Nitrosation and denitrosation of substituted *N*-methylbenzenesulfonamides. Evidence of an imbalanced concerted mechanism

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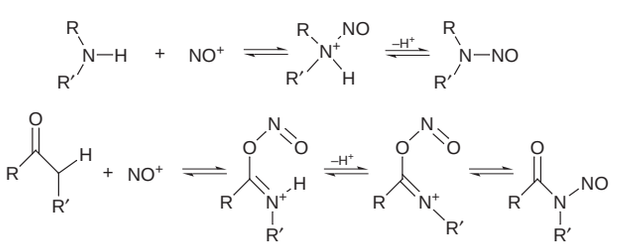
The kinetics of the nitrosation reaction of several substituted sulfonamides and of the denitrosation of the resulting products have been studied. The denitrosation rate is first-order with respect to both the nitroso compound and acid concentration and no effect of added nucleophiles was observed. The denitrosation reaction is general-acid catalysed, with a Brønsted parameter, α_d, of 0.7, which is independent of the substituents on the aromatic ring. Kinetic solvent isotope effects range from $k_d^{H_3O^+}/k_d^{D_3O^+} = 1.20 \pm 0.05$ to 2.04 ± 0.06 for denitrosation by L_3O^+ and from $k_d^{AH}/k_d^{AD} = 1.5 \pm 0.2$ to 2.3 ± 0.3 for denitrosation by dichloroacetic acid, which suggest that a rate-determining proton transfer is involved in this reaction. For nitrosation reaction, the absence of catalysis by nucleophilic anions, the observed general-base catalysis ($\beta_{NO} = 0.3$) and the substituent effects suggest a concerted nitrosation–denitrosation process. The Leffler parameters obtained for N · · · H bond formation ($\alpha_{nuc} = 0.7$) as well as for N · · · N=O bond breaking ($\alpha_{lg} = 0.17$) are in favour of an imbalance in the transition state ($\alpha_{imbalance} = 0.53$) with the development of a positive charge on the nitrogen adjacent to the nitroso group.

Introduction

By far the best-known and most widely studied nitrosation reactions are *N*-nitrosations of amines and related compounds. *N*-Nitrosations occur widely in organic chemistry in many standard synthetic pathways, and a number (including diazotisation and azo dye formation) have large-scale industrial applications. Because of their importance, such reactions have been also much studied mechanistically, and in general are now well understood.[1]

The mechanisms of nitrosation of amides and ureas in an acidic medium have been investigated in recent years[2–5] and a large number of differences have been found between nitrosation of these compounds and amines. In the case of amines the attack of the nitrosating agent on the free amine is rate determining, while for amides this first step is fast, the slow step being a proton transfer from an intermediate to the reaction medium. In the latter case the reaction seems to occur initially on the oxygen atom, and a subsequent rearrangement leads to the thermodynamically more stable *N*-nitrosoamide (Scheme 1).



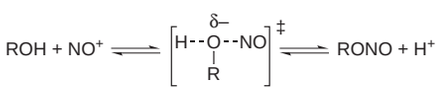
Scheme 1

The reason for this seems to be related to the much lower basicity of amides, compared to amines.

Nitrosation of secondary sulfonamides gives rise to stable *N*-nitroso derivatives.[1] Some nitrosulfonamides are used to generate diazomethane[6] and as nitrosating agents able to transfer their nitroso group at moderate acidities[7,8] where traditional nitrosating agents (NO^+ or alkyl nitrites) are either inefficient or unstable. In spite of the large interest in nitrososulfonamides themselves and their being included in one of the most important classes of mutagenic and carcinogenic compounds,[9,10] there is a clear lack of mechanistic studies of the nitrosation of sulfonamides in the literature.

Similar behaviour would certainly be expected for denitrosation of both sulfonamides and carboxamides, because of their quite similar structure and because the only study known until now demonstrates the same kinetic characteristics for both.[11] Nevertheless, *N*-nitrososulfonamides are the only *N*-nitroso compounds able to transfer their nitroso group to other species acting as nucleophiles, which makes them an important family of transnitrosating agents[7,8] with efficiency similar to that of alkyl nitrites. This peculiar characteristic of nitrososulfonamides may be related with their nitrosation–denitrosation mechanism.

In this paper we try to establish a direct relationship between the denitrosation mechanism and transnitrosation ability of a given compound. The experimental results presented here on nitrosation–denitrosation of a series of 4-substituted *N*-methyl-*N*-nitrosobenzenesulfonamides suggest the existence of a third route for decomposition of some *N*-nitroso compounds. This pathway involves a concerted protonation and fission of the N · · · N=O bond. This mechanism is quite similar to that reported for the main family of transnitrosating agents, alkyl nitrites, for which denitrosation involves a rate-determining protonation with a concerted mechanism in which proton transfer and O · · · N=O bond breaking occur simultaneously, in a slightly imbalanced transition state (Scheme 2).[12]

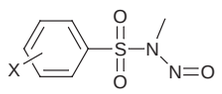


Scheme 2

Experimental

N-Methylbenzenesulfonamides have been synthesized by reaction of the corresponding benzenesulfonyl chlorides with an excess of methylamine in water.[13] The product is extracted with dichloromethane and washed with a solution of sodium hydrogen carbonate and with water. *N*-Methyl-4-methylbenzenesulfonamide and its nitroso derivative **II** were supplied by Ega-chemie and Merck, respectively.

I: X = 4-CH_3O
II: X = 4-CH_3
III: X = 4-Cl
IV: X = 4-NO_2



N-Methyl-*N*-nitrososulfonamides **I**, **III** and **IV** 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 recrystallised from dichloromethane–light petroleum (bp 25–40 °C) with a final yield of 80%. This method has the advantage of preventing the hydrolysis of the nitroso derivatives by sequestering them in the organic phase as soon as they are formed.

N-*Methyl*-4-*methoxybenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 2.64 (3H, d, CH_3-N), 3.87 (3H, s, CH_3O), 6.99 (2H, m, Ph), 7.80 (2H, m, Ph).

N-*Methyl*-N-*nitroso*-4-*methoxybenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 3.12 (3H, s, CH_3-N), 3.89 (3H, s, CH_3O), 7.04 (2H, m, Ph), 7.91 (2H, m, Ph).

