based on the nitrosation mechanisms for DMU and thiols in an acid medium, the observed rate constant can be expressed as

$$k_{obs} = k_{DMU}K_{NO}[H^+][DMU] + k_1K_{NO}[RSH][H^+] + k_{-1}[H^+] \quad (2)$$

where k_{DMU} is the bimolecular rate constant for the nitrosation of dimethyl urea, and k_1 and k_{-1} are the formation and

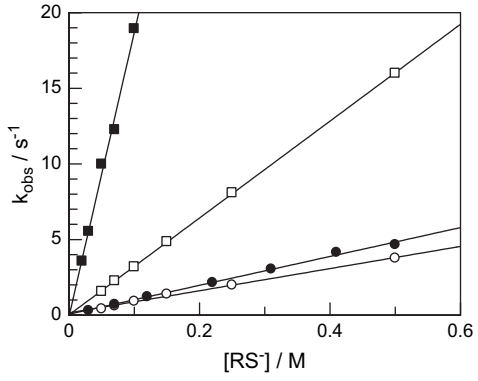


Figure 1. Influence of the thiolate concentration on k_{obs} for the nitrosation of mercaptoethanol (reaction showed in Scheme 1) by (○) 4-MeO, (●) 4-Me, (□) 4-Cl, and (■) 4-NO_2. T=25.0 °C.

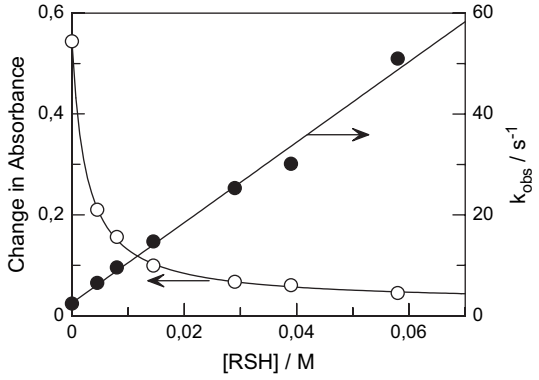


Figure 2. Influence of the mercaptoethanol concentration on k_{obs} and on the variation of the absorbance at 250 nm during the nitrosation of DMU. [DMU]=5.00×10^{-3} M; [$HClO_4$]=0.50 M; [$NaNO_2$]=1.00×10^{-4} M; ionic strength=1.00 M ($NaClO_4$). T=25.0 °C.

Table 1. Bimolecular rate constants, k_2 (M^{-1} s^{-1}), for the nitroso group transfer from *N*-nitrosobenzene-sulfonamides to thiolate ions

pK_a^{lg}	pK_a^{nuc}	7.81	9.45	9.72	10.6	β_{nuc}
		MTG	MMP	MercEt	EtSH	
11.7	4-MeO	9.76±0.05	11.7±0.1	13.5±0.2	14.6±0.5	0.06±0.01
11.6	4-Me	12.6±0.7	15.8±0.2	17.6±0.6	19.2±0.5	0.07±0.01
11.1	4-Cl	34.6±0.3	46.3±0.5	57.9±0.3	64.1±0.7	0.10±0.02
10.7	4-NO_2	194±2	227±8	351±9	375±8	0.10±0.03
	α_{lg}	−1.2±0.1	−1.2±0.1	−1.3±0.1	−1.4±0.1	

decomposition rate constants, respectively, of the nitrosothiol and K_{NO} is the equilibrium constant for the formation of NO^+ from HNO_2 and H^+. Eq. 2 allowed us to calculate the nitrosation rate constant for the thiol, k_1. Because the formation equilibrium constants for nitrosothiols are usually very large, k_{-1} must be very small relative to k_1 and k_{DMU}; this precludes the kinetic determination of k_{-1}.

As can be seen from Figure 2, the addition of RSH decreased the absorbance change at 250 nm due to the nitrosation of DMU. Such a decrease was a result of the formation of the nitrosothiol, which absorbs at 330 nm. Therefore, the absorbance change can be related to the amounts of nitrosodimethyl urea (MNU-NO) and nitrosothiol (RSNO) formed. The variation in absorbance in the absence of added thiol, $(\Delta A)_0$, and in its presence, ΔA, can be related with the nitrosation equilibrium constant of the thiol through the following equation:

$$\frac{(\Delta A)_0-\Delta A}{(\Delta A)_0}=\frac{K_{NO}K_1[RSH]}{1+K_{NO}K_1[RSH]} \quad (3)$$

where K_{NO} is the equilibrium constant for the formation of NO^+ from HNO_2 and H^+, and was taken[15] to be $3.5\times10^{-7}\ M^{-1}$; and K_1 is the equilibrium constant for the formation of the nitrosothiol, $K_1 = k_1/k_{-1}$.

