This may readily be re-written in terms of the stoichiometric concentrations of the reagents if it is remembered that according to the considerations discussed in the previous paragraph the concentration of the intermediate complex must be negligible compared to those of the reagents; that according to the proposed mechanism the intermediate complex is in equilibrium with the reagents, i.e. $k_{-1} \gg k_2[R_2NH]$; and that the total concentration of morpholine is [MOR] = $[R_2NH] + [R_2NH_2^+]$. The resulting rate equation is

$$v = \frac{\alpha [MOR]^2 [NP]}{(K_a + [H^+])^2}$$
(9)

with $\alpha = K_1 k_2 K_a^2$, K_a being the acidity constant of morpholine.

Eq. (9) is identical in form to the experimental rate Eq. (7), and from the constant f that appears in the latter the pK_a of morpholine may therefore be calculated $(pK_a = -\log f)$ as 8.74. This value agrees well with the published result of direct potentiometric measurements at high ionic strength $(pK_a = 8.72$ at $\mu = 0.83$ and 25 °C [17]), and this agreement provides support for the reaction mechanism proposed.

As has already been mentioned, the value of f is not affected by changing the salts present in the medium as long as the ionic strength is held constant. The variation in the rate of reaction observed when the salts are changed under these conditions must therefore be due solely to variation in the product $K_1 k_2$, i.e. it is the value of $K_1 k_2 = k/f^2$ that depends directly on the nature of the salt used to control ionic strength. The data obtained show that

$$K_1 k_2 = (2.75 \pm 0.07) \cdot 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$$

at 25°C and $\mu = 2.0 \text{ M} ((\text{CH}_3)_4 \text{NCl})$
 $K_1 k_2 = (6.37 \pm 0.16) \cdot 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$

at 25°C and $\mu = 2.0$ M (NaCl).

Like Fig. 4, which shows the striking influence of ionic strength on the rate of reaction, these results reflect the latter's great sensitivity to medium effects.

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The Reaction Mechanism of the Nitrosation of Ureas

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The nitrosation of methylurea has been studied under catalysis by acetate and mono-, di- and trichloroacetate buffers. The following general equation for the rate of reaction as a function of the total concentrations of the reagents has been deduced:

$$v = \frac{[\text{MU}] [\text{nit}] [\text{H}^+]^2}{K_1 + [\text{H}^+]} \left[v + \delta \frac{K_1 [\text{nit}]}{K_1 + [\text{H}^+]} + \varepsilon \frac{K_2 [\text{Buf}]}{K_2 + [\text{H}^+]} \right]$$

where K_1 is the acidity constant of nitrous acid and K_2 that of carboxylic acid. The catalysis observed has been found to be due to the organic anions, and Brønsted relation is obeyed with $\beta = 0.24$. – The experimental results have been interpreted in terms of a reaction mechanism which features the rapid formation of a intermediate, MeNH(NO)CONH₂, when the methylurea is nitrosated. The rate controlling step is the transfer of a proton from this intermediate to the solvent or to a basic catalyst (the nitrite ion or the organic anion). That it is this step that controls the overall rate of reaction is supported by the isotopic effect ($k_H/k_D = 3.5$) observed on carrying out kinetic measurements in D₂O.

Introduction

The reactions by which N-nitroso compounds are formed have attracted wide interdisciplinary attention in recent years due, on the one hand, to the fact that most of them are carcinogenic [1, 2], and on the other to some of them being used as drugs to fight cancer [3, 4]. Intensive research has been carried out on the reactions of nitrous acid with amines, whose mechanisms are now well known [5, 6]. The nitrosation of amides and

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ureas, however, has not been investigated in detail. Up till now its mechanism has been taken to be the same as that of the nitrosation of amines, but significant and hitherto unexplained differences have been found in the kinetic behaviour of the two kinds of reaction. Whereas the nitrosation of amines may be of either order one or order two with respect to nitrous acid [6], depending on whether the nitrosating agent is $H_2NO_2^+/NO^+$ or N₂O₃, only first order reactions have been observed for amides and ureas [7, 8]. Again, the rate constants for reactions between amines and NO⁺ or N₂O₃ seem to approach the limit of control by diffusion [6, 9], whereas much lower values are found for the reactions with amides and ureas [6,8]. A further difference, which Yamamoto et al. pointed out in 1976 [10], is that whereas the nitrosation of amines is catalysed by halides but not by carboxylic acids (except under certain conditions [11, 12]), exactly the reverse holds for the nitrosation of amides. A possible explanation for the inoperance of nucleophilic catalysis in the nitrosation of amides has been put forward by Hallett and Williams [13].

