

## Hydroxylaminolysis of Anilides

### II.\* Hydroxylaminolysis of Acetanilide

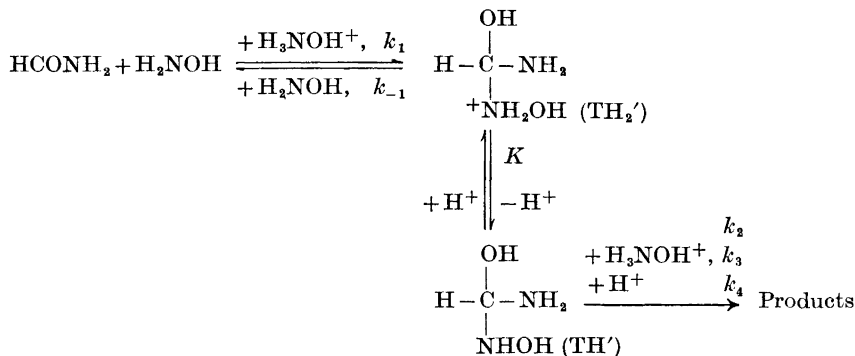
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At 25°C and an ionic strength of 3, the rate of aniline formation from acetanilide is studied in the presence of a hydroxylamine buffer system of base-acid ratios ranging from 2000 to 0.05 and a total concentration of up to 3 M. At small concentrations of the hydroxylamine buffer system or at high pH-values, the rate is close to second order in hydroxylamine, but approaches first order when the concentration is large and pH low. A mechanism is suggested that can quantitatively explain all of the experimental data. This mechanism involves: (1) uncatalyzed nucleophilic attack of hydroxylamine base on the substrate, (2) reaction between the intermediate thus formed and hydroxylammonium ion or hydroxylamine base, producing no less than three new intermediates in protolytic equilibria with each other, and (3) product formation from all three intermediates. In causing breakdown of the primarily formed intermediate to products, hydroxylammonium ion is a much more effective species than hydroxylamine base. The rate constant for the uncatalyzed nucleophilic attack of hydroxylamine base on the substrate is evaluated as well as parameters built up of simple rate and equilibrium constants rendering calculation of rates possible at any pH value and hydroxylamine concentration.

In a previous paper,<sup>1</sup> hydroxylaminolysis of esters and amides was briefly reviewed and commented upon. The hydroxylaminolysis of trifluoroacetanilide there reported showed that at most concentrations of the hydroxylamine system and most ratios of  $[H_3NOH^+]/[H_2NOH]$  almost all aniline formation could be ascribed to a reaction second order in hydroxylamine base. This kinetic dependence is in contrast to that found by Jencks and Gilchrist<sup>2</sup> for a nonacyl-activated amide, *viz.* formamide. They established the presence of an intermediate on the reaction path and proposed two different but kinetically indistinguishable mechanisms, both of which accounted for both hydroxylammonium ion catalyzed formation and partitioning of the intermediate. The mechanisms were commented upon by Fedor and Bruice<sup>3</sup> and depicted by them in a form having two intermediates (Scheme 1).

\* Part I: see Ref. 1.



Scheme 1.

Applying the steady state approximation to  $\text{TH}_2' + \text{TH}'$ , eqn. (1) is derived, where  $K_a$  is the acidity constant of hydroxylammonium ion and  $k_{\text{obs}}$  is a pseudo first order rate constant for the formation of aniline (or disappearance of substrate).

$$k_{\text{obs}} = k_1[\text{H}_2\text{NOH}][\text{H}_3\text{NOH}^+] \frac{k_2K + k_3K[\text{H}_3\text{NOH}^+] + k_4K[\text{H}^+]}{(k_{-1}K_a + k_3K)[\text{H}_3\text{NOH}^+] + k_2K + k_4K[\text{H}^+]} \quad (1)$$

Eqn. (1) is kinetically indistinguishable from those derived by Jencks and Gilchrist.

In another paper,<sup>4</sup> Bruice and Fedor investigated the hydroxylaminolysis of some thioesters and thiolactones. At a given pH, values of  $k_{\text{obs}}$  could be calculated from eqn. (2).

$$k_{\text{obs}} = k_2'[\text{H}_2\text{NOH}] + k_3'[\text{H}_2\text{NOH}]^2 \quad (2)$$

Values of  $k_2'$  and  $k_3'$  varied with pH in a complex manner. Bruice and Fedor could, however, show that the variations were quantitatively in accord with mechanisms involving general catalysis (for  $k_3'$ ) by hydroxylammonium ion and hydroxylamine base in both the formation and partitioning of tetrahedral intermediates and with the existence of protolytic equilibria (for both  $k_2'$  and  $k_3'$ ) for tetrahedral intermediates.

