Alkaline Hydrolysis of *N*-Nitroso-2-imidazolidone

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The hydrolysis of *N*-nitroso-2-imidazolidone has been studied kinetically between pH 8.3 and 12.6. This nitroso compound has an acid–base equilibrium whose constant has been determined spectrophotometrically (pK_a 11.45). Only the acid form is reactive. At pH < 10 hydrolysis is of order less than one with respect to OH^- and is subject to general base catalysis. These results are interpreted in terms of a mechanism involving an initial steady-state hydrate whose decomposition by base leads to the final products. At pH > 10 reaction paths of orders one and two in OH^- appear. The second-order term reflects general base catalysis superimposed on a first-order term in OH^- (the bases dimethylamine, sarcosine, piperidine, and HPO_4^{2-} have been used). The results are interpreted by an initial OH^- attack on the carbonyl group of the nitroso compound to give an intermediate which in the rate-controlling step reacts with bases, among them water (which explains the first-order term with respect to OH^-). The low value of the Brønsted relation (β *ca.* 0) and the fact that the intermediate possesses no proton yielding a low pK_a value suggest that there is inverse classical general base catalysis.

The hydrolysis of nitrosamides in neutral or alkaline media has aroused interest of late due both to their potential carcinogenicity [1] and to the fact that the structure of these molecules, with their two electrophilic centres, increases the mechanistic possibilities of reaction. One group whose alkaline hydrolysis has been studied in great detail is the nitrosoureas, and a number of different reaction mechanisms have been put forward to explain the results obtained. Whereas the studies of Jones *et al.*[2] on the decomposition of *N*-(2,2-diphenylcyclopropyl)-*N*-nitrosourea in organic solvents led them to suggest that the reaction initially involves the nitroso group, Hecht and Kozarich,[3] who investigated the hydrolysis of *N*-methyl-*N*-nitrosourea (likewise in organic solvents), considered the reaction to be triggered by the loss of an amide proton. The detailed study of the hydrolysis of the three methylnitrosoureas carried out over a wide range of pH by Snyder and Stock[4] indicated that the carbonyl group is attacked by OH^- to give the tetrahedral intermediate previously postulated by Garrett *et al.*,[5] and that this process, which is subject to base catalysis, is the rate-limiting step under most experimental conditions. Yoshida and Yano,[6] however, ruled out nucleophilic attack on the carbonyl group as a possible mechanism for the hydrolysis of various arylnitrosoureas in near-neutral aqueous media, and instead repeated Hecht and Kozarich's interpretation in terms of the initial loss of an amide proton. Finally, when Challis and Jones [7] studied the decomposition of *N*-nitroso-2-pyrrolidone in alkaline media, they also reported attack on the carbonyl group catalysed by base. Surprisingly, however, the catalysis was nucleophilic, whereas the hydrolysis of other amides, whether activated or not,[8] usually undergoes general acid–base catalysis.

With these intriguing antecedents, we carried out a kinetic study of the hydrolysis of *N*-nitroso-2-imidazolidone over a wide range of pH (8.3—12.6) and in the presence of a variety of regulating agents. This paper reports the results and discusses the mechanism of the reaction and the nature of the base catalysis to which it is subject.

Experimental

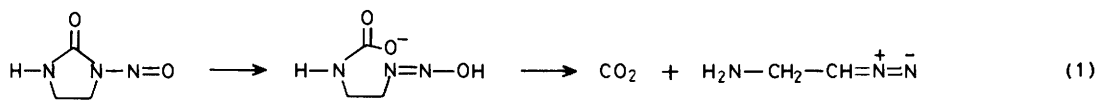
2-Imidazolidone (ethyleneurea) (Merck) was purified by recrystallization from methanol and kept in a vacuum desiccator. Dimethylamine was obtained as its perchlorate by neutralizing the amine with perchloric acid and recrystallizing from methanol. Piperidine was used in the form of its chloride, which was purified by recrystallization from propan-2-ol–ether. Morpholine was distilled. The remaining reagents were Merck products of the highest available purity, which after drying were used without further purification.

