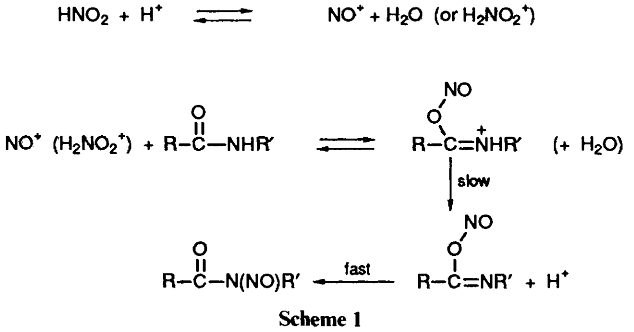
Solvent-induced Mechanistic Changes in Nitrosation Reactions. Part 2.[1] Effect of Acetonitrile–Water Mixtures in the Nitrosation of Ureas

Carlos Bravo, Pablo Hervés, J. Ramón Leis* and M. Elena Peña
Departamento de Química Física, Facultad de Química, Universidad de Santiago, Santiago de Compostela, Spain

The nitrosation of 1,3-dimethylurea in acetonitrile–water mixtures has been studied kinetically. The results obtained show that the addition of acetonitrile until the medium holds 70% acetonitrile by weight inhibits the reaction. The reaction is not catalysed by chloride ions in these circumstances, and the reaction mechanism is probably the same as in pure water. Addition of acetonitrile to a solution already containing more than 70% acetonitrile increases the reaction rate, and catalysis by halides becomes possible. The change in reaction mechanism this suggests was studied in detail in a medium containing 90% acetonitrile. The reaction rate increases non-linearly with increasing halide concentration and acidity, but seems to tend to the same limiting value in all cases, depending only on the nitrous acid and urea concentrations. Nitrosyl halides are therefore good nitrosating agents of ureas, though the catalytic efficiency of the different halides is the reverse of that in water, probably because of solvation-induced changes in their nucleophilicity. The tendency of the reaction rate towards a limiting value is evidence that the mechanism changes with the catalyst or acid concentration. In the limit, the reaction rate will only depend on nitrous acid and urea concentrations; this is consistent with a limiting step consisting of the rearrangement of the 'nitrosourea', the nitroso group transferring from the more nucleophilic O atom to the N atom. Thus, there is direct kinetic evidence that the nitrosation of amides occurs initially on oxygen.

There is considerable evidence in the literature to suggest that the *N*-nitrosation of amides and ureas in water occurs in a different way from that of amines. The absence of catalysis by X^- species (halides, SCN^-, *etc.*), that generally speed up amine nitrosation through formation of efficient nitrosating agents NOX, has been taken[2] as showing that the slow step of the process takes place after the reaction between the nitrosating agent and the amide, the step being proposed to consist of proton transfer of the protonated nitrosamide to the reaction medium. The existence of general base catalysis and the fact that the reaction is subject to a primary solvent isotope effect[3,4] corroborate this mechanism. In a further study we looked at the reaction of different amides and ureas.[5] Applying existing theories concerning proton transfer reactions, we analysed the Brønsted relations described for the catalyst bases of the process and adding to this information the results of studies of the inverse reaction, *i.e.* the denitrosation of nitrosamides, we concluded that nitrosation of these species occurred initially on the O atom of the molecule (Scheme 1), although subsequent rapid rearrangement gives the more thermodynamically stable product, the *N*-nitroso compound.[5] There is controversy in the literature about the exact nature of the nitrosating agent resulting from the protonation of nitrous acid operating in water; arguments for and against nitrosonium ion (NO^+) or nitrous acidium ion ($H_2NO_2^+$) have been put forward.[6] Both possibilities have been considered in Scheme 1.