N-*Methyl*-4-*chlorobenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 2.68 (3H, d, CH_3-N), 7.51 (2H, m, Ph), 7.81 (2H, m, Ph).

N-*Methyl*-N-*nitroso*-4-*chlorobenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 3.14 (3H, s, CH_3-N), 7.57 (2H, m, Ph), 7.94 (2H, m, Ph).

N-*Methyl*-4-*nitrobenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 2.74 (3H, d, CH_3-N), 8.06 (2H, m, Ph), 8.38 (2H, m, Ph).

N-*Methyl*-N-*nitroso*-4-*nitrobenzenesulfonamide*: δ_H(300 MHz, $CDCl_3$) 3.17 (3H, s, CH_3-N), 8.20 (2H, m, Ph), 8.43 (2H, m, Ph).

Nitrite produced by denitrosation of *N*-methyl-*N*-nitrososulfonamides was determined using a modification of Shinn's method.[14] The reaction mixture was brought to pH *ca*. 2 and mixed with sulfanilamide (Merck) and naphthylethylenediamine (Carlo Erba). Absorbance at 550 nm due to the dye formed was measured and nitrite was quantified using the value of 4.6×10^4 dm^3 mol^{-1} cm^{-1} for the molar absorptivity of the dye.

Because of their poor solubility in water, sulfonamides and their nitroso derivatives were dissolved in a small amount of organic solvent (usually dioxane) prior to preparation of aqueous solutions. The final concentration of organic solvent in the medium was usually 3.3% (v/v).

Kinetic runs were monitored following the change in absorbance (λ = 250–275 nm) due to the formation or decomposition of the *N*-nitroso derivative using a Spectronic 3000 Diode-Array UV–VIS spectrophotometer equipped with a multiple cell carrier thermostatted by circulating water. All experiments were carried out at 25.0 ± 0.1 °C. In all kinetic experiments $NaClO_4$ was used to fix the ionic strength of the medium at 0.5 M. All kinetic experiments were performed under pseudo-first-order conditions keeping in deficit either the nitroso derivative concentration $(0.5–1.0) \times 10^{-4}$ M for denitrosation or the nitrite concentration $(6–8) \times 10^{-4}$ M for the nitrosation reaction. In all cases the absorbance–time data fitted accurately the corresponding first-order integrated rate equations. The observed first-order rate constants, k_{obs} were reproducible within 3%. In the experiments to study the effect of buffers, different amounts of buffer solutions were added to mixtures that already contained the amount of acid required to achieve the desired pH. In all cases pH values were measured at the end of the reaction using a Radiometer 82 pH meter with a GK-2401C combined electrode. In experiments with D_2O, pD was calculated by adding 0.4 units to the measured value.[15]

Table 1 Effect of added nucleophiles (Br^- and SCN^-) on k_{obs} of acid denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamides **II** and **III**[a]

Nucleophile		$k_{obs}/10^{-4}$ s^{-1}	
$[Br^-]$/M	$[SCN^-]$/M	4-CH_3 (**II**)	4-Cl (**III**)
—	—		
0.16		(5.1 ± 0.3)	(4.3 ± 0.2)
0.32		(4.7 ± 0.3)	(4.3 ± 0.2)
0.50		(5.1 ± 0.3)	(4.4 ± 0.2)
	0.057	(5.4 ± 0.3)	(4.9 ± 0.3)
	0.114	(5.3 ± 0.2)	(5.7 ± 0.3)
	0.142	(5.4 ± 0.3)	(6.4 ± 0.3)

[a] $[HClO_4] = 1.39 \times 10^{-2}$ M; T = 25 °C.

Table 2 $k_d^{H_3O^+}$ values and kinetic solvent isotope effects in the acid-catalysed denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamides

Substrate	$k_d^{H_3O^+}/10^{-2}$ M^{-1} s^{-1}	$k_d^{H_3O^+}/k_d^{D_3O^+}$	k_d^{AH}/k_d^{AD} [a]
4-CH_3O	4.1 ± 0.1	1.20 ± 0.05	1.5 ± 0.2
4-CH_3	3.5 ± 0.1	1.2 ± 0.1	1.9 ± 0.2
4-Cl	2.80 ± 0.02	1.28 ± 0.04	1.8 ± 0.1
4-NO_2	2.49 ± 0.06	2.04 ± 0.06	2.3 ± 0.3

[a] Obtained with dichloroacetic acid.

Results

The reaction of nitrosation of the *N*-methylbenzenesulfonamides is in equilibrium with the denitrosation process and this must be taken into account when studying their kinetics. Experiments have been carried out using *N*-methyl-*N*-nitrosobenzenesulfonamides as substrates to study the denitrosation reaction while the corresponding *N*-methylsulfonamides were used as substrates when studying the reverse process.

Denitrosation

Under the experimental conditions used ([*N*-methyl-*N*-nitrososulfonamide] = 1.0×10^{-4} M and $[H^+] = 1.0 \times 10^{-2}$ to 0.10 M) denitrosation occurred quantitatively. Formation of NO_2^- as final product together with the total disappearance of the absorption band corresponding to the *N*-nitroso group confirms the irreversibility of the acid denitrosation under these experimental working conditions for all nitrosulfonamides studied as is reported for compound **II**.[11]

The effect of addition of Br^- and SCN^- on the acid denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamides **II** and **III** was studied (Table 1). In neither case was catalysis observed although these nucleophiles are highly effective (even at lower concentrations than those used in this work) in the acid catalysed decomposition of other *N*-nitroso compounds (*i.e.* the catalytic efficiencies of Cl^-, Br^- and SCN^- in the denitrosation of *N*-methyl-*N*-nitrosoaniline are in the ratio 1 : 50 : 5500).[16] The absence of nucleophilic catalysis was also observed by Williams for the acid denitrosation of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide.[11]

Influence of $[HClO_4]$ on the observed rate constants of the acid catalysed denitrosation of *N*-methyl-*N*-nitrososulfonamides (see Fig. 1) leads to a linear relationship implied by eqn. (1). In Table 2 are summarised the second-order rate

$$k_{obs} = k_d^{H_3O^+}[H^+] \quad (1)$$

constants, $k_d^{H_3O^+}$, obtained using eqn. (1) for all the nitrososulfonamides studied.

