1113. *The Mechanism of the Deamination of Acetamide.*

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The kinetics of the reaction of nitrous acid with acetamide have been examined in moderately concentrated perchloric and sulphuric acids. The rate is first-order in amide and first-order in nitrite, the second-order rate constant showing a maximum at 8M-sulphuric acid. At lower acidities, reaction occurs by a rate-determining nitrosation of the free amide by the nitrous-acidium ion. At higher acidities, the dependence of rate upon acidity is more complex. It seems that nitrosation may become reversible, as has been found by other workers in diazotisation.

THE present work was carried out several years ago as part of a general study of the mechanism of *N*-nitrosation reactions by nitrous acid in strongly acid media. After it was completed, it became apparent that the protonation of amides did not follow the Hammett acidity function, thus rendering the interpretation of the results difficult. Edward and Wang[1] reported that plots of log $[BH^+]/[B]$ against H_0 for a number of aromatic amides gave slopes from 0·58 to 0·70, and that similar deviations were observed for propionamide. They accounted for these in terms of differences in hydration between the indicators used to set up the H_0 scale, and the amides that they used. Work by Moodie and Homer[2] leads to the same conclusion. Unfortunately, these results could not be applied quantitatively to the equilibria involving acetamide in our work. A more satisfactory treatment was recently produced by Katritzky, Yates, and Stevens,[3] who used a number of aromatic amides as simple basic indicators, and set up another acidity function, which they called H_A, to describe the protonation of amides:

$$H_A = pK_A - \log[AH^+]/[A]$$

This new acidity function is identical with H_0 at low acidities, but differs appreciably above 2M-sulphuric acid. The differences were again discussed in terms of hydration effects. H_A appears to describe the behaviour of a range of amides quite satisfactorily, and so was used in the interpretation of our kinetic results.

There have been two recent studies of the mechanism of the reaction between nitrous acid and primary amides. Kezdy, Jaz, and Bruylants[4] studied the reaction of acetamide in hydrochloric acid, and showed that it occurs by attack of nitrosyl chloride on the free amide. This work has been extended to other amides.[5]

$$H^+ + HNO_2 + Cl^- \rightleftharpoons NOCl + H_2O \qquad \text{fast} \qquad (1)$$

$$NOCl + CH_3CO{\cdot}NH_2 \longrightarrow \text{Products} \qquad \text{slow} \qquad (2)$$

Bender and Ladenheim[6] investigated the deamination of benzamide in 4·6—8·6M-sulphuric acid, and concluded that the electrophilic reagent is the nitrosonium ion.

$$H^+ + HNO_2 \rightleftharpoons NO^+ + H_2O \qquad \text{fast} \qquad (3)$$

$$C_6H_5CO{\cdot}NH_2 + NO^+ \longrightarrow \text{Products} \qquad \text{slow} \qquad (4)$$

The primary product in each case is probably an *N*-nitroso-compound, $RCO{\cdot}NH_2{\cdot}NO^+$ which, by rapid proton transfers, rearranges to a diazohydroxide. This ionises, the diazonium ion loses nitrogen, and the acylium ion fragment combines with the water.[6] In both of these kinetic studies the authors assumed that the protonation of amides was described by the

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[1] J. T. Edward and I. C. Wang, *Canad. J. Chem.*, 1962, **40**, 966.

[2] R. B. Moodie and R. B. Homer, *J.*, 1963, 4377.

[3] A. R. Katritzky, K. Yates, and J. B. Stevens, *Canad. J. Chem.*, 1964, **42**, 1957.

[4] F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. chim. belges*, 1958, **67**, 687.

[5] A. Bruylants and J. Jaz, *Bull. Soc. chim. belges*, 1961, **70**, 99.

[6] M. L. Bender and H. Ladenheim, *J. Amer. Chem. Soc.*, 1960, **82**, 1895.

Hammett acidity function, H_0, but, as this does not appear to be true, the interpretation of their results needs to be reconsidered. We have re-examined Bender and Ladenheim's results, but as no values of H_A are available for hydrochloric acid we have not done the same for the work of Bruylants and his co-workers.

EXPERIMENTAL

All the chemicals were of AnalaR grade. The acetamide was purified by distillation.

