Nitrosation of *N*-Methyl-4-tolylsulfonylguanidine†

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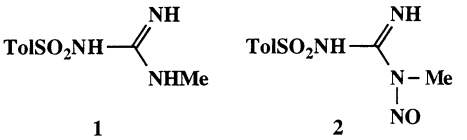
Kinetic studies for the nitrosation of *N*-methyl-4-tolylsulfonylguanidine identify a mechanism involving rapid nitrosation of the *N*-methyl nitrogen atom followed by slow, general-base-catalysed proton transfer.

The nitrosation of amines, amides, amidines and guanidines has received much attention, due in large part to the potential carcinogenic properties of the *N*-nitroso products formed. Nitrosation of amines in acidic medium occurs with rate limiting attack of the nitrosating agent on the substrate, while that of amides involves fast *O*-nitrosation followed by slow proton transfer from the substrate and a fast internal rearrangement to produce the *N*-nitrosamide.[1–3] Clonidine, a guanidine with antihypertensive properties, is nitrosated by nitrous acid *via* slow deprotonation of the *N*-nitrosated substrate.[4] However, guanidines like clonidine provide a bridge between amines and amides, because, in contrast to their behaviour in acidic media, under neutral conditions nitrosation by alkyl nitrites takes place *via* the neutral substrate.[4]

To examine the effect of electron withdrawing groups on the nitrosation of the guanidine moiety, we studied the nitrosation of *N*-methyltoluene-4-sulfonylguanidine (**1**) in acidic medium and herein report our results.



1 **2**

Experimental

N-Methyl-4-tolylsulfonylguanidine (**1**) (TSG) was synthesised from *N*-methylguanidine hydrochloride using toluene-4-sulfonyl chloride in acetone–aqueous sodium hydrochloride. TSG has mp 194–196 °C; δ_H ($CDCl_3$) 2.38 (3 H, s), 2.76 (3 H, s), 7.22 (2 H, d, *J* 8.6 Hz), 7.75 (2 H, d, *J* 8.6 Hz); *m/z* 227, 155, 91, 72. *N*-Methyl-*N*-nitroso-4-tolylsulfonylguanidine (**2**) (NTSG) was synthesised by the method of White.[5] NTSG has mp 168–170 °C; δ_H 2.43 (3 H, s), 3.18 (3 H, s), 7.32 (2 H, d, *J* 8.1 Hz), 7.87 (2 H, d, *J* 8.1 Hz); *m/z* 256 (M^+), 226 ($M^+ - NO$); λ_{max} 257 (log ε 4.08).

For solubility reasons, kinetic studies were carried out at 25 °C in water–dimethylsulfoxide (9:1 v/v) solutions at a constant ionic strength of 0.5 mol dm^{-3}. Kinetic analyses were performed using the initial rate method following the formation of NTSG, thus obviating problems associated with decomposition of nitrous acid.

Results and Discussion

Nitrosation of TSG appears to occur at the *N*-methyl nitrogen atom, as evidenced by the large shift in the ^1H NMR of the *N*-methyl signal of NTSG as compared to that in TSG.

The effect of $[H^+]$ on the initial rate of nitrosation of TSG (holding [TSG] and $[NO_2^-]$ constant) is shown in Fig. 1(*a*). Similar plots for the effects of $[NO_2^-]$ (holding $[H^+]$ and [TSG] constant) and [TSG] (holding $[H^+]$ and $[NO_2^-]$ constant) are shown in Figs. 1(*b*),(*c*). While the reaction is shown to have a simple, linear, first-order dependence upon [TSG] and $[NO_2^-]$, the plot for dependence upon $[H^+]$ is distinctly curved. The plot can be rationalised by a mechanism involving protonation of TSG in which nitrosation occurs *via* the unprotonated form of TSG; *i.e.*