In order to investigate whether the reaction studied is susceptible to general-acid catalysis, we carried out experiments at constant pH in monochloroacetic acid–monochloroacetate buffers of various concentrations for denitrosation of *N*-nitrososulfonamide **II**. In all cases a moderate catalysis was observed (Fig. 2) in accordance with eqn. (2) in terms of the

$$k_{obs} = k_d^{H_3O^+}[H^+] + k_d^{AH}\frac{[H^+][Buffer]}{K_a^{AH} + [H^+]} \qquad (2)$$

total concentration of buffer, where K_a^{AH} is the acidity constant of monochloroacetic acid.

From the slopes of k_{obs} *vs.* [buffer] plots and using eqn. (2) it is easy to obtain the catalytic constant, $k_d^{AH} = (8 \pm 4) \times 10^{-4}$ M^{-1} s^{-1}, for the acid denitrosation of **II** by monochloroacetic acid. From eqn. (2) a pK_a for monochloroacetic acid of 2.42 was also obtained in good agreement with literature values at this ionic strength.

Catalytic constants were also obtained from the slope of the k_{obs} *vs.* [buffer] plots, for a 1 : 1 ratio of the acid and the basic forms of the buffers, using eqn. (2). Table 3 summarises the catalytic constants for denitrosation of *N*-methyl-*N*-nitrososulfonamides **I**–**IV**. In Fig. 3 a representative Brønsted plot for *N*-methyl-*N*-nitrososulfonamide **III** is displayed including all carboxylic acids studied. It is clear that this plot is essentially straight although if the point for H_3O^+ is included a downward curvature is observed. However, the switch from a neutral to a cationic acid (for which temperature and medium effects would be very different) as well as the uncertain statistical correction for H_3O^+ could well account for these differences. From the slope of Brønsted plots for *N*-methyl-*N*-nitrososulfonamides **I**–**IV** α_d values, always $\geqslant 0$, were calculated and they are summarised in Table 3.

To further confirm the hypothesis that a proton transfer is involved in the rate-determining step, the reaction was studied in deuterium oxide both in the presence of either $DClO_4$ (under conditions analogous to those of Fig. 1) or dichloroacetic buffers. The kinetic solvent isotope effect $k_d^{H_3O^+}/k_d^{D_3O^+}$ varies between 1.20 ± 0.05 and 2.04 ± 0.06 (for substrates **I** and **IV** respectively) for hydrolysis by the hydronium ion in the absence of buffer (Table 2). Experimental results are consistent with those reported for compound **II**.[11] The measured kinetic solvent isotope effect on the catalytic constant of dichloroacetic acid k_d^{AH}/k_d^{AD}, varies between 1.5 ± 0.2 and 2.3 ± 0.3 for substrates **I** and **IV** respectively.

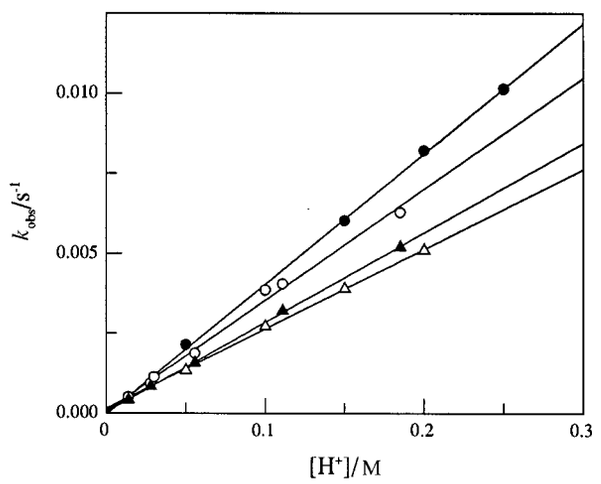


Fig. 1 Influence of [H$^+$] upon k_{obs} in the acid-catalysed denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamides (●) **I**; (○) **II**; (▲) **III**; (△) **IV**, T = 25 °C. Ionic strength 0.50 M ($NaClO_4$).

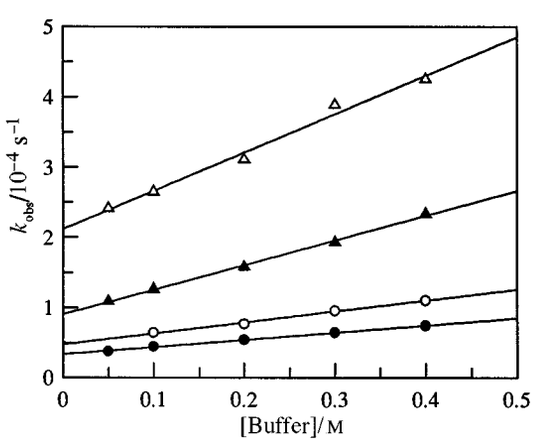


Fig. 2 Influence of the concentration of buffers monochloroacetic acid–monochloroacetate on k_{obs} for the acid-catalysed denitrosation of **II** at T = 25 °C. Ionic strength 0.50 M ($NaClO_4$). pH = (●) 3.30, (○) 3.02, (▲) 2.64 and (△) 2.25.

Nitrosation

The pK_a for the protonation of these sulfonamides varies between −3.4 and −6 (Table 4),[17] which means that these compounds are in their neutral form under the experimental conditions used to study their nitrosation (pH = 1–4). The microscopic reversibility principle suggests that general-base catalysis

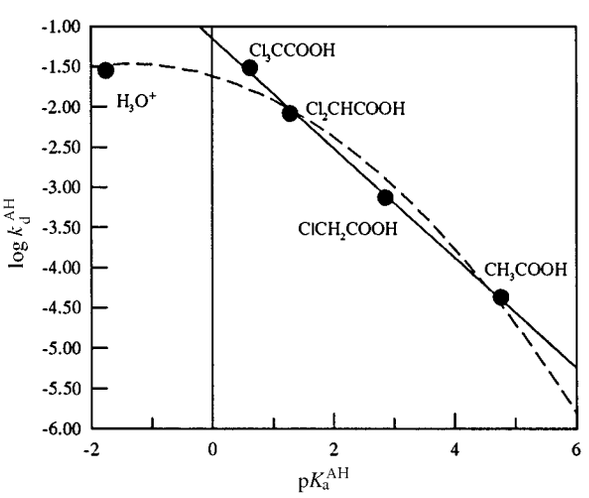


Fig. 3 Brønsted plot for acid-catalysed denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamide **III** using carboxylic acids and including data for H_3O^+ (dotted line)