Solutions of *N*-nitroso-2-imidazolidone (NIM) were prepared immediately before use by the reaction of sodium nitrite with 2-imidazolidone (IM) in acid media under conditions in which the nitrosation reaction proceeds with no interference (*e.g.* [$NaNO_2$] 10^{-4} mol dm^{-3}, [IM] 10^{-3} mol dm^{-3}, pH 2). The concentration of the nitroso compound obtained was checked by measuring the absorbance at 249 nm [ε (824 ± 2) × 10 dm^3 mol^{-1} cm^{-1}], and its thermal and photochemical stability was also verified.

Kinetic measurements were carried out in a Kontron model Uvikon 820 spectrophotometer with a thermostatted cell-carrier, a printer, and a paper trace recorder. The acidity was measured using a radiometer model 82 pH-meter equipped with a GK2401B combined electrode and calibrated with buffer solutions of pH 9.00 and 10.00 from Merck and of pH 12.45 from Beckman. The pH values given below have been corrected for Na^+.

The decomposition of NIM was followed spectrophotometrically at 249 nm, a wavelength only absorbed significantly by the nitroso compound. As expected in view of the acidities used (pH 8.3—12.6), the deamination reaction took place in quantitative agreement with its stoicheiometry. Shinn's method showed [9] that significant denitrosation was only observed for reactions at pH < 2. The hydrolysis reaction is generally accepted as being (1).

Kinetic analysis was carried out using the integration method, the absorbance A_∞ at time $t = \infty$ being optimized by



(1)

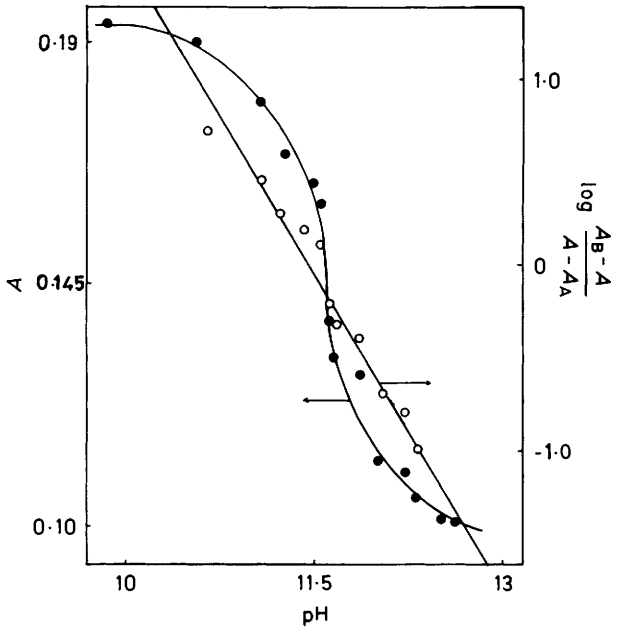


Figure 1. Variation of the absorbance of NIM at 249 nm with pH, together with the same data linearized by plotting $\log(A_B - A)/(A - A_A)$ against pH, where A_A and A_B represent the absorbances of the acid and base forms, respectively. [NIM] 2.43 × 10^{-5} mol dm^{-3}, μ 0.2M, *T* 25 °C

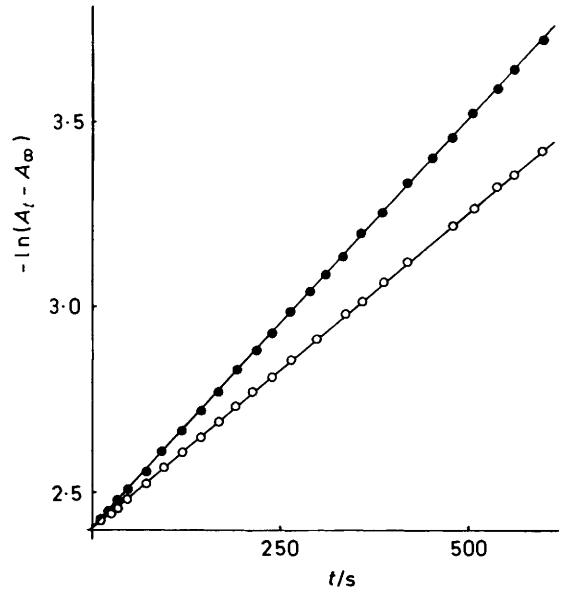


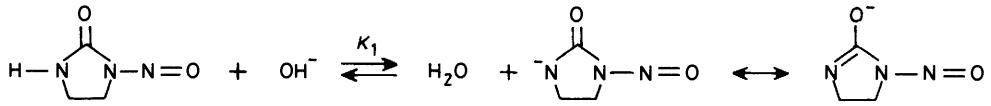
Figure 2. Typical pseudo-first-order plots of the hydrolysis of NIM at 25 °C and μ 0.2M. ●, [NIM] 1.3 × 10^{-5} mol dm^{-3}, pH 11.03. ○, [NIM] 1.3 × 10^{-5} mol dm^{-3}, pH 10.71

