

## Hydrolysis of Anilides

### IV. Hydroxylaminolysis, Hydrazinolysis, and General Acid-Catalysed Alkaline Hydrolysis of Trifluoroacetanilide

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The rate of cleavage of the anilide bond in trifluoroacetanilide is studied at constant ionic strength and at different pH values in the presence of hydroxylamine and hydrazine in concentrations ranging approximately from  $5 \times 10^{-4}$  M to 2 M. The hydrazinium ion ( $pK_a = 8.11$ ) and particularly the hydroxylammonium ion ( $pK_a = 6.05$ ) are very effective in catalysing the breakdown of the tetrahedral intermediate formed between substrate and hydroxyl ions. The constants of this catalysis give, together with the previously obtained constants for acids of the ammonium cation type, a Brønsted plot with slope of 0.9. The two bases cleave the anilide bond and the rate of these reactions can be calculated with an equation containing both a term first-order and a term second-order in base. In the case of hydroxylamine, the constant of the first-order reaction is very small and the contribution to the rate from this reaction is, at most hydroxylamine concentrations, negligible. No general acid catalysis of the amine reaction is found. The hydroxylamine reaction is catalysed by imidazole and this reaction is first-order in hydroxylamine as well as in imidazole. The mechanisms of hydroxylaminolysis and hydrazinolysis are discussed and some comparisons made with what is known from the reactions with esters.

In previous papers<sup>1,2</sup> in this series it was shown that acids catalyse the breakdown of the tetrahedral intermediate formed between trifluoroacetanilide and hydroxyl ions (the substrate-hydroxyl ion complex) and that amine bases also split the anilide bond. This last reaction was characterized as nucleophilic or general basic attack of the amine, and for the amines investigated, the rate did not tend to become more than first-order in amine base. Throughout this paper the word amine is used in a broad sense, including such compounds as ammonia, imidazole, hydroxylamine, and hydrazine. The aminolysis of some phenyl- and thiolesters has during the last few years been investigated in some detail and many different mechanisms have been proposed. Often, different rate expressions have been found to be valid for closely related substrates or amine nucleophiles.<sup>3-15</sup>

Hydroxylamine and hydrazine are in ester aminolysis often found to be unexpectedly effective relative to their base strength, both in reactions first-order in amine and in reactions catalysed by a second molecule of amine base (general base catalysed reactions) or by the corresponding cation (general acid catalysed reactions). In the case of the reaction between hydroxylamine and some thioesters, still more complicated rate expressions have been found to be valid. The mechanisms leading to these expressions include acid-base equilibria between tetrahedral intermediates and general catalysis of both formation and breakdown of these intermediates — so-called crossover mechanisms.<sup>13</sup> The high reactivity of hydroxylamine and hydrazine is explained by the so-called  $\alpha$ -effect, which is shown by amines possessing an unshared electron pair on the  $\alpha$ -atom of the nucleophilic center. The origin of the  $\alpha$ -effect has been discussed by, *e.g.*, Edwards and Pearson<sup>16</sup> and by Bruce and coworkers.<sup>8,15,17</sup>

The kinetics and mechanisms of the reactions of amides with hydroxylamine and hydrazine have by no means been investigated as extensively as those of phenyl- and thioesters. It is well known that hydroxylamine reacts with amides giving hydroxamic acids<sup>18</sup> and, using large concentrations of hydroxylamine and elevated temperatures, this reaction can be used for analytical purposes.<sup>19,20</sup> The formation of hydroxamic acids from amides generally proceeds much more slowly than from esters and the difference in reaction rates sometimes is so large that esters can be determined by this method also in the presence of amides.<sup>21</sup> Jencks and Gilchrist<sup>22</sup> kinetically investigated the reaction of hydroxylamine with formamide and more superficially with acetamide at various pH values and found the reaction to be catalysed by hydroxylammonium ions.