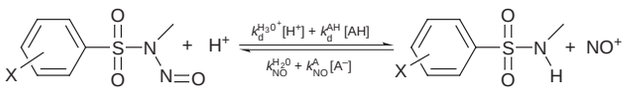
Table 3 Catalytic constants for the carboxylic acid-catalysed denitrosation of *N*-methyl-*N*-nitrosobenzenesulfonamides

	k_d^{AH}/M^{-1} s^{-1}			
Acid	4-CH_3O	4-CH_3	4-Cl	4-NO_2
CH_3COOH	$(3.03 \pm 0.01) \times 10^{-5}$	$(2.93 \pm 0.09) \times 10^{-5}$	$(4.24 \pm 0.02) \times 10^{-5}$	—
$ClCH_2COOH$	$(5.7 \pm 0.2) \times 10^{-4}$	$(5.36 \pm 0.04) \times 10^{-4}$	$(7.4 \pm 0.3) \times 10^{-4}$	$(6.27 \pm 0.08) \times 10^{-4}$
$Cl_2CHCOOH$	$(5.9 \pm 0.5) \times 10^{-3}$	$(6.7 \pm 0.5) \times 10^{-3}$	$(8.2 \pm 0.1) \times 10^{-3}$	$(6.8 \pm 0.2) \times 10^{-3}$
Cl_3CCOOH	$(3.7 \pm 0.3) \times 10^{-2}$	$(3.5 \pm 0.2) \times 10^{-2}$	$(3.05 \pm 0.09) \times 10^{-2}$	$(2.77 \pm 0.04) \times 10^{-2}$
α_d	0.71 ± 0.04	0.72 ± 0.04	0.68 ± 0.02	0.71 ± 0.04

Table 4 $k_{NO}^{H_2O}$ and K_{NO} for nitrosation of *N*-methylbenzenesulfonamides and $pK_a^{BH_2^+}$ of the *N*-methylbenzenesulfonamides

X	$k_{NO}^{H_2O}/M^{-1}\ s^{-1}$	K_{NO}	K_1K_{NO}[a]	$pK_a^{BH_2^+}$	log k_0
4-CH_3O	$(1.1 \pm 0.1) \times 10^7$	$(2.64 \pm 0.26) \times 10^8$	79 ± 7	−3.4	4.93
4-CH_3	$(6 \pm 1) \times 10^6$	$(1.7 \pm 0.3) \times 10^8$	51 ± 9	−4.2	4.85
4-Cl	$(1.5 \pm 0.5) \times 10^6$	$(5.4 \pm 1.8) \times 10^7$	16 ± 5	−5.1	4.11
4-NO_2	1.76×10^5[a]	7.1×10^6[b]	2.13[b]	−6.0	3.81

[a] The equilibrium constant for the overall reaction HNO_2 + sulfonamide. [b] Estimated from a Hammett correlation (see text).



Scheme 3

should be involved in the nitrosation reaction (Scheme 3). For the same reason nucleophilic catalysis should not be expected. The absence of catalysis by nucleophiles was confirmed by studying the influence of Cl^- on the nitrosation of the sulfonamide **II** (data not shown).

From Scheme 3, and considering the formation of NO^+, $K_1 = [NO^+]/[HNO_2][H^+]$, it is easy to calculate the following rate equation [eqn. (3)]. In the absence of acids other than H_3O^+, eqn. (3) can be simplified to eqn. (4).

$$k_{obs} = K_1k_{NO}^{H_2O}[H^+][S] + K_1k_{NO}^{A^-}[H^+][S][A^-] + k_d^{H_3O^+}[H^+] + k_d^{AH}[AH] \quad (3)$$

$$k_{obs} = k_d^{H_3O^+}[H^+] + K_1k_{NO}^{H_2O}[H^+][\text{sulfonamide}] \quad (4)$$

Fig. 4 shows the linear dependence obtained when studying the influence of the concentration of sulfonamide **II** on k_{obs}. The non-zero intercept is clear evidence of reversibility and can be interpreted on the basis of eqn. (4) as the rate of denitrosation under the experimental conditions. A value of $k_d^{H_3O^+} = (3.6 \pm 0.1) \times 10^{-2}\ M^{-1}\ s^{-1}$ was obtained which agrees with the value of $k_d^{H_3O^+} = (3.5 \pm 0.1) \times 10^{-2}\ M^{-1}\ s^{-1}$ reported above when studying denitrosation (Table 2). The slope of the solid line in Fig. 4 gives $K_1k_{NO}^{H_2O} = (1.86 \pm 0.04)\ M^{-2}\ s^{-1}$, which allows us to calculate $k_{NO}^{H_2O} = (6.20 \pm 0.15) \times 10^6\ M^{-1}\ s^{-1}$ using the value of $K_1 = 3 \times 10^{-7}\ M^{-1}$.[18]

Fig. 5 shows the linear plots (k_{obs} *vs.* $[H^+]$) obtained when studying nitrosation of sulfonamides **I**–**III**. Their slopes are related both to the nitrosation and the denitrosation process [eqn. (5)]. From the slope in Fig. 5 and eqn. (5) the rate constant

$$k_{obs} = (k_d^{H_3O^+} + K_1k_{NO}^{H_2O}[\text{sulfonamide}])[H^+] \quad (5)$$

for nitrosation of sulfonamide **II**, $k_{NO}^{H_2O}$, is $(6 \pm 1) \times 10^6\ M^{-1}\ s^{-1}$ which agrees with the value obtained from the variation of k_{obs} with sulfonamide concentration.