In the work described in the present article we have sought detailed explanations of all the differences mentioned above by investigating the kinetics of the nitrosation of methylurea when catalysed by different carboxylate buffers. The results obtained may be of biomedical interest, for they reveal a new catalytic pathway for the formation of nitrosamides, which, given the wide distribution in foodstuffs of nitrates (partially converted to nitrites after ingestion) and of precursors of amides and ureas [14], have been suspected of possibly causing cancer [15, 16].

Reagents

Experimental

The methylurea (Merck p.s.) was recrystallized from ethanol and kept in vacuo in a desiccator. The D_2O (Spanish Junta de Energía Nuclear) contained 99.77% D. The other reagents (Merck p.a. except the mono- and dichloroacetate acids, which were Merck p.s.) were dried and used without further purification. The purity of the carboxylic acids was checked by titration against NaOH. The stability of N-nitroso-N-methylurea (NMU), the product of the reaction, was checked experimentally in the working conditions used.

Apparatus

The kinetic measurements were carried out in a Pye Unicam SP 8-200 UV-VIS spectrophotometer with a thermostatted cell holder. Acidity was measured using a Radiometer model 26 pH-meter with a GK 2401C combined electrode.

Kinetics

The appearance of NMU was followed spectrophotometrically at 260 nm, a wavelength at which its molar absorptivity ($2850 \pm 5 \text{ M}^{-1} \text{ cm}^{-1}$) is much greater than that of nitrite ($\sim 6 \text{ M}^{-1} \text{ cm}^{-1}$) and where absorbance of the other reagents may be considered as negligible for methylurea and constant for carboxylic acids. The kinetic analysis was carried out by the integration method or the initial rate method, depending on which was the most convenient one in each case. Identical results were obtained whichever was used.

In the experimental conditions used the reaction is quantitative:

$$HNO_2 + MeNHCONH_2 \longrightarrow MeN(NO)CONH_2 + H_2O$$
.

The kinetics studied by the integration method were analysed by optimizing the value of the absorbance at time $t = \infty$ using the method of Davies, Swann and Campey [17, 18]. In all cases the graph of $\ln(A_{\infty} - A_t)$ against time was perfectly linear at least as far as 90% reaction, A_t and A_{∞} being the absorbances at times t and infinity respectively. When the initial rate method was used the linearity of the absorbance-time data was ensured by never following the reaction beyond 1%. All kinetic measurements were duplicated, and the discrepancies between the two figures never exceeded 3% whichever of the two methods of analysis was used. All experiments were carried out at 25°C and an ionic strength of 0.20 M (NaClO₄).

Results

The Influence of Acetate Buffer

The influence on the initial rate of reaction, v_0 , of the initial concentration of methylurea, $[MU]_0$, was studied over the range $6 \cdot 10^{-4} - 1 \cdot 10^{-2}$ M at various concentrations of buffer between 0 and 0.2 M. In all cases the reaction was found to be of order one with respect to MU, the same as in the absence of buffer [7, 13].

$$v_0 = a[\mathrm{MU}]_0. \tag{1}$$

The dependence of the reaction rate on the total concentration of buffer, [Buf], was studied, and found to be linear (Fig. 1):

$$v_0 = b + c [Buf]. \tag{2}$$

The dependence of the parameters b and c on $[H^+]$ was studied over the range pH 3.75-4.75. As Fig. 2 shows,

$$b = d [H^+]^2$$
(3)

and

$$b/c = e + f[\mathrm{H}^+] \tag{4}$$

where $d = (9.00 \pm 0.13) \text{ M}^{-1} \text{ s}^{-1}$, $e = (6.3 \pm 0.3) \cdot 10^{-2} \text{ M}$ and $f = (1.50 \pm 0.03) \cdot 10^3$ at $[\text{MU}]_0 = 2.51 \cdot 10^{-2} \text{ M}$ and $[\text{nit}]_0 = 1.176 \cdot 10^{-2} \text{ M}$.



Fig. 1

Dependence of the initial rate of nitrosation of MU on the concentration of buffer at 25 °C and $\mu = 0.2$ M.