From the above, and from the literature given in Ref. 1, it is apparent that mechanisms in hydroxylaminolysis reactions are highly dependent on the nature of the substrate. As very few amides have been investigated with the purpose of elucidating a mechanistic pathway, little only is known about relations between structure and mechanisms for these compounds. As the reaction is also of analytical importance there seems to be more than one reason for studying these reactions. It is supposed that similar information can be obtained from studies of anilides and aliphatic amides. In spite of restricted solubility in aqueous solutions anilides offer advantages over amides because of the ease of determination of small concentrations of aniline formed during reaction. In this paper a study of a simple nonactivated anilide, *viz.* acetanilide, is reported.

## MATERIALS AND METHODS

*Materials.* The acetanilide fulfilled the requirements of the Nordic Pharmacopoeia,<sup>5</sup> and the other chemicals were of the same quality as those used previously.<sup>1</sup>

*Determination of acidity constants.* The stoichiometric  $pK_w$  at 25°C in 3 M KCl (14.13) was determined previously.<sup>6</sup>  $pK_w$  at 39°C in 2 M KCl was determined and found to be 13.46.  $pK_a$  for hydroxylammonium ion at 25°C and ionic strength 3 (with KCl) and at 39°C and ionic strength 2 (with KCl), determined as described previously<sup>1</sup> for another medium, had values of  $6.32 \pm 0.01$  and  $5.82 \pm 0.01$ , resp.

*Kinetic experiments and assay.* The kinetic experiments were performed as previously described.<sup>1,7</sup> In all the experiments, hydroxylammonium chloride was partly neutralized with the calculated volume of a KOH-solution of exactly known concentration. At the smallest concentrations with  $[H_2NOH]/[H_3NOH^+]$  ratios ranging from 0.05 to 20, the obtained pH-values always agreed very well with the calculated ones. When increasing the concentration of the hydroxylamine system, medium effects, however, become very apparent. With the ratio  $[H_2NOH]/[H_3NOH^+]$  small (0.05, 0.1, and 0.125), pH-values smaller by 0.4 units than the calculated ones were obtained at the highest concentrations. With increasing ratios, the deviations decrease and become negligible at the ratio 2. Finally, with a still further increased ratio, the pH-values become larger than the calculated ones (at the ratio 10 a deviation of about 0.15 was obtained at the largest concentrations). No corrections of pH have been performed at ratios from 0.05 to 5. At ratios 10 and higher, the determined  $k_{obs}$ -values refer to solutions that were adjusted to the calculated pH-value. Some experiments at the ratio 10 with unadjusted pH have, however, given  $k_{obs}$ -values differing only slightly from those obtained in solutions with adjusted pH.

At  $[H_2NOH]/[H_3NOH^+] \leq 20$ , the pH did not change significantly during the kinetic runs. Principally because of decomposition of hydroxylamine in alkaline solution,<sup>8,9</sup> there were pH increases at the largest base-acid ratios and therefore small volumes of HCl of suitable concentration had to be added during the runs to keep the pH constant. Due to the successive decrease in the concentration of the hydroxylamine system during these runs the determined  $k_{obs}$ -values are somewhat less accurate at these high pH-values. When these experiments were performed under nitrogen, the rate of decomposition of hydroxylamine was depressed and the required amounts of added HCl were almost negligible. Values of  $k_{obs}$  determined in the usual way and under nitrogen differed only slightly.

The withdrawn samples were analyzed by the previously described aniline method,<sup>1</sup> which involves diazotisation and coupling of the aniline formed. When using a modification of the method utilizing 1 M  $NaNO_2$  and 5 % ammonium sulphamate solution,<sup>1</sup> aniline could be determined in the presence of an amount of hydroxylamine corresponding to a 5 ml sample of a solution 0.75 M in total hydroxylamine concentration. In experiments with larger hydroxylamine concentrations, smaller sample volumes were withdrawn or an aliquot of a withdrawn sample was analyzed. At least 6 samples were analyzed for each determination of a  $k_{obs}$  value. During the time the reaction was followed, which varied between approximately 1 h and 4 days, at most about 4 % of the anilide had reacted. Therefore  $k_{obs}$  was evaluated from graphs where concentration of aniline was plotted against time.