Phenyl- and thioesters have good leaving groups whereas amides and anilides have poor ones. This fact alone is a sufficient reason for the appearance of large differences in the action of nucleophiles upon these groups of compounds. Since the kinetics and mechanisms of hydroxylaminolysis and hydrazinolysis of amides and anilides have not been extensively studied, this investigation, which deals with the action of hydroxylamine and hydrazine on an acyl-activated anilide and which is part of a current study on the hydrolysis and aminolysis of amidic bonds, was undertaken.

## MATERIALS AND METHODS

*Materials.* The trifluoroacetanilide was of the quality described previously.<sup>1</sup> The potassium chloride was of analytical grade and recrystallised from 0.1 M hydrochloric acid. The hydroxylamine hydrochloride was of analytical grade and the hydrazine hydrate was of the best commercially available grade. The determination of their acidity constants showed a high degree of purity. Buffers of these compounds were prepared by addition of standardised hydrochloric acid or potassium hydroxide solution to aqueous solutions of the compounds. Hydroxylamine is unstable in solution and buffers of this compound were always prepared immediately before use.

*Determination of acidity constants.* The stoichiometric  $pK_a$  values of the hydroxylammonium ion and of the monovalent hydrazinium ion at 25°C and ionic strength 1 (with KCl) in a medium of 9.6 % (v/v) ethanol were determined potentiometrically as previously described for some other amines.<sup>2</sup> Values of  $pK_a$  calculated after various additions of sodium hydroxide or hydrochloric acid solution corresponding to 10–90 %

neutralisation did not deviate by more than 0.01  $pK_a$  unit from the values given in Table 1. The ionisation constant of  $HPO_4^{2-}$  used in Fig. 8 was determined in the same medium by the method of half neutralisation and serial dilution. At the smallest concentrations of phosphate species (total concentration 0.02 and 0.01 M) the  $pK_a$  value obtained was 11.3. Larger  $pK_a$  values were obtained in more concentrated phosphate solutions (activity coefficients are not identical in a potassium chloride solution and a phosphate solution of ionic strength 1).

*Kinetic experiments and assay.* The kinetic experiments were performed as previously described<sup>1,2</sup> and the concentration of trifluoroacetanilide was generally about  $10^{-3}$  M. The two previously described assay methods — determination of residual anilide in acidified solutions by UV-spectrophotometry at 242.5  $m\mu$  (the UV-method) and determination of aniline by diazotisation and coupling (the aniline method) — were used also in this investigation. Model experiments have shown that when the aniline method is to be used in the presence of hydrazine the amount of added sodium nitrite has to be increased. The concentrations of the added sodium nitrite and ammonium sulphamate solutions were consequently always ten times those otherwise used, *i.e.* 1 M and 5 %, respectively, and the amount of hydrochloric acid added was such as to give nitrous acid from the nitrite and the desired excess of hydrogen ions. Model experiments have further shown that too small absorbances are obtained when the withdrawn samples have a hydroxylamine concentration exceeding about 0.05 M or a hydrazine concentration greater than about 0.005 M. As in the kinetic experiments, these 5 ml samples also contained 9.6 % ethanol. When no or only very little ethanol is present in the solution to be diazotised, the concentrations of hydroxylamine and hydrazine can be considerably larger than those given above, which is advantageous, especially in the experiments with hydrazine. The aniline method therefore can be used also in experiments with large concentrations of hydroxylamine and hydrazine when the volume of the withdrawn samples to be analysed is much smaller than 5 ml or when the withdrawn samples are poured into dilute hydrochloric acid and an aliquot of this solution taken for analysis.

In the various experiments performed with hydroxylamine, the UV-method always gave very small absorbances at infinite time (after about 8 half-lives or more), and this method of analysis has preferably been used at the larger concentrations of hydroxylamine. In the experiments with hydroxylamine solutions containing imidazole, the absorbances at infinite time were, however, at the largest imidazole concentrations about 10–15 % of the value at zero time. These absorbances after about eight half-lives or more were not quite stable (increased slowly), which, of course, makes the computation of rate-constants somewhat uncertain and many of these experiments therefore have been followed by the aniline assay method. Also when using the aniline method, some experiments have been followed over several half-lives, and when samples have been withdrawn and analysed after infinite time a concentration of aniline agreeing with the initial concentration of anilide has been found.