Kinetic Measurements.—Solutions were made up by dissolving a weighed amount of acetamide in perchloric or sulphuric acid. The solution was cooled to 0° in an ice–water thermostat, and reaction was started by adding ice-cold sodium nitrite solution. Samples were removed at suitable times and analysed for nitrous acid by standard colorimetric methods. Under the conditions used there was no significant interference due to the acid-catalysed hydrolysis of acetamide.

RESULTS AND DISCUSSION

Reaction was carried out with low concentrations of nitrous acid (10^{-2}—10^{-3}M) in the presence of a large excess of acetamide (0·1—0·5M). The reaction was first-order with respect to nitrous acid under all conditions. In a typical run, $[H^+] = 5{\cdot}87$M, [amide] = 0·60M, successive half-lives were 36, 37, 37, and 37 minutes. The first-order rate constant for the disappearance of nitrous acid was independent of initial nitrous acid concentration, and was proportional to the concentration of the amide, as can be seen from Table 1. Thus, the rate equation is of the form

$$v = k_2[\text{nitrite}][\text{amide}]$$

This was established for solutions in perchloric acid and was assumed to apply also to sulphuric acid. It is the same form as was observed by Bender and Ladenheim for benzamide. The products of the reaction are well known to be acetic acid and nitrogen.

TABLE 1.

Rate constants for the deamination of acetamide at 0°.

$[HClO_4]$ (M)	[amide] (M)	[nitrite] (M)	10^4k_1 (sec.$^{-1}$)	10^4k_2 (l. mole^{-1} sec.$^{-1}$)	$[H_2SO_4]$* (M)	10^4k_2 (l. mole^{-1} sec.$^{-1}$)
3·45	0·10	0·01	0·205	2·05	2·45	2·17
3·45	0·50	0·010	1·07	2·14	3·08	2·68
3·45	0·50	0·002	1·04	2·08	3·78	3·61
4·48	0·40	0·002	1·64	4·1	4·98	4·81
5·87	0·20	0·004	1·02	5·1	6·26	6·30
5·87	0·40	0·0016	2·02	5·05	6·90	7·98
5·87	0·40	0·004	2·03	5·08	7·53	8·61
5·87	0·60	0·004	3·17	5·28	8·17	8·21
6·71	0·40	0·0016	1·83	4·57	8·81	5·25
7·12	0·40	0·0016	1·57	3·93	9·45	1·76
7·96	0·40	0·0016	0·87	2·17	10·09	0·41

* Experiments in sulphuric acid carried out with an amide concentration of 0·1M.

In discussing the interpretation of these results in terms of mechanism, it is necessary to know how the equilibria between acetamide and nitrous acid and their ionised forms vary with acidity. It has been claimed on the basis of spectrophotometric evidence[7] that equilibrium (3) follows the H_R acidity function for 4·4—8·1M-perchloric acid, with a pK of −8·11. Thus, it is possible to calculate $[HNO_2]$ and $[NO^+]$ for various sulphuric acid concentrations. In the same study it was shown that the formation of the nitrous-acidium ion occurs to only a small extent:

$$H^+ + HNO_2 \rightleftharpoons H_2NO_2^+ \qquad (5)$$

Equilibrium (5) has been assumed to follow H_0. The protonation of acetamide is assumed to follow the new acidity function H_A with an ionisation constant K_2 for the conjugate acid[1] of

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[7] N. C. Deno, H. E. Berkheimer, W. L. Evans, and H. J. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 2344; K. Singer and P. A. Vamplew, *J.*, 1956, 3971.

3·8 mole l.$^{-1}$. Consider first the results from 2·45 to 6·26M-sulphuric acid. In this concentration range, k_2 increases steadily with acid concentration. The nitrite is present mainly as molecular nitrous acid, *i.e.*, HNO_2, and the amide as the conjugate acid. h_A increases by a factor of 11·5, h_R by a factor of 5900, and k_2 by a factor of 2·9. Clearly, the increase in rate with acidity is much too small to be due to attack by either the nitrous-acidium ion or the nitrosonium ion on protonated acetamide, and is also much too small to be due to attack by the nitrosonium ion on free acetamide. The only reasonable alternative is attack by the nitrous-acidium ion on free acetamide.