- (O) Acetate buffer at $[MU]_0 = 5.66 \cdot 10^{-2} \text{ M}$, $[nit]_0 = 4.45 \cdot 10^{-2} \text{ M}$ and pH = 4.75.
- (\triangle) Dichloroacetate buffer at $[MU]_0 = 5.34 \cdot 10^{-3} \text{ M}$, [nit]₀ = 7.25 \cdot 10^{-3} M and pH = 3.40.
- (•) Trichloroacetate buffer at $[MU]_0 = 4.01 \cdot 10^{-3} \text{ M}$, [nit]_0 = 4.09 \cdot 10^{-3} M and pH = 3.28.



Nitrosation of MU in acetate buffer. Influence of $[H^+]$ on the parameters b and c of Eq. (2) at 25°C, $\mu = 0.2$ M, $[MU]_0 = 2.51 \cdot 10^{-2}$ M and $[nit]_0 = 1.176 \cdot 10^{-2}$ M



Influence of the concentration of nitrite on the initial rate of nitrosation of MU in acetate buffer at 25°C, $\mu = 0.2$ M, [MU]₀ = 9.43 · 10⁻² M, [Buf] = 1.124 · 10⁻² M and pH = 4.54



Nitrosation of MU in acetate buffer. Influence of the concentration of nitrite on the parameters b and c of Eq. (2) at 25°C, $\mu = 0.2$ M, $[MU]_0 = 2.75 \cdot 10^{-2}$ M and pH = 4.18

The dependence of the initial reaction rate on the total initial concentration of nitrite, $[nit]_0$, was also studied (Fig. 3), and found to be of the form:

$$v_0 = g[\text{nit}]_0 + h[\text{nit}]_0^2.$$
 (5)

In order to discover which of these terms is associated with the catalysis exerted by the buffer, the influence of the concentration of nitrite on b and c - Eq. (2) – was investigated, with the result (Fig. 4) that

$$b = i[\operatorname{nit}]_0 + j[\operatorname{nit}]_0^2 \tag{6}$$

and

$$c = l[\operatorname{nit}]_0 \tag{7}$$

with $i = (3.42 \pm 0.05) \cdot 10^{-6} \text{ s}^{-1}$, $j = (1.35 \pm 0.05) \cdot 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ and $l = (2.18 \pm 0.02) \cdot 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at $[\text{MU}]_0 = 2.75 \cdot 10^{-2} \text{ M}$ and pH = 4.18.

The above results imply an experimental rate equation for the reaction of methylurea with nitrite in the presence of acetate buffer of the form

$$v_0 = [MU]_0[nit]_0[H^+]^2 \left(m + n[nit]_0 + \frac{p[Buf]}{q + [H^+]} \right).$$
(8)

The Influence of Chloroacetate Buffer

The influence of this buffer was studied at concentrations of nitrite of the order of 10^{-4} M, much lower than those used for acetate buffer. For this reason the second order term in Eq. (6) is not detectable in this case. The integration method, with an excess of MU over nitrite, therefore revealed a first order reaction. Plots of $\ln(A_{\infty} - A_t)$ versus time were linear (Fig. 5) and their slopes were the first-order rate coefficients, k',

$$= k' [nit] . (9)$$



Typical pseudo-first order plots of the nitrosation of MU in monochloroacetate buffer at 25 °C, $\mu = 0.2$ M, $[nit]_0 = 2.63 \cdot 10^{-4}$ M, $[MU] = 3.34 \cdot 10^{-2}$ M, [Buf] = 0.1151 M and (\odot) pH = 1.98, (\bullet) pH = 2.09 and (\triangle) pH = 2.24

Since the reaction is also of order one with respect to MU,

$$v = k''[\operatorname{nit}][\operatorname{MU}]. \tag{10}$$

In a series of experiments at various values of pH, the dependence of k'' on the concentration of buffer was found to be of the form:

$$k^{\prime\prime} = r + s[\text{Buf}] \tag{11}$$

and in the range of pH studied (1.98 - 3.11)

$$r = [H^+]^2 / (t + u[H^+])$$
(12)

and

$$r/s = w + z[H^+]$$
 (13)

with $t = (3.2 \pm 0.2) \cdot 10^{-5} \text{ M}^3$ s, $u = (3.66 \pm 0.04) \cdot 10^{-2} \text{ M}^2$ s, $w = (0.132 \pm 0.006) \text{ M}$ and $z = 52.3 \pm 1.3$ (Fig. 6).