Hydrazine itself has in the concentrations used only a very small absorbance at 242.5  $m\mu$  in acid solution but at infinite time, absorbances which are not negligible are always obtained. These absorbances after about 8 half-lives or more change only very slowly with time. The absorbances at infinite time, which at the higher concentrations of hydrazine range between 5 and 10 % of the absorbance at zero time, are largest when the experiments are run at low pH and rather small hydrazine concentrations and can in extreme cases be of an order of 25 % of the value at zero time. However, in the cases with large UV-absorbances after infinite time, the  $k_{obs}$ -values reported were obtained by the aniline method, which in these cases tends to give somewhat smaller values of the constant. At the larger concentrations of hydrazine, both methods give results agreeing with each other within the experimental errors.

## RESULTS

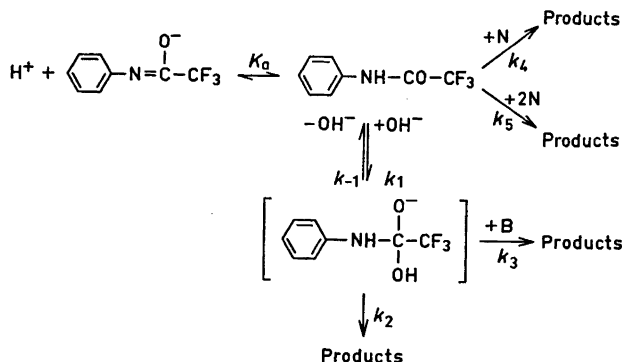
In Figs. 1–6 the pseudo first-order rate constant  $k_{obs}$  for the formation of aniline (or disappearance of anilide) is plotted against total concentration of amine or concentration of free hydroxylamine and hydrazine. Figs. 3 and

6 show the effect of hydroxylamine and hydrazine over the whole concentration range, Figs. 2 and 5 give a more detailed picture at concentrations up to 0.25 M base and Figs. 1 and 4 show the effect of very small concentrations. From the diagrams it is apparent that very small concentrations — of the acidic forms — greatly enhance the reaction rate and that the rate of increase declines with increasing concentrations. Diagrams 2—3 and 5—6, however, also show that after this initial period in which  $k_{\text{obs}}$  increases at a diminishing rate, it increases more rapidly than the concentration of amine upon further addition thereof. The curves of  $k_{\text{obs}}$  as a function of concentration of amine at a given pH therefore first have a section with decreasing slope, go through a point of inflection and then have a section with increasing slope.

The great influence on rate exerted by small concentrations of amine — as cation — is in accordance with the previously advanced theory of general acid catalysis of the breakdown of a tetrahedral substrate-hydroxyl ion complex. The shape of the profiles further indicates that the rate equation may contain a term second-order in amine base. With these premises, eqn. (1) is derived.

$$k_{\text{obs}} = \frac{k_1 K_w}{K_a + [\text{H}^+]} \times \frac{k_2 + \sum k_{3,i} [\text{B}_i]}{k_{-1} + k_2 + \sum k_{3,i} [\text{B}_i]} + \frac{[\text{H}^+]}{K_a + [\text{H}^+]} (k_4 [\text{N}] + k_5 [\text{N}]^2) \quad (1)$$

The significance of these symbols, which, with the exception of  $k_5$ , were also used in the previous paper<sup>2</sup>, in this series, is evident from the following scheme, where B represents general acids and hydroxyl ions and N represents hydroxylamine or hydrazine base.