## RESULTS

Determined pseudo first-order rate constants,  $k_{obs}$ , for the formation of aniline (which equals disappearance of acetanilide) at constant pH and constant hydroxylamine concentration are given in Figs. 1–3. In Figs. 1 and 2,  $k_{obs}$ -values are reported for 15 different values of the ratio  $[H_2NOH]/[H_3NOH^+]$ , with  $[H^+]$  ranging from  $10^{-5.02}$  to  $10^{-9.62}$ . For the three largest ratios, there is no significant difference in  $k_{obs}$ -values for a given concentration of the hydroxylamine system and these three series are represented by one curve. At small concentrations of the hydroxylamine system, the curves in Figs. 1 and

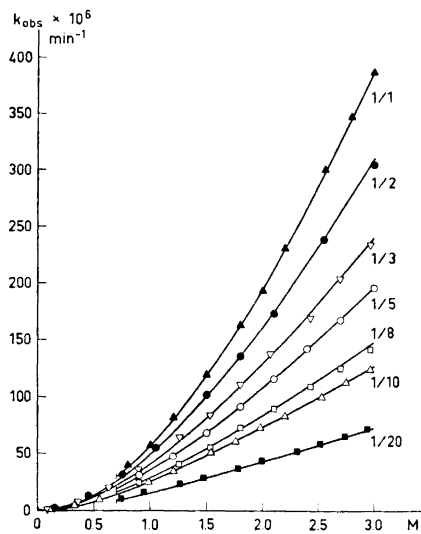


Fig. 1. Plot of  $k_{\text{obs}}$  against total concentration of hydroxylamine ( $C$ ). The curves are calculated from eqn. (3) and  $p$ -values given in Table 1. The  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$  ratios are given to the right of each curve.

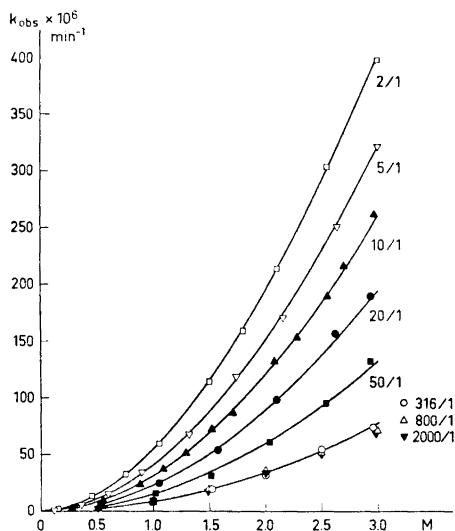


Fig. 2. Plot of  $k_{\text{obs}}$  against total concentration of hydroxylamine ( $C$ ). The curves are calculated from eqn. (3) and  $p$ -values given in Table 1. The  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$  ratios are given to the right of each curve.

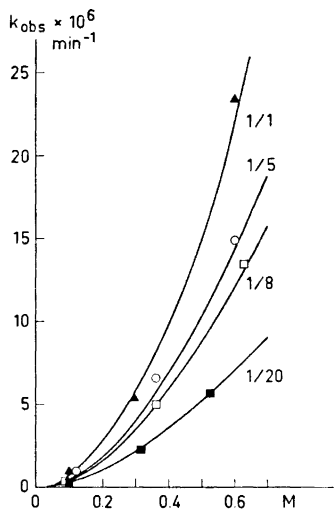


Fig. 3. Plot of  $k_{\text{obs}}$  against total concentration of hydroxylamine ( $C$ ). The curves, which only refer to small hydroxylamine concentrations, are calculated from eqn. (3) and  $p$ -values given in Table 1. The  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$  ratios are given to the right of each curve.

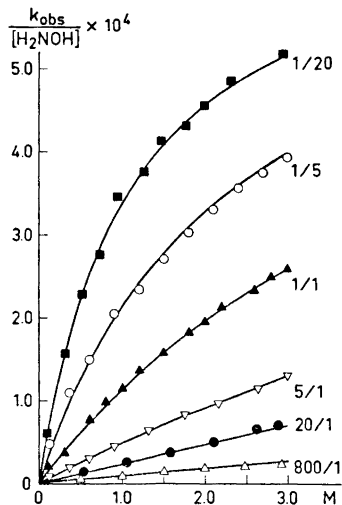


Fig. 4. Plot of  $k_{\text{obs}}/[\text{H}_2\text{NOH}]$  against total concentration of hydroxylamine ( $C$ ) for six different ratios of  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$ . These ratios are given to the right of each curve.

2 lie very closely together and cannot be drawn at the smallest concentrations without being superimposed. Therefore the omitted sections of the curves in Fig. 1 cut at as large a concentration as 0.7 M are shown in Fig. 3 at an expanded scale.

