Deamination of *N,O*-Dialkylhydroxylamines *via* *N*-Nitroso-*N,O*-dialkylhydroxylamines: a New Reaction

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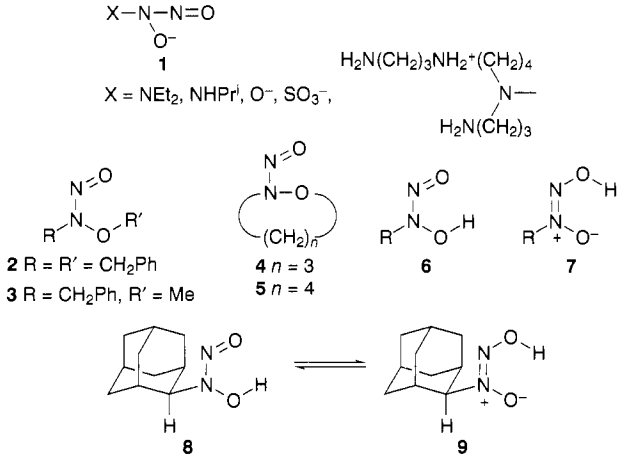
N-Nitroso-*N,O*-dialkylhydroxylamines undergo acid catalysed deaminative solvolysis in aqueous solution.

Derivatives of *N*-nitrosohydroxylamines containing the anion **1** have been found to release nitric oxide under mild conditions[1] and, due to the discovery of the importance of nitric oxide in a range of physiological processes,[2] these may be pharmaceutically useful alternatives to traditional drugs. In view of the similarity between these compounds and *N*-nitrosoamines, it is perhaps surprising that their chemistry has remained largely unexplored for so long.[3] We report here findings from the initial stages of a broadly based investigation into the chemistry of nitrosohydroxylamines, in particular the mechanisms of reactions of **2–5** and **8** under acidic conditions in aqueous solution.

It was already known that compounds named *N*-nitroso-*N*-alkylhydroxylamines **6** actually exist as the *N*-alkylhydroxydiazenium oxides **7**[4] though interconversion between the two forms is expected to be very rapid in protic solvents. In order to avoid structural ambiguities, we prepared four *N*-nitroso-*N,O*-dialkylhydroxylamines **2–5**; we have also investigated the *N*-adamantyl analogue which, as indicated, exists as **9**. All five parent hydroxylamines were known compounds,[5] and the nitrosations were carried out by conventional preparative methods. The spectroscopic and analytical data for all compounds are in accord with the structures shown.

Compounds **2–5** decompose in aqueous acidic solution, and rates were measured by monitoring the UV absorbance of solutions initially *ca.* 10^{-4} mol dm^{-3} in the substrate in the thermostatted cell block of a UV spectrophotometer. Rates were shown to be cleanly first order in the substrate and first order in hydronium ion with no appreciable reaction at $[H_3O^+] = 0$; typical results are shown in Fig. 1. The observed pseudo-first order rate constants were found to be sensitive to the ionic strength of the medium which was subsequently kept constant using sodium perchlorate. Second-order rate constants were determined in the normal way for each compound over a range of temperatures which allowed activation parameters and rate constants at a common temperature to be determined; a summary of results is shown in Table 1.

Reaction of a more concentrated solution of **2** evolved a colourless gas which was not oxidized by air; gas injection mass spectrometry allowed us to conclude that it is not nitric oxide.



These early results suggested that the reactions were ionic, *e.g.* denitrosation, rather than homolytic. In view of the known reversibility of *N*-nitrosation/denitrosation in general, and of the easy reactions of our parent hydroxylamines in nitrosation, sulfamic acid was used as a trap for any liberated nitrosating agent in our early experiments on **2**, **3** and **5**.[6] As the results in Table 2 show, however, the presence of sulfamic acid at concentrations up to twenty times that of the substrate had no effect upon the rates. We concluded that either the reactions do not liberate a reactive nitrosating agent, or that the reactions are carried out at sufficiently high a dilution that the reverse reaction is insignificant. The reaction is only slightly affected by chloride at constant ionic strength, and methanol as co-solvent has a modest rate-retarding effect, Table 2.

At ionic strength = 2.5 mol dm^{-3} (sodium perchlorate), the second-order rate constant for the adamantyl analogue **9** is lower than that for **3** by a factor of about 20 at 25 °C but otherwise the reaction appears similar. The product from **9** in a largely aqueous medium (1.25% methanol) was isolated as a single pure compound and was expected to be *N*-(2-adamantyl)-hydroxylamine, the product of simple denitrosation. However, it proved to be identical in all respects with an authentic sample