Due to the low solubility of the *N*-methylbenzenesulfonamides, the rate constants of nitrosation, $k_{NO}^{H_2O}$, were determined by varying the acid concentration while keeping the sulfonamide concentration constant (Table 4). Taking into account the second-order rate constants for nitrosation, $k_{NO}^{H_2O}$ (Table 4), and denitrosation, $k_d^{H_3O^+}$ (Table 2), one can obtain the values for the equilibrium constants for the process $K_{NO} = k_{NO}^{H_2O}/k_d^{H_3O^+}$ (Table 4). K_{NO} correlates quite well with the $pK_a^{BH_2^+}$ of sulfonamides **I**, **II** and **III** [eqn. (6)]. From this correlation it is possible

$$\log K_{NO} = -(10.6 \pm 0.5) - (0.6 \pm 0.1)pK_a^{BH_2^+} \quad (r = 0.96) \quad (6)$$

to estimate the value of K_{NO} for sulfonamide **IV** allowing the calculation of its nitrosation rate constant (Table 4). The

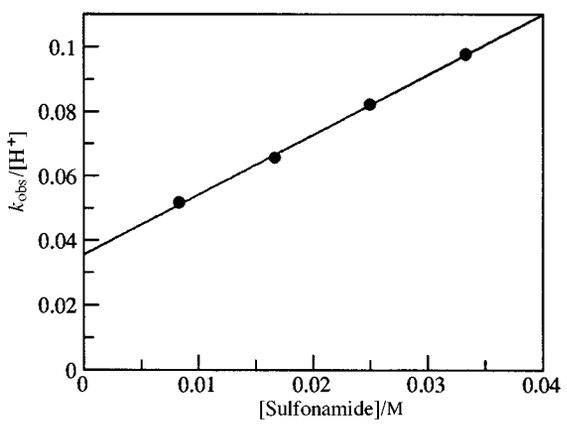


Fig. 4 Influence of *N*-methyl-4-methylbenzenesulfonamide concentration upon k_{obs} in nitrosation by NO^+. $[H^+] = 7.5 \times 10^{-2}$ M, $T = 25$ °C. Ionic strength 0.50 M ($NaClO_4$).

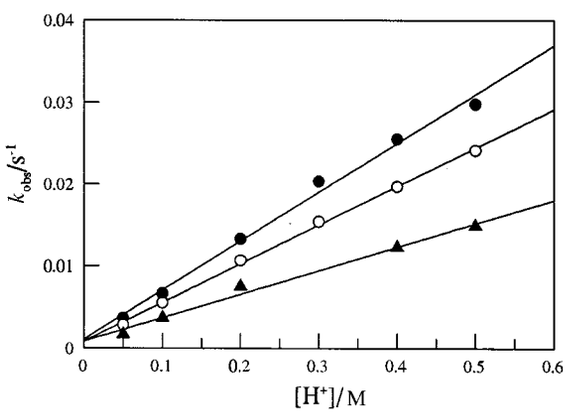


Fig. 5 Influence of $[H^+]$ upon k_{obs} in the nitrosation of (●) *N*-methyl-4-methoxybenzenesulfonamide, (○) *N*-methyl-4-methylbenzenesulfonamide and (▲) *N*-methyl-4-chlorobenzenesulfonamide. [Sulfonamide] + 6.67×10^{-3} M; $T = 25$ °C, ionic strength 0.50 M ($NaClO_4$).

second-order rate constants for both nitrosation, $k_{NO}^{H_2O}$, and denitrosation, $k_d^{H_3O^+}$, seem to correlate also with the $pK_a^{BH_2^+}$ [eqns. (7) and (8)].

$$\log k_{NO}^{H_2O} = (9.5 \pm 0.5) + (0.7 \pm 0.1)pK_a^{BH_2^+} \quad (r = 0.97) \quad (7)$$

$$\log k_d^{H_3O^+} = -(1.10 \pm 0.03) + (0.08 \pm 0.007)pK_a^{BH_2^+} \quad (r = 0.97) \quad (8)$$

The possibility of the existence of general-base catalysis similar to that found in the nitrosation of amides was also investigated. Fig. 6 shows the influence of the total concentration of monochloroacetic acid on the ratio $k_{obs}/[H^+]$ for the nitrosation of **II**. For this set of experiments, eqn. (9) can be derived from

$$\frac{k_{obs}}{[H^+]} = k_d^{H_3O^+} + K_1k_{NO}^{H_2O}[S] + \left(\frac{k_d^{AH}}{K_a^{AH}} + K_1k_{NO}^{A^-}[S]\right)\frac{K_a^{AH}}{K_a^{AH} + [H^+]}[\text{buffer}] \quad (9)$$

Table 5 Catalytic constants, $k_{NO}^{A^-}$, for nitrosation of *N*-methylbenzenesulfonamides

	$k_{NO}^{A^-}/M^{-1}\ s^{-1}$				
	4-CH_3O	4-CH_3	4-CH_3 [a]	4-Cl	4-NO_2
CH_3COO^-	$(4.6 \pm 0.15) \times 10^8$	$(2.9 \pm 0.6) \times 10^8$	—	$(1.3 \pm 0.4) \times 10^8$	—
$ClCH_2COO^-$	$(1.1 \pm 0.15) \times 10^8$	$(6.6 \pm 1.2) \times 10^7$	$(9.4 \pm 2) \times 10^7$	$(2.9 \pm 1.0) \times 10^7$	3.2×10^6
Cl_2CHCOO^-	$(3.0 \pm 0.5) \times 10^7$	$(2.2 \pm 0.5) \times 10^7$	2.2×10^7	$(8.6 \pm 3.0) \times 10^6$	9.4×10^5
Cl_3CCOO^-	$(4.2 \pm 0.7) \times 10^7$	$(2.5 \pm 0.5) \times 10^7$	2.9×10^7	$(7.0 \pm 2.4) \times 10^6$	8.4×10^5
β_{NO}	0.28 ± 0.05	0.28 ± 0.04	—	0.32 ± 0.02	0.27 ± 0.06

[a] Experimentally determined (see text).

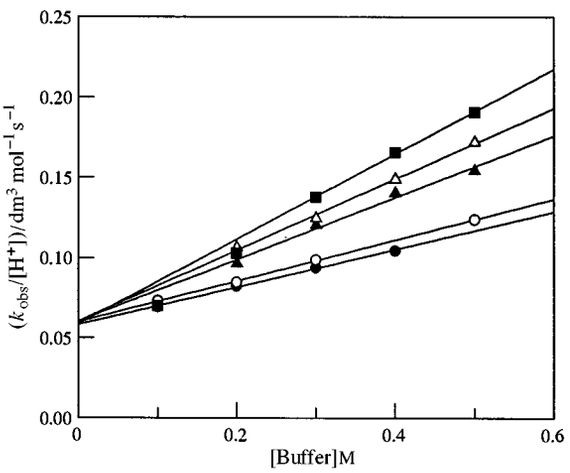


Fig. 6 Influence of the concentration of buffers monochloroacetic acid–monochloroacetate on k_{obs} for the nitrosation of the *N*-methyl-4-methylbenzenesulfonamide at $T = 25$ °C. [Sulfonamide] = 6.67×10^{-3} M. Ionic strength 0.50 M ($NaClO_4$). (●) pH = 2.10, (○) pH = 2.25, (▲) pH = 2.64, (△) pH = 2.78 and (■) pH = 3.30.

eqn. (3), where K_a^{AH} is the dissociation constant of the acid used, and [S] is the concentration of the sulfonamide that is being nitrosated.