Scheme 1

This mechanism provides no way of distinguishing whether only the species resulting from protonation of nitrous acid or other, less electrophilic, nitrosating agents NOX can nitrosate deactivated species such as amides. The answer emerged recently[1] in our study of the nitrosation of 1,3-dimethylurea (DMU) in dioxane–water mixtures. The change of medium causes the slow step of the reaction to change, and at high dioxane concentrations catalysis by chloride and bromide is observed, providing direct evidence for the participation of the corresponding nitrosyl derivatives in the nitrosation of DMU. Changing the solvent has therefore been shown to be a useful tool for elucidating nitrosation reaction mechanisms, as Williams and co-workers had already demonstrated regarding other aspects.[7,8]

Scheme 1 is novel in that it proposes an initial *O*-nitrosation. This idea is not without merit, since O is probably the centre of greatest nucleophilicity in the molecule[9] and, furthermore, the scheme established would be similar to the observed behaviour in the reaction of amides with electrophiles, since processes such as alkylation[10] and protonation[11] also occur on this atom. Nevertheless, it would be desirable to have more direct evidence on that point, rather than that based on theoretical interpretations of the Brønsted relations. The work described here studies the nitrosation of DMU in acetonitrile–water mixtures and provides direct kinetic evidence concerning this aspect, as well as discussing the mechanistic changes brought about by the presence of acetonitrile in the mixtures.

Experimental

DMU (Merck) was purified by recrystallization in ethanol. All other reagents were from Merck and were used without further purification after drying. Kinetic measurements were taken in a Kontron Uvikon 930 spectrophotometer at 25 °C, following the increase in absorbance at 270 nm corresponding to formation of 1,3-dimethyl-1-nitrosourea. Reactions were

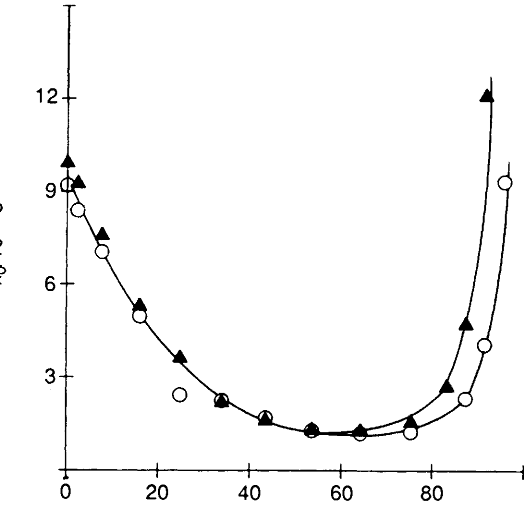


Fig. 1 Influence of the percentage of acetonitrile upon the pseudo-first-order rate constant for nitrosation of DMU ion water–acetonitrile mixtures. [DMU] = 3.2 × 10^{-3} mol dm^{-3}; [$HClO_4$] = 1.2 × 10^{-2} mol dm^{-3}; ○ [NaCl] = 0; ▲ [NaCl] = 2.7 × 10^{-2} mol dm^{-3}.

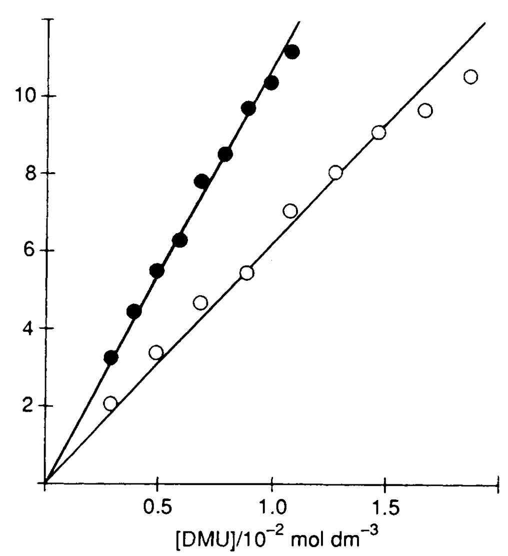


Fig. 2 Influence of the concentration of DMU upon k_0 at [$HClO_4$] ○ 6.2 × 10^{-3} mol dm^{-3}; ● 1.2 × 10^{-2} mol dm^{-3}

performed with a large deficiency of nitrous acid (in the range 10^{-5}–10^{-4} mol dm^{-3}) with respect to the other reagents. Under these conditions the absorbance–time data were a perfect fit to the first-order integrated equation until the reaction was at least 90% complete. The values of the pseudo-first-order rate constant, k_0, were reproducible to within ±4%. The composition of the solvent mixture is expressed as the percentage by weight of acetonitrile.