The curves and  $k_{\text{obs}}$ -values in Fig. 2 show that when  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$  has a large value the rate is purely or almost purely second order in hydroxylamine at all concentrations. From Fig. 1, on the other hand, it is apparent that when the ratio is small and the concentration large,  $k_{\text{obs}}$  approaches a linear function in hydroxylamine concentration. These trends are further visualized graphically for six different ratios in Fig. 4, where  $k_{\text{obs}}/[\text{H}_2\text{NOH}]$  is plotted against total concentration of hydroxylamine. At the two largest ratios (20:1 and 800:1) the curves seem to be straight lines passing through the origin, which is expected for a reaction second order in hydroxylamine. At the smaller ratios, the slope decreases with increasing concentration of the hydroxylamine system and at the smallest ratio (1:20) the curve apparently approaches a limiting value (slope approaching zero).

The rate enhancing effect of weak acids and of a second hydroxide ion in anilide hydrolysis has previously been interpreted as breakdown of a tetrahedral substrate-hydroxide ion intermediate catalyzed by these species.<sup>6,7,10</sup> The results now obtained also strongly indicate the presence of an intermediate on the reaction path and might be in accord with hydroxylammonium ion as well as hydroxylamine base catalyzed breakdown of a substrate-hydroxylamine intermediate. Eqn. (3), which is used in the calculation of the curves in Figs. 1–4, is analogous to the equation obtained for weak acid or superimposed hydroxide ion catalyzed breakdown of a tetrahedral substrate-hydroxide ion intermediate when neglecting the uncatalyzed pathway (see, *e.g.*, eqn. (2) in Ref. 6).

$$k_{\text{obs}} = k_1[\text{H}_2\text{NOH}] \frac{pC}{1 + pC} \quad (3)$$

In eqn. (3)  $C = [\text{H}_2\text{NOH}] + [\text{H}_3\text{NOH}^+]$ . As  $\text{H}_3\text{NOH}^+$  apparently is a more powerful agent than  $\text{H}_2\text{NOH}$  in the breakdown of the intermediate,  $p$  must be a pH-dependent parameter. If the fraction expression in eqn. (3) at small pH-

Table 1. Values of  $p$  in eqn. (3) used in the calculation of the curves in Figs. 1–4. The value of  $k_1 = 7 \times 10^{-4} \text{ M}^{-1} \text{ min}^{-1}$  has been used in all calculations.

$\frac{[\text{H}_2\text{NOH}]}{[\text{H}_3\text{NOH}^+]}$	$-\log [\text{H}^+]$	$p \text{ M}^{-1}$	$\frac{[\text{H}_2\text{NOH}]}{[\text{H}_3\text{NOH}^+]}$	$-\log [\text{H}^+]$	$p \text{ M}^{-1}$
0.05	5.02	0.94	2.0	6.62	0.133
0.10	5.32	0.68	5.0	7.02	0.077
0.125	5.42	0.58	10	7.32	0.053
0.20	5.62	0.44	20	7.62	0.036
0.286	5.78	0.36	50	8.02	0.023
0.50	6.02	0.27	316	8.82	0.013
1.0	6.32	0.20	800	9.02	0.013
			2000	9.62	0.013

values and large concentrations of the hydroxylamine system can approach 1, then  $k_{\text{obs}}$  would become a linear function of the hydroxylamine concentration. From such sections of the plots of  $k_{\text{obs}}$  against concentration or from an estimation of a limiting value in plots like those in Fig. 4, it would be possible to evaluate  $k_1$ . This is done from the plots at the smallest ratios of  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$ , Fig. 1. After trying different reasonable values of  $k_1$  for calculating  $k_{\text{obs}}$ -values from eqn. (3), the value  $7 \times 10^{-4} \text{ M}^{-1} \text{ min}^{-1}$  was chosen as that giving the best fit to the experimental values. Values of  $k_1$  approximately 10 % smaller or larger give a less good fit to the experimental values. Using this value of  $k_1$  and values of  $p$  given in Table 1 all curves in Figs. 1–4 are calculated from eqn. (3). Values of  $p$  differing from those in Table 1 by approximately 5 % generally give a less good fit to the experimental values. Eqn. (3) and the mechanism of the reaction will be discussed in more detail later in this paper.

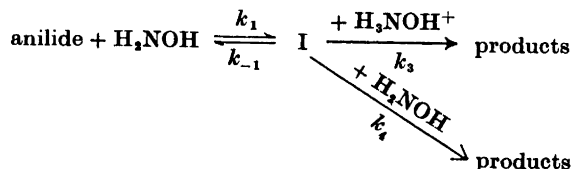
## DISCUSSION

*Previously proposed mechanisms.* It is generally accepted that one molecule hydroxylamine base acts as a nucleophile in the hydroxylaminolysis reaction. Assuming that the N-atom is the nucleophilic one, hydroxamic acid and aniline then are the reaction products. That hydroxylammonium ion is a better catalyst of the reaction than hydroxylamine base is in contrast to what was found in hydroxylaminolysis of trifluoroacetanilide,<sup>1</sup> where no hydroxylammonium ion catalysis of the reaction was detected.