In accordance with this equation, reciprocals of the slopes from Fig. 6 show a linear dependence on $[H^+]$ [eqn. (10)] (not shown). From this plot a value for the dissociation constant of monochloroacetic acid was obtained ($pK_a = 2.60$) in good agreement with literature values. Moreover, the second-order rate constant for the reaction catalysed by the monochloroacetic anion was also determined as $k^{A^-} = (9 \pm 2) \times 10^7\ M^{-1}\ s^{-1}$.

$$1/\text{slope} = K_a^{AH}/(k_d^{AH} + K_a^{AH}k_{NO}^{A^-}[S]) + [H^+]/(k_d^{AH} + K_a^{AH}k_{NO}^{A^-}[S]) \quad (10)$$

Catalytic constants of dichloroacetic and trichloroacetic buffers for nitrosation of sulfonamide **II** were obtained from the linear relationship between k_{obs} and buffer concentration using eqn. (9) (Table 5). These constants can also be obtained from the values of the denitrosation catalytic constants, the equilibrium constant of the nitrosation reaction and the acidity constant of the buffer used [eqn. (11)]. Both sets of values for

$$k_{NO}^{A^-} = \frac{K_{NO}k_d^{AH}}{K_a^{AH}} \quad (11)$$

sulfonamide **II** agree well (Table 5). In the Discussion section we will use constants $k_{NO}^{A^-}$ obtained from eqn. (11).

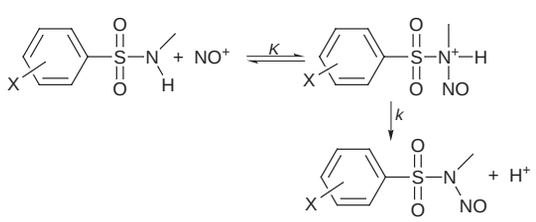
Discussion

According to the principle of microscopic reversibility, the transition state (**TS**) of both the nitrosation and denitrosation reactions must be the same. At a first glance, the results obtained for denitrosation: absence of catalysis by nucleophiles, general-acid catalysis, and the kinetic solvent isotope effect, suggest a rate-determining protonation of the substrate. This mechanism is similar to that of amides. However, a more detailed analysis of the results leads to a quite different proposal.

Evidence of a concerted mechanism

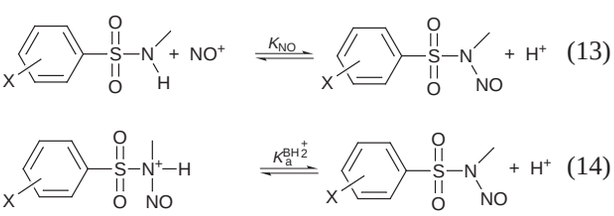
Results in Tables 2 and 4 clearly show that both processes, denitrosation and nitrosation, show similar substituent effects. Electron withdrawing groups retard both denitrosation and nitrosation. If a single proton transfer were involved in the rate determining step, electron withdrawing groups would certainly increase the rate of the nitrosation process because of the enhanced acidity of the protonated *N*-nitrososulfonamide. Then the sequence of nitrosation rates of sulfonamides would be the opposite of what was observed (Table 4).

The substituent effects in the nitrosation process could be achieved by a stepwise mechanism involving a fast nitrosation pre-equilibrium followed by a slow proton transfer to the medium [eqn. (12)]. In that case electron withdrawing groups



(12)

will disfavour the formation of the protonated nitroso intermediate, and substituent effects will arise from the balance of the pre-equilibrium constant and the deprotonation rate constant. We can calculate the pre-equilibrium constant *K* from K_{NO} and $(pK_a^{BH_2^+})_{NO}$ of the nitroso derivatives [eqns. (13)–(15)



(13)

(14)

$$K = K_{NO}(K_a^{BH_2^+})_{NO} \quad (15)$$

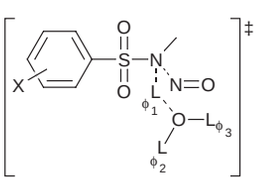
$(pK_a^{BH_2^+})_{NO} = pK_a^{BH_2^+} - 10]$ where the obtained values for *K* vary from 1.05×10^{-5} to 7.10×10^{-10} for the 4-MeO and 4-NO_2 derivatives, respectively. Since the measured rate constants for the overall reaction have a 70-fold variation, the rate constants for the slow process must vary by three orders of magnitude, this is not consistent with a process that should be diffusion controlled because of the difference of pK_a of the involved species ($\Delta pK_a > 12$). A protonated nitrososulfonamide with $pK_a < -13$ according to Eigen theory [19] would deprotonate in water at a diffusion-controlled rate and no intermediate would be formed.

With regard to the denitrosation process the observed

sequence of reactivity is in keeping with a rate-determining protonation although the difference in reactivity between the 4-CH_3O and 4-NO_2 is only 1.65, which is rather small when compared with the corresponding difference in acidity, 1000 between the 4-CH_3O and 4-NO_2.

The concomitant substituent effects on both rates of denitrosation and nitrosation lead us to think that the rate-determining step is not a simple proton transfer. Moreover, for denitrosation the rate-limiting step should be a concerted process where substrate protonation must be simultaneous with N···NO bond breaking. This mechanism accounts for the effect of the substituents assuming an asymmetric **TS** with protonation advanced to N···NO bond breaking. Obviously, for nitrosation the **TS** will also be asymmetric, with N···NO bond formation advanced to the deprotonation.