Results and Discussion

As the proportion of acetonitrile was increased, at constant concentrations of DMU and $HClO_4$ (source of acidity in the medium), the reaction rate decreased sharply at first, then more gradually. At acetonitrile proportions above 70% the reaction rate increased very quickly with increasing amount of acetonitrile (Fig. 1). The whole curve described a minimum, of similar characteristics to that obtained for the reaction with dioxane.[1] The initial reactivity was 4.2 times greater than its minimum value. The reactivity in the absence of acetonitrile corresponds exactly with the value obtained in a more detailed study of the nitrosation of DMU in water.[5] Adding 2.7 × 10^{-2} mol dm^{-3} NaCl to the reaction mixture (results shown in Fig. 1) did not change the reaction rate at all until the mixture contained 75% acetonitrile, when the reaction was progressively catalysed by the NaCl. The behaviour in mixtures containing less than 75% acetonitrile is like that in pure water, suggesting that the mechanism proposed for the reaction in water is also valid under these conditions. The catalysis suggests that NOCl intervenes as an efficient nitrosating agent of DMU under this range of experimental conditions, and that its reactivity is kinetically detectable. Hence, the reaction mechanism changes when the composition of the medium is changed.

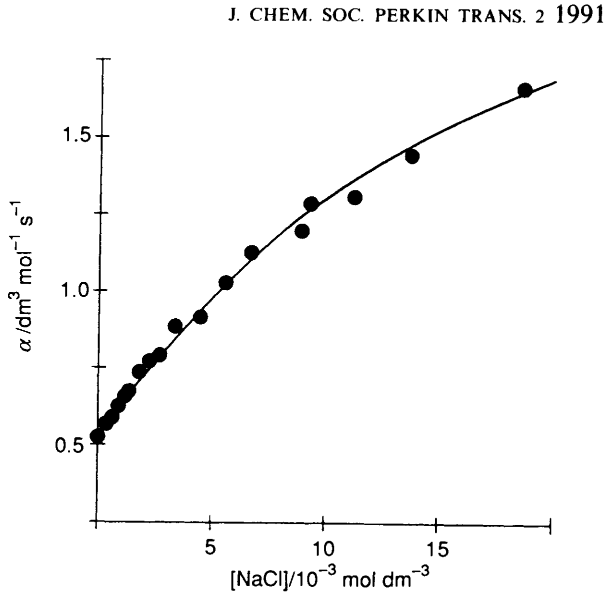


Fig. 3 Variation of α with [NaCl]; [$HClO_4$] = 5.8 × 10^{-3} mol dm^{-3}

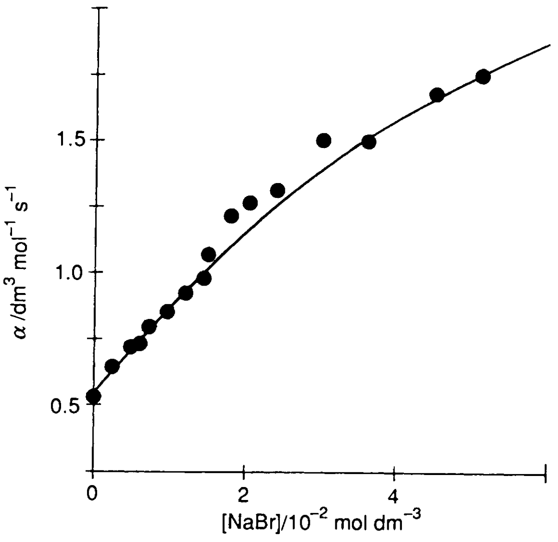


Fig. 4 Variation of α with [NaBr]; [$HClO_4$] = 5.8 × 10^{-3} mol dm^{-3}

The reaction at high concentration of acetonitrile was studied in more detail, choosing 90% by weight of acetonitrile as representative. Fig. 2 shows the influence of the concentration of DMU on the reaction rate at two acidities. The reaction is first-order with respect to DMU at both acidities. Interestingly, both lines pass through the origin, demonstrating that the reaction is irreversible.* Therefore, we can derive eqn. (1).