The curves in Figs. 1—6 are calculated with eqn. (1) using the values of the constants presented in Table 1. From the values of  $k_{\text{obs}}$  at small total concentrations of hydroxylamine or hydrazine the value of  $k_3/k_{-1}$  can be estimated as previously shown. From the straight lines obtained when the second term on the right-hand side of eqn. (1) divided by  $[\text{N}]$  is plotted against  $[\text{N}]$ , the value of  $k_4$  can be estimated from the intercept, and of  $k_5$  from the slope. No such plots, however, are given in this paper. After a few successive approximations the “best” values of the three parameters are obtained. The value of  $k_4$  for hydroxylamine is very small and the plots are then not

Table 1. Dissociation constants and rate parameters experimentally determined and used in the construction of Figs. 1–7 together with the previously<sup>1,2</sup> determined dissociation constants and rate parameters:  $pK_w = 13.92$ ,  $pK_{a,\text{trifluoroacetanilide}} = 9.51$ ,  $k_1 = 930 \text{ l mole}^{-1} \text{ min}^{-1}$ ,  $k_2/k_{-1} = 0.025$ ,  $k_{3,\text{OH}^-}/k_{-1} = 93 \text{ l mole}^{-1}$ , and  $k_{4,\text{imidazole}} (= k_I) = 0.0014 \text{ l mole}^{-1} \text{ min}^{-1}$ .

Catalytic compound	$pK_a$	$k_2/k_{-1}$ $\text{l mole}^{-1}$	$k_4 \times 10^3$ $\text{l mole}^{-1} \text{ min}^{-1}$	$k_5 \times 10^3$ $\text{l}^2 \text{ mole}^{-2} \text{ min}^{-1}$	$k_{NI} \times 10^3$ $\text{l}^2 \text{ mole}^{-2} \text{ min}^{-1}$
Hydroxylamine	6.05	10 000	1.0	39	72.5
Hydrazine	8.11	375	11	73	(18)

suiting for an estimation of this constant. Of the experiments depicted in Figs. 1 and 2, it is only some at the smallest pH value that give a comparatively large contribution to  $k_{\text{obs}}$  from a  $k_4$ -term and thus are suited for an accurate

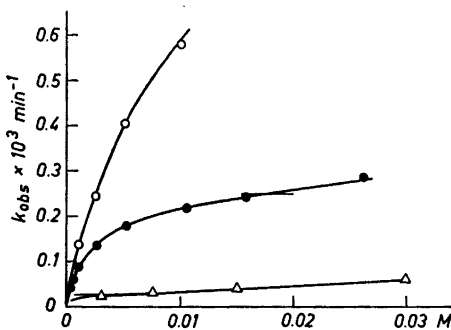


Fig. 1. Plot of  $k_{\text{obs}}$  against total concentration of hydroxylamine. The lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of  $k_1 K_w / (K_a + [\text{H}^+])$ . Breakdown at ratio [base]/[acid] = 2.00 ( $[\text{OH}^-] = 10^{-7.67}$ )  $\Delta$ , at ratio 20.0 ( $[\text{OH}^-] = 10^{-6.57}$ )  $\bullet$ , at ratio 89 ( $[\text{OH}^-] = 10^{-5.92}$ )  $\circ$ .

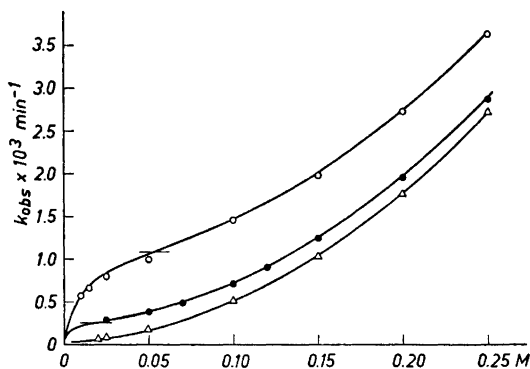


Fig. 2. Plot of  $k_{\text{obs}}$  against concentration of hydroxylamine base. The lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of  $k_1 K_w / (K_a + [\text{H}^+])$ . Breakdown at  $[\text{OH}^-] = 10^{-7.57}$   $\Delta$ , at  $[\text{OH}^-] = 10^{-6.57}$   $\bullet$ , at  $[\text{OH}^-] = 10^{-5.92}$   $\circ$ .