Figure 3 illustrates the good fitting of the absorbance changes of Figure 2, and those obtained using different dimethyl urea concentrations to Eq. 3. The fit allows the product K_1K_{NO} to be established, $K_1K_{NO} = (270 \pm 17)\ M^{-1}$. By using the value of K_{NO}, we can get the nitrosation equilibrium constant for mercaptoethanol, $K_1 = 7.71 \times 10^8$. From similar plots to that of Figure 3 we have obtained the formation equilibrium constants for the nitrosothiols used in this work (see Table 2).

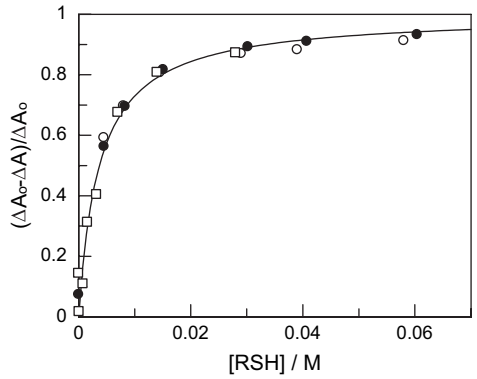


Figure 3. Plot of $(\Delta A)_0-\Delta A/(\Delta A)_0$ versus the thiol concentration, Eq. 3, for the nitrosation of DMU in the presence of variable concentrations of mercaptoethanol. $[HClO_4]$=0.50 M; $[NaNO_2]=1.00\times10^{-4}$ M; ionic strength=1.00 M ($NaClO_4$). T=25.0 °C. (○) $[DMU]=5.00\times10^{-3}$ M; (●) $[DMU]=3.00\times10^{-3}$ M; (□) $[DMU]=2.00\times10^{-3}$ M.

Table 2. Formation equilibrium constants for the studied nitrosothiols at an ionic strength of 1.00 M ($NaClO_4$) at 25.0 °C

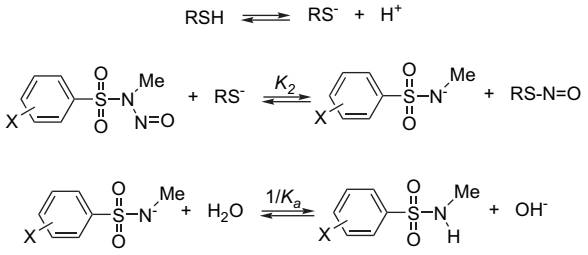
Thiol	MTG	MMP	MercEt	EtSH
pK_a	7.81	9.45	9.72	10.6
K_1	1.8×10^8	6.1×10^8	7.7×10^8	9.0×10^8

3. Discussion

The bimolecular rate constants k_2 for the nitroso group transfer from *N*-nitrosobenzene-sulfonamides to thiolate ions (Table 1) were much greater than those obtained with secondary amines as the nucleophiles. In fact, the rate constant for the nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide to mercaptoethanol ($pK_a = 9.72$) is roughly 300 times greater than that for another nucleophile such as piperazine ($pK_a = 9.82$).[12] This higher strength of the sulfur nucleophiles is well documented in the literature as evidenced by the different values in Ritchie's N_+ scale.[16]

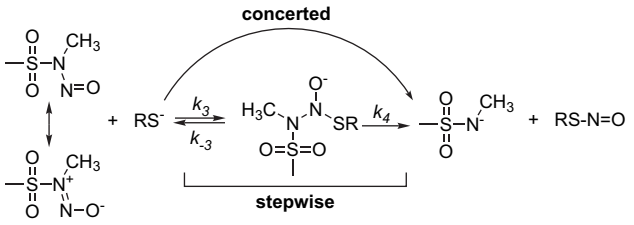
3.1. Reaction mechanism

The mechanism by which a nitroso group is transferred from an *N*-nitrosobenzenesulfonamide to a thiol involves the nucleophilic attack of the thiolate ion to the nitroso group and the release of the anion from the sulfonamide, which constitutes the rate-determining step of the process. Subsequently, the sulfonamide ion is protonated to an extent proportional to the acidity of the medium (see Scheme 3).



