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Howard Maskill, Juan Crugeiras, William Mcfarlane, Ana Rios, Miguel Rios, et al.. Nitrosation of dialkylhydroxylamines, and computational and NMR investigations of the interconversion of conformational isomers of N nitroso dimethylhydroxylamine. *Journal of Physical Organic Chemistry*, 2010, 24 (2), pp.162. 10.1002/poc.1723 . hal-00599800

**HAL Id: hal-00599800**

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Submitted on 11 Jun 2011

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**Nitrosation of dialkylhydroxylamines, and computational and NMR investigations of the interconversion of conformational isomers of N nitroso dimethylhydroxylamine**

|                               |   |
|-------------------------------|---|
| Journal:                      | <i>Journal of Physical Organic Chemistry</i>  |
| Manuscript ID:                | POC-10-0030.R1  |
| Wiley - Manuscript type:      | Research Article  |
| Date Submitted by the Author: | 26-Mar-2010   |
| Complete List of Authors:     | Maskill, Howard; Newcastle University, Chemistry<br>Crugeiras, Juan<br>McFarlane, William<br>Rios, Ana<br>Rios, Miguel<br>Menneer, Iain |
| Keywords:                     | nitrosation, NMR kinetics   |
|                               |   |



Nitrosation of dialkylhydroxylamines, and computational and NMR investigations of the interconversion of conformational isomers of *N*-nitroso-dimethylhydroxylamine.

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**Keywords:** dialkylhydroxylamines, nitrosation, nitrosohydroxylamines, NMR kinetics, conformational isomers, computational chemistry.

### Abstract

The effect of acidity upon the rate of nitrosation of *N*-benzyl,*O*-methylhydroxylamine (**3**) in 1:1 (v/v) H<sub>2</sub>O:MeOH at 25 °C has been investigated. The *pseudo*-first-order rate constant ( $k_{\text{obs}}$ ) for loss of HNO<sub>2</sub> as the limiting reagent decreases as [H<sub>3</sub>O<sup>+</sup>] increases. This is compatible with two parallel reaction channels, Scheme 2. One involves direct reaction of the free hydroxylamine with HNO<sub>2</sub> ( $k_1 = 1.4 \times 10^2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , 25 °C) and the other involves reaction of the free hydroxylamine with NO<sup>+</sup> ( $k_2 = 5.9 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ). In contrast, there is only a very slight increase in  $k_{\text{obs}}$  with increasing [H<sub>3</sub>O<sup>+</sup>] for nitrosation of *N,O*-dimethylhydroxylamine (**4**) in dilute aqueous solution at 25 °C to give *N*-nitroso-dimethylhydroxylamine, **5**. This also fits a two-channel mechanism, Scheme 3. Again, one involves nitrosation of the free base by NO<sup>+</sup> ( $k_2 = 8 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , 25 °C) but the other channel now involves catalysis by chloride ( $k_3 = 1.3 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ). Arising from these results, we propose an estimate of  $\text{p}K_{\text{a}} \sim -5$  for protonated nitrous acid, (O=N-OH<sub>2</sub><sup>+</sup>), which is appreciably different from the literature value of +1.7.

The interconversion of *cis* and *trans* conformational isomers of **5** has been investigated by temperature-dependent NMR spectroscopy in CDCl<sub>3</sub>, methanol-d<sub>4</sub>, toluene-d<sub>8</sub>, and dimethyl sulfoxide-d<sub>6</sub>. Enthalpies and entropies of reaction and of activation have been

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3 determined, and compared with computational values obtained at the B3LYP/6-31G\* level of  
4 theory. The *cis* form is slightly more stable at normal temperatures and no solvent effects  
5 upon the thermodynamics or kinetics of the conformational equilibrium were predicted  
6 computationally or detected experimentally. In addition, key geometric parameters and dipole  
7 moments have been calculated for the *cis* and *trans* forms, and for the lowest energy transition  
8 structure for their interconversion, in the gas phase and in chloroform. These results indicate  
9 electronic delocalisation in the ground states of **5** which is lost in the transition structure for  
10 their interconversion.  
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## 17 Introduction

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19 There are many known nitrosating agents, *e.g.* nitrosyl compounds (halides, thiocyanate, and  
20 acetate), nitrogen oxides (nitric oxide, dinitrogen trioxide, and dinitrogen tetroxide), the  
21 nitrosonium ion ( $\text{NO}^+$ ), and nitroso sulphur compounds, but by far the most common reagent  
22 is the undissociated weak acid, nitrous acid ( $\text{HNO}_2$ ). Nitrosation of organic compounds has  
23 been studied since the earliest days of systematic organic chemistry,<sup>[1,2,3]</sup> the first report being  
24 by Behrend and König who prepared *N*-nitroso-dibenzylhydroxylamine by treating *N,O*-  
25 dibenzylhydroxylamine (**1** in Fig. 1) with nitrous acid.<sup>[1]</sup> Catalysis of nitrosation by  
26 nucleophiles has also been investigated.<sup>[4]</sup>  
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34 Nitrous acid ( $\text{p}K_a = 3.3$ ) is readily formed in aqueous solution by adding a nitrite salt  
35 (typically sodium nitrite) to an aqueous solution of a strong acid.<sup>[5]</sup> Under these conditions, it  
36 exchanges oxygen with the water, a reaction which can be exploited when oxygen isotope  
37 labelling is desired in the nitroso group.<sup>[6]</sup> Under acidic conditions, nitrous acid has been  
38 reported to be in equilibrium with its protonated form,  $(\text{H}_2\text{NO}_2)^+$ ,<sup>[4]</sup> its anhydride ( $\text{N}_2\text{O}_3$ ),<sup>[7,8]</sup>  
39 and the nitrosonium ion ( $\text{NO}^+$ ),<sup>[9]</sup> all of which are potential nitrosating agents; in addition, it  
40 undergoes decomposition to nitric oxide and nitric acid. There have been many wide-ranging  
41 discussions of nitrosation of amino compounds (including hydroxylamine) notably by Ridd  
42 and Stedman and their colleagues,<sup>[9-12]</sup> and the field has been comprehensively reviewed by  
43 Williams.<sup>[13]</sup> Particularly relevant to our current investigation is the effect of acidity upon the  
44 rate of nitrosation of *O*-alkylhydroxylamines by nitrous acid reported by Stedman.<sup>[10,11]</sup>  
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53 We reported recently an investigation of the mechanism of the acid-catalysed  
54 decomposition of a series of *N*-nitroso-dialkylhydroxylamines.<sup>[14,15]</sup> We now report the  
55 kinetics and mechanism of nitrosation of *N,O*-dialkylhydroxylamines (**1-3**) in acidic 1:1 (v/v)  
56 aqueous methanol and of *N,O*-dimethylhydroxylamine (**4**) in aqueous acid without the  
57 methanol cosolvent.  
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We also report an investigation of the conformational properties of *N*-nitroso-dimethylhydroxylamine (**5**) by NMR spectroscopy and theoretical methods; dynamic, thermodynamic, and structural parameters have been determined.

## Methods and Results

*Kinetics of nitrosation of N,O-dibenzylhydroxylamine (1), tetrahydro-1,2-oxazine (2), and N-benzyl,O-methylhydroxylamine (3).* Of the range of *N*-nitroso-dialkylhydroxylamines we had prepared for solvolytic studies,<sup>[15]</sup> the formations of three by nitrosation of the parent dialkylhydroxylamines (*N,O*-dibenzylhydroxylamine (**1**), tetrahydro-1,2-oxazine (**2**), and *N*-benzyl,*O*-methylhydroxylamine (**3**)) were selected as representative for mechanistic investigation and comparison with literature results. All were available as the substituted hydroxylammonium chlorides which, given their  $pK_a$  values (typically  $\approx 5$ ),<sup>[5,11]</sup> remain very largely in their protonated forms in aqueous acidic solution. In each case, therefore, the total initial concentration of all hydroxylamine species was taken to be equal to the initial concentration of the hydroxylammonium chloride and represented henceforth as  $[RNH_2OR^+]_0$ . And since  $[RNH_2OR^+]_0 \gg [NaNO_2]_0$ , it will (like  $[H_3O^+]_0$ ) remain approximately constant throughout the reaction. However, a high level of methanol in water (1:1, v/v) was needed to achieve the concentrations of hydroxylammonium chlorides that were required to ensure they were in large excess over the initial concentrations of nitrous acid. Similarly, as  $[H_3O^+]_0 \gg [NaNO_2]_0$  and  $pK_a = 3.3$  for  $HNO_2$ ,<sup>[5]</sup> the initial concentration of nitrous acid,  $[HNO_2]_0$ , was taken to be equal to the initial concentration of the sodium nitrite,  $[NaNO_2]_0$ , (and it decreased to zero as the reaction went to completion).

The UV range 300-400 nm was monitored and the crown-shaped absorbance attributed to nitrous acid (the limiting reactant) was seen to decrease by a clean first-order rate law (even though the overall changes in absorbances were small) as broad absorbances due to the nitroso-products increased. As seen in Table 1, the range in reactivity for compounds **1-3** is modest, as anticipated from the earlier work by Stedman.<sup>[11]</sup> Compounds **1** and **2** were then shown to be first order in hydroxylammonium by using different initial excess concentrations of  $RNH_2OR^+ Cl^-$  in the usual way (results not shown),<sup>[16]</sup> and **3** was studied at different initial excess perchloric acid concentrations (Table 2). Results in Tables 1 and 2 indicate that precision and reproducibility are satisfactory. Although nitrosation is first order in both hydroxylammonium and nitrous acid, Table 2 and Fig. 2 indicate that increasing initial hydronium ion concentrations lead to lower *pseudo*-first-order rate constants for **3**, so a complex rate law is implicated.

