# Kinetics and Mechanism of the Formation and Decomposition of N-Nitroso-amides and Related Compounds

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Kinetic studies of the nitrosation reactions of ethyl N-ethylcarbamate, N,N'-dimethylurea, and 2-imidazolidone have shown that all are subject to primary solvent isotope effects and to general base catalysis with bases of $pK_a$ in the range 0.6—4.6. Both these features are indicative of a slow proton transfer. The characteristics of this proton transfer and the reactivity of the substrate depend to a large extent on the nature of the substrate: for ethyl N-ethylcarbamate the Brønsted plot is linear ($\beta$ = 0.34) and the solvent isotope effect is 5.5; for N,N'-dimethylurea the curved Brønsted plot suggests that the reaction with acetate ion is diffusion-controlled, and the isotope effect is 3.2 in the absence of added base and 1.1 when the reaction is catalysed by acetate; for 2-imidazolidone the slightly curved graph of reaction rate against base concentration shows the proton donor to be an intermediate in the steady state, and the solvent isotope effects for the uncatalysed and acetate-catalysed reactions are 2.9 and 1.4, respectively. These facts suggest that the protonated intermediate has a near-zero $pK_a$ value. Complementary studies of the denitrosation of N-nitroso-N-methylurea, N-nitroso-N,N'-dimethylurea, and N-nitroso-2-imidazolidone have shown that the rate-controlling step of each of these reactions is protonation of the substrate. These data, together with those from the nitrosation experiments, imply a $pK_a$ of ca. −12 for the nitroso-amide. The discrepancy between the two results suggests that nitrosation initially takes place at the oxygen atom; this is followed first by a slow proton transfer and subsequently by a fast internal rearrangement to produce the thermodynamically more stable N-nitroso-amide.

It is now well established that the N-nitrosation mechanism for amides is different from that for amines.[1-3] The rate-controlling step for amines is usually the reaction between the nitrosating agent and the substrate, whereas the N-nitrosation of amides involves a slow proton transfer from the protonated nitroso-amide intermediate to the reaction medium, as shown both by the absence of nucleophilic catalysis[1] and by the existence of primary isotope effects and general base catalysis, complying with Brønsted's law.[2,3] The experimental results for the two amides hitherto investigated suggest that both the isotope effect and the base catalysis are strongly influenced by the nature of the substrate: for N-methylurea the primary solvent isotope effect and the Brønsted slope of 0.24 suggest that in the transition state the characteristics of the reagents are relatively little altered;[2] for N-methylacetamide, on the other hand, the isotope effect is much greater and the Brønsted slope of 0.49 implies a symmetrical transition state in the slow step.[2] The urea, moreover, reacts some 4 000 times faster than the acetamide; the great range of reactivities exhibited by amides has been further demonstrated by Mirvish,[4] who observed differences of up to a factor of 3 × 10⁵ that were not correlated with the basicity of the amide substrates. The present paper describes experiments undertaken to investigate the causes of these enormous variations by studying both the nitrosation of three substrates selected for their potentially widely differing reactivities, and the corresponding denitrosation reactions of two of the N-nitrosated products and one other N-nitrosourea.

## Experimental

Ethyl N-ethylcarbamate (EEC) (Fluka, *purum*) was purified by double distillation at reduced pressure. N,N'-Dimethylurea (DMU) (Merck, p.s.) and 2-imidazolidone (Im) were purified by recrystallization from methanol. Heavy water supplied by the Spanish nuclear energy board was 99.77% D₂O. The nitroso compounds N-nitroso-N-methylurea (NMU), N-nitroso-N,N'-dimethylurea (NDMU) and N-nitroso-2-imidazolidone (NIm)

were synthesized by treating the corresponding ureas with less than an equivalent amount of nitrous acid (Nit) at pH ca. 2 under conditions in which the reaction suffered no interference. The concentration of nitroso compound thus obtained was determined by measuring absorbance at 249 nm ($\varepsilon_{NMU}$ 4 100; $\varepsilon_{NDMU}$ 4 800; $\varepsilon_{NIm}$ 8 240 dm³ mol⁻¹ cm⁻¹). Other reagents were obtained from Merck with the best available purity and were used as supplied with no further purification other than drying.