Scheme 3.

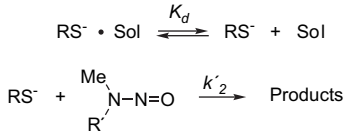
There are at least two possible mechanisms for the nitroso group transfer. One is of the addition–elimination type and the other involves the direct (concerted) displacement of the N═O group as in the alkaline hydrolysis of alkyl nitrites.[17] Because the Bronsted slopes, α_{lg}, of Table 1 are smaller than −1, the formation of the transition state is more strongly influenced by the development of negative charge than the acidity equilibrium of the sulfonamide. *N*-nitroso compounds stabilize by resonance between two different structures:[18] R–N–N═O↔R–N^+═N–O^-. A possible explanation is that the transnitrosation 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–$N(CH_3)^-$) (Scheme 4). This change or charge of more than one unit, $\alpha_{lg} \approx -1.3$, in the reaction versus only one in the reference reaction, pK_a^{lg} (the acid dissociation of the sulfonamide), is only compatible with a concerted mechanism for nitroso group transfer, ruling out the stepwise mechanism shown in Scheme 4.



Scheme 4.

The variation of the nucleophilic reactivity with the basicity of the nucleophile shows behavior clearly different from that of the nitrogen or carbon nucleophiles. The nitroso group transfer rate constant increases slightly by 55% by increasing the basicity of the nucleophile approximately 615 times. The same increase in basicity brings a rise of more than 10^4% in the rate constants of amine[19] or carbanion nitrosation[20] by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. Such a difference of behavior is made clear when establishing a Bronsted correlation giving values of $\beta_{nuc} \approx 0.8$ for the nitrosation of primary and secondary amines by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[12] whereas the values obtained for the nitrosation of the sulfur nucleophiles studied is close to $\beta_{nuc} \approx 0.08$.

This change in the sensitivity of the reaction to the basic strength of the nucleophile is unusual although not without precedent and it has traditionally been regarded as a consequence of the effect of desolvation on the reaction rate or on reactivity–structure correlations. In fact, there are many cases where the rate of certain nucleophilic attacks has been found to decrease as the basicity of the nucleophile is increased, leading to negative Bronsted exponents. This behavior has been observed for some phosphoryl transfer reactions to amines,[21] and for reactions of highly reactive carbocations with amines[22] and for reactions of thiolate ions with Fischer carbene complexes.[23] In the same way, values of the Bronsted exponent close to zero have been found for reactions of diphenylketene with amines.[24] Studies carried out by Jencks[21] indicate that these anomalous Bronsted exponents result form a requirement for partial desolvation of the nucleophile prior to reaction. The desolvation is usually considered to be a pre-equilibrium that occurs in a separate step, in such a way that a two-step model like that illustrated in Scheme 5 can be adopted for a nucleophilic attack.



Scheme 5.

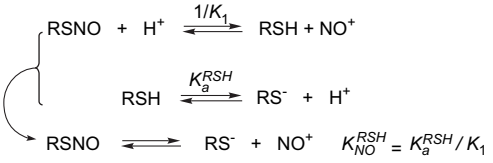
As Scheme 5 shows, the experimental value of the rate constant for the process of nucleophilic attack corresponds to the product $K_d k'_2$, where K_d is the equilibrium constant for the partial desolvation of the nucleophile. Taking into account this approach, we can assume that β_{nuc} is given by Eq. 4:

$$\beta_{nuc} = \frac{d \log k_2}{d\, pK_a^{RSH}} = \frac{d \log K_d k'_2}{d\, pK_a^{RSH}} = \frac{d \log K_d}{d\, pK_a^{RSH}} + \frac{d \log k'_2}{d\, pK_a^{RSH}} = \beta_d + \beta'_{nuc} \quad (4)$$

In view of the fact that the higher the basicity of RS^-, the more difficult the desolvation is, $\beta_d < 0$ can be expected. Thus, if β_{nuc} is low, β_{nuc} may be dominated by β_d and be close to zero or even negative. The values reported in the literature where β_{nuc} values are quite low for thiolate ion addition to a variety of electrophiles are very common.[25]