determination of  $k_4$ . In order to get some more values of  $k_{\text{obs}}$ , where the contribution from the  $k_4$ -term is important, some experiments at still smaller pH values have been performed and the values of  $k_{\text{obs}}$  obtained in these experiments are presented in Table 2 together with values from some other experiments. The six experimentally determined values of  $k_{\text{obs}}$  with a large contribution from the  $k_4$ -term (55–20 %) are in very good agreement with the calculated values, which indicates that  $k_4$  can be determined with good accuracy. In these experiments the contribution to  $k_{\text{obs}}$  from the cation-catalysed alkaline hydrolysis is only a minor part ( $0.0042 \times 10^{-3}$  at  $[\text{OH}^-] = 10^{-8.35}$  and  $0.0125 \times 10^{-3} \text{ min}^{-1}$  at  $[\text{OH}^-] = 10^{-7.87}$ ) of the total value and the error in these values is certainly very small. From the profiles in Figs. 2 and 3 it is apparent that the error in the value of  $k_5$  must be small (an error of 5 % can be regarded as an upper limit) and therefore the calculated contribution to the values of  $k_{\text{obs}}$  from this term can, for the six experiments, give at most an error of about 4 % in these calculated values. The six values of  $k_{\text{obs}}$  in Table 2 now discussed, together with the values in Figs. 1 and 2 which have a large contribution from the  $k_4$ -term, seem to permit the conclusion that the value of  $k_4$  reported in Table 1 is correct within an error of approximately  $\pm 20$  %.

The values at the large concentrations of hydroxylamine in Table 2 and the values at the largest hydroxyl ion concentration ( $10^{-5.50} \text{ M}$ ) are not suitable for the determination of  $k_4$ . All the experiments reported in Table 2, however, further demonstrate that eqn. (1) is applicable over a broad pH range and at very large concentrations of hydroxylamine, and that these experiments as

Table 2. Experimentally determined pseudo first-order rate constants ( $k_{\text{obs.exp.}}$ ) and the calculated ones ( $k_{\text{obs.calc.}}$ ) for the breakdown of trifluoroacetanilide in the presence of hydroxylamine; eqn. (1) and parameter values from Table 1 were used in the computation.

Total concentration of hydroxylamine M	Ratio [base]/[acid]	$[\text{OH}^-]$ M	$k_{\text{obs.exp.}}$ $\times 10^3 \text{ min}^{-1}$	$k_{\text{obs.calc.}}$ $\times 10^3 \text{ min}^{-1}$	% of reaction via $k_4$
0.04	0.33	$10^{-8.35}$	0.0182	0.0181	55
0.10	0.33	$10^{-8.35}$	0.0542	0.0535	47
0.20	0.33	$10^{-8.35}$	0.159	0.152	33
1	0.33	$10^{-8.35}$	2.84	2.69	9
0.04	1	$10^{-7.87}$	0.0501	0.0481	42
0.10	1	$10^{-7.87}$	0.160	0.160	31
0.20	1	$10^{-7.87}$	0.515	0.503	20
1	1	$10^{-7.87}$	10.6	10.3	5
1.89	20	$10^{-6.57}$	129	128	1.4
2.10	20	$10^{-6.57}$	158	161	1.3
0.05	234	$10^{-5.50}$	0.197	0.199	2.3
0.30	234	$10^{-5.50}$	6.23	6.06	4.6
0.60	234	$10^{-5.50}$	17.1	16.2	3.4
1	234	$10^{-5.50}$	41.0	39.7	2.3

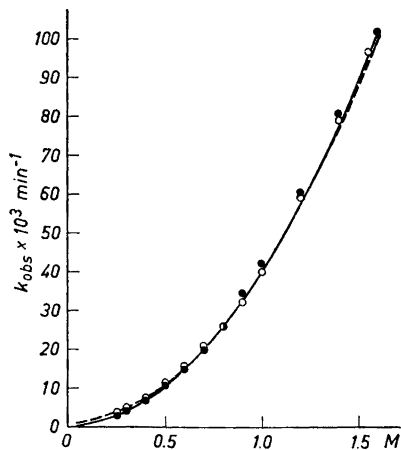


Fig. 3. Plot of  $k_{\text{obs}}$  against concentration of hydroxylamine base. The lines are calculated from eqn. (1) and parameter values given in Table 1. Breakdown at  $[\text{OH}^-] = 10^{-6.57}$  —●—, at  $[\text{OH}^-] = 10^{-5.92}$  —○—.