Reaction rates were obtained spectrophotometrically with a Kontron Uvikon 820 spectrophotometer by recording the absorbance at 249 or 265 nm due to the nitroso compound being formed or decomposed. Acidities were measured with a Radiometer 82 pH-meter equipped with a GK2401C combined electrode. In all kinetic experiments NaClO₄ was used to maintain the ionic strength of the medium at either 0.2 mol dm⁻³ (for the nitrosation experiments) or 2.6 mol dm⁻³ (for denitrosation). All experiments were carried out at 25 °C. Reaction rates were reproducible to within ±3%.

In the case of the nitrosation of EEC the initial-rate technique was employed, because of the slowness of this reaction (no more than 1% was ever followed). The nitrosation of the other amides was studied almost exclusively by the integration technique: the method of Davies, Swann, and Campey[5] was used to optimize the value of $A_\infty$, the absorbance at infinite time and the corresponding graphs of $\ln(A_\infty - A_t)$ against $t$ were linear for at least 90% of the reaction ($A_t$ being the absorbance at time $t$). The slopes of those graphs were the pseudo-first-order rate constants $k_{obs.}$. Those experiments in which the nitrosation of these amides was studied by the initial-rate method (when acetic buffer of pH > 4 was used) yielded results totally compatible with those obtained by the integration method. The nitrosation of EEC was studied for [EEC] 0.0130—0.200 mol dm⁻³, [Nit] (3.74—11.0) × 10⁻³ mol dm⁻³, pH 1.85—3.98; that of DMU for [DMU] (1.60—43.4) × 10⁻³ mol dm⁻³, [Nit] (1.00—22.9) × 10⁻⁴ mol dm⁻³, pH 1.89—4.66; and that of Im for [Im] (1.39—22.3) × 10⁻³ mol dm⁻³, [Nit] (1.00—43.2) × 10⁻⁴

**Table 1.** Values of $a$ [equation (1)] and $pK_1$ for the nitrosation of various amides in water and in $D_2O$ at ionic strength 0.2 mol $dm^{-3}$ and 25 °C

| Amide | $pK_1$ in $H_2O$ | $a(H_2O)/$ $dm^6$ $mol^{-2}$ $s^{-1}$ | $a(D_2O)/$ $dm^6$ $mol^{-2}$ $s^{-1}$ | $pK_1$ in $D_2O$ | $\Delta pK_1$ |
|---|---|---|---|---|---|
| EEC | 3.20 | 0.29 ± 0.04 | 0.140 ± 0.004 | 3.68 | 0.48 |
| DMU | 3.05 | 280 ± 10 | 235 ± 1 | 3.52 | 0.47 |
| Im | 3.09 | 660 ± 20 | 601 ± 2 | 3.60 | 0.50 |
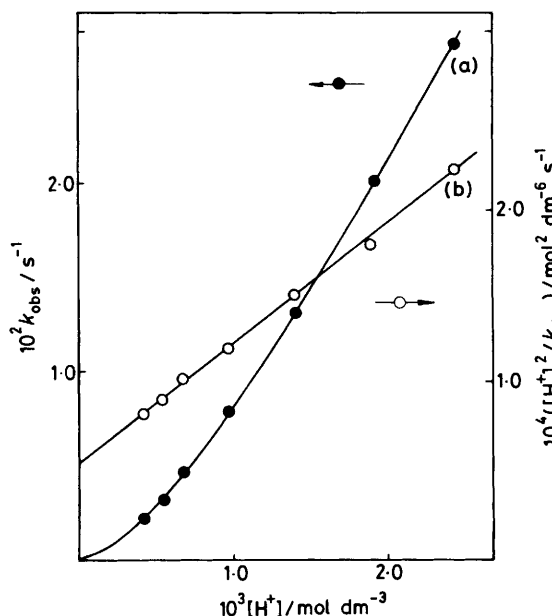


**Figure 1.** (a) Influence of acidity on the pseudo-first-order rate constant for nitrosation of Im; [Im] = 2.23 × $10^{-2}$M, $I$ = 0.2M, $T$ = 25 °C; (b) the same data in linear form

mol $dm^{-3}$, pH 2.61—4.58. For all denitrosation experiments the integration method was employed.