*Kinetics of nitrosation of N,O-dimethylhydroxylamine (4) in aqueous acid.* Our results for the effect of acidity upon the rate of nitrosation of **3** in aqueous methanol (Table 2 and Fig. 2) were not as anticipated from results reported earlier by Stedman who detected minimal dependence of  $k_{\text{obs}}$  upon  $[\text{H}_3\text{O}^+]_0$  for a series of *O*-alkylhydroxylamines in water.<sup>[11]</sup> Consequently, we reinvestigated the nitrosation of the simpler *N,O*-dialkylhydroxylamine (**4**) in aqueous acid without methanol as cosolvent. The reaction was monitored by following the increase in absorbance due to the formation of the *N*-nitroso product (**5**), and results for different starting concentrations of sodium nitrite in the range  $(0.05\text{--}5.0)\times 10^{-3}$  mol dm<sup>-3</sup> are shown in Table 3. As seen, the value of  $k_{\text{obs}}$  increases slightly with increasing  $[\text{NaNO}_2]_0$ ; however, the absorbance-time data deviated from first-order behaviour at higher values of  $[\text{NaNO}_2]_0$ , especially at the higher acidity. This effect had been noted earlier by Stedman for nitrosation of the parent hydroxylamine and attributed to competing nitrosation by  $\text{N}_2\text{O}_3$ .<sup>[12]</sup> Consequently, our further experiments were all carried out at  $[\text{NaNO}_2]_0 = 5\times 10^{-5}$  mol dm<sup>-3</sup>.

Figure 3 shows the effect of  $[\mathbf{4H}^+]_0$  (the initial concentration of the hydroxylammonium ion) upon  $k_{\text{obs}}$  at  $[\text{H}_3\text{O}^+]_0 = 0.05$  mol dm<sup>-3</sup>; the results appear to be in accord with a rate law comprising first and second order terms in  $[\mathbf{4H}^+]_0$ , *i.e.* rate =  $k_{\text{obs}} [\text{HNO}_2]$  with  $k_{\text{obs}}$  given by eqn 1, and a plot of  $k_{\text{obs}}/[\mathbf{4H}^+]_0$  versus  $[\mathbf{4H}^+]_0$  was indeed linear with  $a = (2.75 \pm 0.06)\times 10^{-2}$  dm<sup>3</sup> mol<sup>-1</sup> s<sup>-1</sup> and  $b = (2.80 \pm 0.02)$  dm<sup>6</sup> mol<sup>-2</sup> s<sup>-1</sup> (Fig. 4).

$$k_{\text{obs}} = a [\mathbf{4H}^+]_0 + b [\mathbf{4H}^+]_0^2 \quad (1)$$

However, since the initial concentration of the hydroxylammonium is equal to that of chloride,  $b [\mathbf{4H}^+]_0^2 = b [\mathbf{4H}^+]_0 [\text{Cl}^-]$ , so the second term in eqn 1 could be due to nucleophile catalysis by  $\text{Cl}^-$  as previously reported by Stedman for halides and  $\text{SCN}^-$  in the nitrosation of several hydroxylamines by nitrous acid.<sup>[11]</sup> To test this,  $\text{Cl}^-$  was replaced by perchlorate using Amberlyte IRA-410 anionic resin. Although 100% exchange was not achieved, the value of  $b$  in eqn 1 was much reduced whereas  $a$  was unchanged. In addition, Fig. 5 shows the effect of increasing concentrations of NaCl upon  $k_{\text{obs}}$  for nitrosation of **4** at  $[\text{H}_3\text{O}^+]_0 = 0.05$  mol dm<sup>-3</sup> and  $[\mathbf{4H}^+]_0 = 0.01$  mol dm<sup>-3</sup>. The intercept divided by  $[\mathbf{4H}^+]_0$  gave the result  $a = 4.5$  ( $\pm 2.1$ ) $\times 10^{-2}$  dm<sup>3</sup> mol<sup>-1</sup> s<sup>-1</sup> which, although of low precision, compares favourably with the result given above,  $(2.75 \pm 0.02)\times 10^{-2}$  dm<sup>3</sup> mol<sup>-1</sup> s<sup>-1</sup>. The slope divided by  $[\mathbf{4H}^+]_0$  gave the result  $b = 2.56$  ( $\pm 0.07$ ) dm<sup>6</sup> mol<sup>-2</sup> s<sup>-1</sup> in fair agreement with the value given above,  $2.80$  ( $\pm 0.02$ ) dm<sup>6</sup> mol<sup>-2</sup> s<sup>-1</sup>.

Finally in this context, Fig. 6 shows the effect of  $[\text{H}_3\text{O}^+]_0$  upon  $k_{\text{obs}}$  for nitrosation of **4** at  $[\mathbf{4H}^+\text{Cl}^-]_0 = 0.05$  mol dm<sup>-3</sup> in water; clearly, the effect is only small up to  $0.9$  mol dm<sup>-3</sup> in

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3 agreement with previous observations by Stedman for related compounds,<sup>[11]</sup> and quite  
4 different from what we had found for **3** in aqueous methanol.  
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7 *Determination of thermodynamic and kinetic parameters for the conformational*  
8 *isomerisation of N-nitroso-dimethylhydroxylamine (5) by NMR spectroscopy and related*  
9 *computational methods.* *N*-Nitrosamines and *N*-nitroso-hydroxylamines have been  
10 investigated in the past by <sup>1</sup>H and <sup>15</sup>N NMR spectroscopy,<sup>[17]</sup> and conformational isomerism  
11 of several *N*-nitroso-dialkylhydroxylamines was reported by Axenrod *et al.*<sup>[18]</sup> We have  
12 carried out new <sup>1</sup>H measurements on **5** at 500 MHz and -50 °C, and isotropic NMR  
13 parameters were calculated using B3LYP/6-311++G(d,p) in Gaussian03 with the Gauge-  
14 Invariant Atomic Orbital (GIAO) scheme and geometries optimised at the B3LYP/6-  
15 311++G(d,p) level.<sup>[19]</sup> Identical calculations were also carried out on tetramethylsilane and  
16 the results used as references to calculate proton and carbon chemical shifts. As seen in Table  
17 4, the computed and new experimental <sup>1</sup>H chemical shifts for *cis*- and *trans*-**5** are in good  
18 agreement with each other and with earlier experimental values. We have also measured <sup>13</sup>C  
19 NMR spectra of **5** at 125.77 MHz and 23 °C in CDCl<sub>3</sub> (assignments were confirmed by two-  
20 dimensional HSQC experiments) for comparison with our computed results in the gas (Table  
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34 In order to determine the thermodynamic and kinetic parameters for the conformational  
35 isomerisation of compound **5**, Scheme 1, <sup>1</sup>H NMR spectra were recorded at 500.16 MHz at  
36 different temperatures in deuteriochloroform (263-328 K), methanol-d<sub>4</sub> (263-328 K), toluene-  
37 d<sub>8</sub> (238-373 K), and dimethyl sulfoxide-d<sub>6</sub> (295-336 K; this relatively high lower temperature  
38 is enforced by the melting point of DMSO). At the lowest temperatures in each solvent, we  
39 see two sharp singlets (>NCH<sub>3</sub> and -OCH<sub>3</sub>) for each of the two conformational isomers of  
40 CH<sub>3</sub>N(NO)OCH<sub>3</sub> (see Fig. 7 for the spectrum in CDCl<sub>3</sub> at 253 K). Integration of the signals  
41 gives the relative proportions of the conformational isomers and hence the equilibrium  
42 constant at the measured temperature, which is the ratio of forward and reverse rate constants  
43 for the conformational equilibration ( $K = k_f/k_r$ ).  
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51 As the temperature is raised, the signals broaden as they begin to coalesce due to  
52 interconversion of the conformational isomers becoming faster compared with the time-scale  
53 of the NMR process; spectra in all solvents at the highest temperatures comprise only two  
54 broad signals (one for -O-CH<sub>3</sub> and one for >N-CH<sub>3</sub>). At each temperature, a first-order  
55 exchange rate constant,  $k_{ex}$ , was determined by line-shape analysis and simulation of the  
56 spectrum. The simulations of the <sup>1</sup>H NMR spectra were performed using Program gNMR,<sup>[20]</sup>  
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allowance being made for the variation of the proportions of *cis*- and *trans*-**5** with temperature, and also for the temperature dependence of the various chemical shifts which was particularly marked in the case of solutions in toluene. These latter effects can be attributed to reversible association of the solvent and solute and the large anisotropic diamagnetic susceptibility of toluene. In CDCl<sub>3</sub> and methanol, the chemical shifts of the >N-Me and -O-Me resonances of the more abundant *cis*-**5** were quite close, and their assignments were confirmed by two-dimensional EXSY experiments at 5 °C which related them to the corresponding widely separated resonances in the less abundant *trans* isomer. Representative experimental and simulated spectra in deuteriochloroform at specified temperatures, along with calculated exchange rate constants, are shown in Fig. 7. The <sup>13</sup>C NMR spectra at 125 MHz showed similar line broadening and coalescence behaviour fully consistent with the results from the <sup>1</sup>H spectra, although the signal-to-noise ratios attainable in the times available were insufficient to achieve comparable precision in spectral simulations.