the algorithm of Davies *et al.*[10,11] Graphs of $\ln(A_t - A_\infty)$ against time were linear for at least 90% reaction. All kinetic measurements were duplicated (error ±3%).

All experiments were carried out at a constant ionic strength of 0.2M controlled with $NaClO_4$, and at 25 °C.

Results and Discussion

The absorption spectrum of NIM was observed to vary considerably with the pH of the medium. The peak at 247 nm (ε 8 278 dm^3 mol^{-1} cm^{-1}) in neutral media diminished with increasing concentration of OH^- until at pH 12.5 it was flat (ε 4 237 dm^3 mol^{-1} cm^{-1}). A pH-dependent kinetic process was thus superimposed on the thermodynamic deprotonation equilibrium (2).



(2)

Other activated amides have been found to be involved in similar equilibria.[12] The equilibrium constant K_1 was obtained from the initial absorbance at 249 nm for the various pH values used. The results (Figure 1) imply that K_1 = 354.8 dm^3 mol^{-1} ($pK_a = pK_1 + pK_w$ = 11.45).

Under all the experimental conditions employed the hydrolysis of NIM was of order one with respect to NIM itself {[equation (3)], where k_{obs} is the pseudo-first-order constant}. Figure 2 shows the linearity of plots of $\ln(A_t - A_\infty)$ *vs. t*. Concentrations of NIM between 10^{-4} and 10^{-5} mol dm^{-3} were used.

$$r = k_{obs}[NIM] \quad (3)$$

Hydrolysis at pH < 10.—Between pH 8.30 and 9.53 the hydrolysis of NIM was studied in the presence of morpholine and boric acid buffers to maintain constant acidity throughout the reaction. The reaction rate increased with the total concentration of buffer [Buf] towards a maximum which was the same for all pH (Figure 3).* The algorithm of Davies *et al.*[11] was used to fit equation (4) to the experimental data, whose standard deviation from the curve was always <2%. The limiting value of the reaction rate, *b*:*c*, was confirmed as being independent of both pH and buffer reagent (*b*:*c* = 1.5 × 10^{-3} s^{-1}). A plot of *a*, the reaction rate in the absence of buffer, against $[OH^-]$ passes through the origin and also tends to a limiting value with increasing $[OH^-]$ (Figure 4), so that equation (5) holds, where *d* = 50 ± 3 dm^3 mol^{-1} s^{-1} and *e* = (3.0 ± 0.5) × 10^4 dm^3 mol^{-1}. The limiting value of *a* (*d*:*e*) coincides numerically with *b*:*c*.

These results suggest a mechanism in which both OH^- and the active form of the buffer (be it base or acid) react with a single steady-state species whose rate of formation is independent of the concentration of hydroxide ions. This would seem

$$k_{obs} = \frac{a + b[Buf]}{1 + c[Buf]} \quad (4)$$

$$a = \frac{d[OH^-]}{1 + e[OH^-]} \quad (5)$$

to rule out the possibility of nucleophile catalysis, and we accordingly propose the reaction mechanism of Scheme 1, in

* One referee has rightly suggested that the behaviour in the presence of borate buffers might be influenced by the formation of polyborates (see ref. 13, p. 470). The experiments carried out in morpholine buffers, as well as the results in the absence of buffer (Figure 4) and the pK_a value deduced for boric acid from kinetic measurements, allow us to confirm the proposed mechanism.

which a base B (either OH^-, morpholine, or borate ion) reacts with the hydrate (I) derived from the reaction of the nitroso compound with a molecule of water. This mechanism implies the rate equation (6), which for constant pH is of the same form as equation (4) and reduces to equation (5) when [Buf] = 0.

$$b = \frac{k_1k_{OH}[OH^-] + k_1k_B[B]}{k_{-1} + k_{OH}[OH^-] + k_B[B]} \quad (6)$$

The constant k_1 is thus the limiting value of k_{obs} (b:c or d:e). The effect of both B and OH^- is to increase the rate of decomposition of the tetrahedral intermediate (I), whose formation may become the rate-limiting step.