## Results and Discussion

With concentrations of nitrite of less than $10^{-2}$ mol $dm^{-3}$ the rate equations inferred experimentally for the nitrosations of EEC, DMU, and Im were all of the form of equation (1), where

$$\text{rate} = a[\text{Nit}][\text{Amide}][H^+]/(K_1 + [H^+]) \qquad (1)$$

[Nit] represents the sum of the concentrations of $HNO_2$ and $NO_2^-$ and $K_1$ is the acidity constant of nitrous acid (with greater concentrations of nitrite a second-order Nit term appears which has been interpreted[2,3] as due to base catalysis by $NO_2^-$ facilitating the loss of a proton from the protonated nitrosamide). Equation (1) is based on the observation of first-order dependence on Nit and amide and on a rather peculiar acidity dependence which, as Figure 1 shows for Im, gives rise to linear graphs of $[H^+]^2/k_{obs.}$ against $[H^+]$. The values of $pK_1$ deduced for $HNO_2$ from these graphs and the corresponding values of the parameter $a$ of equation (1) are listed in Table 1.

The accepted mechanism for the nitrosation of this kind of substrate (Scheme 1) is compatible with equation (1) ($a = K_2K_3k_4$) and is confirmed by the results of experiments carried out to investigate the influence of acidity on the reaction rate in heavy water (pD = $pH_{meas.}$ + 0.40)[6] (Table 1). The differences between the $pK_a$ values of $HNO_2$ in $H_2O$ and those of $DNO_2$ in

**Table 2.** Values of $a$ [equation (1)], isotope effects, and Brønsted behaviour for the nitrosation of various amides at ionic strength 0.2 mol $dm^{-3}$ and 25 °C

| Amide | $a(H_2O)/$ $dm^6$ $mol^{-2}$ $s^{-1}$ | Brønsted plot | $(k_{4H}/k_{4D})$* |
|---|---|---|---|
| N-Methylacetamide (ref. 3) | 5.50 × $10^{-3}$ | Linear, β = 0.49 | 7.7 |
| EEC | 0.29 | Linear, β = 0.34 | 5.5 |
| N-Methylurea (ref. 2) | 27 | Linear, β = 0.24 | 4.6 |
| DMU | 280 | Curve | 3.3 |
| Im | 660 | | 2.9† |

* Calculated using $K_1(D_2O)/K_1(H_2O)$ = 2.7 (ref. 8).
† $(a_H/a_D)$ × 2.7 = 2.9, but the true value may be somewhat different owing to the intermediate's steady-state condition.

$D_2O$ are all close to 0.48, in good agreement with the results of direct measurements;[7] and the values of the isotope effects on the $k_4$ step (obtained by multiplying $a(H_2O)/a(D_2O)$ by 2.7, the ratio of the equilibrium concentrations of $NO^+$ in $D_2O$ and water[8]) are all typical of primary isotope effects indicative of slow proton transfers (Table 2).
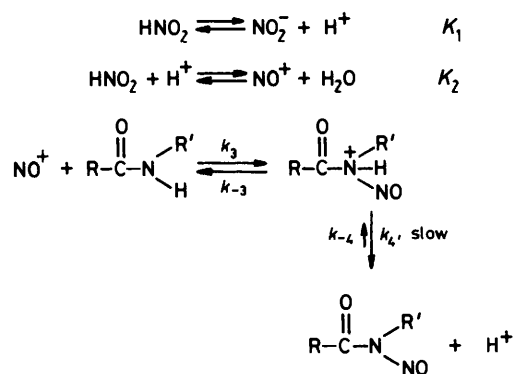


**Scheme 1.**

The values of $k_{4H}/k_{4D}$ shown in Table 2 decrease appreciably as the reactivity of the substrate increases. In order better to relate this tendency to differences in the nature of the corresponding proton transfers,[9] experiments were carried out to investigate the behaviour of these reactions in the presence of added bases. The nitrosation of EEC was found to be subject to pronounced linear catalysis by acetate and chloroacetates (see Figure 2 for examples), the variation of the percentage catalysis with acidity showing it to be the basic form of the buffer that was responsible for catalysis. Figure 3 shows that the catalytic efficiency of the various carboxylic bases is satisfactorily described by a linear Brønsted dependence on their basicity (β = 0.34). The deviation of the value for water is probably due to the same causes as are responsible for its exceptional behaviour in other contexts.[9]