Each exchange rate constant corresponds to a rate of conformational equilibration and is the sum of the rate constants for forward and reverse processes ( $k_{\text{ex}} = k_{\text{f}} + k_{\text{r}}$ ) shown in Scheme 1.<sup>[16]</sup> From these and the ratios of the rate constants from the equilibrium constants,  $k_{\text{f}}$  and  $k_{\text{r}}$  can be separately determined at each temperature. The enthalpies and entropies of activation for  $k_{\text{f}}$  and  $k_{\text{r}}$  processes in the various solvents were then obtained from plots using the Eyring equation:  $\ln(k/T) = 23.73 - (\Delta H^{\ddagger}/8.31T) + (\Delta S^{\ddagger}/8.31)$ ; in all cases, the least squares fits to straight lines had  $R^2 > 0.994$ . and results for the  $k_{\text{f}}$  process are included in Table 5. Results for  $\Delta H^{\circ}$  ( $= \Delta H_{\text{f}}^{\ddagger} - \Delta H_{\text{r}}^{\ddagger}$ ) and  $\Delta S^{\circ}$  ( $= \Delta S_{\text{f}}^{\ddagger} - \Delta S_{\text{r}}^{\ddagger}$ ) were the same as results obtained by the more usual van't Hoff method from values of  $K$  at different temperatures shown (with experimental values for  $\Delta G^{\circ}_{298}$ ) in Table 6.

*Computational structural investigation on N-nitroso-dimethylhydroxylamine (5).* Structures were optimized using the B3LYP method with a 6-31G(d) basis set using the Gaussian03 program.<sup>[19]</sup> For geometry optimizations in chloroform, the Polarized Continuum Model (PCM) approximation was used (TABS = 300.0, ALPHA = 1.21, TSNUM = 70, RADII = PAULING). Vibrational frequency calculations were performed on all stationary points at the B3LYP level to characterise them as minima (all real frequencies) or as transition structures (one imaginary frequency). Stable *cis* and *trans* conformational isomers, and two transition structures (TS1 and TS2) for their interconversion, were identified (Fig. 8). TS2 was found to be less stable than TS1, which was confirmed by results of higher level calculations (QCISD/6-311+G(d,p) and B3LYP/6-311++G(d,p)), and is not considered further. Key



geometric parameters (B3LYP/6-31G(d)) and dipole moments for *cis*-**5**, *trans*-**5**, and **TS1** in the gas phase are given in Table 7.

Zero-point vibrational energies, entropies, and thermal corrections to enthalpy and Gibbs free-energy values were obtained from the unscaled harmonic frequencies and moments of inertia by standard methods.<sup>[21]</sup> These led to the computed thermodynamic parameters for the conformational isomerisation *cis*-**5**  $\rightleftharpoons$  *trans*-**5** included in Table 6 (along with NMR experimental values), and computed activation parameters are compared with NMR experimental results in Table 5.

## Discussion

*Mechanism of nitrosation of N,O-dibenzylhydroxylamine (1), tetrahydro-1,2-oxazine (2), and N-benzyl,O-methylhydroxylamine (3) in aqueous methanol.* In aqueous acidic solution, nitrite anions will be essentially fully protonated ( $pK_a = 3.3$  for  $\text{HNO}_2$ )<sup>[5]</sup> and it has been previously assumed that the  $\text{HNO}_2$  so formed will be further protonated on the hydroxyl but to only a small degree, eqn 2.<sup>[4]</sup> On this assumption, a kinetic scheme involving  $\text{ONOH}_2^+$  as a reactive intermediate nitrosating agent may be derived (see later). However, the  $pK_a$  of  $\text{ONOH}_2^+$  has recently been reported to be 1.7,<sup>[22]</sup> in which case its concentration would be appreciable in aqueous acidic solutions of nitrites (even though it had eluded previous attempts at detection), and the steady state approximation may not be applied to it. This  $pK_a$  value requires that replacement of a hydrogen in  $\text{H}_2\text{O}$  by a nitroso group is both strongly acid-enhancing ( $pK_a = 15.7$  for  $\text{H}_2\text{O}$  and 3.3 for  $\text{HONO}$ ) and appreciably base-enhancing ( $pK_a = -1.74$  for  $\text{H}_3\text{O}^+$  and +1.7 for  $\text{ONOH}_2^+$ ). In contrast, our recent computational studies indicate that  $\text{ONOH}_2^+$  is not only a stronger acid than  $\text{H}_3\text{O}^+$ , but that it is also very unstable with respect to dissociation into  $\text{NO}^+$  and water, eqn 3.<sup>[23]</sup> Consequently, we combine eqns 2 and 3 into eqn 4 and, following earlier workers,<sup>[9]</sup> propose  $\text{NO}^+$  as the nitrosating agent additional to nitrous acid in dilute aqueous solutions of nitrite salts (but see later).



Hydroxylammonium ions ( $pK_a \approx 5$ ) are the conjugate acids of moderately strong bases,<sup>[5,11]</sup> so will be deprotonated in aqueous acids to only a very small degree; however, the free base will be the most reactive nucleophile present even though its concentration is very low. We

propose, therefore, the mechanism shown in Scheme 2 with two parallel reaction channels. A third possible channel involving catalysis by chloride to give ClNO can be ruled out by the finding that there is no kinetic term second-order in  $[\text{RNH}_2\text{OR}^+\text{Cl}^-]_0$  for the nitrosation of **3** as was observed for the nitrosation of **4** (see later). The rate law derived from the mechanism in Scheme 2 for compounds **1-3** in aqueous methanol is included in Scheme 2.

The experimental rate law for loss of nitrous acid is *pseudo*-first order, *i.e.* rate =  $k_{\text{obs}}[\text{HNO}_2]$ , so, if the mechanism of Scheme 2 is correct and assuming  $[\text{HNO}_2] \approx [\text{HNO}_2]_{\text{T}}$ ,  $k_{\text{obs}}$  is related to the parameters in Scheme 2 and eqn 4 by eqn 5.

$$k_{\text{obs}} = \frac{[\text{RNHOR}']_0 \cdot K_{\text{a1}} \cdot (k_1 + k_2 \cdot K_{\text{NO}} \cdot [\text{H}_3\text{O}^+])}{(K_{\text{a1}} + [\text{H}_3\text{O}^+]) \cdot (1 + K_{\text{NO}} \cdot [\text{H}_3\text{O}^+])} \quad (5)$$

As  $[\text{H}_3\text{O}^+] \gg K_{\text{a1}}$  and  $K_{\text{NO}} \cdot [\text{H}_3\text{O}^+] \ll 1$  (see below),

$$k_{\text{obs}} = [\text{RNHOR}']_0 \cdot K_{\text{a1}} \left\{ \frac{k_1}{[\text{H}_3\text{O}^+]} + k_2 \cdot K_{\text{NO}} \right\} \quad (6)$$

Equation 6 predicts a linear relationship between  $k_{\text{obs}}$  and the reciprocal of  $[\text{H}_3\text{O}^+]$  with a finite intercept. The plot is shown in Fig. 9, which indicates that the experimental results obtained for **3** are indeed compatible with the mechanism in Scheme 2. Moreover, the two second order rate constants  $k_1$  and  $k_2$  may be determined from the gradient and intercept of the plot, respectively, with values for  $K_{\text{a1}}$  and  $K_{\text{NO}}$ .

Using  $[\text{RNHOR}']_0 = 0.075 \text{ mol dm}^{-3}$ ,  $K_{\text{a1}} = 3.2 \times 10^{-5} \text{ mol dm}^{-3}$ ,<sup>[21]</sup> and  $K_{\text{NO}} = 3.5 \times 10^{-7} \text{ dm}^3 \text{ mol}^{-1}$ ,<sup>[13]</sup> we obtain  $k_1 = 1.4 \times 10^2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  and  $k_2 = 5.9 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ . We conclude that reaction between dialkylhydroxylamines and nitrosonium ion is diffusion controlled, and the lower overall reactivity of **3** at higher values of  $[\text{H}_3\text{O}^+]$  is because the increasing concentrations of  $\text{NO}^+$  do not compensate for the decreasing concentrations of the free hydroxylamine.

*Mechanism of nitrosation of N,O-dimethylhydroxylamine (4) in aqueous acid.* We saw above in the nitrosation of  $3\text{H}^+\text{Cl}^-$  in aqueous methanol that  $k_{\text{obs}}$  decreased with increasing  $[\text{H}_3\text{O}^+]$  (Fig. 2) and that this is due to the  $k_1$  term in eqn 6 corresponding to reaction of the decreasing concentrations of the free base with  $\text{HNO}_2$  (the  $k_1$  route in Scheme 2). This was not observed in the reaction of  $4\text{H}^+\text{Cl}^-$  in water; in fact  $k_{\text{obs}}$  increased slightly with increasing  $[\text{H}_3\text{O}^+]$  (Fig. 6), the anticipated result on the basis of earlier findings by Stedman for related compounds.