The values observed for the solvent isotope effect are $k_d^{H_3O^+}/k_d^{D_3O^+} = 1.20–2.04$ for the denitrosation by H_3O^+ and $k_d^{AH}/k_d^{AD} = 1.5–2.3$ for the reaction catalysed by dichloroacetic acid. Any pre-equilibrium protonation would be characterised by a solvent isotope effect of less than 0.5.[20] The value observed for the isotope effect, $k_d^{H_3O^+}/k_d^{D_3O^+} = 1.20–2.04$, is small for a rate-limiting proton transfer, but is in fact quite typical of protonation by L_3O^+.[20,21]



For the transition state shown above the ratio $k_d^{H_3O^+}/k_d^{D_3O^+}$ is given by eqn. (16) where l is the fractionation factor of L_3O^+

$$\frac{k_d^{H_3O^+}}{k_d^{D_3O^+}} = \frac{l^3}{\varphi_1\varphi_2^2} \qquad (16)$$

($l = 0.69$), φ_1 is that of the proton being transferred (the 'in-flight' proton) and φ_2 is that of the other L atoms. Since the 'in-flight' proton is loosely bound, the value of φ_1 is assumed to be small and that of φ_2 is intermediate between l and 1.[22] The fractionation factor of the *N*-nitrososulfonamide is assumed to be unity, as is usual for uncharged substrates. Only the small numerator on the right-hand side of eqn. (16) can bring about a low $k_d^{H_3O^+}/k_d^{D_3O^+}$ ratio by balancing the small value of φ_1 in the denominator.[20] Proton transfer to *N*-nitrososulfonamide from some other general acid LA with a fractionation factor, φ_{LA}, close to unity would give rise to a larger primary isotope effect.[23]

About the transition state

The situation of the **TS** along the reaction coordinate can be schematically represented by a typical Jencks and More O'Ferrall[24,25] (Fig. 7) diagram. In our case protonation and bond-breaking processes are represented by each axis. The location of the **TS** can be approximately plotted using Brønsted α_d values as a measure of proton transfer and α_{lg} of Leffler for the N···NO bond breaking. The Brønsted α_d values for denitrosation of *N*-methyl-*N*-nitrososulfonamides are close to 0.7 (Table 3). These values show that protonation of sulfonamide is nearly complete in the **TS**. From the values of $k_d^{H_3O^+}$ for denitrosation by H_3O^+ we obtain a value for $\alpha^v_{lg} \cong 0.1$ [eqn. (8)]. However, whereas Brønsted α_d values are by definition normalised, α^v_{lg} values must be normalised with respect to the α_{eq} of a suitable calibration equilibrium. We have used the value of $\alpha_{eq} = 0.6$ corresponding to the variation of K_{NO} with the $pK_a^{BH_2^+}$ of sulfonamides [eqn. (6)]. In this way, a normalised value for $\alpha_{lg} = 0.17$ was obtained. This can be considered an index of the degree of N···NO bond breaking in the **TS** for denitrosation.

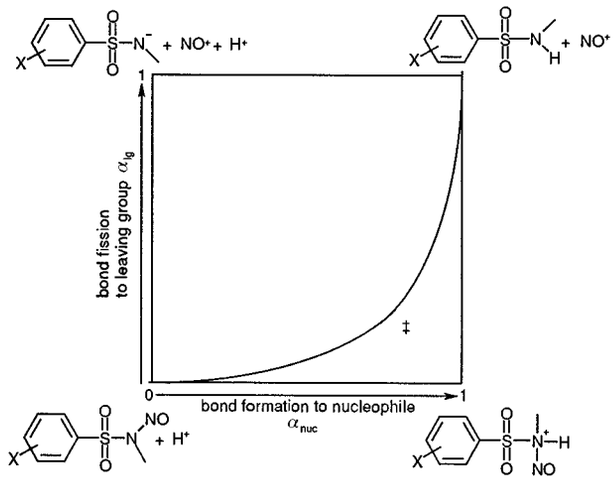
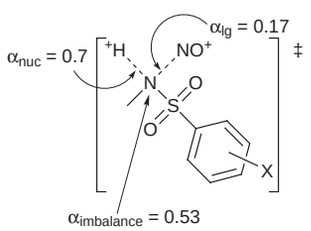


Fig. 7 Jencks and More O'Ferrall diagram for the **TS**

Considering both values, the position of the **TS** in a typical Jencks and More O'Ferrall diagram is shown in Fig. 7.

Leffler methodology[26] has been frequently used for the discussion of asymmetric reactions, such as phenolysis of sulfurylpyridines[27] or aminolysis of triazenes.[28] If the extent of bond formation (α_{nuc}) and bond fission (α_{lg}) are not the same in the **TS**, the Leffler parameters α_{nuc} and α_{lg} will not be the same and an imbalance in the effective charge will result.[29] The difference $\alpha_{nuc} - \alpha_{lg}$ provides the apparent Leffler parameter $\alpha_{imbalance}$ which is a measure of the sign and amount of charge accumulated in the **TS** relative to the total amount possible if the transition structure resembled either the dissociative intermediate (resulting from N···NO fission when $\alpha_{imbalance}$ would be -1) or the associative intermediate (resulting from the *N*-nitrosamine protonation when $\alpha_{imbalance}$ would be $+1$). The ratio α_{nuc}/α_{lg} for the denitrosation reaction is greater than unity ($\alpha_{nuc}/\alpha_{lg} = 4.12$). This indicates that there is an imbalance[29] with bond formation being advanced over bond breaking. The resultant build-up of a positive charge on the nitrogen atom adjacent to the nitroso group corresponds to a hypothetical Leffler value '$\alpha_{imbalance}$' of 0.53 as is illustrated below.



Intrinsic rate constants for nitrosation of *N*-methylsulfonamides

The catalytic constants for nitrosation, $k_{NO}^{A^-}$, and for denitrosation, k_d^{AH}, of sulfonamides by carboxylic acids fit linear Brønsted relationships. The values of α_d and β_{NO} (Tables 3 and 5, respectively) allow us to calculate a β for the equilibrium equal to one. The intersection of the two Brønsted plots in Fig. 8 allows a direct determination of the intrinsic rate constant for nitrosation of *N*-methylsulfonamides according to Marcus theory, defined as $k_0 = k^{A^-} = k_d^{AH}$ when $pK_a^{AH} + \log K_{NO} = 0$.[29]

Additional insights may be gained from consideration of the intrinsic rate constants for nitroso group transfer. The intrinsic rate constant, k_0, provides a measure of the purely kinetic barrier (intrinsic reactivity) of the reaction. The log k_0 values are included in Table 4. It is difficult to give precise error limits for these parameters, because they depend not only on uncertainties in the rate constants and pK_a^{AH} values but also on the linear extrapolation and on the assumptions made to calculate the intrinsic rate constants. Log k_0 decreases following

