Nitrosation of 2-hydroxyethylpiperidine

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The kinetics of the nitrosation of 2-hydroxyethylpiperidine have been studied in acidic (0.05–0.30 mol dm^{-3} $HClO_4$) aqueous media. The reaction rate is first order with respect to nitrite and amine and independent of acidity and shows an experimental isotope effect of 1.73. The most plausible mechanism involves the fast formation of an alkyl nitrite in the protonated amine (equilibrium constant estimated as 0.014 dm^3 mol^{-1}). The loss of a proton from this intermediate is the rate-limiting step, and it is followed by a fast internal nitroso group transfer from the oxygen to the nitrogen atom to give the corresponding *N*-nitroso compound. A comparison of this nitrosation pathway of secondary amines in acid media with the nitrosation of thiomorpholine and piperidine, and with that of amines by alkyl nitrites in basic media is also discussed.

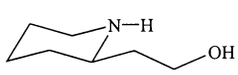
Introduction

Internal nitroso group transfer is a well-known process in substrates that possess two nucleophilic positions, one of them usually being a protonated nitrogen atom. This internal rearrangement to the final *N*-nitroso compound can occur from an aromatic ring,[1–4] an oxygen atom,[5–8] a sulfur atom[9,10] or another nitrogen atom.[6,11]

It is also well known that when the nitrogen atom is not protonated, and less nucleophilic than other atoms in the molecule, the *N*-nitroso compound is obtained after an initial O-, *S*- or C-nitrosation. Typical examples are the nitrosation of amides and ureas,[12–14] thioureas[15] and tryptophan.[16]

Nitrosation of thiomorpholine in aqueous media at pH = 2.3–3.6 takes place, as with other amines, through a mechanism in which the rate-limiting step is the attack of the substrate by dinitrogen trioxide.[10] At higher acidities, however, the reaction occurs *via* an *S*-nitroso intermediate, which rearranges to the final and more stable *N*-nitrosothiomorpholine.[10] The low isotope effect measured for this reaction in D_2O confirms that the loss of the proton from the *S*-nitroso intermediate is only part of the rate-determining step in the reaction. This result indicates that the intermediate must adopt a boat conformation to facilitate the migration of the NO group from the sulfur to the nitrogen atom.[10]

In this paper we present the results of our study of the nitrosation of 2-hydroxyethylpiperidine **I** at high acidities. This



I

substrate was chosen because it has an oxygen atom located in a flexible lateral chain and, therefore, the possible rearrangement of the NO group from that atom to the heterocyclic nitrogen would not require a conformation as restrictive as in the case of thiomorpholine. Of course, this could give rise to a change in the rate-limiting step or in the reaction mechanism. The investigation of these possibilities is one of the objectives of our work. At the same time, the reaction could imply the study of an internal nitrosation by an alkyl nitrite, for which there is no information in the literature.

Experimental

2-Hydroxyethylpiperidine (2-HEP) was from Aldrich, and $NaNO_2$, $HClO_4$ and $NaClO_4$ from Panreac. Deuterium oxide (>99.90%) was supplied by SDS.

The kinetics of the reactions were followed spectrophotometrically in a Varian Cary 1E apparatus using 1 cm path-length cells kept at 25.0 °C by recirculating water from a Heto thermostat. Ionic strength was maintained at 0.5 mol dm^{-3}, adjusted with $NaClO_4$.

The acidity constants of the amine in H_2O and D_2O were obtained from conductimetry–potentiometry; the resulting values of pK_a were 10.21 and 10.56, respectively. Conductimetric and pH measurements were carried out with a Crison model 525 apparatus provided with a platinum cell and a Radiometer PHM-82 with a GK2401C combined electrode, respectively. pD in D_2O was obtained accordingly with the equation pD = pH + 0.4.[17]

The nitroso compound was synthesised by reacting 2-HEP with an excess of sodium nitrite in concentrated $HClO_4$. The product was extracted with light petroleum, dried with anhydrous sodium sulfate and concentrated down to dry powder with the rotavapor. The UV-Vis spectrum showed maxima at 231.7 and 365 nm.