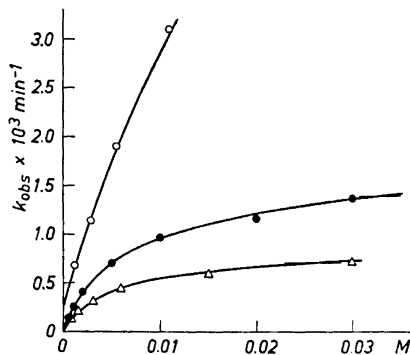


Fig. 4. Plot of  $k_{\text{obs}}$  against total concentration of hydrazine. The lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of  $k_1 K_w / (K_a + [\text{H}^+])$ . Breakdown at ratio  $[\text{base}]/[\text{acid}] = 0.50$  ( $[\text{OH}^-] = 10^{-6.11}$ )  $\Delta$ , at ratio 1.00 ( $[\text{OH}^-] = 10^{-5.81}$ )  $\bullet$ , at ratio 10.0 ( $[\text{OH}^-] = 10^{-4.81}$ )  $\circ$ .

well as those reported in Figs. 1–3 do not reveal any general acid or hydroxyl ion catalysis of the amine reaction.

Breakdown of the anilide *via*  $k_4$  is more important with hydrazine than with hydroxylamine. Calculations using the parameter values given in Table 1 show that breakdown *via*  $k_4$  and  $k_5$  proceeds at the same rate at  $[\text{H}_2\text{NOH}] = 0.025$  M and at  $[\text{H}_2\text{NNH}_2] = 0.15$  M.

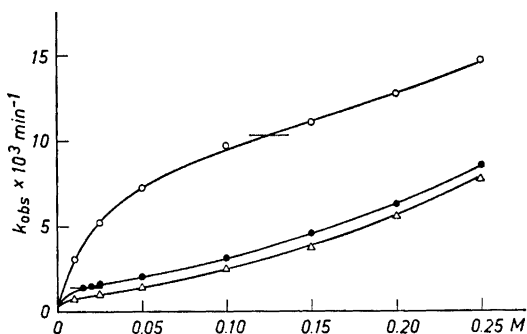


Fig. 5. Plot of  $k_{\text{obs}}$  against concentration of hydrazine base. The lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of  $k_1 K_w / (K_a + [\text{H}^+])$ . Breakdown at  $[\text{OH}^-] = 10^{-6.11}$   $\Delta$ , at  $[\text{OH}^-] = 10^{-5.81}$   $\bullet$ , at  $[\text{OH}^-] = 10^{-4.81}$   $\circ$ .

The values of  $k_{\text{obs}}$  in Fig. 3 at hydroxylamine concentrations of 1 M or higher, as well as the two values at  $[\text{OH}^-] = 10^{-6.57}$  in Table 2 and the values in Fig. 6 at  $[\text{OH}^-] = 10^{-5.81}$  and hydrazine concentrations higher than 1 M correspond to ionic strengths larger than 1. Some experiments with hydroxylamine at  $[\text{OH}^-] = 10^{-6.57}$  and a base concentration of 1 M or more have also been performed at ionic strength 2 (obtained by addition of KCl). This increase in the ionic strength had no noticeable effect on the rate. In addition to the experiments at ionic strength 1, some kinetic runs with hydrazine at  $[\text{OH}^-] = 10^{-5.81}$  and a hydrazine concentration of 1 M have been performed also at ionic strengths 1.5 and 2, obtained by the addition of either KCl or excess of hydrazinium chloride (pH is also somewhat decreased then). These experiments have shown no or only a small (always less than 10 %) positive influence on rate as a result of the increased ionic strength. It can therefore be concluded that rate constants used in calculating the values at the ionic strength 1 also can be used at the largest concentrations in Figs. 3 and 6 with an ionic strength somewhat higher than 1.