Consequently, we rule out any appreciable reaction between the free base **4** and HNO<sub>2</sub> under these reaction conditions. However, like Stedman, we observed catalysis by chloride so propose the mechanism in Scheme 3 for **4** with two principal reaction channels. If the mechanism of Scheme 3 is correct,  $k_{\text{obs}}$  of the experimental rate law (rate =  $k_{\text{obs}}$  [HNO<sub>2</sub>]) is related to the parameters in Scheme 3 by eqn 7.

$$k_{\text{obs}} = [\text{RNHOR}']_0 \cdot K_{\text{a1}} \cdot [\text{H}_3\text{O}^+] \cdot \frac{(k_2 \cdot K_{\text{NO}} + k_3 \cdot K_{\text{CINO}} \cdot [\text{Cl}^-])}{(K_{\text{a1}} + [\text{H}_3\text{O}^+])} \quad (7)$$

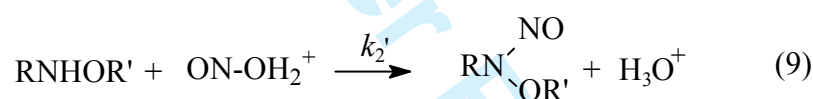
$$k_{\text{obs}} = [\text{RNHOR}']_0 \cdot K_{\text{a1}} \cdot (k_2 \cdot K_{\text{NO}} + k_3 \cdot K_{\text{CINO}} \cdot [\text{Cl}^-]) \quad (8)$$

This complex rate law may be approximated to eqn 8 since  $K_{\text{a1}} \ll [\text{H}_3\text{O}^+]$  (see below). Equation 8 predicts a linear plot of  $k_{\text{obs}}$  versus total chloride concentration,  $[\text{Cl}^-]_{\text{T}}$ , as is observed in Fig. 5. From the gradient of the plot ( $2.56 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ),  $[\text{4H}^+]_0 = 0.01 \text{ mol dm}^{-3}$ , and literature values for  $K_{\text{a1}}$  ( $1.78 \times 10^{-5} \text{ mol dm}^{-3}$ ),<sup>[24]</sup>  $K_{\text{NO}}$  ( $3.5 \times 10^{-7} \text{ dm}^3 \text{ mol}^{-1}$ ),<sup>[13]</sup> and  $K_{\text{CINO}}$  ( $1.1 \times 10^{-3} \text{ dm}^6 \text{ mol}^{-2}$ ),<sup>[13]</sup> we calculate  $k_3 = 1.3 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  at 25 °C which compares well with the result of  $1.5 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  at 0 °C reported by Stedman.<sup>[11]</sup> From the intercept in Fig. 5 ( $5 \times 10^{-4} \text{ s}^{-1}$ ) and the values for  $K_{\text{NO}}$  and  $K_{\text{a1}}$  given above,<sup>[13,24]</sup> we obtain  $k_2 = 8 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , *i.e.* diffusion control, in excellent agreement with the result obtained for **3** (see above). The mechanism of Scheme 3, therefore, accounts for the experimental results for nitrosation of compound **4** under the experimental conditions we used.

*Comparison of the nitrosation of compounds 1-3 and 4.* Nitrosation of compounds **1-3** was carried out in 1:1 (v/v) aqueous methanol; compound **4** was nitrosated in aqueous solution without the methanol; all substrates were used as their hydrochloride salts (RNH<sub>2</sub>OR<sup>+</sup> Cl<sup>-</sup>). For **3** in aqueous methanol, we have shown that a mechanism involving HNO<sub>2</sub> and NO<sup>+</sup> as the effective nitrosating agents satisfactorily accommodates the experimental findings, and HNO<sub>2</sub> is more than 10<sup>7</sup> times less reactive than NO<sup>+</sup> which reacts under diffusion control. Significantly, there was no evidence of catalysis by the counter-ion of the substrate, Cl<sup>-</sup>. In contrast, a second-order term in [RNH<sub>2</sub>OR<sup>+</sup> Cl<sup>-</sup>] implicates Cl<sup>-</sup> as a nucleophile catalyst for nitrosation of **4** in water. Under these conditions, both CINO (formed in the catalytic route) and NO<sup>+</sup> react with **4** close to or at the diffusion limit, and the much less reactive HNO<sub>2</sub> cannot compete as a nitrosating agent. Apart from the relatively minor differences in structure between **3** and **4**, the only obvious difference between the two reactions is the presence of methanol as cosolvent for **3**. Consequently, we have to conclude that the

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3 difference in solvents affects the relative magnitudes of the various equilibrium and rate  
4 constants sufficiently to determine the subtle balance between the competing nitrosation  
5 routes for **1-3** on the one hand and **4** on the other. There are insufficient data, however, either  
6 in the literature or from our own work, to allow extrapolation and accurate prediction of likely  
7 results in aqueous methanol solutions of other compositions.  
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12 *Base strength of nitrous acid.* In Scheme 2 and the associated text, we invoked  $\text{NO}^+$  as the  
13 reactive nitrosating agent (in addition to  $\text{HNO}_2$ ) rather than its precursor,  $\text{ONOH}_2^+$ , eqns 2-4.  
14 This was based upon a computational investigation of the protonation of  $\text{HONO}$ .<sup>[23]</sup> In the  
15 event that  $\text{ONOH}_2^+$  is trapped by  $\text{RNHOR}'$  faster than it fragments to  $\text{NO}^+$  and  $\text{H}_2\text{O}$ , eqn 9,  
16 and  $\text{ONOH}_2^+$  rather than  $\text{NO}^+$  is the reactive nitrosating agent, a mechanism analogous to that  
17 in Scheme 2 can be readily devised. With the usual approximations, the experimental rate  
18 constant is then given by eqn 10, rather than eqn 6, where  $K_{a2}$  is the equilibrium constant for  
19 the reverse of eqn 2 above, *i.e.* the acid dissociation constant of protonated nitrous acid. If we  
20 assume that  $\text{ONOH}_2^+$  is comparable with  $\text{ClNO}$  as a nitrosating agent,<sup>[26]</sup> *i.e.*  $k_2' \sim 10^8 \text{ dm}^3$   
21  $\text{mol}^{-1} \text{ s}^{-1}$ , we calculate  $\text{p}K_{a2} \sim -5$ . Whilst this is an approximate result, we suggest it is more  
22 credible than the value of 1.7 recently reported.<sup>[22]</sup>  
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$$k_{\text{obs}} = [\text{RNHOR}']_0 \cdot K_{a1} \left\{ \frac{k_1}{[\text{H}_3\text{O}^+]} + \frac{k_2'}{K_{a2}} \right\} \quad (10)$$

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43 *Conformational isomerisation of N-nitroso-dimethylhydroxylamine (5) by temperature-*  
44 *dependent <sup>1</sup>H NMR spectroscopy and computational methods.* Computed and experimental  
45 thermodynamic parameters for *cis-5*  $\rightleftharpoons$  *trans-5* are given in Table 6. Agreement amongst the  
46 experimental results in the several solvents and the computed results is within the probable  
47 experimental error of the NMR results. The computed results indicate no major effect of  
48 solvation by chloroform upon the equilibrium and none is found experimentally in non-polar,  
49 H-bonding, and dipolar aprotic solvents employed. Equilibrium favours the *cis* isomer but  
50 there is still about 20% of the less stable *trans* form present at 25 °C. Resolution of the free  
51 energy of reaction into enthalpy and entropy terms indicates no huge compensating effects or  
52 differences amongst the solvents: the entropy change for the *cis* to *trans* conversion is positive  
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3 but very small so compensates to only a small degree for the small positive enthalpy change  
4 associated with the conversion.  
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7 The agreement between the experimental and simulated NMR spectra shown in Fig. 7 is  
8 satisfactory indicating that the derived rate constants are reliable. Computed and  
9 experimental activation parameters for the *cis*-**5** → *trans*-**5** conversion are compared in Table  
10 5. As with the enthalpies and entropies of reaction, agreement amongst the experimental  
11 results in the several solvents, and with the computed values, is within the probable  
12 experimental error of the NMR results. Again, we see no computational prediction of a  
13 solvent effect upon the conformational interconversion and none is found. This is perhaps  
14 surprising in view of the computed greater dipolarity of the ground state forms compared with  
15 the transition structure for their interconversion (see above and Table 7).  
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19 *Structure of N-nitroso-dimethylhydroxylamine (5)*. The interconversion of *cis* and *trans*  
20 conformational isomers of compound **5** is shown in Scheme 4 along with their alternative  
21 resonance structures. We note that the degree of planarity at the central N and the dihedral  
22 angles in *cis* and *trans* forms will reflect the contribution of the alternative resonance  
23 canonicals, *i.e.* the degree of delocalisation. We also note that internal rotation about the  
24 central N-N bond which interconverts *cis* and *trans* forms of **5** reduces the degree of  
25 delocalisation, which will be close to zero in the transition structures when the dihedral angle  
26 is about 90 °.  
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30 The N-N bonds in the two stable conformers are very similar in length (Table 7), and  
31 shorter than a normal N-N bond,<sup>[27]</sup> *i.e.* as expected for partial double bond character indicated  
32 in Scheme 4. In contrast, the N-N bond in **TS1** is appreciably longer and corresponds to no  
33 discernable resonance interaction in the transition structure. Correspondingly, the nitroso N-  
34 O bond in **TS1** is normal for a double bond between O and N whereas the very similar N-O  
35 bonds in *cis*-**5** and *trans*-**5** are longer than normal indicating partial single bond character.<sup>[27]</sup>  
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37 In accordance with these findings, the sums of angles at N1 shown in Table 7 indicate (i) a  
38 high degree of pyramidity in **TS1** but only little in *cis*-**5** and *trans*-**5**, (ii) dihedral angles in  
39 *cis*-**5** and *trans*-**5** only about 15 ° out of planarity, and (iii) appreciably greater dipolarity in  
40 *cis*-**5** and *trans*-**5** than in **TS1**.  
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## 58 Experimental

59 *Representative kinetics measurement of the nitrosation of N-benzyl-O-methylhydroxylamine*  
60 (**3**). Aqueous perchloric acid (5.0 cm<sup>3</sup>, 0.4 mol dm<sup>-3</sup>) was mixed with methanolic *N*-benzyl-