According to the above mechanism, it is the basic form of the buffer which catalyses the reaction. That this is so is confirmed by examining the equation deduced from equation (6) for b [equation (7)], where K_a is the acidity constant of the buffer

$$k_{obs} = \frac{k_1k_B}{(k_{-1} + k_{OH}[OH^-])} \frac{K_a}{(K_a + [H^+])} \quad (7)$$

acid. Figure 5, which shows the experimental data corresponding to the reorganization of equation (7) into form (8) for boric acid, implies a value of 9.3 for pK_a, which agrees well with published values,[14] and a value of 0.14 dm^3 mol^{-1} s^{-1} for k_1k_B/k_{-1}. Values of 8.5 for pK_a and 1.0 dm^3 mol^{-1} s^{-1} for k_1k_B/k_{-1} are obtained in the case of morpholine. Comparison of this latter result with the value of 50 dm^3 mol^{-1} s^{-1} calculated for k_1k_{OH}/k_{-1} from the data obtained in the absence of buffer

$$b^{-1}\left[1 + \frac{k_{OH}}{k_{-1}}[OH^-]\right]^{-1} = \frac{K_a + [H^+]}{K_aK_B(k_1/k_{-1})} \quad (8)$$

confirms that the strength of the catalyst increases with its basicity. The fact that morpholine is a better catalyst than borate ion is probably due to the 'true' pK_a value of boric acid.[13]

Hydrolysis at pH > 10.—At pH between 10 and 12.6 the hydrolysis of NIM was studied kinetically in the absence of buffer but with the constancy of the pH throughout each reaction guaranteed by the concentration of hydroxide ions being very much greater than that of NIM. Figure 6 shows the plot of k_{obs} against $[OH^-]$ to be clearly non-linear and to have an intercept at the origin (1.4×10^{-3} s^{-1}) compatible with the value of k_1 obtained for the hydrate pathway at lower pH. As already mentioned, the initial absorbance of the reaction mixture varied with pH due to the formation of the conjugate base of the nitroso compound [equation (2)], and this will contribute to the deviation of the k_{obs}–$[OH^-]$ data from linearity if, as in the case of other amides,[12] the base is not reactive. Figure 7 shows the result of correcting k_{obs} on this assumption to $k_{obs}(1 + K_1[OH^-])$ using the value of K_1 obtained above. Figure 7 is linear up to pH 11.7 (see insert) with a slope of 1.65 dm^3 mol^{-1} s^{-1}, but at higher pH has an upward

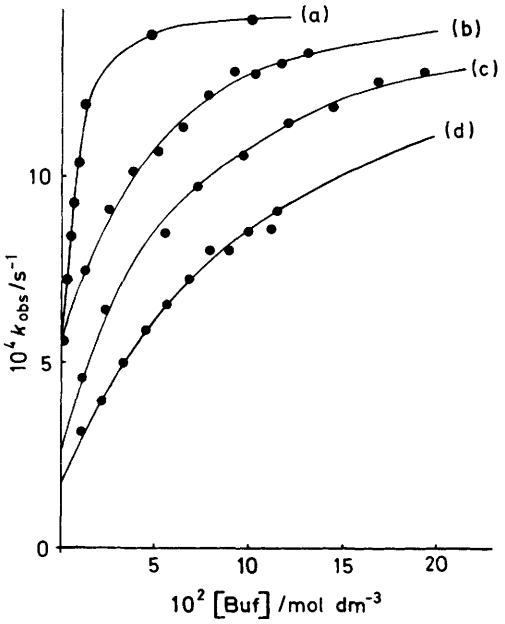


Figure 3. Influence of the total concentration of buffer on k_{obs} at 25 °C and μ 0.2M, [NIM] 1.5×10^{-5} mol dm^{-3} for (a) morpholine, pH 8.40; (b) boric acid, pH 9.22; (c) boric acid, pH 8.80; (d) boric acid, pH 8.52