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* In our study using dioxane[1] there was a small intercept at the origin in a similar plot, which we attributed to the reversibility of the process. However, studies since then show that this intercept is probably due to the competitive decomposition of the nitrous acid in these media, which becomes significant when the concentration of DMU is low and shows roughly first-order kinetics. The solutions of nitrous acid in 90% acetonitrile are stable for several hours under the experimental conditions employed in this study.

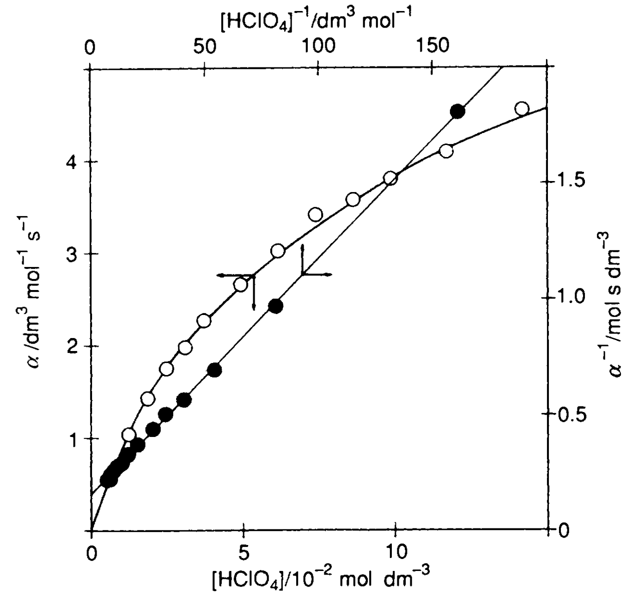


Fig. 5 Influence of the acidity on the kinetic parameter α in the absence of halide ion. Linearization of the data according to eqn. (3) is also shown.

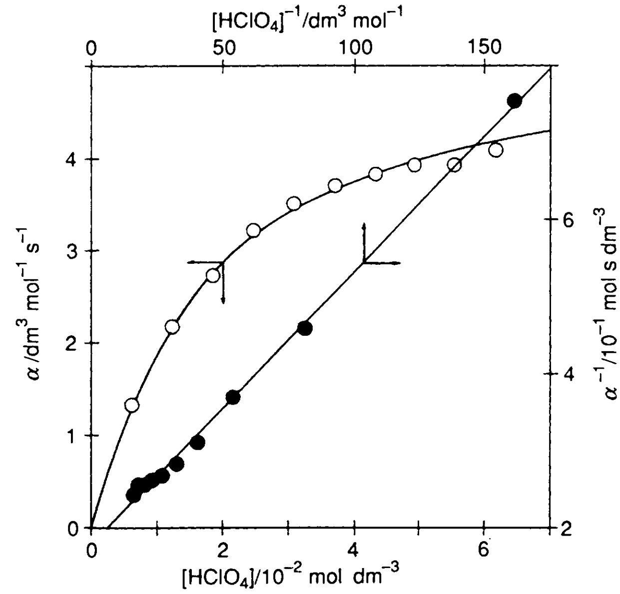


Fig. 6 Influence of the acidity upon α at [NaCl] = 9.3 × 10-3 mol dm-3. Linearization of the data according to eqn. (3) is also shown.

$$k_o = \alpha[\mathrm{DMU}] \qquad (1)$$

The influence of NaCl and NaBr on α was also studied under the same experimental conditions. The reaction was halide-catalysed (Figs. 3 and 4), but the catalysis was non-linear, tending to a limiting value as the concentration of halide is increased. Though concentrations placing the reaction in the flat part of the curve could not be attained because of solubility problems, it seems likely that the limits are similar for both catalytic species. Nevertheless, it is possible to calculate the slope at the origin, to give the catalytic efficiency of the two halides for nitrosating DMU. At the working acidity (5.8×10^{-3} mol dm^{-3} $HClO_4$) the values were 150 dm^6 mol^{-2} s^{-1} for chloride ion and 56 dm^6 mol^{-2} s^{-1} for bromide ion, hence chloride ion is almost three times more efficient than bromide ion at catalysing this reaction, this result being the opposite of results obtained in water for other nitrosation reactions,[6] in which the greater catalytic efficiency in water of bromide compared with chloride is attributed to its greater nucleophilic nature. This inversion in the order of catalysis, though more marked, is in keeping with our recent findings for the nitrosation of the same substrate in mixtures containing 90% dioxane,[1] and we attribute it to the smaller role played by ionic solvation in media with low water content. In this case deactivation of the nucleophile by solvation is minimized and the natural order of nucleophilicity (that in the gas phase) is restored.[12]