3.2. Determination of equilibrium constants

Accurately interpreting Bronsted exponents with a view to characterizing the structure of the transition state entails normalizing β_{nuc} and α_{lg} through β_{eq}. In the nitroso group transfer reactions studied here, the equilibrium is displaced to the formation of the nitrosothiol to such an extent that it precludes its experimental determination. Moreover, nitrosothiols are unstable compounds and decompose under a wide variety of conditions. The equilibrium constant for a process involving the loss of an NO^+ group from a nitrosothiol can be calculated from the equilibrium constant for the formation of the nitrosothiol from its parent thiol and NO^+, K_1, and the acidity constant for the thiol, K_a^{RSH} (see Scheme 6).



Scheme 6.

Table 3 lists the K_{NO}^{RSH} values obtained for various thiols in the form of pK_{NO}^{RSH}, as well as the previously reported values for the corresponding nitrososulfonamides.[12] Based on the results, the most basic sulfonamides or thiols produce the most stable *N*-nitroso compounds, which is consistent with the above-described behavior of *N*-nitrosamines. The dependence of the stability of *N*-nitrosamines on the basicity of the parent amines was previously demonstrated in the nitroso group transfer from an *N*-nitrosamine to another amine in an acid medium.[26,27] The structure and stereochemistry of *N*-nitrosamines should reflect delocalization

Table 3. Equilibrium constants for the loss of an NO^+ group from a nitrosothiol or *N*-nitrososulfonamide and for the nitroso group transfer from a nitrososulfonamide to a thiol, K_2

pK_{NO}		16.1	18.23	18.61	19.55	β_{nuc}^{norm}
		MTG	MMP	MercEt	EtSH	
		$\log K_2 = \Delta pK_{NO} = pK_{NO}^{acceptor} - pK_{NO}^{donor}$				
20.12	4-MeO	−4.02	−1.89	−1.51	−0.57	0.05±0.01
19.83	4-Me	−3.73	−1.6	−1.22	−0.28	0.05±0.01
18.83	4-Cl	−2.73	−0.6	−0.22	0.72	0.08±0.02
17.55	4-NO_2	−1.45	0.68	1.06	2.00	0.08±0.03
	α_{lg}^{norm}	0.51±0.03	0.50±0.01	0.54±0.02	0.55±0.03	

of the lone-pair electrons of the amino nitrogen into the π-system of the N=O group. Electron diffraction studies[28] have shown that N–N and N–O bond orders are ca. 1.5, which is consistent with a structure in between the valence structures of Scheme 7.

Scheme 7.

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

The equilibrium constant for the rate-determining step of the nitroso group transfer reaction, K_2, can be calculated from pK_{NO} for the *N*-nitrososulfonamide (the nitroso group donor) and the nitrosothiol (the acceptor), using the relation $\log K_2 = \Delta pK_{NO} = pK_{NO}^{acceptor} - pK_{NO}^{donor}$. Table 3 lists the $\log K_2$ values thus obtained. As can be seen, based on the equilibrium constant for the nitroso group transfer, the process will be thermodynamically unfavorable and lead to a mixed equilibrium between the *N*-nitrososulfonamide and the nitrosothiol in most cases. However, the sulfonamide will be protonated in a diffusion-controlled step at a later stage of the process. As a result, the backward reaction of the nitroso group transfer from a nitrosothiol to the neutral form of the sulfonamide will simply not occur. Also, nitrosothiols decompose rapidly,[30] so the nitroso group transfer will be quantitative.

3.3. Characterization of the transition state

The equilibrium constant for the rate-determining step in the nitroso group transfer, K_2, allows one to derive rate–equilibrium relationships. In fact, the resulting plots can be used to calculate α_{lg}^{norm} and β_{nuc}^{norm} (see Fig. 4), which are measures of charge development on the nitrogen atom of the *N*-nitrososulfonamide and the sulfur atom of the thiolate ion, respectively. The α_{lg}^{norm} and β_{nuc}^{norm} values thus obtained are listed in Table 3. As can be seen, the α_{lg}^{norm} values are close to 0.50 and