The mechanisms in the hydroxylaminolysis of formamide proposed by Jencks and Gilchrist<sup>2</sup> postulate hydroxylammonium ion catalysis in the addition step (formation of the tetrahedral intermediate). According to such mechanisms (see Scheme 1) and to eqn. (1), values of  $k_{\text{obs}}$  at a given concentration of the hydroxylamine system plotted against pH will give bell shaped profiles with  $k_{\text{obs}}$  approaching zero with increasing pH. From Fig. 2 and values of  $p$  in Table 1 it is apparent that  $k_{\text{obs}}$ -values for acetanilide at constant total hydroxylamine concentration decrease with increasing pH but only down to a given limit, which is far from zero. Thus the mechanisms proposed by Jencks and Gilchrist for hydroxylaminolysis of formamide cannot be applied to the whole pH range now investigated for hydroxylaminolysis of acetanilide.

As already mentioned, Bruice and Fedor<sup>4</sup> obtained a very complex pH-dependence in hydroxylaminolysis of thioesters and thiolactones. Plots like those in Fig. 4, *i.e.*  $k_{\text{obs}}/[\text{H}_2\text{NOH}]$  versus hydroxylamine concentration, however, gave straight lines from which  $k_2'$  (intercept) and  $k_3'$  (slope) in eqn. (2) could be calculated. Apparently the mechanism for hydroxylaminolysis of acetanilide is different from that of thioesters and thiolactones.

*Conceivable but not operating mechanisms.* As already mentioned under RESULTS, mechanisms involving hydroxylammonium ion and hydroxylamine base catalyzed breakdown of a substrate-hydroxylamine intermediate lead to eqn. (3). The simplest among such mechanisms is given in Scheme 2.



Scheme 2.

Applying the steady state approximation to the tetrahedral intermediate I, utilizing the conservation equation  $[\text{H}_3\text{NOH}^+] + [\text{H}_2\text{NOH}] = C$ , and introducing the acidity constant  $K_a$  for hydroxylammonium ion, Scheme 2 gives the following expression for  $p$  in eqn. (3)

$$p = \frac{k_4 K_a}{k_{-1}(K_a + [\text{H}^+])} + \frac{k_3 [\text{H}^+]}{k_{-1}(K_a + [\text{H}^+])} \quad (4)$$

According to eqn. (4) a plot of  $p(K_a + [\text{H}^+])$  against  $[\text{H}^+]$  should give a straight line with intercept  $k_4 K_a / k_{-1}$  and slope  $k_3 / k_{-1}$ . The plot is given in Fig. 5 and

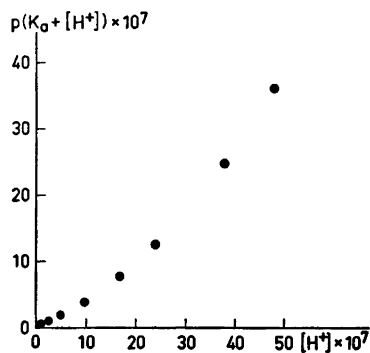
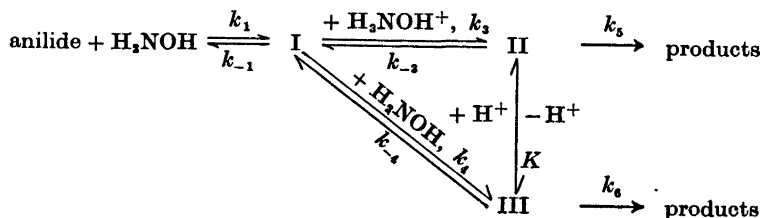


Fig. 5. Plot of  $p(K_a + [\text{H}^+])$  against  $[\text{H}^+]$ . Values of  $p$  are taken from Table 1.

it is obvious that the experimentally determined values of  $p$  cannot be calculated from eqn. (4). Thus the mechanism in Scheme 2 is not in accord with the rate data obtained. This conclusion is in agreement with what can be expected from the  $p$ -values in Table 1, since according to Scheme 2 and eqn. (4) values of  $p$  larger than twice the value at  $[\text{H}^+] = K_a$  should not be possible.

With new intermediates formed in the  $k_3$ - and  $k_4$ -step of Scheme 2 and with these intermediates in protolytic equilibrium with each other, a pH-dependence of  $p$  more complex than that in eqn. (4) is expected.



Scheme 3.