The influence of acidity on reaction rate was studied in the presence and absence of chloride. The results obtained are shown in Figs. 5 and 6; α increased with increasing acidity, describing a curve passing through the origin and levelling off at high proton concentrations. The degree of curvature was much more marked in the presence of catalyst (Fig. 6). A function such as that shown in eqn. (2) is a good fit to the experimental data, and the data plotted according to the transformed function [eqn. (3)] lie on a straight line (Figs. 5 and 6).

$$\alpha = \frac{a[\mathrm{H^+}]}{1 + b[\mathrm{H^+}]} \qquad (2)$$

$$\frac{1}{\alpha} = \frac{b}{a} + \frac{1}{a[\mathrm{H^+}]} \qquad (3)$$

Fitting gave $a = 93 \pm 3$ dm^6 mol^{-2} s^{-1} and $b = 13.9 \pm 0.7$ dm^3 mol^{-1} for the reaction in the absence of chloride and $a = 311 \pm 16$ dm^6 mol^{-2} s^{-1} and $b = 59 \pm 4$ dm^3 mol^{-1} in the presence of 9.3×10^{-3} mol dm^{-3} NaCl. The quotient a/b represents the limiting value of α at a high concentration of protons in the two cases. The values were 6.6 and 5.3 dm^3 mol^{-1} s^{-1}, respectively, which may be treated as being similar, especially when the different ionic strengths are taken into account. The value of α tends to a limiting value around 5–6 dm^3 mol^{-1} s^{-1} when the acidity is increased. The acidity necessary to reach this limiting value is lower if there are halides in the medium. These facts together suggest that the system undergoes a change of rate-limiting step as the acidity of the medium is increased and that protons and halides act co-operatively to promote the transition to the new situation. Furthermore, a limiting value of *ca.* 5 dm^3 mol^{-1} s^{-1} is a reasonable estimate for the limiting value of α (Figs. 3 and 4), when the halide concentration, not the acidity, is varied. Thus, a change in the limiting step is produced by increasing the acidity, the catalyst concentration or both of these together; the limiting step in each case is the same. In the limit the reaction rate depends only on the concentrations of DMU and nitrous acid. Under these conditions, the transition state through which the reaction passes in its slow step will have a molecular composition equivalent to one molecule of nitrous acid and one of DMU, without the presence of halide ions or protons. The simplest explanation is that this step implies the migration of the nitroso group from one part of the molecule to another, *i.e.* the *O* to *N* rearrangement suspected for nitrosation of DMU in water,[5] but which cannot be detected kinetically. A reaction mechanism which explains all the experimental results is shown in Scheme 2, in which ionic species have been written as the free ions. Ionic association in this medium of relatively high relative permittivity (*ca.* 39) is not predominant for conventionally strong acids or electrolytes. For example, experimental evidence indicates that $HClO_4$ behaves as a strong acid even in pure acetonitrile[13] and the same would happen to sulfuric acid at the concentrations used by us.[14] The situation is therefore completely different to that described by us when the same reaction was studied in mixtures of dioxane–water[1] with 90% dioxane (*ca.* 6).

Table 1 Values of kinetic parameters corresponding to the nitrosation of DMU at 90% acetonitrile

Nitrosating agent	k_1K_{NO}/ $dm^6\ mol^{-2}\ s^{-1}$	k_{-1}/K_3k_4 $dm^3\ mol^{-1}$	k_2K_{XNO}/ $dm^9\ mol^{-3}\ s^{-1}$	k_{-2}/K_3k_4 $dm^6\ mol^{-2}$
NO^+	93	13.9	—	—
NOCl	—	—	2.5×10^4	5×10^3
NOBr	—	—	9.75×10^3	$\approx 2.5 \times 10^3$