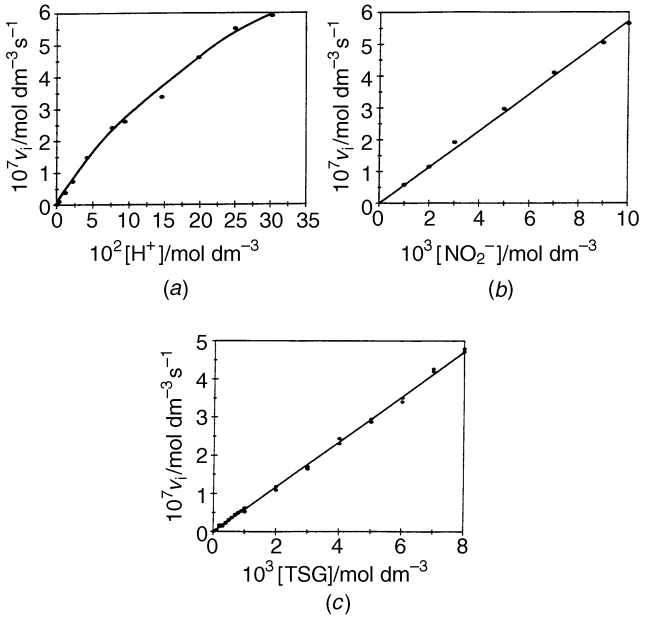


Fig. 1 Dependence of initial rates of nitrosation of TSG upon (*a*) $[H^+]$, (*b*) $[NO_2^-]$ and (*c*) [TSG]

$$TSG + H^+ \rightleftharpoons TSGH^+ \qquad (K_a = [TSG][H^+]/[TSGH^+])$$

$$TSG \xrightarrow{\text{nitrosation}} NTSG$$

Under the conditions of the reaction for the variation of $[H^+]$, the total concentration of TSG, $[TSG]_T$, is given by

$$[TSG]_T = [TSG] + [TSGH^+]$$

Thus, $[TSG] = [TSG]_T/(1 + [H^+]/K_a)$; as $[H^+]$ increases the amount of unprotonated TSG, the form which undergoes nitrosation, decreases. The data in Fig. 1(*a*) can be fitted to the rate equation

$$v_i = k_3[TSG]_T[NO_2^-][H^+]/(1 + [H^+]/K_a)$$

from which a value of 0.39 mol dm^{-3} for the acid dissociation constant, K_a, for TSG can be obtained. This corresponds to a pK_a of 0.4. The third-order rate constant, k_3, so obtained is contained in Table 1, together with those from the slopes of Figs. 1(*b*),(*c*) corrected for the concentration of unprotonated TSG, [TSG], at the acidity studied. The constant value of k_3 from the three different investigations reveals that the nitrosation of TSG has a first-order dependence upon [TSG], $[NO_2^-]$ and $[H^+]$.

Data for the influence of Cl^- and Br^-, ions that catalyse the nitrosation of amines but not of amides, upon the initial

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Table 1 Dependence of observed rate constants for the nitrosation of TSG upon the concentrations of reacting species

Varying species	$[H^+]$	$[TSG]_T$	$[NO_2^-]$	$10^5 k'/s^{-1}$[a]	$10^2 k'_3/dm^6$ [a] $mol^{-2}\ s^{-1}$	$10^2 k_3/dm^6$ $mol^{-2}\ s^{-1}$
H^+	—	0.005	0.01	—	—	6.9
TSG	0.1	—	0.01	5.90	5.90	7.41
	0.422	—	0.01	1.28	3.03	3.11[b]
NO_2^-	0.1	0.001	—	0.572	5.72	7.19

[a] k' is the pseudo-first-order rate constant obtained from the slope of v_i *vs.* the concentration of the varying species. k'_3 is the third-order rate constant obtained by dividing k' by the concentrations of the invariant species, uncorrected for the protonation of TSG. [b] In D_2O.

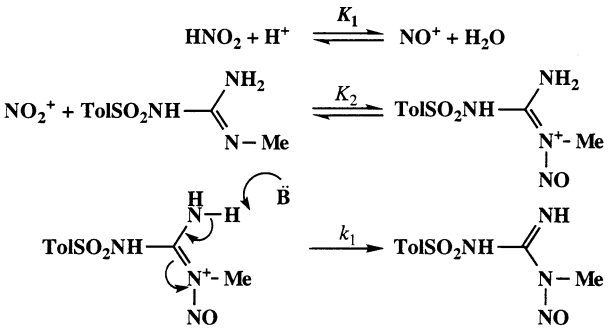
Table 2 Effect of added Cl^- and Br^- ions on the initial rate of nitrosation of TSG