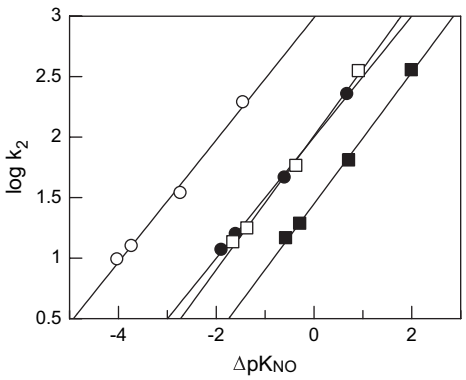


Figure 4. Plot of log k_2 versus ΔpK_{NO} for the nitroso group transfer from *N*-nitrososulfonamides to (○) MTG, (●) MMP, (□) MercEt, and (■) EtSH. The slopes of the lines provide an α_{lg}^{norm} value of 0.50.

independent of the particular substituent of the *N*-nitrososulfonamide, consistent with the previous results for the nitroso group transfer from *N*-nitrososulfonamides to amines.[12]

The β_{nuc}^{norm} values obtained for the nitroso group transfer from *N*-nitrososulfonamides to amines are also close to 0.50, which is consistent with a symmetric transition state for the reaction. The small values obtained in this work ($\beta_{nuc}^{norm} = 0.05$) suggest the presence of a thiolate desolvation equilibrium encompassed by the rate constant. Based on Scheme 5, $\beta_{nuc}^{norm} = \beta_d + \beta_{nuc}^{\prime norm}$, where β_d is the Bronsted slope for the desolvation of the thiolate ion and $\beta_{nuc}^{\prime norm}$ that for the nitroso group transfer.

Previous studies on the nitroso group transfer from *N*-nitrososulfonamides[12] revealed that stabilization by the SO_2 group of the negative charge that develops on the nitrogen atom of the sulfonamide during the reaction must be the result of polarization effects rather than of conjugative dπ–pπ bonding or negative hyperconjugation. This is consistent with the results for the mechanism by which carbanions with a sulfur atom[31] or sulfonyl group[32] in α are stabilized.[32] The absence of resonance effects from the stabilization of negative charge in α to sulfur atoms is supported by the fact that $\alpha_{lg}^{norm} + \beta_{nuc}^{norm} = 1$. One can therefore assume that the Bronsted exponent for the nitroso group transfer from *N*-nitrososulfonamides to thiolate ions (Scheme 5), $\beta_{nuc}^{\prime norm}$, should be 0.50. Accordingly, β_d should be −0.45, which is consistent with the expectations ($\beta_d < 0$) as the difficulty of desolvating the thiolate ion should increase with increasing basicity of RS^-.

3.4. Intrinsic rate constants

The Marcus theory[33] for *outer sphere electron transfer reactions* relates kinetic and thermodynamic barriers in a chemical reaction. This theory has allowed the experimental results for a large number of processes including proton,[34] hydride ion,[35] and methyl group[36,37] transfers to be explained. Such a wide scope suggests that the Marcus theory should also be applicable to nitroso group transfers.

The Marcus theory[33] predicts non-linearity in free energy relations by introducing a quadratic term:

$$\Delta G^{\neq} = \Delta G_0^{\neq} + \frac{\Delta G^0}{2} + \frac{\Delta G^{0^2}}{16\Delta G_0^{\neq}} \quad (5)$$

where $\Delta G^{\neq}$ is the free energy of activation for the reaction concerned, ΔG^0 the free energy change for the process and $\Delta G_0^{\neq}$ the *intrinsic barrier* corresponding to the free energy of activation at $\Delta G^0 = 0$. The associated rate constant and intrinsic rate constant are k and k_0, respectively. In proton transfer reactions, ΔG^0 is determined by the pK_a difference between the proton donor and acceptor. An identical formalism can be used with nitroso group transfers. In our case, ΔG^0 will be determined by the pK_{NO} difference between the nitroso group donor (i.e., the *N*-nitrososulfonamide) and acceptor (thiolate ion).

We used the results of Figure 4 to calculate the intrinsic rate constant, k_0, for the nitroso group transfer from *N*-nitrososulfonamides to thiols as the rate constants at $\Delta pK_{NO} = 0$.