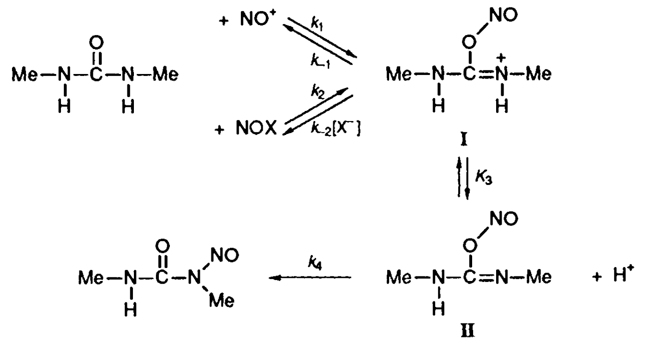
Table 2 Influence of the concentration of HCl upon the pseudo-first-order rate constant for nitrosation of DMU at 90% acetonitrile[a]

$[HCl]/10^{-3}\ mol\ dm^{-3}$	$k_0/10^{-3}\ s^{-1}$ (experimental)	$k_0/10^{-3}\ s^{-1}$ (calculated)[b]
1.78	0.73	0.74
3.87	2.06	2.04
5.35	3.49	3.13
7.13	4.55	4.50
8.92	5.87	5.81
10.7	6.93	7.04
12.5	7.78	8.16
14.3	8.75	9.13
16.1	9.95	9.94
17.8	11.8	10.6
19.6	12.2	11.2

[a] $[DMU] = 3.14 \times 10^{-3}\ mol\ dm^{-3}$. [b] Predicted by eqn. (6).

$$HNO_2 + H^+ \rightleftharpoons NO^+ + H_2O \quad K_{NO} \tag{4}$$

$$HNO_2 + H^+ + X^- \rightleftharpoons NOX + H_2O \quad K_{XNO} \tag{5}$$



Scheme 2

Scheme 2 contains exactly the same steps as Scheme 1 proposed for the reaction in water, but the nature of the limiting steps of the process has been altered and the intervention of nitrosyl halides in the reaction has been explicitly recognized. Intermediates **I** and **II** in such a scheme are found in the steady state and its interconversion is considered to be fast, explaining the changes in the slow step as the proton and halide concentrations are varied. In keeping with Scheme 2, at low concentrations of X^- and H^+ the slow step will be the attack by the nitrosating agents (NO^+ or NOX) on DMU; the reaction is first-order in DMU and protons, and presents components of order zero (reaction not catalysed) and order one (catalysis by halides) in X^-. The first-order dependence on H^+ and X^- disappears at high concentrations of these species, in which case internal rearrangement of the nitroso group becomes the controlling step. This scheme shows similarities with that proposed to explain the nitrosation of 2-naphthol in water,[15] a reaction in which the reaction rate also depends non-linearly on acidity and halide concentrations. The rate equation derived from this mechanism is eqn. (6) and indicates a dependence of the reaction rate upon the acidity, whether X^- is present or not, that coincides with the experimental rate equation [eqn. (2)].

$$k_0 = \frac{k_1k_4K_3K_{NO}[H^+][DMU] + k_2k_4K_3K_{XNO}[H^+][X^-][DMU]}{K_3k_4 + k_{-1}[H^+] + k_{-2}[H^+][X^-]} \tag{6}$$

Fitting the equation to the experimental results gives the kinetic parameters shown in Table 1. The value of $K_{XNO}k_2$ is greater for chloride than for bromide, as we have mentioned. That this behaviour is due to the greater nucleophilicity of chloride in this solvent becomes clear when the ratio k_{-2}/K_3k_4 is compared for both ions. Since the constants K_3 and k_4 are independent of the nitrosating agent, k_{-2} is approximately twice as great for Cl^- than for Br^-. This rate constant is that directly governing the attack of the nucleophile X^- on a common electrophile (intermediate **I**) and, therefore, it can be considered as a straightforward measure of the relative nucleophilicity of the two ions in this medium.

A further test for the correctness of this mechanism was performed by studying the reaction using hydrochloric acid instead of perchloric acid; in this way both Cl^- and H^+ ions are supplied together from one source. In Table 2 the results obtained are compared with the theoretical values calculated from eqn. (6) using the data in Table 1. The agreement is good in all cases, in support of the proposed mechanism.