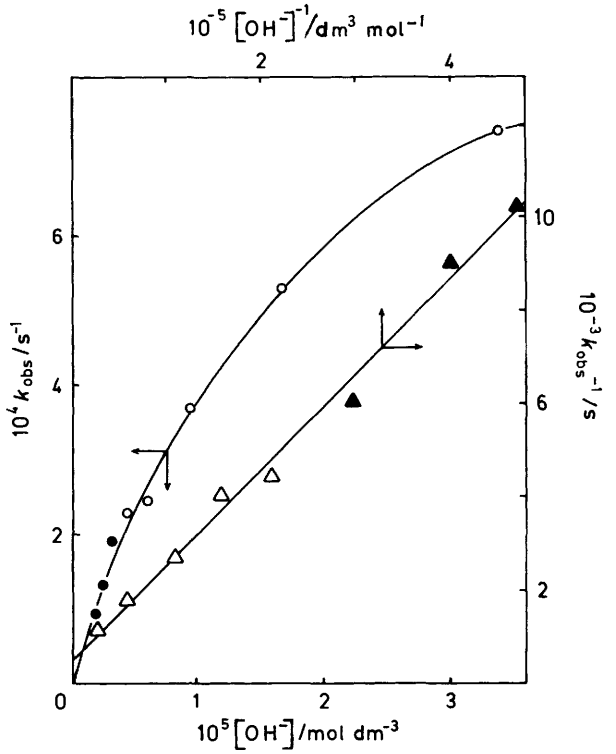
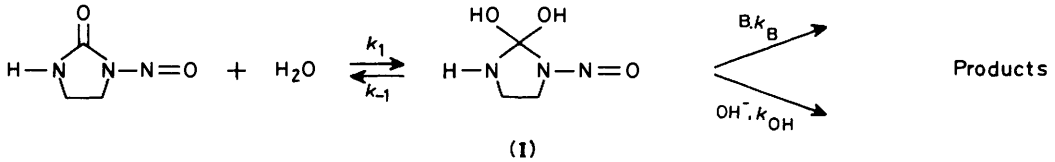


Figure 4. Influence of $[OH^-]$ on k_{obs} at [NIM] 1.5×10^{-5} mol dm^{-3}, pH < 10, T 25 °C, and μ 0.2M, together with the same data linearized in accordance with equation (5). ●, Morpholine buffer, ○, borate buffer



(I)

Scheme 1.

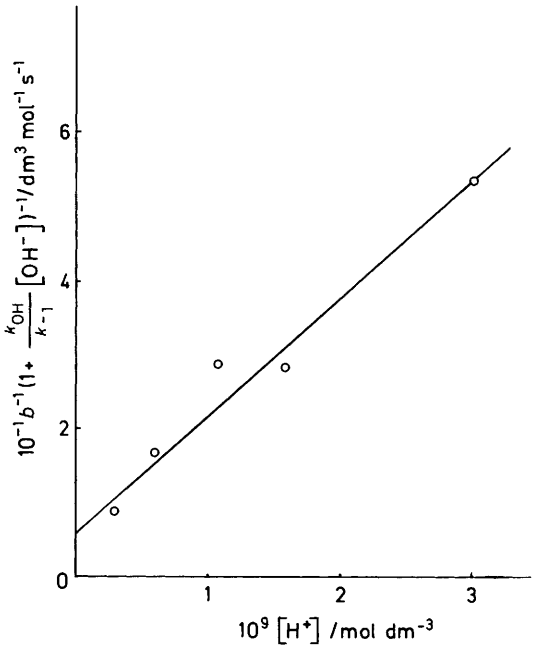


Figure 5. Data for the base catalysis by the borate ion of the hydrolysis of NIM at pH <10, 25 °C and μ 0.2M, linearized in accordance with equation (8)

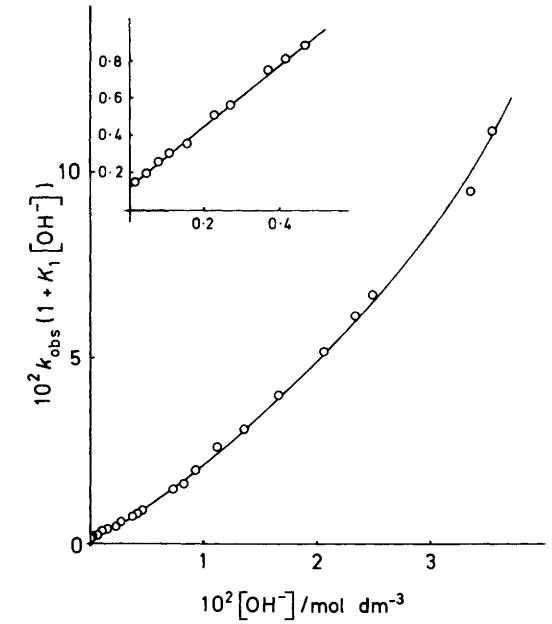


Figure 7. Dependence on [OH$^-$] of k_{obs} as corrected to allow for only the acid form of NIM being reactive