$$H^+ + HNO_2 \rightleftharpoons H_2NO_2^+ \qquad \text{fast} \qquad (6)$$

$$H_2NO_2^+ + CH_3CO{\cdot}NH_2 \longrightarrow CH_3CO{\cdot}NH_2{\cdot}NO^+ \qquad \text{slow} \qquad (7)$$

$$CH_3CO{\cdot}NH_2{\cdot}NO^+ \longrightarrow CH_3CO_2H + N_2 + H^+ \qquad \text{fast} \qquad (8)$$

The rate equation can be written as

$$v = kh_0[K_2/(K_2+h_A)]\,(f_1f_2/f_*)\,[\text{nitrite}]\,[\text{amide}],$$

where f_1, f_2, and f_* are the activity coefficients of the nitrous-acidium ion, free acetamide, and the transition state for (7), respectively. Making the usual assumption that the activity-coefficient term does not vary, one can predict the variation in rate from K_2, h_0, and h_A. However, this is not entirely satisfactory. The concentration of the nitrous-acidium ion should increase by a factor of 55, assuming that equilibrium (6) follows h_0, while the concentration of free acetamide, which should follow $[K_2/(K_2+h_A)]$, decreases by 12. Thus, the rate constant k_2 should increase by 55/12, *i.e.*, 4·6, which is substantially greater than the observed factor of 2·9. This cannot be due to the incursion of another mechanism at higher acidities, such as one involving the nitrosonium ion, as the increase in rate is smaller than predicted. It may well be that the protonation of nitrous acid deviates appreciably from h_0, but as there is no direct physical evidence for the existence of this species it is difficult to see how this can be proved. It might be due to a variation in the activity-coefficient term. The fact that the rates in perchloric and sulphuric acids are similar is reasonable, as the h_0 values are similar at the same molarity in this concentration range. As the activity of water is also similar for the two acids[8] at a given molarity in this concentration range, the h_A values are also probably similar. At higher concentrations of sulphuric acid, an appreciable fraction of the nitrite exists as the nitrosonium ion. This is the most reactive electrophilic nitrosating agent that can exist in these solutions, and as it is a major component of the nitrite it must be responsible for the nitrosation. However, the results are not consistent with a rate-determining attack on either the free amide or its conjugate acid. The dependence of k_2 on sulphuric acid concentration, predicted from a knowledge of the pK values for acetamide and nitrous acid, and the H_A and H_R acidity functions, is shown in Table 2 and is quite different from the observed variation of k_2. As the nitrosonium ion is a major component of the nitrite, the calculated concentration will not be very sensitive to errors in pK_1 or in H_R. The H_A function looks to be quite well established, and should presumably describe the ionisation of an aliphatic amide reasonably well. Errors in pK_2 of the conjugate acid of acetamide should not affect the predicted variation of k_2, because at these high acidities the acetamide is nearly 100% protonated.

TABLE 2.

Nitrosation of acetamide in sulphuric acid at 0°.

$[H_2SO_4]$ (M)	7·53	8·17	8·81	9·45	10·09
10^4k_2 (l. mole^{-1} sec.$^{-1}$)	8·61	8·21	5·35	1·76	0·41
$10[NO^+]/[\text{nitrite}]$	0·87	3·29	7·15	9·30	9·85
$10^3[CH_3CO{\cdot}NH_2]/[\text{amide}]$	8·83	5·99	3·96	2·68	1·73
$10^3[CH_3CO{\cdot}NH_2]\,[NO^+]/[\text{amide}]\,[\text{nitrite}]$	0·77	1·97	2·83	2·49	1·70

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[8] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956.

A second difficulty concerns the relative rates of the nitrous-acidium ion and nitrosonium ion mechanisms. From the results in the range 2·45—6·26M-sulphuric acid, one can predict approximately the rate of reaction to be expected at higher acidities by the nitrous-acidium ion mechanism. One can do this either from the known values of H_A and H_0, or by a simple linear extrapolation of the plot of k_2 against sulphuric acid concentration, including a correction for the fact that at higher acidities the concentration of molecular nitrous acid is reduced owing to ionisation to the nitrosium ion. If one uses the simple linear extrapolation, then at 8·17, 8·81, and 9·45M-sulphuric acid the predicted k_2 values are 5·6, 2·5, and $0{\cdot}7 \times 10^{-4}$ $\text{l.mole}^{-1}\text{sec.}^{-1}$ compared with the observed values of 8·21, 5·35, and $1{\cdot}76 \times 10^{-4}$. Thus, the rate by the nitrous-acidium ion mechanism is similar in magnitude to the rate by the nitrosium ion mechanism, even though the nitrous-acidium ion should be a less reactive electrophilic reagent and should be present, according to the spectrophotometric evidence, in much smaller concentration. This is not reasonable. If the extrapolation is carried out using the known values of H_A and H_0 it is even greater.