Kinetic data were analysed by the initial rate method, never exceeding 2% of the reaction. Data were recorded at 231.7 nm, a wavelength at which the difference between the molar absorptivities of the products and reactants is the maximum and equal to 1157 ± 6 dm^3 mol^{-1} cm^{-1}. The rapid formation of an alkyl nitrite from nitrous acid and the hydroxy group of the substrate (Scheme 1) does not invalidate the method due to the low value of its equilibrium constant (see Results and discussion section).

Results and discussion

The results obtained at $[H^+]$ = 0.05 mol dm^{-3} show (Figs. 1 and 2) that the reaction is first order with respect to both 2-HEP and nitrite. At constant concentrations of amine and nitrite, the influence of the acidity on the initial rate was investigated; Table 1 shows that the reaction is zero-order with respect to H^+. By fitting all these data rate eqn. (1) was deduced, with

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Table 1 Initial rates for the nitrosation of 2-HEP at 25 °C for several conditions of acidity ($[2\text{-HEP}]_o = 6.00 \times 10^{-3}$ mol dm^{-3} and $[\text{nitrite}]_o = 5.00 \times 10^{-4}$ mol dm^{-3})

$[HClO_4]$/mol dm^{-3}	0.05	0.10	0.15	0.20	0.25	0.30
$10^8 r_o$/mol dm^{-3} s^{-1}	1.83	1.69	1.65	1.75	1.72	1.75

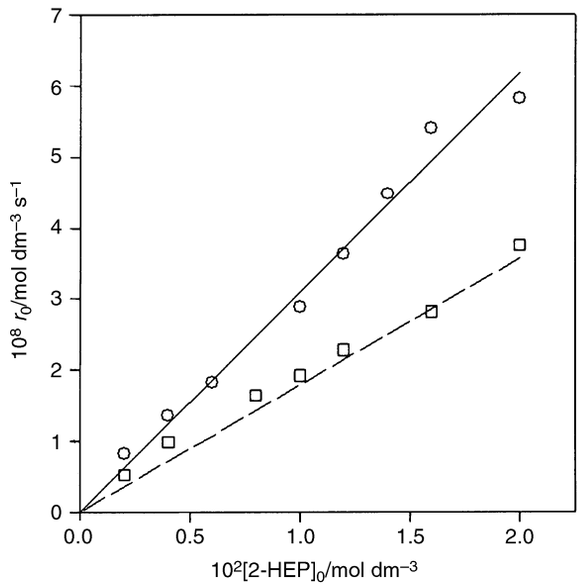


Fig. 1 Influence of the amine concentration on the initial rate of the nitrosation of 2-HEP in H_2O (circles) and D_2O (squares) at 25 °C, $[\text{nitrite}]_o = 5 \times 10^{-4}$ mol dm^{-3} and $[HClO_4] = 0.05$ mol dm^{-3}.

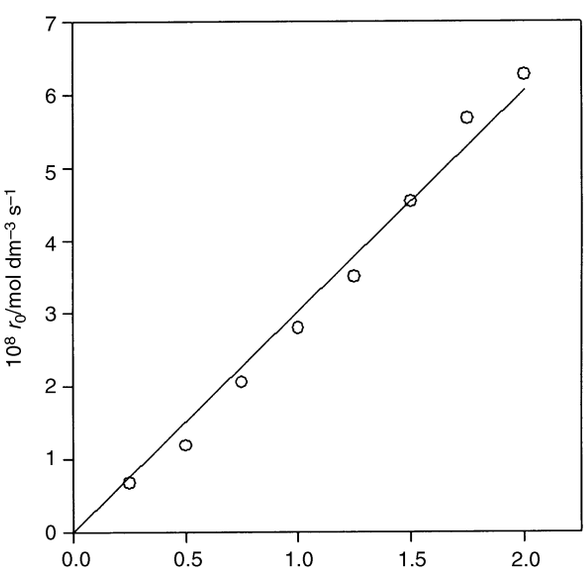


Fig. 2 Influence of the nitrite concentration on the initial rate of the nitrosation of 2-HEP at 25 °C, $[2\text{-HEP}]_o = 4 \times 10^{-3}$ mol dm^{-3} and $[HClO_4] = 0.10$ mol dm^{-3}.

$$r_o \text{ (mol dm}^{-3}\text{ s}^{-1}) = k_H[2\text{-HEP}]_o[\text{nitrite}]_o \qquad (1)$$

$k_H = (6.51 \pm 0.03) \times 10^{-3}$ dm^3 mol^{-1} s^{-1} (the subscript H refers to H_2O as solvent).