Applying the steady state approximation to I and to (I + II + III) in Scheme 3, eqn. (3) is still found to be valid, and  $p$  is defined by eqn. (5).

$$p = \frac{a + b[\text{H}^+] + c[\text{H}^+]^2}{1 + (eK_a + 1/K_a)[\text{H}^+] + e[\text{H}^+]^2} \quad (5)$$

$a$ ,  $b$ ,  $c$ , and  $e$  in eqn. (5) denote groups of rate and equilibrium constants that cannot be separated from each other. Thus.

$$a = \frac{k_4 k_6}{k_{-1}(k_{-4} + k_6)}; \quad b = \frac{k_3 k_6 K + k_4 k_5 K_a}{k_{-1} K K_a (k_{-4} + k_6)}; \quad c = \frac{k_3 k_5}{k_{-1} K K_a (k_{-4} + k_6)}; \quad e = \frac{k_{-3} + k_5}{K K_a (k_{-4} + k_6)}$$

In Fig. 6, experimentally determined  $p$ -values are plotted against  $[\text{H}^+]$  for the whole pH range used and in Fig. 7 only for the higher pH-values using

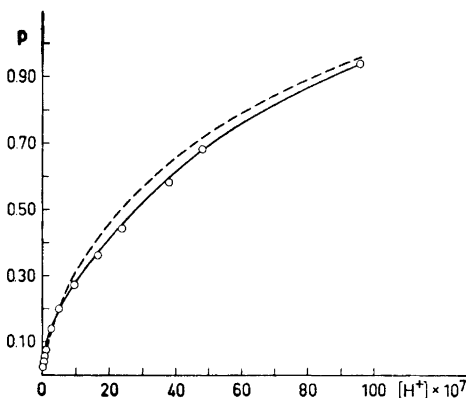


Fig. 6. Plot of  $p$  (values taken from Table 1) against  $[\text{H}^+]$ . The dotted curve is constructed from eqn. (5) using the following parameter values:  $a = 0.0129 \text{ M}^{-1}$ ;  $b = 0.66 \times 10^6 \text{ M}^{-2}$ ;  $c = 0.417 \times 10^{12} \text{ M}^{-3}$ ;  $e = 0.262 \times 10^{12} \text{ M}^{-2}$ . The solid curve is constructed from eqn. (6) using the following parameter values:  $a = 0.0129 \text{ M}^{-1}$ ;  $b = 0.959 \times 10^6 \text{ M}^{-1}$ ;  $c = 1.153 \times 10^{12} \text{ M}^{-3}$ ;  $d = 0.980 \times 10^{18} \text{ M}^{-4}$ ;  $e = 4.38 \times 10^6 \text{ M}^{-1}$ ;  $f = 0.589 \times 10^{18} \text{ M}^{-3}$ .

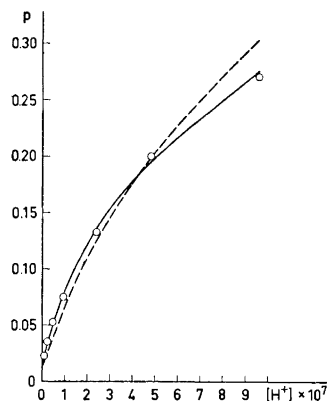


Fig. 7. Plot of  $p$  (values taken from Table 1) against  $[\text{H}^+]$  for  $[\text{H}^+]$ -values smaller than  $10^{-6}$ . The dotted curve is constructed from eqn. (5) and the solid one from eqn. (6), using the parameter values given in the text to Fig. 6.

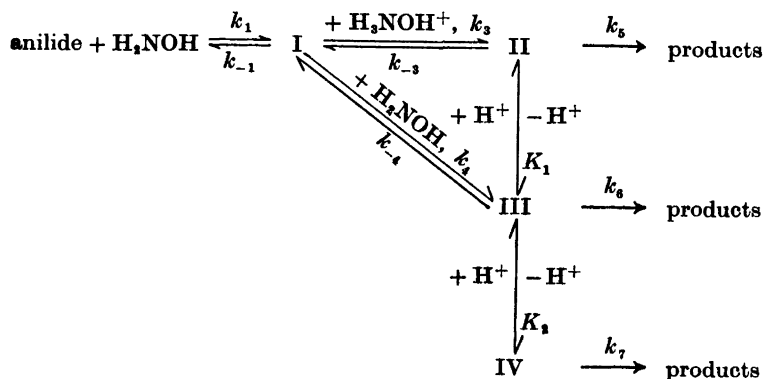
an expanded scale. The dotted curves in these figures are calculated from eqn. (5). The parameter  $a$  is directly obtained from the experiments at the three highest pH-values in Fig. 2, and the other parameter values in eqn. (5) are chosen so that they give a good fit around  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+] = 1$  and the best possible at other ratios. Apparently eqn. (5) can only give a rather approximative fit to the experimentally determined  $p$ -values.