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3 *O*-methylhydroxylammonium chloride ( $5.0 \text{ cm}^3$ ,  $0.30 \text{ mol dm}^{-3}$ ) to give solution A ( $10 \text{ cm}^3$ )  
4 which is  $0.2 \text{ mol dm}^{-3}$  in perchloric acid and  $0.15 \text{ mol dm}^{-3}$  in *N*-benzyl-*O*-  
5 methylhydroxylammonium chloride in 1:1 aqueous methanol.  
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9 Sodium nitrite (13.8 mg) was dissolved in 1:1 methanol:water ( $25 \text{ cm}^3$ ) to give solution  
10 B which is  $8.0 \times 10^{-3} \text{ mol dm}^{-3}$  in  $\text{NaNO}_2$ . Typically,  $1 \text{ cm}^3$  of each of the solutions A and B  
11 was injected into a 1 cm pathlength quartz UV cell whereupon the data acquisition was started  
12 at a wavelength in the range 320-330 nm (corresponding to the wavelength of greatest change  
13 in absorbance as the reaction proceeds) in the usual manner.<sup>[16]</sup> (The initial concentrations in  
14 the 1:1 methanol:water in the cell were  $[\text{HClO}_4] = 0.1 \text{ mol dm}^{-3}$ ;  $[\text{hydroxylammonium salt}]_0 =$   
15  $0.075 \text{ mol dm}^{-3}$ , and  $[\text{NaNO}_2]_0 = 4.0 \times 10^{-3} \text{ mol dm}^{-3}$ .)  
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19 The absorbance-time data were fitted to the exponential form of the first-order rate law  
20 equation to determine the *pseudo* first order rate constant.  
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25 *NMR spectroscopic measurements of the conformational equilibration of N-Nitroso-N,O-*  
26 *dimethylhydroxylamine (5)*. Pulsed FT  $^1\text{H}$  (500.16 MHz) NMR spectra were obtained from  
27 samples containing *ca.* 5 % of **5** in 5 mm o.d. tubes on a JEOL Lambda spectrometer using  
28  $70^\circ$  flip angles and a digital resolution in the transformed spectra of 0.15 Hz per point.  
29 Temperature calibration was done using the  $^1\text{H}$  spectra of samples of neat MeOH and 1,2-  
30 ethanediol. The number of transients recorded depended upon the amount of line-broadening  
31 at the different temperatures and was adjusted to give a satisfactory signal-to-noise ratio in  
32 each case. Any exponential window applied to the FID prior to transformation was adjusted  
33 to ensure the resulting additional line-broadening was insignificant in each case.  $^{13}\text{C}$  spectra  
34 were measured at 125.77 MHz, and the EXSY and HSQC experiments used standard pulse  
35 sequences.  
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#### 45 **Acknowledgements**

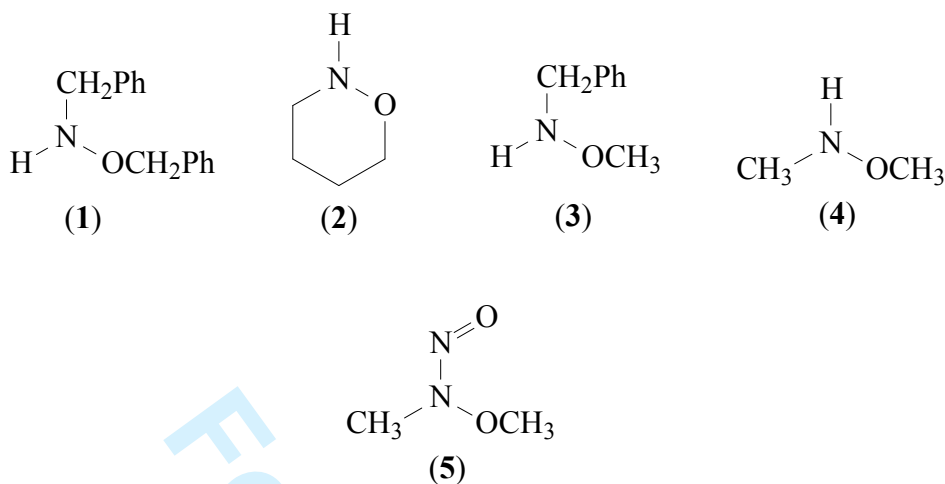
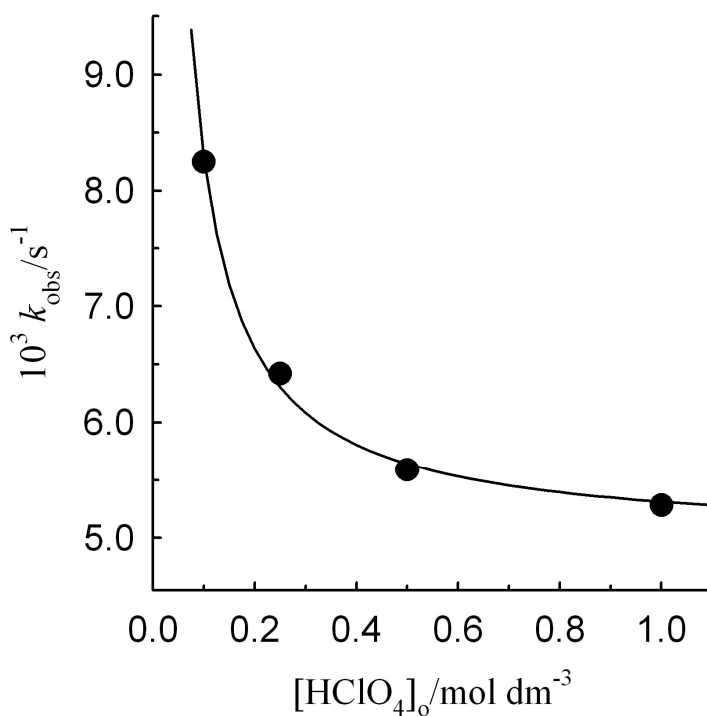
46 We thank the Centro de Supercomputacion de Galicia (CESGA) for computing facilities, and  
47 the EPSRC (UK) for partial funding of NMR facilities at Newcastle.  
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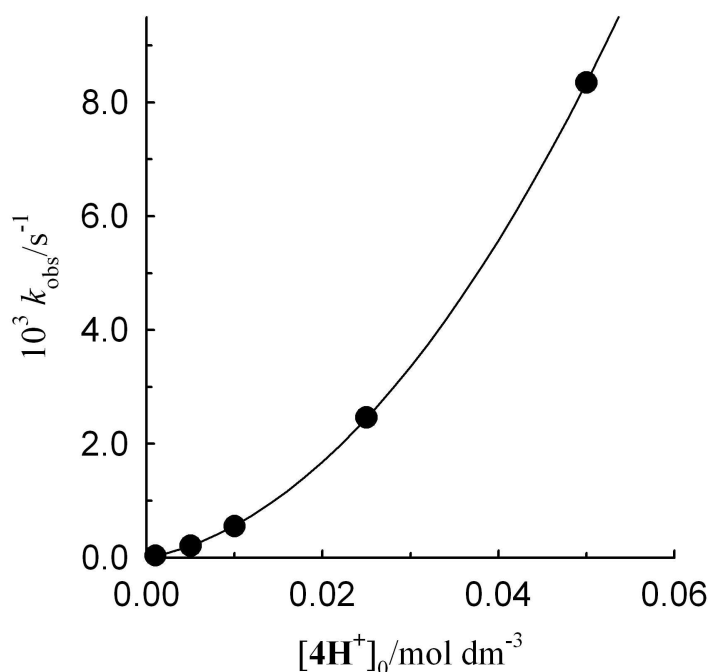
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  26. We thank Drs T. W. Bentley and R. A. McClelland for helpful discussions on this issue.
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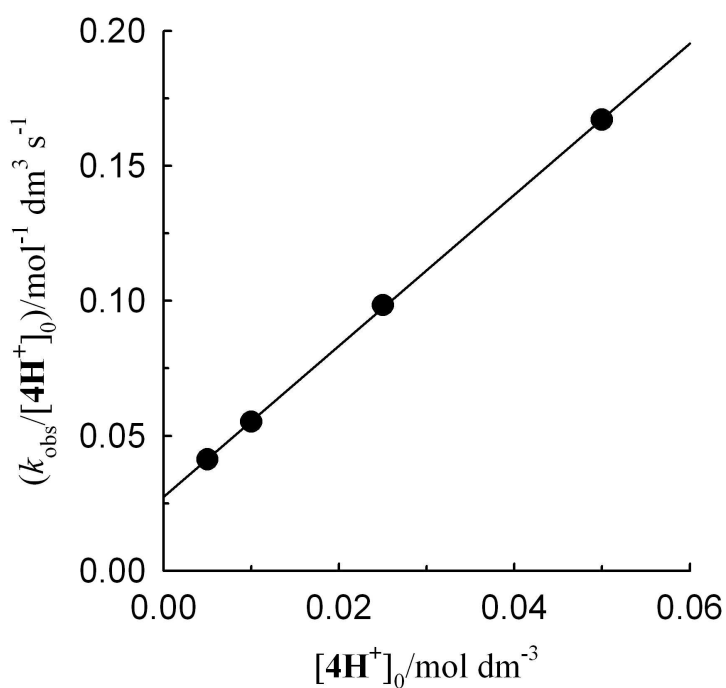
**Figure 1:** Hydroxylamines 1–4 and *N*-nitroso,dimethylhydroxylamine, 5**Figure 2:** Plot of *pseudo*-first-order rate constants against initial hydronium ion concentrations for nitrosation of *N*-benzyl-*O*-methylhydroxylamine (3) by sodium nitrite in 1:1 (v/v) aqueous methanolic perchloric acid at 25.0 °C.<sup>[a]</sup>

<sup>a</sup>  $[\text{NaNO}_2]_0 = 4 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\mathbf{3}]_0 = 0.075 \text{ mol dm}^{-3}$ .