$10^2[Cl^-]/mol\ dm^{-3}$	$10^2[Br^-]/mol\ dm^{-3}$	$10^8 v_i/mol\ dm^{-3}\ s^{-1}$
—	—	5.44
—	2.0	5.24
—	4.0	5.53
3.3	—	5.48
20.0	—	5.26

Table 3 Effect of TCA buffers on the initial rate of nitrosation of TSG[a]

$10[TCA]/mol\ dm^{-3}$	$10^8 v_i/mol\ dm^{-3}\ s^{-1}$
0.429	4.56
0.858	4.90
1.287	5.11
1.717	5.28
2.575	6.13

[a] $[TSG]_T = 0.001\ mol\ dm^{-3}$, $[NO_2^-] = 0.01\ mol\ dm^{-3}$, pH 1.0.



Scheme 1 Mechanism of the nitrosation of TSG

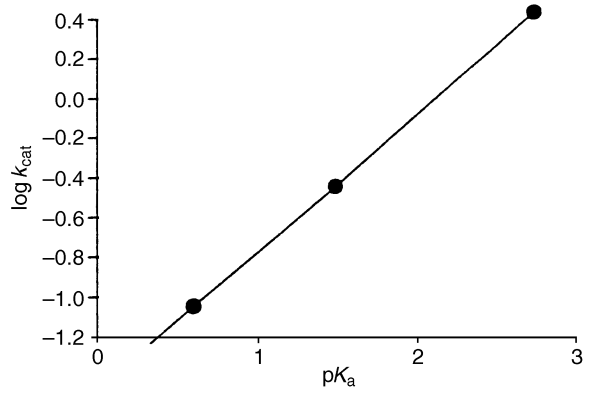


Fig. 2 Brønsted plot for general base catalysis of nitrosation of TSG

rates of reaction (Table 2) reveal that these ions have no catalytic effect. Thus, towards nitrosation, TSG behaves like an amide, and its nitrosation should be subject to buffer catalysis. The data in Table 3 for trichloroacetic acid (TCA) buffers are consistent with this expectation. Similar correlations are observed with dichloro- (DCA) and monochloro- (MCA) acetic acid buffers, and the catalytic rate constants, k_{cat}, for the catalysis by the basic form of the buffer, $[B^-]$, is obtained from plots of v_i *vs.* $[B^-]$ using $k_{cat} = \text{slope}/[NO_2^-][H^+][TSG]_{corrected}$. A Brønsted plot for the three buffers (Fig. 2) gives a value for β of 0.68. This is similar to that for clonidine,[4] and implies a slow proton transfer in the rate determining step.

The most likely mechanism for the nitrosation of TSG is shown in Scheme 1. We cannot be sure of the exact structure of the prototropic tautomer that reacts with NO^+, but that shown in Scheme 1 is the simplest that is consistent with the experimental data. Fast, pre-equilibrium nitrosation of TSG at the most nucleophilic, methyl-bearing nitrogen atom is followed by slow protonation transfer to the medium. According to Scheme 1, the rate of nitrosation can be expressed as

$$v = k_1K_1K_2[TSG][NO_2^-][H^+][H_2O] + k_{cat}[TSG][NO_2^-][H^+][B^-]$$

For the reaction in the absence of general bases (other than solvent water) the observed deuterium isotope effect, k_3^H/k_3^D is 2.38. However, $k_3 = k_1K_1K_2[H_2O]$, so $k_3^H/k_3^D = k_1^HK_1^HK_2^H[H_2O]/k_1^DK_1^DK_2^D[D_2O]$. The value of $[H_2O]/[D_2O] = 1.00$, and $K_1^H/K_1^D = 0.39$,[6] so assuming that there is a negligible isotope effect upon K_2, *i.e.* $K_2^H/K_2^D = 1$, because it does not involve a proton transfer, then the isotope effect upon the step involving proton transfer, k_1^H/k_1^D, is $2.38/0.39 = 6.1$. This is consistent with the proposed step being a slow proton transfer from an acidic species to water.

Thus, the sulfonylguanidine moiety behaves like amides and ureas towards nitrosation. It also has similar behaviour to that of the cyclic guanidine, clonidine. However, clonidine is a much more basic guanidine than TSG, *cf.* pK_1s of 8.7 and 0.4 respectively; whereas it is the protonated form of clonidine that is nitrosated, it is the unprotonated form of TSG that is nitrosated.

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