If intermediate III in Scheme 3 is formed only in the equilibrium reaction but not directly from I, the parameter  $a$  in eqn. (5) will be zero and  $p$  will



be smaller and smaller with decreasing  $[H^+]$ . Thus such a mechanism cannot explain the experimental data at high pH-values. If, on the other hand, II is formed only in the equilibrium reaction, the parameter  $c$  will be zero and in that form eqn. (5) cannot at all predict  $p$ -values at small pH-values.

*An operating mechanism.* Scheme 4 shows the next natural step along the trodden path in the developing of mechanisms. This scheme postulates that intermediate III in Scheme 3 has a corresponding negatively charged base, which directly can break down to products.



Scheme 4.

Applying the steady state approximation to intermediate I and to the sum of intermediates I, II, III, and IV in Scheme 4, an equation for calculating  $k_{\text{obs}}$ -values has been derived, that has the same form as eqn. (3),  $p$  now being defined by eqn. (6).

$$p = \frac{a + b[H^+] + c[H^+]^2 + d[H^+]^3}{1 + e[H^+] + (fK_a + e/K_a - 1/K_a^2) [H^+]^2 + f[H^+]^3} \quad (6)$$

Of course,  $a$ ,  $b$ ,  $c$ , and  $e$  do not stand for the same combinations of constants as in eqn. (5). They now denote the following expressions:

$$\begin{aligned}
 a &= \frac{k_4}{k_{-1}}; & b &= \frac{k_3k_7K_2 + k_4k_6K_a}{k_{-1}k_7K_2K_a}; & c &= \frac{k_3k_6K_1 + k_4k_5K_a}{k_{-1}k_7K_1K_2K_a}; \\
 d &= \frac{k_3k_5}{k_{-1}k_7K_1K_2K_a}; & e &= \frac{k_7K_2 + K_a(k_{-4} + k_6)}{k_7K_2K_a}; & f &= \frac{k_{-3} + k_5}{k_7K_1K_2K_a}
 \end{aligned}$$

Curves calculated from eqn. (6) give, as shown in Figs. 6 and 7 (solid curves) very good fits to the experimentally determined  $p$ -values.

*Data from hydroxylaminolysis of formamide.* The dependence of  $k_{\text{obs}}$  on hydroxylamine concentration and on pH, as shown in Figs. 1–4, is undoubtedly similar to that obtained for formamide by Jencks and Gilchrist.<sup>2</sup> The mechanisms proposed by them and the equation used for the calculations are, as already mentioned, not compatible with the results now obtained—nor

were they so for formamide at pH-values outside  $pK_{a, \text{H}_3\text{NOH}^+} \pm 1$ . The question arises: Is the mechanism now proposed also applicable to the data obtained by Jencks and Gilchrist? Before trying to answer this, the data must be discussed in some detail. The largest concentrations of the hydroxylamine system used by them is 1.75 M and the proposed mechanisms refer to experiments performed at the following  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$ -ratios: 0.11, 0.25, 0.67, 1, 1.5, 4, and 9. Values of  $k_{\text{obs}}$  at the two smallest ratios permit a rough estimation of  $k_1$ , giving a value around  $0.3 \text{ M}^{-1} \text{ min}^{-1}$ . Using that value of  $k_1$  and the following  $p$ -values (in order of decreasing pH): 0.12, 0.20, 0.32, 0.39, 0.48, 0.83,  $1.40 \text{ M}^{-1}$ , curves which reasonably well fit the experimental values can be calculated from eqn. (3). When plotted against  $[\text{H}^+]$  these values of  $p$  give, as shown in Fig. 8, a curve similar in shape to that in Fig. 6. Jencks and Gilchrist performed in the presence of tris(hydroxymethyl)aminomethane a few experiments at ratios of  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+] > 100$ . The values of  $k_{\text{obs}}$  obtained are about 25 times larger than those calculated from their equation corresponding to eqn. (1). Jencks and Gilchrist supposed that additional terms became significant at "extreme" pH-values. Of course the buffer species used may also raise the  $k_{\text{obs}}$ -values. However, some experiments with acetanilide as substrate have shown that as far as acetanilide is concerned the presence of tris(hydroxymethyl)aminomethane has no significant effect on rate. Furthermore, all their experiments at high pH-values give  $p$ -values of the same magnitude, *viz.*  $0.04 \text{ M}^{-1}$ , which would be expected if one of the mechanisms of Schemes 3 or 4 were operating. In Fig. 8, theoretical curves have been