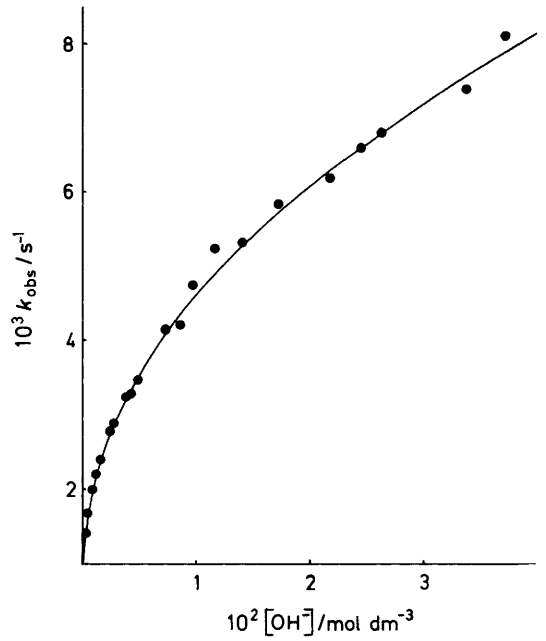


Figure 6. Dependence of k_{obs} on [OH$^-$] at pH >10. [NIM] 2.6 × 10^{-5} mol dm^{-3}, T 25 °C, μ 0.2M

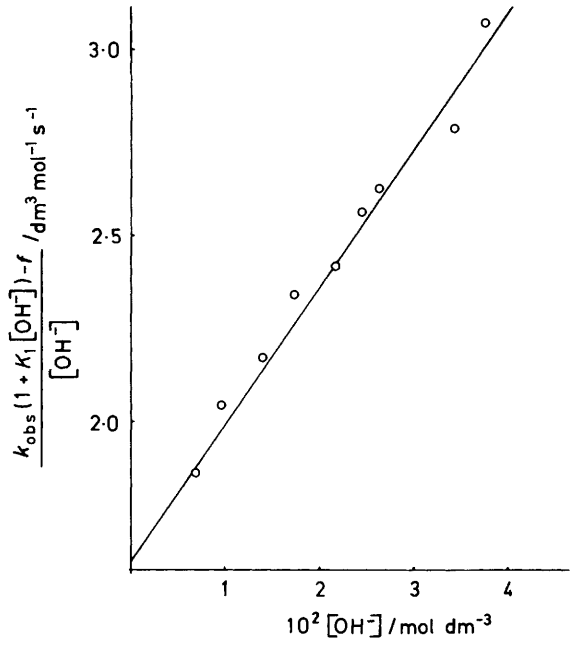


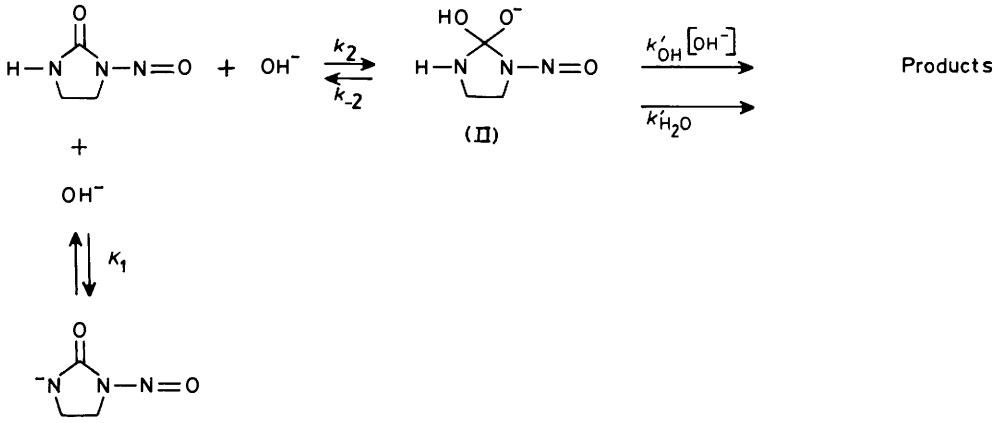
Figure 8. Data for the hydrolysis of NIM at pH > 11.7, linearized in accordance with equation (9). μ 0.2M, T 25 °C