Fig. 6 Nitrosation of MU in monochloroacetate buffer. Influence of [H⁺] on the parameters r and s of Eq. (11) at 25°C and $\mu = 0.2$ M

The above results yield the rate equation:

$$v = \frac{[MU][nit][H^+]^2}{\frac{l}{u} + [H^+]} \left(\frac{1}{u} + \frac{1}{zu} \cdot \frac{[Buf]}{\frac{w}{z} + [H^+]}\right).$$
 (14)

The Influence of Di- and Trichloroacetate Buffers

These were found to have the same catalytic effect, linearly dependent on the concentration of buffer, as the previous buffers studied - Eqs. (2) and (11) -, though to a lesser degree (Fig. 1).

Discussion

Eqs. (8) and (14) show that the catalysis due to the buffer is greater as the concentration of hydrogen ions decreases, which would seem to mean that the effective catalyst must be the anion corresponding to each buffer. Since it is well known [10, 13], and we ourselves have confirmed, that the nitrosation of amides and ureas is not catalysed by halides or pseudohalides, then the catalytic effect of the buffers cannot involve the formation of the corresponding nitrosyl compound (e.g. nitrosyl acetate) and its subsequent reaction with MU, for in the nitrosation of amines the catalysis due to this kind of nitrosyl compounds is much weaker than that due to nitrosyl halides [5, 11] and there is no reason to suppose that in the case of ureas this order is inverted to the point of the former being effective and the halides having no effect at all.

The above considerations lead us to believe that the mechanism involved may be basic catalysis by carboxylate anions, which is possible if the rate controlling step is not the reaction of the nitrosating agent with the substrate, as in the nitrosation of amines, but the subsequent step in which the intermediate formed loses a proton, i.e.

$$\frac{\text{NO}^{+} + \text{MeNHCONH}_{2} \underbrace{\xrightarrow{\text{IASU}}}_{|} \text{MeNCONH}_{2} \underbrace{\xrightarrow{\text{IASU}}}_{B} \frac{\text{MeNCONH}_{2} + \text{BH}^{+}}_{NO}}_{NO} \frac{\text{MeNCONH}_{2} + \text{BH}^{+}}_{NO}$$

If this is so, the nitrite ion should also have a catalytic effect in these conditions in which it acts as a base, so that a second order term with respect to this reagent should appear. As Eq. (8) shows, such a term has indeed been found in the present study. The fact that it has not been observed by other authors may be attributed to their working with lower concentrations of nitrite and higher acidities than ourselves.

The results obtained in this study may thus be interpreted in terms of the following mechanism:

$$\frac{\text{HNO}_2}{\text{max}} \xrightarrow{\text{NO}_2^-} + \text{H}^+ \qquad \qquad K_1$$

$$\frac{HRCO_2}{HNO_2 + H^+} \xrightarrow{RCO_2 + H^+} \frac{K_2}{K_1} \int_{ast}^{ast} \frac{fast}{K_2}$$

$$NO^+ + CH_3NHCONH_2 \longrightarrow CH_3NH(NO)CONH_2 K_4$$

$$\begin{array}{c} CH_{3}\dot{N}H(NO)CONH_{2} + H_{2}O \longrightarrow CH_{3}N(NO)CONH_{2} + H_{3}O^{+} & k_{5} \\ CH_{3}\dot{N}H(NO)CONH_{2} + NO_{2}^{-} \longrightarrow CH_{3}N(NO)CONH_{2} + HNO_{2} & k_{6} \\ CH_{3}\dot{N}H(NO)CONH_{2} + RCO_{2}^{-} \longrightarrow CH_{3}N(NO)CONH_{2} + HRCO_{2} & k_{7} \\ \end{array}$$

This scheme explains the halides not acting as catalysts, for the appearance of new nitrosating agents, ONX, capable of reacting with MU to form the intermediate according to

$$X^{-} + NO^{+} + CH_{3}NHCONH_{2} \implies CH_{3}NH(NO)CONH_{2} + X^{-}$$

ONX + CH_{3}NHCONH_{2}

does not determine a rise in the concentration of intermediate, and thus in the rate of reaction, because the intermediate is in equilibrium (the concentration of nitrosyl halides is too small to affect that of NO⁺). This means that when $X^- = NO_2^-$ the reaction may take place via N₂O₃ even though it is of order one with respect to nitrite, contrary to what has hitherto been supposed (see e.g. Refs. [7, 8, 13]). As a result, in these conditions we cannot in fact know the true nitrosating agent, though in the scheme shown above we have written NO⁺ for simplicity. It is also worth pointing out that in view of these conclusions it is pointless to try to interpret the different reactivities of amines and amides in their nitrosation reactions upon the basis of an assumed identity of mechanism.