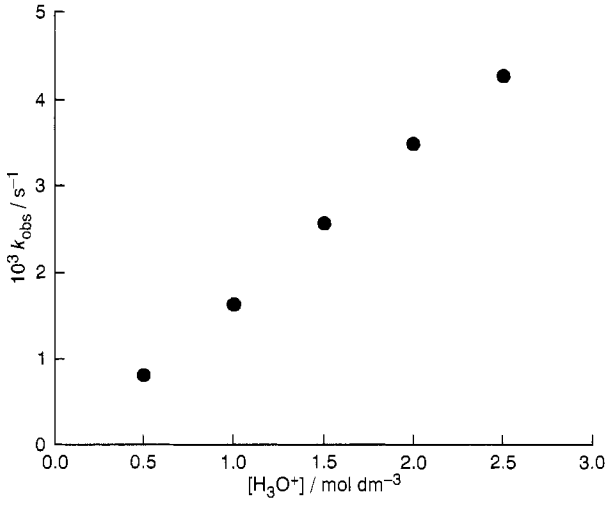


Fig. 1 Decomposition of *N*-nitrosotetrahydro-1,2-oxazine **5** in aqueous perchloric acid at 55 °C

Table 1 Summary of kinetic results for H_3O^+-catalysed reactions of *N*-nitrosohydroxylamines **2–5**, and compound **9** in water (1.25% methanol), I = 2.5 mol dm^{-3} ($NaClO_4$)

Substrate	$10^5 k_2$ (25 °C)/ dm^3 mol^{-1} s^{-1}	$\Delta S^{\ddagger a}$/ J K^{-1} mol^{-1}	$\Delta H^{\ddagger b}$/ kJ mol^{-1}
2	8.97	−57[c]	79[c]
5	5.85	−24[c]	90[c]
3	2.82	−38[c]	88[c]
4	181	−56[d]	72[d]
9	0.15	−18[e]	101[e]

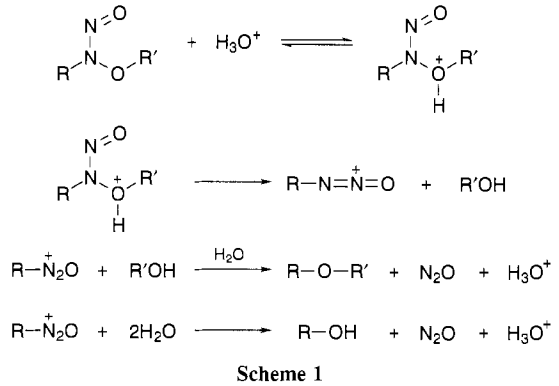
[a] Estimated uncertainty *ca.* 10 J K^{-1} mol^{-1}. [b] Estimated uncertainty *ca.* 4 kJ mol^{-1}. [c] Determined over the range 25–55 °C. [d] Determined over the range 15–45 °C. [e] Determined over the range 35–65 °C.

of adamantan-2-ol and was obtained in high yield (>96%). *Reaction of the dibenzyl* analogue **2** gave two organic products in aqueous acid neither of which was the product of denitrosation. They were isolated and identified spectroscopically and by comparison with authentic samples. One was benzyl alcohol and the other dibenzyl ether; they were formed in relative yields 4 : 1 (by NMR), there being no other detectable organic product. These product analytical results require that the reactions of the *N*-nitrosohydroxylamines are deaminative rather than denitrosations and, as far as we are aware, are the first such reactions of organic hydroxylamines to be reported. The similarity in kinetic parameters and the correspondence between the reaction products from **9** on the one hand and **2** on the other indicate analogous mechanisms of reaction even though **2** is unambiguously an *N*-nitroso compound and **9** is not. This suggests that **9** reacts through its less stable tautomer **8**. A mechanism involving pre-equilibrium protonation followed by fragmentation is indicated in Scheme 1 which accounts for the results so far. This mechanism includes the oxodiazonium ion as an intermediate; such a species has been implicated in other reactions.[7] In accord with this mechanism, reaction of **8** specifically labelled with ^{17}O in the nitroso group leads to adamantan-2-ol with no incorporation of the ^{17}O. The product analytical results for **2** require that the intermediates in these reactions are trappable by the nucleofuge of the fragmentation step before it has time to diffuse away and hence are exceedingly short lived. We are presently investigating further the mechanistic details, for example whether or not carbenium ions intervene.

Table 2 Effect of solutes and solvent composition upon rates of H_3O^+-catalysed reactions of compounds **2**, **3** and **5**[a]

Compound	$[Cl^-]$/ mol dm^{-3}	10^4 $[NH_2SO_3H]$/ mol dm^{-3}	vol.% MeOH in H_2O	I/mol dm^{-3}	10^5 k_{obs}[b]/ s^{-1}
3	0				6.61
	1.00				8.08
	1.75				8.75
	2.50				9.07
3		0			6.64
		2.0			6.68
		10.0			6.65
		20.0			6.61
2			2.5		7.05
			19.2		7.00
			35.8		6.13
			49.5		5.37
5[c]				1.0	2.97
				1.5	3.61
				2.0	4.28
				2.5	5.05

[a] Initial [substrate] = 10^{-4} mol dm^{-3}; 25 °C; 1.25% MeOH in H_2O; $[H_3O^+]$ = 2.5 mol dm^{-3} except where otherwise indi- cated. [b] Observed pseudo-first order rate constant. [c] $[H_3O^+]$ = 1.0 mol dm^{-3}, ionic strength modified by $NaClO_4$.



Scheme 1

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