The intrinsic constants thus obtained increased with decreasing basicity of the thiol; thus, $\log k_0$ was 3.0 for MTG ($pK_a = 7.81$), 2.0 for MMP ($pK_a = 9.45$), 2.0 for MercEt ($pK_a = 9.72$), and 1.75 for EtSH ($pK_a = 10.6$). These results are consistent with the need to desolvate thiolate ions, the desolvation increasing in difficulty with increase in the basicity of the thiol. In order to suppress the effect of desolvation on $\log k_0$, we used a β_d value of -0.45 to establish the following equation

$$\log k_2 + 0.45pK_a^{RSH} = \text{intercept} + \beta'_{nuc}pK_a^{RSH} \quad (6)$$

Figure 5 illustrates the good correlation between $\log k_2 + 0.45pK_a^{RSH}$ and ΔpK_{NO} for the nitroso group transfer from *N*-nitrososulfonamides to various thiolate ions. The figure is similar to the traditional log plots of proton transfer rate constants versus acid ionization constants. As can be seen, the rate constant for the nitroso group transfer and the equilibrium constants are linearly related. This is consistent with the previous results for the nitroso group transfer from *N*-nitrososulfonamides to secondary amines.[12] The linearity of the rate–equilibrium constant empirical correlation apparent from Figure 5 includes both thermodynamically favorable and unfavorable reactions. It should be noted that this linear relationship contradicts reported Bronsted exponent changes for a wide range of proton transfers from carbon acids.[38] However, a number of absolutely linear rate–equilibrium plots for proton abstraction by OH^- ions exist[39,40] that span 19 pK_a units and include favorable and unfavorable proton transfer processes.

The results of Figure 5 can be used to calculate the intrinsic rate constants for the nitroso group transfer from *N*-nitrososulfonamides to secondary amines ($\log k_0 = -0.5$) and thiols ($\log k_0 = 6.3$). The large difference between the reactivity of amines and thiolate ions is a result of the latter being highly effective nucleophiles and superior to oxyanions or amines of comparable pK_a in many nucleophilic addition reactions.[41] One of the reasons for such a high reactivity is their high carbon basicity (i.e., their high equilibrium constants for nucleophilic addition).[42] Within the framework of hard–soft acid–base interactions,[43] this can be understood as the soft (polarizable) electrophile having stronger affinity for the soft sulfur bases than for the hard nitrogen or oxygen bases.

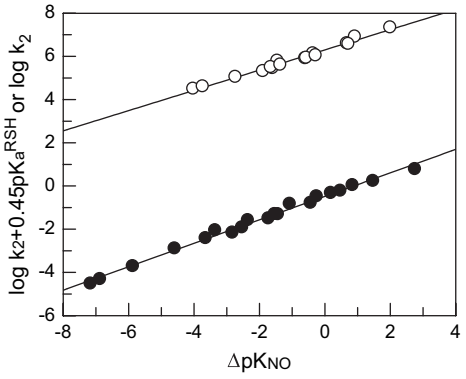


Figure 5. Plot of (○) $\log k_2 + 0.45pK_a^{RSH}$ versus ΔpK_{NO} for nitroso group transfer from *N*-nitrososulfonamides to thiolate ions and (●) $\log k_2$ versus ΔpK_{NO} for nitroso group transfer from *N*-nitrososulfonamides to secondary amines.

Albery and Kreevoy[36] examined methyl transfer reactions in the light of the Marcus theory and determined the intrinsic barriers $\Delta G_0^{\neq}$ for various identity reactions where the nucleophile and leaving group were the same. In this way, they obtained the $\Delta G_0^{\neq}$ values 147, 213, 133, 111, 99, and 97 kJ mol^{-1} (corresponding to the $\log k_0$ values -12.98, -24.45, -10.53, -6.67, -4.57, and -4.22) for H_2O, CN^-, F^-, Cl^-, Br^-, and I^-, respectively. These results for methyl group transfers show that the intrinsic rate constant is very strongly dependent on the nature of the nucleophile, in fact, it varies by a factor of 10^6 from F^- to I^-.

The above-described high thermodynamic affinity was recently shown not to fully account for the high nucleophilicity of thiolate ions.[25f] In fact, an important contribution comes from an enhanced intrinsic rate constant. This was demonstrated for the reaction of thiolate ions with α-nitrostilbene in 1:1 Me_2SO/water, for which $\log k_0 = 3.43$, is much greater than for the reaction of piperidine/morpholine with the same substrate ($\log k_0 = 1.43$).[44] An attractive explanation for the enhanced k_0 value is that the soft acid–soft base interaction, which is responsible for the high thermodynamic stability of the thiolate ion adduct develops ahead of C–S bond formation. This is interesting because it contrasts with most other product-stabilizing factors development of which typically lags behind bond formation at the transition state, thereby lowering k_0.[45] One common feature of product-stabilizing factors such as resonance, solvation or intramolecular hydrogen bonding is that they are 'created' by the reaction (i.e., they would not exist in the absence of bond formation). At best, these factors could conceivably develop synchronously with bond formation, but not possibly ahead of it. By contrast, soft–soft interactions are rooted in the polarizability of the interacting molecules and may not require a substantially developed bond to make themselves felt.