According to the mechanism proposed, the rate of reaction is given by

$$v = (k_5 + k_6[NO_2^-] + k_7[RCO_2^-])[CH_3\dot{N}H(NO)CONH_2].$$
 (15)

When this is expressed in terms of the total concentrations of the reagents, considering that the concentration of the intermediate is negligible compared to those of the reagents (no spectrophotometric evindence to the contrary was observed), and that $[nit] = [HNO_2] + [NO_2^-]$ and $[Buf] = [HRCO_2] + [RCO_2^-]$, the result is:

$$v = \frac{[\mathrm{MU}][\mathrm{nit}][\mathrm{H}^+]^2}{K_1 + [\mathrm{H}^+]} \left[\gamma + \delta \frac{K_1[\mathrm{nit}]}{K_1 + [\mathrm{H}^+]} + \varepsilon \frac{K_2[\mathrm{Buf}]}{K_2 + [\mathrm{H}^+]} \right]$$
(16)

with $\gamma = K_3 K_4 k_5$, $\delta = K_3 K_4 k_6$ and $\varepsilon = K_3 K_4 k_7$.

Eq. (16) may be considered as being compatible with the experimental equation obtained in the study of the influence of acetate buffer, Eq. (8), for the highest concentration of hydrogen ions present in those experiments, $1.7 \cdot 10^{-4}$ M, is almost negligible compared with the acidity constant of nitrous acid $(K_1 \approx 10^{-3} \text{ M})$. In fact, closer examination of the graph of b against $[H^+]^2$ (Fig. 2) shows that at the highest $[H^+]$ the experimental points fall a little below the regression line, which is no doubt due to $[H^+]$ not being totally negligible compared with K_1 at these acidities. Eq. (16) is also compatible with that obtained experimentally when monochloroacetate buffer was used, Eq. (14), the absence of the second order nitrite term being due to its low concentration and the low pH.

Eq. (16) was fitted to the data obtained in the four groups of experiments carried out (one for each buffer) by means of a non-linear optimization procedure based on Marquardt's method [6, 17] using the weighting factor $w_i = 1/y_i^2$, where y is v_0 or k'. The optimized values of the parameters are listed in Table 1, together with previously published values for y and the acidity constants K_1 and K_2 , whose agreement with our values constitutes further support for the mechanism proposed. For those sets of experiments in which the pH used did not permit optimization of K_1 and K_2 their values were taken as those found in the literature and shown in Table 1. The constant δ was only obtained for the experiments with acetate buffer, since in the other cases the concentration of nitrite and pH were too low to allow the corresponding kinetic term to be detected.

The data of Table 1 show that the catalytic constants of the various carboxylate anions increase with their basic strength. Fig. 7 shows that Brønsted relation [22] is obeyed, with a slope $\beta = 0.24$, and the values corresponding to NO₂⁻ and H₂O are shown in the same figure. The slight deviation of NO₂⁻ from the line defined by the carboxylic compounds is probably due to its different structure. The much greater deviation of H₂O has frequently been observed and attributed to a number of different causes [23]. No statistical corrections have been applied to

Brønsted relation since, apart from the uncertainty of such corrections [23], they would only modify the relative position of the point corresponding to H_2O , which in any case still differ from the behaviour of the other bases.



Brønsted plot for general basic catalysis of the nitrosation of MU



Influence of pD on the rate of nitrosation of MU in D₂O at 25°C, $\mu = 0.2$ M, [MU]₀ = 2.33 · 10⁻² M and [nit]₀ = 3.79 · 10⁻³ M

| Reference | This paper | | | | [7] | | | (21) |
|-----------------------------|---------------------------------|-------------------------------|----------------|----------------|----------------|-----|------|------|
| | (a) | (b) | (c) | (d) | [/] | [8] | [13] | [21] |
| $\gamma/M^{-2} s^{-1}$ | 26.3 ± 0.2 | 27.4 ± 0.3 | 23.8 ± 0.4 | 26.3 ± 0.3 | 15.6 ± 0.5 | 10 | 36 | - |
| $\delta/M^{-3} s^{-1}$ | 116 ± 2 | - | - | - | - | - | - | - |
| $\varepsilon/M^{-3} s^{-1}$ | $(6.2 \pm 0.2) \cdot 10^2$ | 226 ± 14 | 122 ± 3 | 66 ± 2 | - | - | - | - |
| $10^4 K_1 / M$ | - | 8.4 ± 0.3 | 8.0 ± 0.2 | - | 10.6 ± 0.8 | - | - | 11.6 |
| K,/M | $(2.80 \pm 0.16) \cdot 10^{-5}$ | $(2.0 \pm 0.2) \cdot 10^{-3}$ | - | - | - | - | - | - |
| μ/M | 0.2 | 0.2 | 0.2 | 0.2 | 1.0 | - | - | 0.2 |
| T/K | 298 | 298 | 298 | 298 | 288 | 298 | 304 | 298 |