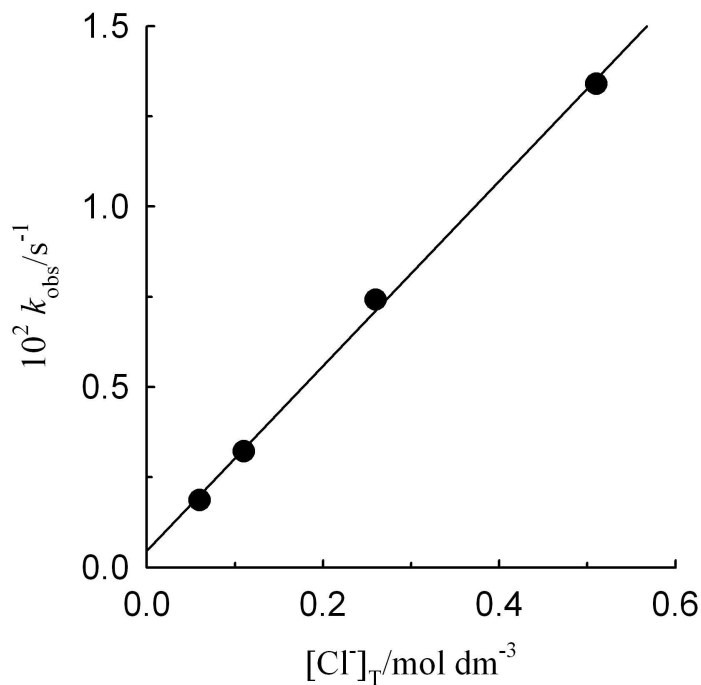
**Figure 3:** The effect of  $[4H^+]_0$  upon  $k_{obs}$  for nitrosation of **4** in aqueous solution at  $[H_3O^+]_0 = 0.05 \text{ mol dm}^{-3}$ ,  $[NaNO_2]_0 = 5 \times 10^{-5} \text{ mol dm}^{-3}$ ,  $25 \text{ }^\circ\text{C}$ ,  $I = 1.0$  ( $NaClO_4$ ).



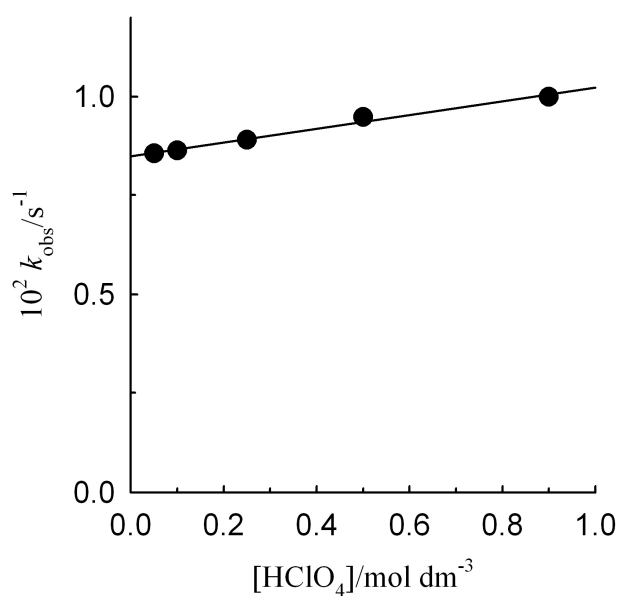
**Figure 4:** Plot of  $k_{obs}/[4H^+]_0$  versus  $[4H^+]_0$  for nitrosation of **4** in aqueous solution at  $[H_3O^+]_0 = 0.05 \text{ mol dm}^{-3}$ ,  $[NaNO_2]_0 = 5 \times 10^{-5} \text{ mol dm}^{-3}$ ,  $25 \text{ }^\circ\text{C}$ ,  $I = 1.0$  ( $NaClO_4$ ).



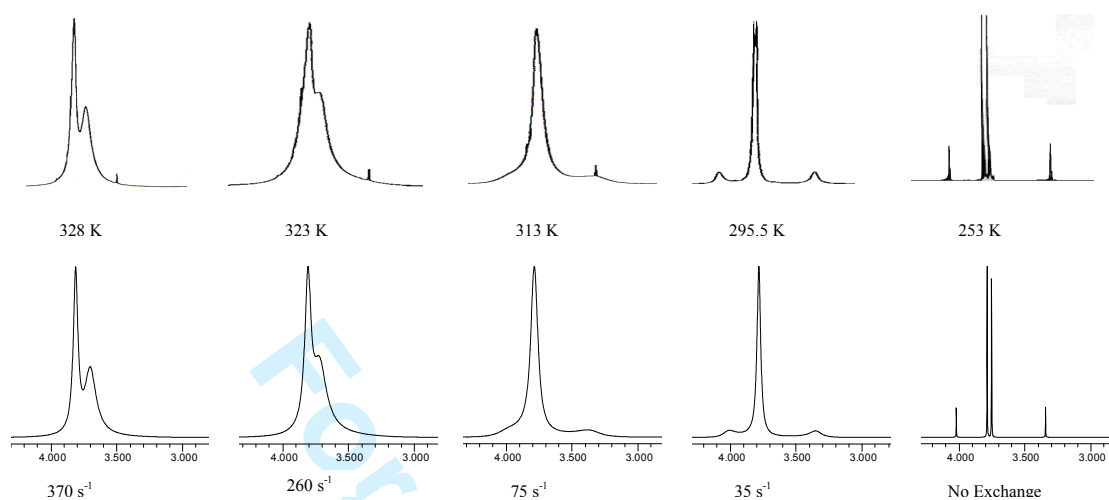
**Figure 5:** The effect of increasing concentrations of NaCl upon  $k_{\text{obs}}$  for the nitrosation of **4** at  $[\text{H}_3\text{O}^+]_0 = 0.05 \text{ mol dm}^{-3}$ ,  $[\text{4H}^+]_0 = 0.01 \text{ mol dm}^{-3}$ ,  $[\text{NaNO}_2]_0 = 5 \times 10^{-5} \text{ mol dm}^{-3}$ ,  $25 \text{ }^\circ\text{C}$ ,  $I = 1.0$  ( $\text{NaClO}_4$ ).



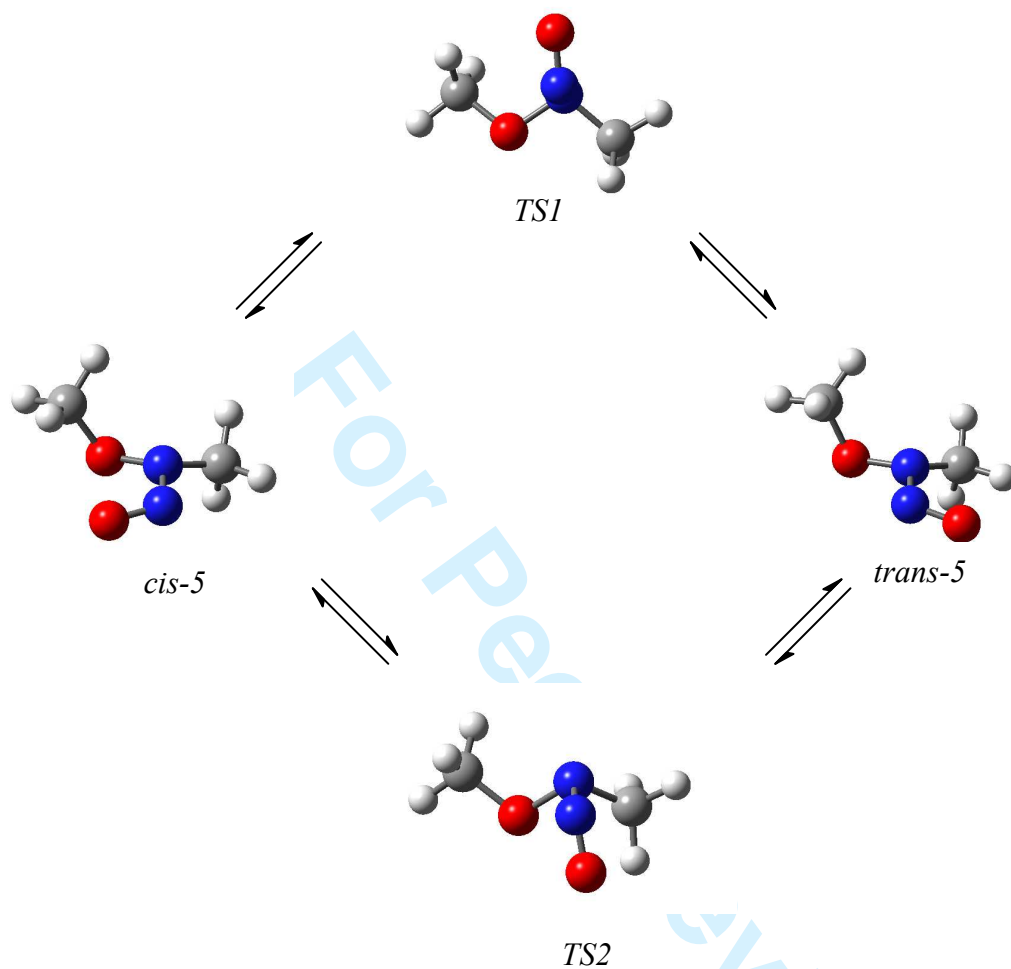
**Figure 6:** The effect of  $[\text{H}_3\text{O}^+]_0$  upon  $k_{\text{obs}}$  for nitrosation of **4** in water at  $[\text{4H}^+]_0 = 0.05 \text{ mol dm}^{-3}$ ,  $[\text{NaNO}_2]_0 = 5 \times 10^{-5} \text{ mol dm}^{-3}$ ,  $25 \text{ }^\circ\text{C}$ ,  $I = 1.0$  ( $\text{NaClO}_4$ ).