The nitrosation of DMU was also found to be subject to linear catalysis by all the bases added (both the acetate buffers used with EEC and sulphate). In this case, however, the Brønsted graph is slightly curved, with a tendency to level off at the higher basicities (Figure 4). In order to determine whether this effect is merely due to experimental errors (in some cases the catalysis was very weak) or whether it is truly indicative of the reaction rates being limited by diffusion at higher basicities,[9] experiments were carried out to compare the catalytic actions of the acetate ion in water and in $D_2O$. Figure 5 shows that
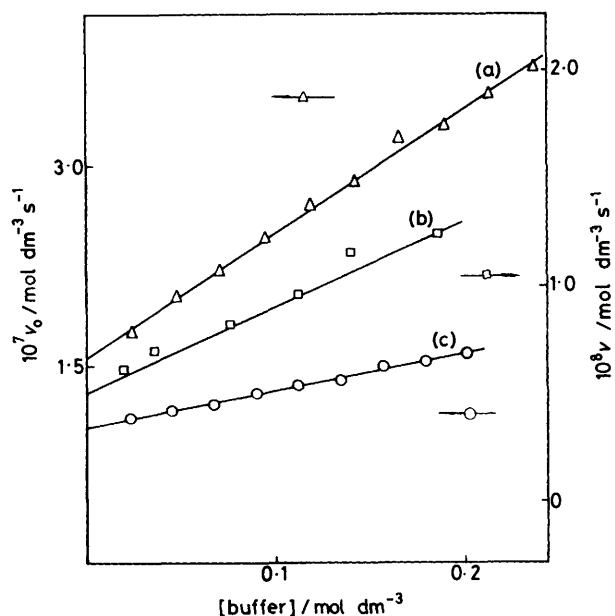
**Figure 2.** Influence of buffers on the initial rate of nitrosation of EEC at 25 °C and ionic strength 0.2M; (a) monochloroacetate (pH 2.72, [EEC] 7.78 × $10^{-2}$M, [Nit] 4.37 × $10^{-3}$M); (b) dichloroacetate (pH 2.46, [EEC] 2.59 × $10^{-2}$M, [Nit] 4.37 × $10^{-3}$M); (c) acetate (pH 3.98, [EEC] 0.200M, [Nit] 6.76 × $10^{-3}$M)
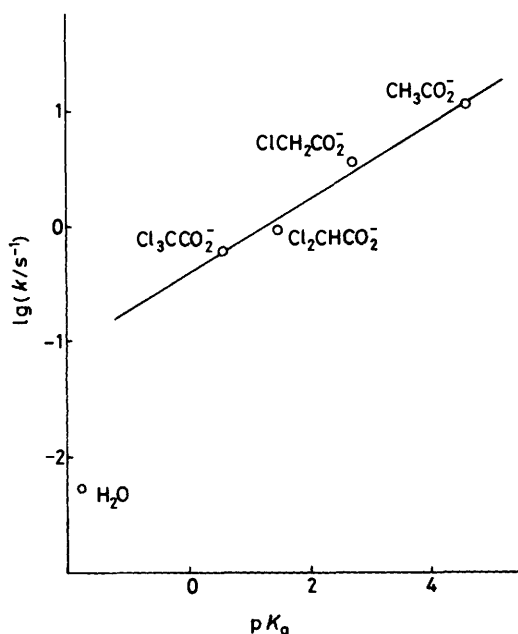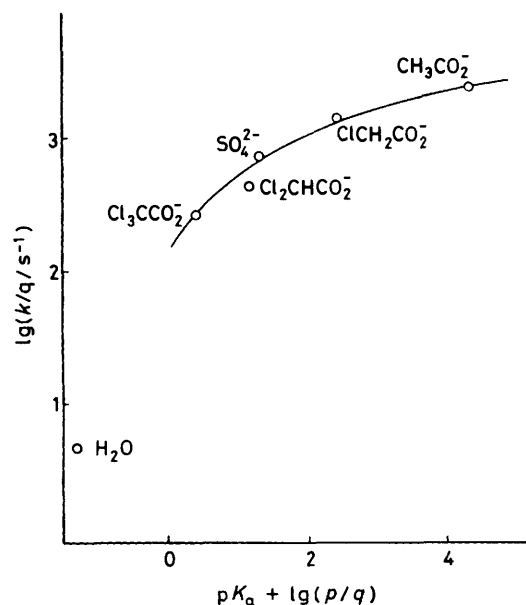


**Figure 4.** Brønsted plot for the general base catalysis of the nitrosation of DMU. $P$ = number of equivalent acidic pictons. $q$ = number of equivalent basic sites in the conjugate base