Table 1 Values obtained in this study for the kinetic and thermodynamic constants of Eq. (16), with some published values

(a) Based on 239 experiments with acetate buffer. $K_1 = 8.4 \cdot 10^{-4}$ M, by optimization in (b). Previously published value of $K_2 = 3.2 \cdot 10^{-5}$ M [19].

(b) Based on 84 experiments with monochloroacetate buffer. Previously published value of $K_2 = 1.4 \cdot 10^{-3}$ M [20].

(c) Based on 58 experiments with dichloroacetate buffer. $K_2 = 3.32 \cdot 10^{-2} \text{ M}$ [20].

(d) Based on 19 experiments with trichloroacetate buffer. $K_1 = 8.4 \cdot 10^{-4}$ M, by optimization in (b). $K_2 = 0.20$ M [20].

As the rate controlling step of the mechanism proposed is a proton transfer, it was thought useful to study the kinetics of the reaction when D_2O is substituted for H_2O , so as to determine the solvent deuterium isotope effect. Experimental conditions were chosen in which the second order term with respect to nitrite was negligible. No buffer was present. The righthand side of Eq. (16) then reduces to its first term. On studying the effect on the reaction rate of pD (pD = pH_{measured} + ΔpH , with $\Delta pH = 0.4$ [24]), the values of K_1 and γ in D_2O were found (Fig. 8) to be

$$\gamma(D_2O) = (15.2 \pm 0.2) M^{-2} s^{-1}$$

 $K_1(D_2O) = (2.3 \pm 0.1) \cdot 10^{-4} M$.

This value of K_1 is 3.6 times lower than its value in H₂O, a similar factor to that found for other acids and agreeing with direct measurements of K_1 (D₂O) carried out in our laboratory [25].

The above results also show that $\gamma(H_2O)/\gamma(D_2O) = 1.7$. Since $\gamma = K_3 K_4 k_5$, this ratio includes both the effect on the rate constant k_5 and on the equilibrium constants K_3 and K_4 . Challis et al. [26] found that $K_3(D_2O)/K_3(H_2O) = 2.2$, and since the value of K_4 ought hardly to be affected by the change of solvent, we find that

 $k_5(H_2O)/k_5(D_2O) = 3.5$

value which shows that the rate controlling step involves a proton transfer [27]. The value of the slope in Brønsted relation, $\beta = 0.24$, seems to indicate an asymmetric transition state structurally similar to the products of reaction [28].

The mechanism proposed in this article for the nitrosation of ureas is also supported by the results of authors who have studied the denitrosation of amides and ureas [13, 29-33] in which the rate controlling step is deduced to be the transfer of a proton from the solvent to the nitrogen atom of the amide:

$$\begin{array}{c} O \\ R^{i} - C \\ R \end{array} \xrightarrow{N-N=O} \xrightarrow{H^{*}, slow} \begin{array}{c} R^{i} - C \\ R \end{array} \xrightarrow{N-N=N} \begin{array}{c} O \\ R^{i} - C \\ R \end{array} \xrightarrow{N-N=N} \begin{array}{c} O \\ R^{i} - C \\ R \end{array} \xrightarrow{N-H} + NO^{+} \end{array}$$

This interpretation is supported by the isotopic effect observed $(k_{\rm H}/k_{\rm D} = 1.9$ for N-n-butyl-N-nitrosoacetamide [29], 1.5 for N-methyl-N-nitrosotoluene-p-sulphonamide [31] and 1.3 for N-nitroso-N-methylurea [32]; by there being no catalysis by anions (unlike in the denitrosation of N-nitrosamines [34]); and by the general acid catalysis observed, with $\alpha = 0.64$ for various carboxylic acids in the denitrosation of N-nitroso-2-pyrrolidone [30]. According to the principle of microscopic reversibility, these results are coherent with our own.

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