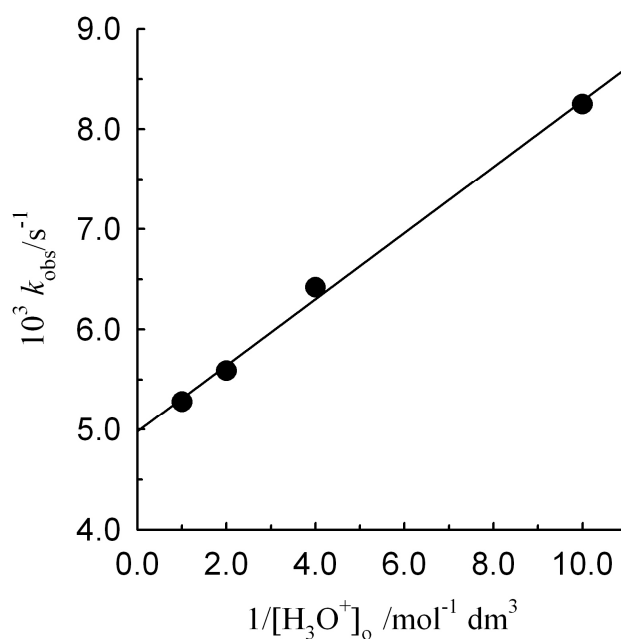
**Figure 7:** Comparison of experimental and simulated NMR spectra for *N*-nitroso-dimethylhydroxylamine (**5**) in CDCl<sub>3</sub>. (Temperatures are given below experimental spectra and corresponding calculated exchange rate constants are given below the simulated spectra.)



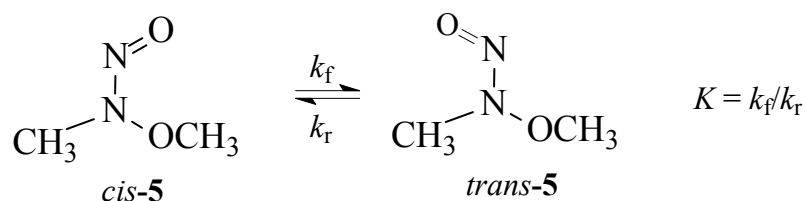
**Figure 8:** Gas phase optimized structures (B3LYP/6-31G(d)) for the *cis* and *trans* conformational isomers of  $\text{CH}_3\text{N}(\text{NO})\text{OCH}_3$  (**5**) and two transition structures (**TS1** and **TS2**) for their interconversion



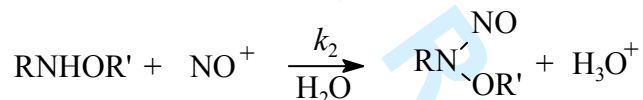
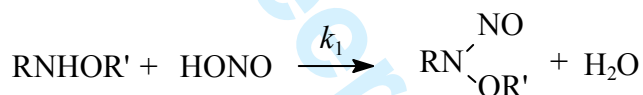
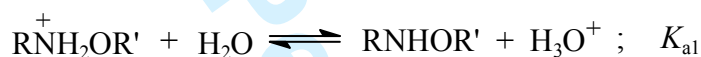
**Figure 9:** Plot of *pseudo*-first-order rate constants against the reciprocal of the initial hydronium ion concentrations for nitrosation of *N*-benzyl-*O*-methylhydroxylamine (**3**) in 1:1 (v/v) aqueous methanol at 25.0 °C. ( $[\text{NaNO}_2]_0 = 4 \times 10^{-3} \text{ mol dm}^{-3}$ ;  $[\text{RNH}_2\text{OR}^+]_0 = 0.075 \text{ mol dm}^{-3}$ ; gradient =  $3.30 \times 10^{-4} \text{ mol dm}^{-3} \text{ s}^{-1}$  (standard error =  $1.4 \times 10^{-5}$ ); intercept =  $4.98 \times 10^{-3} \text{ s}^{-1}$  (standard error =  $7.6 \times 10^{-5}$ ); correlation coefficient > 0.99).



**Scheme 1:** Conformational isomerisation of *N*-nitroso-dimethylhydroxylamine (**5**). (See footnote <sup>[a]</sup> to **Table 4** regarding *cis* and *trans* nomenclature.)



**Scheme 2.** Proposed mechanism and derived rate law for nitrosation of **1-3** by nitrous acid and nitrosonium ion in aqueous methanol.



$$\text{mechanistic rate} = k_1 [\text{RNHOR}'] [\text{HNO}_2] + k_2 [\text{RNHOR}'] [\text{NO}^+]$$

Substituting in this equation using

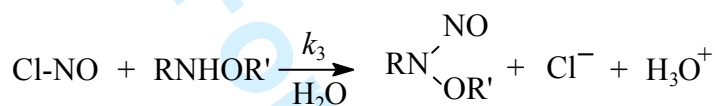
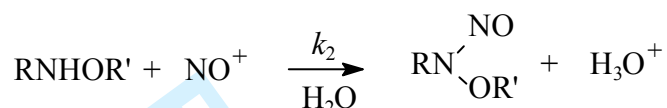
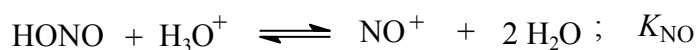
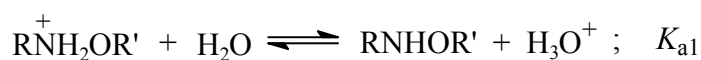
$$[\text{RNHOR}']_0 = [\text{RNH}_2\text{OR}'] + [\text{RNHOR}'], \quad [\text{HNO}_2]_T = [\text{HNO}_2] + [\text{NO}^+],$$

$$K_{a1} = \frac{[\text{RNHOR}'] [\text{H}_3\text{O}^+]}{[\text{RNH}_2\text{OR}']}, \quad \text{and (from eqn 4)} \quad K_{\text{NO}} = \frac{[\text{NO}^+]}{[\text{H}_3\text{O}^+] [\text{HNO}_2]},$$

we obtain

$$\text{mechanistic rate} = \frac{[\text{HNO}_2]_T \cdot [\text{RNHOR}']_0 \cdot K_{a1} \cdot (k_1 + k_2 \cdot K_{\text{NO}} \cdot [\text{H}_3\text{O}^+])}{(K_{a1} + [\text{H}_3\text{O}^+]) \cdot (1 + K_{\text{NO}} \cdot [\text{H}_3\text{O}^+])}$$

**Scheme 3.** Proposed mechanism and derived rate law for nitrosation of **4** in aqueous perchloric acid containing sodium nitrite with catalysis by chloride.



$$\text{mechanistic rate} = k_2 [\text{RNHOR}'] [\text{NO}^+] + k_3 [\text{RNHOR}'] [\text{ClNO}]$$

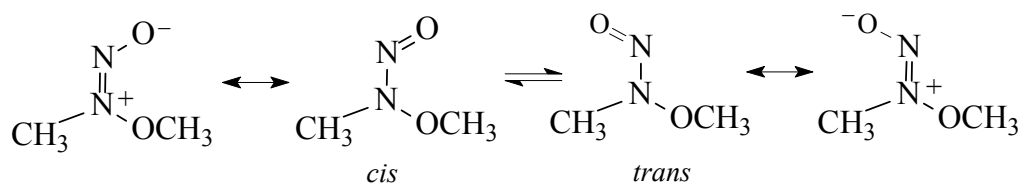
Substituting into this equation using  $[\text{RNHOR}']_0 = [\text{RNH}_2\text{OR}'] + [\text{RNHOR}']$ ,

$$K_{a1} = \frac{[\text{RNHOR}'] [\text{H}_3\text{O}^+]}{[\text{RNH}_2\text{OR}']}, \quad K_{\text{NO}} = \frac{[\text{NO}^+]}{[\text{H}_3\text{O}^+][\text{HNO}_2]}, \quad \text{and} \quad K_{\text{ClNO}} = \frac{[\text{ClNO}]}{[\text{H}_3\text{O}^+][\text{HNO}_2][\text{Cl}^-]},$$

$$\text{mechanistic rate} = \frac{[\text{HNO}_2] \cdot [\text{RNHOR}']_0 \cdot K_{a1} \cdot [\text{H}_3\text{O}^+] \cdot (k_2 \cdot K_{\text{NO}} + k_3 \cdot K_{\text{ClNO}} \cdot [\text{Cl}^-])}{(K_{a1} + [\text{H}_3\text{O}^+]}$$



1  
2  
3  
4  
5 **Scheme 4.** Electronic structures and interconversion of conformational isomers of *N*-nitroso-  
6 dimethylhydroxylamine (**5**). (See footnote <sup>[a]</sup> to **Table 4** regarding *cis* and *trans*  
7 nomenclature.)  
8  
9



**Table 1:** Kinetics of nitrosation of *N,O*-dibenzylhydroxylamine (**1**), tetrahydro-1,2-oxazine (**2**), and *N*-benzyl,*O*-methylhydroxylamine (**3**) under *pseudo*-first-order conditions in 1:1 (v/v) aqueous methanol containing perchloric acid, 25.0 °C.<sup>[a]</sup>

| Hydroxylamine  | $10^3 k_{\text{obs}}/\text{s}^{-1}$ | $10^4$ Standard Error | Wavelength <sup>[b]</sup> /nm |
|--|-------------------------------------|-----------------------|-------------------------------|
| <i>N,O</i> -Dibenzylhydroxylamine ( <b>1</b> )               | 22.5                                | 11.1                  | 345                           |
| Tetrahydro-1,2-oxazine ( <b>2</b> )                          | 1.48                                | 0.764                 | 322                           |
| <i>N</i> -Benzyl, <i>O</i> -methylhydroxylamine ( <b>3</b> ) | 8.01                                | 2.43                  | 333                           |

<sup>a</sup> In all cases,  $[\text{HClO}_4]_0 = 0.1 \text{ mol dm}^{-3}$ ;  $[\text{RNH}_2\text{OR}^+]_0 = 0.075 \text{ mol dm}^{-3}$ ;  $[\text{NaNO}_2]_0 = 4.0 \times 10^{-3} \text{ mol dm}^{-3}$ .