Finally, the mechanisms proposed can lead to a better understanding of the role of the amount of water in the process. When the mechanism in Scheme 2 is operating, the addition of water (Fig. 1) inhibits the reaction considerably. Similar inhibition was observed in other nitrosation reactions in pure organic solvents.[16] After studying the reactions between alkyl nitrites and alcohols Allen and Schonbaum[17] interpreted this inhibition as being a consequence of the greater basicity of water compared to alcohols, which lowers the effective acidity of the medium. In our case we can suppose that when the mechanism in Scheme 2 is operating the limiting step of the reaction is initially the attack of the nitrosating agent on the urea. In these conditions the only way water can take part in the mechanism is in the steps forming the nitrosating agents. Adding water would displace equilibria (4) and (5) to the left reducing the concentration of nitrosating agent (NO^+ or NOX) in the medium and inhibiting the reaction. The situation is different for amounts of acetonitrile below 70%, in which case water catalyses the reaction. At these concentrations the mechanism of Scheme 1 is that which operates, with the slow step of the reaction being proton transfer to the medium. Water, in the absence of other bases in the medium, would be the proton-collecting species, enabling it to catalyse the process and making more difficult the prediction of the overall effect on the reaction rate. The key point in this discussion is, therefore, why the slow step changes upon changing the solvent composition. One can speculate on the basis of the old nitrosonium ion/nitrous acidium ion controversy, *i.e.* $H_2NO_2^+$ is the predominant species in water or water-rich mixtures whereas NO^+ acts in acetonitrile-rich mixtures (as in pure acetonitrile).[7] In such a case, according to the microreversibility principle, at high water content water would act as a nucleophile assisting intermediate **I** in NO^+ loss and making the corresponding step (rate constant k_{-1}) fast. On the contrary, under conditions for which NO^+ was the effective nitrosating agent, in the absence of added catalyst, the system should have to undergo a unimolecular (and difficult) NO^+ loss (see Scheme

2). This would lower the value of k_{-1}, so that the slow step of the reaction would be, at least partially, the nitrosation step.

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References

1 Part 1: C. Bravo, P. Hervés, J. R. Leis and M. E. Peña, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1969.

2 G. Hallett and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1372.

3 J. Casado, A. Castro, M. Mosquera, M. F. Rodríguez Prieto and J. Vázquez Tato, *Ber. Bunsenges. Phys. Chem.*, 1983, **87**, 1211.

4 J. Casado, A. Castro, J. R. Leis, M. E. Peña and J. Vázquez Tato, *Monatsh. Chem.*, 1984, **115**, 1047.

5 A. Castro, E. Iglesias, J. R. Leis, M. E. Peña and J. Vázquez Tato, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1725.

6 D. L. H. Williams, *Nitrosation*, Cambridge University Press, Cambridge, 1988.

7 M. J. Crookes and D. L. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1988, 571; M. J. Crookes and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1319.

8 S. S. Johal, D. L. H. Williams and E. Buncel, *J. Chem. Soc., Perkin Trans. 2*, 1980, 165.

9 B. C. Challis, J. N. Iley, H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1037.

10 P. Beak, J. K. Lee and B. G. McKinnie, *J. Org. Chem.*, 1978, **43**, 1367.

11 R. B. Homer and C. D. Johnston, in *The Chemistry of Amides*, ed. J. Zabicky, Wiley, New York, 1970.

12 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 1988, ch. 5.

13 I. M. Kolthoff, S. Bruckenstein and M. K. Chantooni, *J. Am. Chem. Soc.*, 1961, **83**, 3927.

14 I. M. Kolthoff and M. K. Chantooni, *J. Am. Chem. Soc.*, 1968, **90**, 5961.

15 A. Castro, E. Iglesias, J. R. Leis, M. Mosquera and M. E. Peña, *Bull. Soc. Chim. Fr.*, 1987, 83.

16 M. J. Crookes and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1989, 759.

17 A. D. Allen and G. R. Schonbaum, *Can. J. Chem.*, 1961, **39**, 947.

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