**Figure 3.** Brønsted plot for the general base catalysis of the nitrosation of EEC
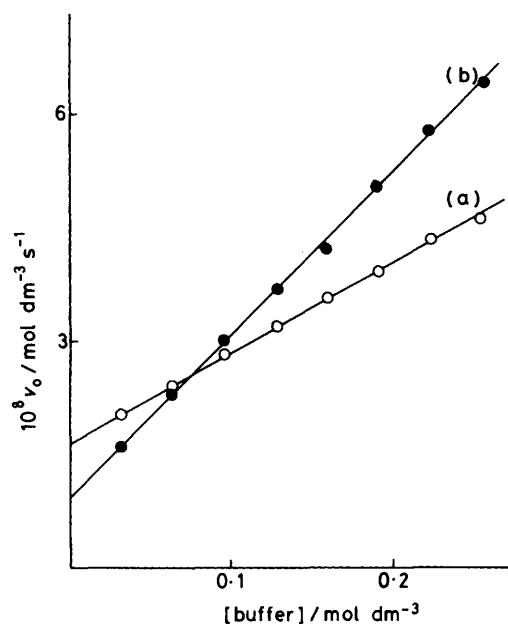


**Figure 5.** Influence of the concentration of acetate buffer on the initial rate of nitrosation of DMU at 25 °C and ionic strength 0.2M; (a) in water (pH 4.67, [DMU] 4.34 × $10^{-2}$M, [Nit] 2.29 × $10^{-3}$M); (b) in $D_2O$ (pD 5.11, [DMU] 4.39 × $10^{-2}$M, [Nit] 3.50 × $10^{-3}$M)

catalysis is much greater in $D_2O$, with an inverse isotope effect $k_{AcO}-(H_2O)/k_{AcO}-(D_2O) = 0.41$, which when multiplied by 2.7 to correct for the greater concentration of $NO^+$ in $D_2O$ yields a final value of 1.1 for the isotope effect on the reaction between the acetate and the protonated intermediate. This approaches the ratio of the viscosities of heavy water and water, showing that these reactions are indeed diffusion-controlled. The fact that the isotope effect for DMU is governed by the nature of the active base (3.22 for water, 1.1 for acetate) implies that the characteristics of the transition state depend on the base withdrawing the proton. This suggests that $\Delta pK_a = [pK_{a(base)} - pK_{a(intermediate)}] \simeq 0$, in keeping with the $pK_a$ of

$ca.$ 0 implied by the curved Brønsted plot for the protonated intermediate.

The catalysis of the nitrosation of Im by acetate buffer was found to be slightly non-linear in both water and $D_2O$ [Figure 6; equation (2)]. In terms of Scheme 1, this means that the

$$\text{rate} = (b + c[\text{buffer}])/(1 + d[\text{buffer}]) \quad (2)$$

reaction intermediate is in the steady state, so that the proton transfer only partially controls the reaction rate. Fitting equation (2) to the data by means of the algorithm of Davies, Swann, and Campey[5] yielded the value of $c/d$, which is the
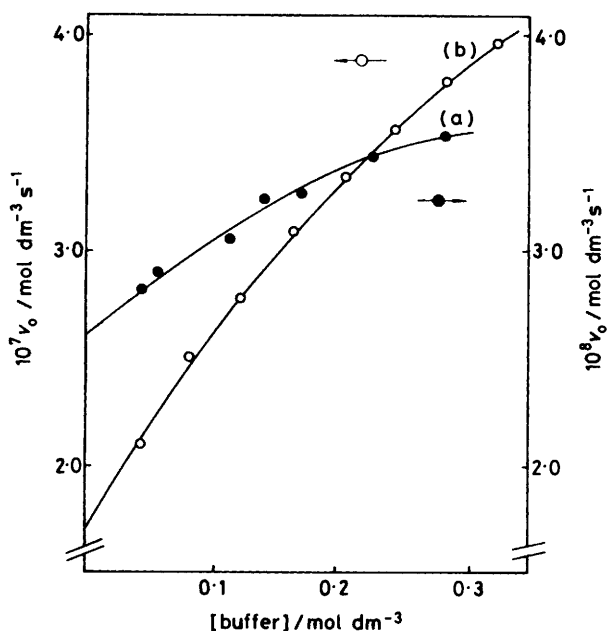
**Figure 6.** Influence of the concentration of acetate buffer on the initial rate of nitrosation of Im at 25 °C and $I = 0.2M$; (a) in water (pH 4.51, [Im] $5.98 \times 10^{-3}M$, [Nit] $6.00 \times 10^{-3}M$); (b) in $D_2O$ (pD 5.09, [Im] $3.43 \times 10^{-2}M$, [Nit] $3.27 \times 10^{-2}M$)
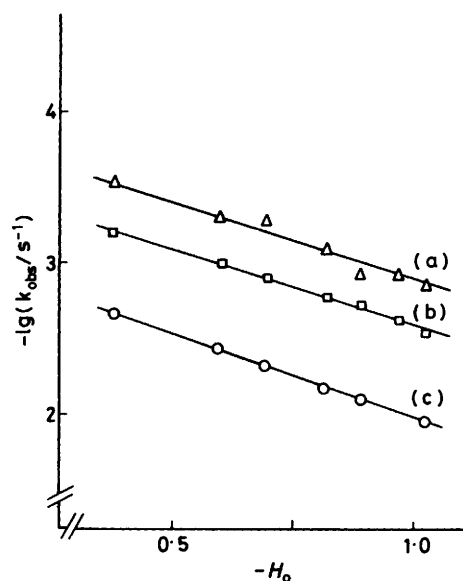