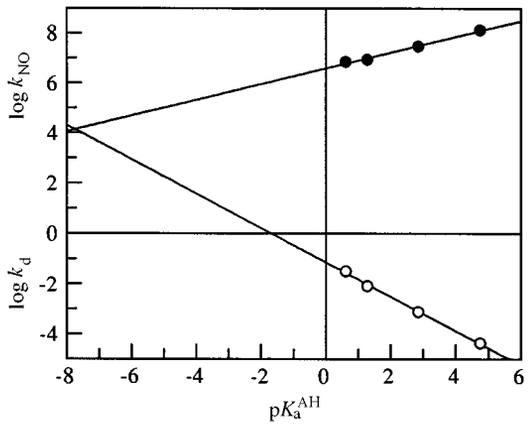


Fig. 8 Brønsted plots for nitrosation–denitrosation of **III**

the sequence: 4-MeO > 4-Me > 4-Cl > 4-NO_2. The main contributing factor to this decrease is destabilisation of the positive charge generated on the nitrogen atom adjacent to the nitroso group by electron withdrawing substituents.

Formation of nitroso compounds

It is interesting to compare the mechanism of nitrosation and denitrosation of *N*-methyl-*N*-nitrososulfonamides with that of other families of *N*-nitroso compounds. The absence of reaction intermediates during the denitrosation of nitrososulfonamides is in contrast to what is observed for *N*-nitrosamines and *N*-nitrosamides. For *N*-nitrosamines the mechanism of denitrosation involves a rapid protonation equilibrium followed by nucleophilic attack on the nitroso group.[2–5] The presence of a nitroso group diminishes the protonation pK_a of amines by about 10 units[19] and one can conclude that the pK_a of a protonated nitrosamine must be around 0, making it sufficiently stable in aqueous medium. Using a similar approach, a protonated *N*-methyl-*N*-nitrosobenzenesulfonamide would have p$K_a = -14$, and thus, its water deprotonation should be diffusion-controlled.[30] Such an intermediate would be too unstable and the reaction presumably occurs by an 'enforced concerted mechanism'.[24,31] It is not expected that the N···NO bond breaking occurs during denitrosation of *N*-nitrosamines with partial generation of the negative charge on the nitrogen atom simply because the second pK_a of deprotonation of amines (p$K_a = 26$ and approx. 16 for a nitrosamine) is high in comparison with that of sulfonamides (p$K_a = 11$ and approx. 1 for *N*-methyl-*N*-nitrosobenzenesulfonamide).[13] Amides and ureas possess a protonation pK_a around 3 that could account for the occurrence of concerted mechanisms of nitrosation and denitrosation. A protonated nitrosamide would have a p$K_a = -12$ and consequently following Eigen theory[30] would deprotonate in water at a diffusion-controlled rate and no intermediate is formed. This apparent disagreement was interpreted in the past[29] by considering that nitrosation takes place on oxygen and then is followed by a slow proton transfer. This mechanism implies that it is the iminium (pK_a close to 0) and not the nitrosamide which is losing the proton.

All these arguments are in keeping with a concerted mechanism. Furthermore, the hydrolysis of *N*-methyl-*N*-nitrosobenzenesulfonamides fulfils Jencks criteria[24] for the possibility of proton transfer occurring concertedly with the formation or breaking of covalent bonds: the site of protonation undergoes a large change in pK_a during the course of the reaction and the pK_a of the catalyst lies between the initial and final pK_a values of the protonation site. The hydrolysis of *N*-methyl-*N*-nitrosobenzenesulfonamides under the conditions employed certainly satisfies these criteria since the pK_a of the N atom changes from *ca.* −15 to *ca.* 11 and the catalyst is H_3O^+ (p$K_a = -1.74$) or a carboxylic acid.

Transnitrosation and denitrosation

N-Nitrososulfonamides are well known for their ability to transfer their nitroso group to nucleophiles in slightly acidic or basic media, which makes them as good nitrosating agents as alkyl nitrites. Acidic hydrolysis of alkyl nitrites occurs by a concerted mechanism with an asymmetric transition state where the protonation on the oxygen adjacent to the nitroso group and the O···NO bond breaking occur simultaneously with a slight development of charge on the oxygen, in a quite similar way to the mechanism proposed here for *N*-methyl-*N*-nitrososulfonamides.[12] For a given nitroso compound the ability to transfer the nitroso group seems to be related to its capacity for stabilising negative charge on the atom adjacent to the nitroso group during transnitrosation. The alcohols used to prepare alkyl nitrites have pK_a values between 12 and 16. Those with the larger pK_a values generate the less reactive alkyl nitrites. Sulfonamides[7,8] have deprotonation pK_a values ranging between 10 and 12. Both alkyl nitrites and nitrososulfonamides easily stabilise negative charge on the oxygen of the alkoxide group and on the nitrogen of the sulfonamide, respectively. We therefore conclude that both the ability of transnitrosation and the concerted mechanism for denitrosation involving protonation and N···NO or O···NO bond breaking are related to the ability to stabilise negative charge.

Conclusions

The kinetic studies and in particular the substituent effects on the nitrosation–denitrosation of sulfonamides led us to propose a concerted mechanism for this process. The proton transfer and the N···NO bond breaking occur simultaneously in the transition state, though not synchronously. The results also show the existence of a significant imbalance between formation and fission of bonds, generating an important positive charge on the nitrogen adjacent to the nitroso group. Generation of this positive charge is due to the extent of protonation of the nitrososulfonamide (*ca.* 70%) in the denitrosation process and the extent of the nucleophilic attack of the sulfonamide on the NO^+ (*ca.* 83%) in the transition state for nitrosation. Thus we propose a third denitrosation pathway between those of nitrosamines and nitrosoureas. This concerted mechanism comes from the instability of a possible intermediate of nitrososulfonamide protonation and the capacity of the sulfonyl group to stabilise the negative charge on the nitrogen atom adjacent to the nitroso group. The mechanistic similarities found between acid denitrosation of nitrososulfonamides and alkyl nitrites suggest a relationship between nitrosation–denitrosation mechanisms and the ability to transfer their nitroso group.

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