<sup>b</sup> In each case, the wavelength at which the decreasing absorbance change was greatest was selected.

**Table 2:** Effect of initial hydronium ion concentration on kinetics of nitrosation of *N*-benzyl,*O*-methylhydroxylamine (**3**) under *pseudo*-first-order conditions, 1:1 (v/v) aqueous methanol, 25.0 °C.<sup>[a]</sup>

| $[\text{HClO}_4]_0 / \text{mol dm}^{-3}$ | $10^3 k_{\text{obs}} / \text{s}^{-1}$ | $10^5$ Standard Error |
|--|---------------------------------------|-----------------------|
| 0.10 <sup>[b,c]</sup>                    | 8.25                                  | 7.52                  |
| 0.25 <sup>[b]</sup>                      | 6.42                                  | 5.06                  |
| 0.50 <sup>[b]</sup>                      | 5.59                                  | 20.9                  |
| 1.00 <sup>[d]</sup>                      | 5.28                                  | 4.92                  |

<sup>a</sup> For all cells,  $[\text{RNH}_2\text{OR}^+]_0 = 0.075 \text{ mol dm}^{-3}$ ;

<sup>b</sup>  $[\text{NaNO}_2]_0 = 4.0 \times 10^{-3} \text{ mol dm}^{-3}$ ;

<sup>c</sup> repeat of experiment 3 in **Table 1** using different solutions and spectrophotometer, etc.;

<sup>d</sup>  $[\text{NaNO}_2]_0 = 3.87 \times 10^{-3} \text{ mol dm}^{-3}$ .

**Table 3:** Dependence of  $k_{\text{obs}}$  for nitrosation of **4** on  $[\text{NaNO}_2]_0$  in aqueous acidic solution at 25 °C,  $I = 1.0 \text{ mol dm}^{-3}$  ( $\text{NaClO}_4$ ).<sup>[a]</sup>

| $[\text{H}_3\text{O}^+]_0 = 0.10 \text{ mol dm}^{-3}$ |                                    | $[\text{H}_3\text{O}^+]_0 = 0.010 \text{ mol dm}^{-3}$ |                                    |
|---|------------------------------------|--|------------------------------------|
| $10^3[\text{NaNO}_2]_0/\text{mol dm}^{-3}$            | $10^3k_{\text{obs}}/\text{s}^{-1}$ | $10^3[\text{NaNO}_2]_0/\text{mol dm}^{-3}$             | $10^3k_{\text{obs}}/\text{s}^{-1}$ |
| 0.05 <sup>[b]</sup>                                   | 8.58                               | 0.05 <sup>[b]</sup>                                    | 8.35                               |
| 0.5 <sup>[c]</sup>                                    | 9.35                               | 0.5 <sup>[c]</sup>                                     | 12.7                               |
| 5.0 <sup>[d]</sup>                                    | 14.0                               | 5.0 <sup>[d]</sup>                                     | 24.0                               |

<sup>a</sup>  $[\text{MeNH}_2\text{OMe}^+ \text{Cl}^-]_0 = 5 \times 10^{-2} \text{ mol dm}^{-3}$ ;

<sup>b</sup> monitored at 240 nm;

<sup>c</sup> monitored at 250 nm;

<sup>d</sup> monitored at 330 nm.

**Table 4:** Experimental and computed  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts (ppm relative to TMS) for *cis*- and *trans*-*N*-nitroso-dimethylhydroxylamines (**5**) in  $\text{CDCl}_3$ .<sup>[a]</sup>

|   | <i>cis</i> - <b>5</b> |                    | <i>trans</i> - <b>5</b> |                    |
|---|-----------------------|--------------------|-------------------------|--------------------|
|   | >N-CH <sub>3</sub>    | -O-CH <sub>3</sub> | >N-CH <sub>3</sub>      | -O-CH <sub>3</sub> |
| $\delta_{\text{H}}$ observed <sup>[b]</sup>   | 3.91                  | 3.87               | 3.46                    | 4.13               |
| $\delta_{\text{H}}$ observed <sup>[c]</sup>   | 3.80                  | 3.75               | 3.36                    | 4.02               |
| $\delta_{\text{H}}$ calculated <sup>[d]</sup> | 3.77                  | 3.75               | 3.13                    | 4.05               |
| $\delta_{\text{C}}$ observed <sup>[e]</sup>   | 38.60                 | 61.76              | 33.80                   | 64.43              |
| $\delta_{\text{C}}$ calculated <sup>[d]</sup> | 39.5                  | 63.3               | 30.2                    | 65.6               |

<sup>a</sup> The *cis* and *trans* short-hand descriptors here indicate the relationship between the oxygens bonded to the respective N atoms in the approximately planar forms (see Schemes 1 and 4 and text); earlier authors have used *cis* and *trans* to describe the relationships between the >N-CH<sub>3</sub> and the O of the nitroso.<sup>[18]</sup>

<sup>b</sup> -30 °C, 60 MHz,<sup>[18]</sup>

<sup>c</sup> present work, -50 °C, 500 MHz;

<sup>d</sup> present work, gas phase;

<sup>e</sup> present work, 23 °C, 125.77 MHz.

**Table 5:** Computed and NMR experimental activation parameters for the conformational isomerisation *cis-5* → *trans-5*

|   | B3LYP<br>(gas) | B3LYP<br>(CHCl <sub>3</sub> ) | NMR<br>(CDCl <sub>3</sub> ) | NMR<br>(toluene) | NMR<br>(DMSO-d <sub>6</sub> ) <sup>[a]</sup> | NMR<br>(CD <sub>3</sub> OD) |
|---|----------------|-------------------------------|-----------------------------|------------------|--|-----------------------------|
| $\Delta H^\ddagger/\text{kJ mol}^{-1}$              | 62.4           | 68.2                          | 65.9                        | 63.6             | 66.5   | 64.1                        |
| $\Delta S^\ddagger/\text{J K}^{-1} \text{mol}^{-1}$ | -9             | -13                           | 5                           | 2                | -5   | -4                          |

<sup>a</sup> Limited temperature range.

**Table 6:** Computed and NMR experimental thermodynamic parameters for the conformational isomerisation *cis-5* ⇌ *trans-5*.

|  | B3LYP<br>(gas) | B3LYP<br>(CHCl <sub>3</sub> ) | NMR<br>(CDCl <sub>3</sub> ) | NMR<br>(toluene) | NMR<br>(DMSO-d <sub>6</sub> ) <sup>[a]</sup> | NMR<br>(CD <sub>3</sub> OD) |
|--|----------------|-------------------------------|-----------------------------|------------------|--|-----------------------------|
| $\Delta H^\circ/\text{kJ mol}^{-1}$              | 3.9            | 4.3                           | 4.1                         | 4.0              | 5.7  | 5.1                         |
| $\Delta S^\circ/\text{J K}^{-1} \text{mol}^{-1}$ | 8.1            | 8.3                           | 2.8                         | 2.4              | 7.6  | 5.4                         |
| $\Delta G^\circ_{298}/\text{kJ mol}^{-1}$        | 1.5            | 1.8                           | 3.3                         | 3.3              | 3.4  | 3.5                         |
| (equil. constant)                                | (0.55)         | (0.48)                        | (0.26)                      | (0.26)           | (0.25)                                       | (0.24)                      |

<sup>a</sup> Limited temperature range.

**Table 7:** Key geometric parameters (B3LYP/6-31G(d)) and dipole moments for *cis-5*, *trans-5*, and the transition structure **TS1** for their interconversion in the gas phase.<sup>[a]</sup>

| Parameter                     | <i>cis-5</i> | <b>TS1</b> | <i>trans-5</i> |
|-------------------------------|--------------|------------|----------------|
| d(N-N)/Å                      | 1.351        | 1.571      | 1.347          |
| d(N=O)/Å                      | 1.220        | 1.183      | 1.225          |
| $\Phi(\text{O-N-N-O})/^\circ$ | -15.3        | -119.2     | 165.8          |
| $\mu/\text{D}$                | 3.4          | 1.3        | 3.6            |
| $\sum\theta/^\circ$ at N1     | 350.3        | 306.7      | 351.8          |

<sup>a</sup> calculated results in chloroform are only slightly different.