**Figure 7.** Influence of acidity on the pseudo-first-order rate constants for denitrosation of (a) NMU, (b) NDMU, and (c) NIm at 25 °C and ionic strength 2.6M

limiting reaction rate ideally attained at high concentration of buffer, when the rate-controlling step would be electrophilic attack by $NO^+$. The inverse isotope effect reflected by the corresponding limiting values of $a(H_2O)$ and $a(D_2O)$ (1 300 and 3 000 $dm^6$ $mol^{-2}$ $s^{-1}$, respectively) implies a value of 2.3 for $K_1(D_2O)/K_1(H_2O)$, in good agreement with published values.[8] The fact that these limiting values for $a$ are of the same order as those found for amines (2 000—6 000 $dm^6$ $mol^{-2}$ $s^{-1}$ in water[10]) suggests that the lower reactivity of many amides in nitrosation reactions is due not so much to their being less nucleophilic as to the mechanism by which their nitrosation takes place. The parameter $c$ allows the isotope effect on the

**Table 3.** Values of $e$ [equation (3)] and solvent isotope effects for the denitrosation of various $N$-nitrosoureas at ionic strength 2.6 mol $dm^{-3}$ and 25 °C ($n$ represents the proportion of $D_2O$ in the medium)

| Nitrosourea | $10^3$ $e$/dm$^3$ mol$^{-1}$ s$^{-1}$ | $e_H/e_D$ |
|---|---|---|
| NMU | 0.5 | 1.19 ($n = 0.83$) |
|  |  | 1.26 ($n = 0.91$) |
| NDMU | 1.0 | 1.08 ($n = 0.83$) |
| NIm | 3.5 | 1.05 ($n = 0.91$) |

reaction between the acetate and the protonated intermediate to be known. This effect has a value of 1.4, suggesting again a diffusion-controlled reaction.

Table 2 summarizes the results of the present study together with those obtained previously[2,3] for two similar substrates. The pronounced decline in the solvent isotope effect as reactivity increases has already been noted. The first three substrates also exhibit a parallel decrease in the value of the Brønsted $\beta$ value, reflecting transition states progressively closer to the structure of the separate reagents and hence, according to Hammond's postulate,[11] easier proton transfer. In the case of DMU the curvature of the Brønsted plot over a small range of base $pK_a$ values is a sign of intrinsically faster proton transfer,[12] and in the case of Im the proton transfer is no longer the only step controlling the reaction rate. For these two substrates, however, the fact that the reaction with acetate has been shown to take place at a rate close to the encounter rate ($10^{10}$ $dm^3$ $mol^{-1}$ $s^{-1}$) means that comparison of the data for the acetate-catalysed and uncatalysed reactions enables $k_4$ to be calculated. The values so obtained (ca. $10^9$ $dm^3$ $mol^{-1}$ $s^{-1}$ in both cases) will be used later.

The information obtained from the foregoing experiments was supplemented by studying the denitrosation of the $N$-nitroso compounds formed by the three ureas of Table 2. All these experiments were carried out using a great deficiency of nitroso compound with respect to the quantity of sodium azide or cysteine used to trap nitrous acid. In all cases the rate equations observed were of the form of equation (3).

$$\text{rate} = e[\text{nitroso compound}][H^+] \qquad (3)$$

These results for NMU agree with those reported by Hallett and Williams[1] and by Snyder and Stock;[13] at high concentrations of acid the rates of all three reactions follow the acidity function $H_0$ (Figure 7). It was also confirmed experimentally that the values of the isotope effect decrease in the same sequence as suggested by the nitrosation results (NMU > NDMU > NIm). Table 3 summarizes all these results.