4. Conclusions

On the basis of this study, the following results are particularly worthy of note.

(1) The nitroso group transfer from *N*-nitrososulfonamides to thiolate ions takes place directly via concerted mechanism. The rate of the reaction is strongly dependent on the nature of the leaving group, but virtually independent of the basicity of the thiolate ion. This is a result of the presence of a prior equilibrium for the desolvation of thiolate ions.

(2) The calculated equilibrium constants for the nitroso group transfers allowed charge development on the nucleophile and leaving group in the transition state to be quantified. Because the sulfonyl group is not involved in the establishment by resonance of the negative charge on the nitrogen atom in α, the nucleophilic sensitivity of the reaction can be resolved into a desolvation term and a bond formation term.

(3) The establishment of a rate–equilibrium relation for the nitroso group transfer allowed us to derive a quantitative explanation for the observed reactivity similarly to proton transfer reactions. The absolute linearity of the rate–equilibrium correlation was interpreted in the light of the

Marcus theory of electron transfer as applied to the nitroso group transfer process. The accelerating effect of substituents withdrawing charge from the aromatic ring of the *N*-nitrososulfonamide is mainly due to the greater thermodynamic driving force of the reaction. Hence, the intrinsic reactivities of nitrososulfonamides remain virtually constant.

5. Experimental

N-methylbenzenesulfonamides were synthesized by reacting the corresponding benzenesulfonyl chlorides with excess methylamine in water. The resulting products were extracted with dichloromethane and washed with a solution of sodium hydrogen carbonate and water. *N*-methyl-*p*-toluenesulfonamide and its nitroso derivative were supplied by Ega-Chemie and Merck, respectively. *N*-Methyl-*N*-nitrososulfonamides were prepared from a biphasic water/dichloromethane mixture. The aqueous phase, containing sodium nitrite, and the organic phase, containing the parent sulfonamide, were mixed together and slowly supplied with concentrated (5 M) perchloric acid. Following stirring for 1 h, the organic phase was separated and washed with water, *N*-methyl-*N*-nitrososulfonamides being finally recrystallized in a 80% yield from a dichloromethane/petroleum ether mixture. This method has the advantage that it avoids the hydrolysis of the nitroso derivatives by sequestering them in the organic phase as they form. All other reagents were obtained in the highest available purity from Aldrich and used as received.

The pK_a values of thiols in water at 25.0 °C, ionic strength = 1.00 M ($NaClO_4$) were determined potentiometrically. The obtained values are compatible with those existing in the bibliography.[46] The pK_a values of the sulfonamides were known from the previous studies.[46c]

All kinetic experiments were performed with a large excess of nucleophile relative to *N*-methyl-*N*-nitrososulfonamide, the concentration of the latter ranged from $(1–2)\times10^{-4}$ M. The pH was controlled by using the nucleophile itself as buffering agent in solutions with NaOH. Because of their low solubility in water, the *N*-methyl-*N*-nitrososulfonamides were dissolved in a small amount of organic solvent (dioxane) prior to preparing the aqueous solutions. The final concentration of organic solvent in the reaction medium was smaller than 3.3% (v/v) in all instances. The reaction kinetics was studied by monitoring the formation of the nitrosothiol via the absorbance at 330 nm, which was measured with an Applied Photophysics stopped-flow spectrophotometer. The reaction was found to be first order up to about 90% conversion. Each kinetic run was repeated at least five times in order to obtain an average value for the *pseudo* first-order rate constant, k_{obs}. The standard error for k_{obs} was always less than 3%. All experiments were performed at 25.0 °C.

The equilibrium constant of nitrosothiol formation was determined from the nitrosation of 1,3-dimethyl urea (DMU) in the presence of variable concentrations of a thiol. Experiments were conducted with [$NaNO_2$] much smaller than those of DMU and RSH. The reaction was monitored at 250 nm, where nitrosothiols absorb negligibly.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.060.

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