curve that can only be explained by the appearance of an OH$^-$ term of order greater than one. Equation (9) was therefore fitted

$$k_{obs}(1 + K_1[OH^-]) = f + g[OH^-] + h[OH^-]^2 \quad (9)$$

to the data for pH > 11.7, f being the maximum reaction rate attained *via* the hydrate pathway. Figure 8, which shows $\{k_{obs}(1 + K_1[OH^-]) - f\}/[OH^-]$ plotted against [OH$^-$], confirms the action of a second-order hydroxide term and implies a value of 1.64 dm^3 mol^{-1} s^{-1} for g, virtually the same as that calculated from the data for acidities between pH 10 and 11.7, where the second-order OH$^-$ term is negligible. Fitting equation (9) to the totality of the experimental data for all values of pH > 10 yielded the results $f = (1.35 \pm 0.03) \times 10^{-3}$ s^{-1}, $g = 1.58 \pm 0.02$ dm^3 mol^{-1} s^{-1}, $h = 28.8 \pm 0.8$ dm^6 mol^{-2} s^{-1}, and $K_1 = 312 \pm 0.3$ dm^3 mol^{-1}. This value of K_1 coincides reasonably with that determined spectrophotometrically. There is also good agreement between the value of $f = k_1$ and that calculated previously from data obtained at pH <10.

No second-order OH$^-$ term has hitherto been reported for



Scheme 2.

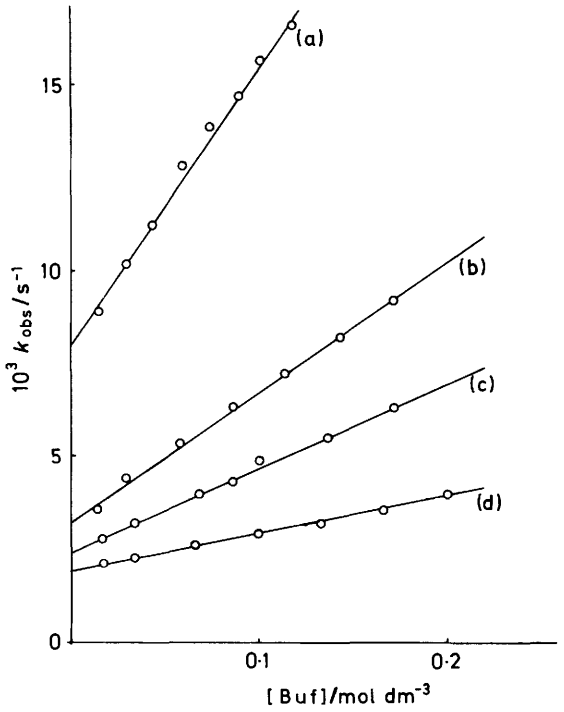


Figure 9. Influence of the concentration of dimethylamine buffer on k_{obs} at 25 °C and μ 0.2M: (a) pH 12.56; (b) pH 11.42; (c) pH 11.14; (d) pH 10.90

the hydrolysis of nitrosamides or nitrosoureas, though it has frequently been found in the case of amides with electron-withdrawing substituents.[12,15]

By analogy with mechanisms put forward for the latter, we therefore propose that shown in Scheme 2, according to which $g = k_2k'_{H_2O}:k_{-2}$ and $h = k_2k'_{OH}:k_{-2}$.