Scheme 1, together with the principle of microreversibility, implies that the protonation of the nitroso compound should be the step controlling the rate of the denitrosation reaction, in which case $e = k_{-4}$. On this assumption, DMU and Im values are thus available for both $k_4(10^9$ $s^{-1})$ and $k_{-4}$ (1.0 × $10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$ for NDMU and 3.5 × $10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$ for NIm), and it is accordingly possible to arrive at the first kinetically determined values of $pK_a$ of $N$-nitroso-amides, if of course Scheme 1 is accepted. However, the values so obtained ($-12$ for NDMU and $-11.3$ for NIm), though apparently logical (since the drop in basicity of about 11 $pK$ units with respect to the non-nitrosated amides is similar to that observed between nitrosamines and the corresponding amines)[14] are nevertheless at odds with the experimental facts already commented on. According to Eigen,[15] substrates as acidic as this would lose protons to water at the encounter rate, so that there would be no catalysis by added bases (at least at the low concentrations
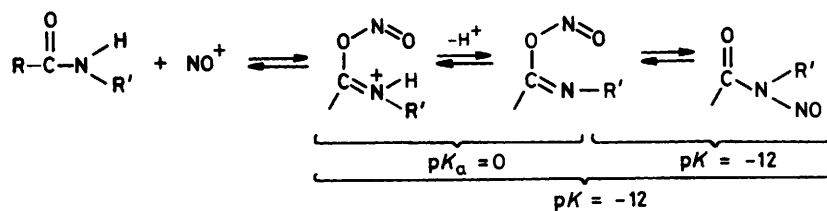
Scheme 2.

used) and the isotope effect on the slow step would always be close to unity. As we have seen, the isotope effects observed for all the substrates used were in fact large, which together with the clearly non-zero values of β for the less reactive of them suggests $pK_a$ values of ca. 0 for all. Furthermore, the $pK_a$ value $-12$ deduced for DMU from the denitrosation data together with the acetate-catalysed nitrosation results is wildly different from the value of ca. 0 deduced from the Brønsted curve.

The paradox presented in the previous paragraph may be resolved in the same way as various other cases in which kinetic and overall $pK_a$ values differ (see, for example, ref. 16) by postulating a mechanism in which the proton-transfer step (which determines the Brønsted behaviour and solvent isotope effects) is followed by an internal rearrangement, the overall $pK_a$ also being affected by this second step. In the present case we propose the reaction mechanism of Scheme 2, in which an O-nitroso compound formed by nitrosation at the oxygen atom is later transformed into the thermodynamically more stable N-nitroso-amide during a fast equilibrium step. The initial nitrosation at the oxygen atom is in fact more plausible a priori than N-nitrosation, since it is the oxygen atom that seems to be the more nucleophilic and is the site of protonation[17] and initial attack by methylating agents.[18] O-Nitrosation is also in keeping with the behaviour of thioureas, which give rise to S-nitrosated products.[19] When reinterpreted in accord with Scheme 2, the results of our experiments imply that it is the iminium ion losing the proton that has a $pK_a$ close to 0, not the N-nitroso-amide, the protonated form of which is not an intermediate of the reaction, and the fast internal rearrangement that has an equilibrium constant of the order of $10^{12}$. This rearrangement perhaps takes place via a four-centred intermediate similar to those postulated for reactions between alkyl nitrites and amines[20] and for the nitrosation of iminium ions by the nitrite ion.[21] So, denitrosation takes place via N $\longrightarrow$ O transfer of the N=O group to yield an intermediate in equilibrium with the N-nitroso-amide, but at a concentration $10^{-12}$-times smaller than that of the nitroso compound.

Although it is difficult to explain the differences amongst the reactivities of the substrates investigated, the only correlation that appears to exist is a relationship with the Taft constants of the substituents 'α' to the amide group as regards their capacity for charge donation by resonance, with a strongly negative slope. The importance of this capacity might stem from its effect on a possible degree of intramolecular hydrogen bonding in the intermediate of Scheme 2, for any donor-induced increase in the charge density at the nitrogen atom would weaken such a bond and hence facilitate proton transfer to the medium.

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