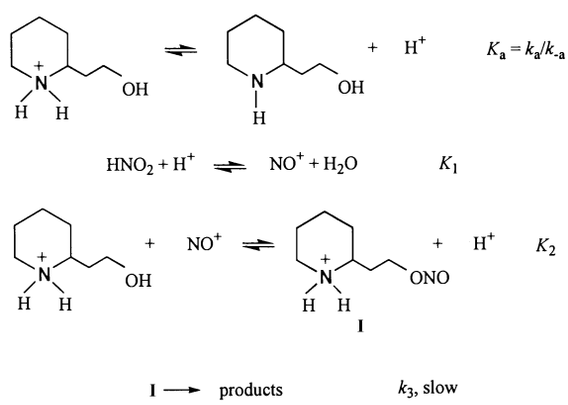
This rate equation is compatible with a mechanism in which the rate-limiting step (k) is the attack of nitrosonium (or nitrous acidium) ion on free amine. It must be remembered that all the kinetic runs were carried out at acidities at which the nitrite is present as nitrous acid ($pK_a = 2.94$ at the ionic strength of this work [18]). The nitrosating agent is formed by the protonation of the nitrous acid with an equilibrium constant $K_1 = 3 \times 10^{-7}$ dm^3 mol^{-1}.[19] Under these conditions relation (2) is easily deduced,

$$k_H = K_1K_ak \qquad (2)$$

where K_a is the acidity constant of 2-HEP, which we have determined as $10^{-10.21}$ dm^{-3} mol. This implies a value of 3.5×10^{14} dm^3 mol^{-1} s^{-1} for k, which exceeds by far the accepted value for a diffusion-controlled process in aqueous solution.[19] Therefore, the mechanism of a direct attack of NO^+/$NO_2H_2^+$ on free amine as the rate-limiting step must be ruled out.

On the other hand, as alkyl nitrites can act as nitrosating agents, the reaction could proceed by the reaction of two amine molecules, one of them being the nitrosating agent (formed from the reaction between the hydroxy group of 2-HEP and nitrous acid) and the other one being the nitrosatable substrate. However, this would imply a second-order dependence on total amine concentration, which was not observed. Furthermore, alkyl nitrites are very poor nitrosating agents and they need a high concentration of free amine,[20,21] which is only available in basic media. In fact, at acid pH the nitrosation of amines is inhibited by the presence of alcohols because the alkyl nitrites formed are not effective nitrosating agents, *i.e.*, alcohols act as nitrous acid scavengers.[22–24]

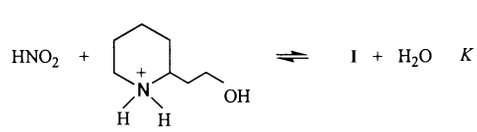
The most simple reaction mechanism in agreement with the experimental rate equation is the one sketched in Scheme 1, leading to eqn. (3).



Scheme 1

$$k_H = K_1K_2k_3 \qquad (3)$$

Alternatively, the two equilibria defined by K_1 and K_2 (Scheme 1) may be condensed into one (Scheme 2) similar to that representing the formation of alkyl nitrites.



Scheme 2

Obviously, $K = K_1K_2$, and, therefore, eqn. (4) follows.

$$k_H = Kk_3 \qquad (4)$$

Since the internal nitroso group transfer needs a lone electron pair on the nitrogen atom, this step must follow the loss of a proton from the protonated amine. The relevance of the loss of this proton as the rate-limiting step can be investigated by studying the reaction in D_2O. Fig. 1 shows the results obtained by modifying the concentration of 2-HEP at constant nitrite and perchloric acid concentrations. The kinetic constant is now $k_D = (3.76 \pm 0.11) \times 10^{-3}$ dm^3 mol^{-1} s^{-1}, which implies the experimental kinetic isotope effect given in eqn. (5).

$$\frac{k_H}{k_D} = \frac{K_H}{K_D}\frac{k_{3H}}{k_{3D}} = 1.73 \pm 0.06 \qquad (5)$$

The values of k_{3H}, k_{3D} and their ratio may be estimated by assuming that they are close to k_a, the deprotonation rate constant of 2-HEP (Scheme 1), which may be calculated because the reverse step is diffusion controlled and the acidity constant is known (*i.e.*, $k_3 \approx k_a = k_{-a}K_a$). The resulting values are given by eqns. (6) and (7).