Since the nature of the catalysis exercised by the second OH^- ion has given rise to a certain amount of controversy in the case of amides,[12,15,16] we studied the effects of various buffer solutions at these pH values. Figure 9 shows that with dimethylamine buffers of pH between 10.88 and 12.56 k_{obs} depends linearly on [Buf]. The corresponding values of slope and intercept (Table 1) show a first-order OH^- term to be undergoing base catalysis, which implies the general rate equation (10) (the values of i obtained in accordance with this equation are likewise included in Table 1). It therefore appears

Table 1. Slopes and intercepts for the linear base catalysis by dimethylamine buffers of the hydrolysis of NIM at various values of pH [equation (10)], μ 0.2M, T 25 °C

pH	10^2 Slope ($dm^3\ mol^{-1}\ s^{-1}$)	10^3 Intercept (s^{-1})	i
10.88	0.831	1.93	25.5
10.90	0.975	1.92	29.4
11.06	1.91	2.35	31.8
11.14	2.29	2.39	34.0
11.42	3.51	3.21	34.9
11.62	3.50	3.30	23.4
12.56	7.52	8.05	25.1

Table 2. Values of the base catalysis parameter i [equation (10)] for the hydrolysis of NIM at pH >10, μ 0.2M, T 25 °C

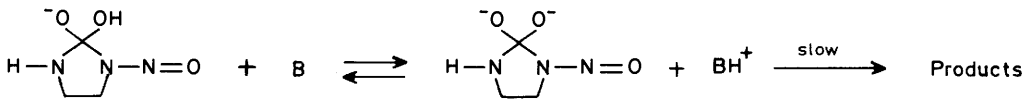
Basic entity	pK_a	log i
HPO_4^{2-}	7.21	1.1
Sarcosine	10.20	1.1
Dimethylamine	10.73	1.5
Piperidine	11.20	1.4
OH^-	15.75	1.4
H_2O	−1.75	−1.5

$$k_{obs} = \frac{f + g[OH^-] + h[OH^-]^2 + i[OH^-][B]}{1 + K_1[OH^-]} \quad (10)$$

that the second OH^- ion acts like any other base B, favouring the destruction of the intermediate (**II**) and showing up kinetically as a second-order term. These experiments were repeated with piperidine, phosphate, and sarcosine buffers, and Table 2 lists the values of i obtained for all the bases used. The strength of the catalyst does not seem to depend on their pK_a, and the Brønsted relation is satisfied with $\beta = 0.04 \pm 0.02$.

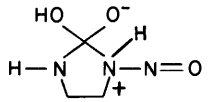
The deviation of the value given for water in Table 2 from those of the other bases used may reflect a particular pattern of behaviour, that of the water molecule helping to transfer a proton from O to N.

Two mechanisms emerge as initial candidates for the interpretation of the above results, classical general base catalysis and inverse classical general base catalysis (see ref. 16 and references mentioned therein). However, according to Eigen[17,18] a value of $\beta = 0$ for general base catalysis suggests that the pK_a of the intermediate from which the proton is lost is at least one unit less than the lowest pK_a among those of the buffers involved, which in the present case means that



(II)

Scheme 3.



(III)

intermediate (**II**) ought to have a proton of $pK_a < 6$. Since none of the protons of intermediate (**II**) can in fact be reasonably supposed to have a pK_a in this range, it must be concluded that the actual mechanism is the inverse base catalysis of Scheme 3, in which the slow step is the protonation of the departing group to assist its removal. According to this hypothesis, the slope of the Brønsted equation for catalysis by the acid form of the buffer would be α *ca.* 1, which by similar reasoning to that set out above suggests that the protonation of the >N–N=O group is completed in the transition state or that the pK_a involved is < 6 (which boils down to the same thing). Since a very low pK_a is expected of an *N*-nitroso compound, the mechanism proposed is compatible with the results.

The proposed mechanism seems to suggest that the departing group must be assisted by protonation. The general base catalysis of the hydrate pathway observed at pH < 10 therefore probably involves the tautomeric form (**III**) of intermediate (**I**). Stuctures analogous to that resulting from the loss of a proton by the OH group of intermediate (**III**) have frequently been suggested to be involved in the hydrolysis of amides.[8,19]

Finally, it is worth emphasizing that the data here allow the slow loss of an amide proton to be ruled out for this substrate since the results suggest that such a loss would lead to a species not susceptible to hydrolysis. At the same time, the differences between the mechanism put forward in the present study for NIM and that found by Snyder and Stock[4] for methyl- and dimethyl-nitrosoureas (carbonyl group attack by OH^- as rate-controlling step) may be due to the latter compound's intramolecular hydrogen bridge,[20] which must be destroyed during the formation of the tetrahedral intermediate.

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