We think that the answer to these difficulties is that, in the more concentrated sulphuric acid solutions, we are observing the transition from a rate-determining nitrosation to a rate-determining loss of a proton or protons from an equilibrium concentration of the nitroso-compound. Ridd and Challis[9] observed that, in the diazotisation of aniline and the toluidines in 8·6—9·5M-perchloric acid and in 9·7—11·5M-sulphuric acid, the rate decreases rapidly with increasing acidity, and they presented evidence suggesting that the mechanism was:

$$RNH_3^+ + NO^+ \underset{\text{fast}}{\rightleftharpoons} RNH_2{\cdot}NO^+ + H^+ \xrightarrow[\text{slow}]{} RN_2^+ \qquad (9)$$

It was suggested that the slow step was the removal of a proton or protons from an equilibrium concentration of the primary nitrosation product. The rate decreased approximately with the square of h_0 in perchloric acid, and somewhat more rapidly in sulphuric acid. The rate was faster in the latter case, presumably owing to catalysis, by the bisulphate ion, of the removal of a proton. In our system the rate in sulphuric acid is greater than the rate in perchloric acid. If we assume that, above 7·53M-sulphuric acid, reaction occurs by mechanism (9), then, after correcting our k_2 values for the different proportion of nitrosonium ion, the rate decreases with h_0 to a power of 1·7. We suggest, therefore, that at higher sulphuric acid concentrations the decrease in rate is due to a transition from a rate-determining nitrosation to a mechanism formally similar to (9).

We have re-examined the results of Bender and Ladenheim, using the new H_A acidity function for the ionisation of amides. Qualitatively, the results are similar to those for acetamide. The k_2 values increase almost linearly with sulphuric acid concentration, and level off in the region 7·5—8·5M-acid. Bender and Ladenheim did not extend their measurements to higher acidities, so it is not known whether the rate then decreases as it does for acetamide. The pK value for the conjugate acid of benzamide has been recalculated from the data of Edward and Meacock,[10] assuming protonation to follow H_A. The values are reasonably constant over the range 1·6—6·5M-sulphuric acid, the mean value being −1·63. In Table 3 we summarise the percentage of free benzamide, and of nitrosonium ion under the conditions of Bender and Ladenheim's experiments. Inspection of the figures shows that k_2 increases much too slowly to be due to a rate-determining attack by the nitrosonium ion on

TABLE 3.

Bender and Ladenheim's results on the deamination of benzamide at 25°.

$[H_2SO_4)$ (M)	4·58	5·40	6·02	6·70	7·45	8·55
10^2k_2 (l. mole^{-1} sec.$^{-1}$)	2·36	5·17	6·47	9·07	35·1	32·1
$10^5[NO^+]/[\text{nitrite}]$	8·7	58·9	256	1120	4880	52300
$[C_6H_5CO{\cdot}NH_2]/[\text{amide}]$	0·419	0·289	0·211	0·139	0·095	0·050

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[9] J. H. Ridd and B. Challis, *Proc. Chem. Soc.*, 1960, 245.
[10] J. T. Edward and S. C. R. Meacock, *J.*, 1957, 2002.

free benzamide. A plot of log $[K_3/(K_3+h_A)]$ $[h_R/(K_1+h_R)]$ against k_2 has a slope of 0·4, instead of the ideal value of 1.

Other values of the pK_3 of benzamide, if recalculated to the H_A scale, would make it less basic, and hence increase the discrepancy. We think that the results of Bender and Ladenheim are not consistent with a rate-determining nitrosation of free benzamide by the nitrosonium ion. The alternative mechanism, involving the nitrous-acidium ion, and similar to (6)—(8), fits better. A plot of log k_2 against log$[K_3/(K_3+h_A)]h_0$ gives a slope of 0·85 for the points up to 6·70M-sulphuric acid. At higher concentrations there is an appreciable proportion of the nitrite present as the nitrosonium ion, so presumably this must be responsible for the nitrosation, though the same difficulties arise as for acetamide. This probably accounts for the sharp increase in k_2 from 6·70 to 7·45M-sulphuric acid.

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