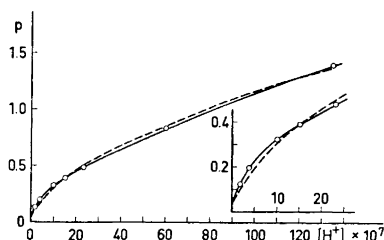
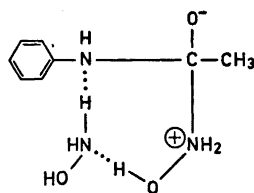


Fig. 8. Plot of  $p$  (values estimated from a paper by Jencks and Gilchrist<sup>2</sup>) for hydroxylaminolysis of formamide against  $[\text{H}^+]$ . The dotted curve is constructed from eqn. (5) using the following parameter values:  $a = 0.040 \text{ M}^{-1}$ ;  $b = 0.418 \times 10^6 \text{ M}^{-2}$ ;  $c = 0.055 \times 10^{12} \text{ M}^{-3}$ ;  $e = 0.007 \times 10^{12} \text{ M}^{-2}$ . The solid curve is constructed from eqn. (6) using the following parameter values:  $a = 0.040 \text{ M}^{-1}$ ;  $b = 0.634 \times 10^6 \text{ M}^{-2}$ ;  $c = 0.210 \times 10^{12} \text{ M}^{-3}$ ;  $d = 0.0649 \times 10^{18} \text{ M}^{-4}$ ;  $e = 1.40 \times 10^6 \text{ M}^{-1}$ ;  $f = 0.0141 \times 10^{18} \text{ M}^{-3}$ . In the inserted figure, the left part of the plot is shown in greater detail.

calculated from eqns. (5) and (6) using the value of  $K_a$  at  $39^\circ\text{C}$  given under Materials and Methods and  $[\text{H}^+]$ -values calculated from  $K_a$  and the known  $[\text{H}_2\text{NOH}]/[\text{H}_3\text{NOH}^+]$ -ratios. The parameter  $a$  of both eqns. (5) and (6) has been given the value of  $p$  obtained from the experiments performed at high pH-values and the other parameters have been chosen to give the best possible fit to the experimental  $p$ -values. Also now eqn. (5) can only give a rough fit to the experimental values whereas that obtained by eqn. (6) is very good.

Even though the  $p$ -values are rather few and somewhat uncertain and the pH-range narrow, the data now discussed seem to permit the conclusion that the mechanism in Scheme 4 as well as that in Scheme 1 can be used in the pH-range  $pK_{a, \text{H}_2\text{NOH}^+} \pm 1$  and, in contrast to that in Scheme 1, can also predict rates outside this pH-range.

*General remarks.* Scheme 3 must be regarded as a reasonable and attractive pathway, where intermediates II and III might be cyclic. One such structure of several possible ones is the following where the assisting molecule as well



as the nucleophile are the base form of hydroxylamine. The existence of cyclic intermediates in hydrolysis as well as hydroxylaminolysis reaction has been discussed previously.<sup>1,4,11</sup> In the depicted structure product formation is facilitated by the second base molecule, partly by donation of a hydrogen bonded hydrogen to the anilide nitrogen, partly by attack on a hydrogen in the molecule acting as nucleophile. The donating of a hydrogen is of course more easily accomplished by a hydroxylammonium ion and is for the actual substrate probably a more important step in the breakdown process than attack on a hydrogen in the nucleophile.

The existence of medium effects is, as mentioned previously, very apparent from the pH-measurements. These effects imply a limitation for very accurate calculations and it might be argued that the discrepancy between the values calculated from eqn. (5) and the experimental ones are due only to these effects. The effects should, however, if at all important, manifest themselves at least as much in curves like those in Figs. 1–4 as those in Figs. 6–7.

It has been proposed that thiolester-hydroxylamine intermediates can exist in a negatively charged form<sup>4</sup> and that anilide-hydroxide ion-hydrogen carbonate ion intermediates can function as acids.<sup>6,12,13</sup> Therefore, for intermediate III to function as an acid giving intermediate IV in Scheme 4 is not too astonishing. In that form the intermediate as a total carries one negative charge and can directly break down to aniline, hydroxylamine, and acethydroxamic acid anion –  $pK_a$  of acethydroxamic acid is about 9.3.<sup>14</sup> In the hydroxylaminolysis of trifluoroacetanilide, an intermediate corresponding to III in Schemes 3 and 4 was discussed as a predecessor to products.<sup>1</sup> From the experimental results, however, it cannot be decided if the intermediate preceding product formation is III or its corresponding base.

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