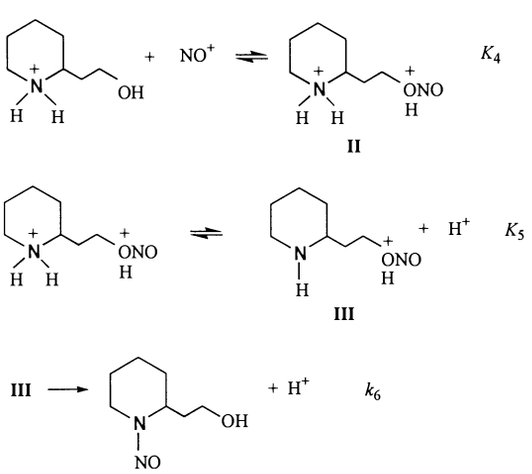
$$k_{3H} = 0.456\ s^{-1} \quad (6)$$

$$k_{3H}/k_{3D} = 2.76 \quad (7)$$

With this result, and using eqn. (5) we obtain $K_H/K_D = 0.63$, a value not too far from ≈1, expected for that equilibrium. This supports our proposal that the loss of the proton is involved in step k_3.

On the other hand, from the estimated value for k_3 in H_2O [eqn. (6)] and eqn. (4), a value of 0.014 $dm^3\ mol^{-1}$ can be obtained for the equilibrium constant *K*. Reported equilibrium constants for the formation of alkyl nitrites are in the range 0.03–5 $dm^3\ mol^{-1}$.[24] The lower value estimated here can be explained in terms of a certain degree of intramolecular hydrogen bonding between the hydroxy group and the nitrogen protons, which would make nitrosation at the alcohol more difficult. Again, this supports the proposed mechanism.

Another possibility to bear in mind is the mechanism shown in Scheme 3, in which the nitrosating agent attacks the



Scheme 3

oxygen atom of the protonated amine, forming the *O*-nitroso intermediate **II**.

Intermediate **II** undergoes the loss of a proton in a rapid equilibrium step (K_5). The so-formed intermediate **III** would yield the reaction products in the rate-limiting step, by loss of a further proton and the internal rearrangement of the NO group from the oxygen to the nitrogen atom, in a similar way to that for thiomorpholine.

Although this mechanism could explain the experimental rate equation, it seems to be very improbable. Since the pK_a of an alcohol is close to −2,[25] the pK_a of the nitroso intermediate will be −6 or −7. The intermediates **II** and **III** must be very unstable under the experimental conditions and, therefore, their lifetimes would be short enough to rule out the internal NO transfer.

The internal NO transfer from an alkyl nitrite proposed in the reaction mechanism of the Scheme 1 can be compared with the nitrosation of amines by alkyl nitrites in basic media.[20] The main difference between intermolecular and intramolecular nitroso group transfer to an amine is that in the former a basic medium is required in order to achieve high concentrations of free amine, while in the latter the transfer can occur in acidic media. Therefore, the hydroxyalkyl chain in 2-HEP acts as a source of the nitroso group leading to a new nitrosation pathway of secondary amines in acidic media.

On the other hand, the results obtained in this work indicate that the rate of formation of the *N*-nitroso compound for 2-HEP is ≈5 orders of magnitude higher than for piperidine under similar experimental conditions.[26] This quite important difference is due to the presence of an alcoholic group in the molecule, allowing the formation of the corresponding alkyl nitrite, which is responsible for the final internal nitrosation. Therefore, the rate of nitrosation of amines in acid media can be much higher than expected when hydroxy groups are presents in the same molecule.

Acknowledgements

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