The curves in Figs. 3 and 6 intersect. At small concentrations of hydroxylamine or hydrazine, a large part of the value of  $k_{\text{obs}}$  derives from the cation catalysed alkaline hydrolysis and the maximum contribution to  $k_{\text{obs}}$  from this source increases with increasing pH. At  $[\text{H}^+]$  about  $10^{-8}$ , ionisation of trifluoroacetanilide begins to be of importance and with decreasing value of  $[\text{H}^+]$ , the ratio  $[\text{H}^+]/(K_a + [\text{H}^+])$  becomes smaller and smaller. From

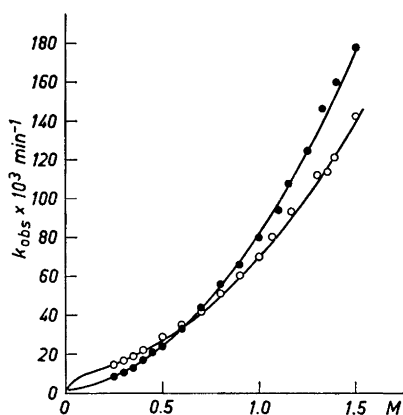


Fig. 6. Plot of  $k_{\text{obs}}$  against concentration of hydrazine base. The lines are calculated from eqn. (1) and parameter values given in Table 1. Breakdown at  $[\text{OH}^-] = 10^{-5.81}$   
 ●, at  $[\text{OH}^-] = 10^{-4.81}$  ○.

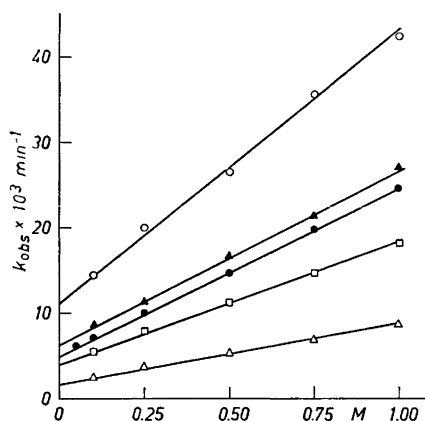


Fig. 7. Plot of  $k_{\text{obs}}$  against total concentration of imidazole. The lines are calculated from eqn. (2) and parameter values given in Table 1.

	$-\log [\text{OH}^-]$	$[\text{H}_2\text{NOH}]$
△	5.92	0.1
□	6.57	0.3
●	5.92	0.3
▲	5.50	0.3
○	5.92	0.5



eqn. (1) and the parameter values in Table 1, it is apparent that these effects of changes in pH will lead to intersection of profiles obtained at different pH values.

In Fig. 7, values of  $k_{\text{obs}}$  obtained in experiments with mixtures of imidazole and hydroxylamine are presented, each line representing a fixed concentration of hydroxylamine and variable concentrations of imidazole. The experiments were performed at three different pH values, and at one of these, at three different hydroxylamine concentrations. At all these experiments, the concentration of hydroxylammonium ion is large enough to give almost the limiting value of the cation catalysed alkaline hydrolysis, hence rate increase can only to a very small extent be due to imidazolium ion catalysed alkaline hydrolysis. The increase in rate with increasing concentration of imidazole is in these experiments much larger than what can be ascribable to the reaction between substrate and imidazole. For this last reaction the constant has been determined previously<sup>2</sup> and found to have the value of  $1.4 \times 10^{-3} \text{ l mole}^{-1} \text{ min}^{-1}$ . The most reasonable explanation for the great influence of imidazole in these experiments seems to be that the reaction between hydroxylamine and substrate is catalysed by imidazole, *i.e.* that the rate equation contains a term first-order in substrate, hydroxylamine and imidazole.

$$k_{\text{obs}} = \frac{k_1 K_w}{K_a + [\text{H}^+]} \times \frac{k_2 + \sum k_{3,i} [\text{B}_i]}{k_{-1} + k_2 + \sum k_{3,i} [\text{B}_i]} + \frac{[\text{H}^+]}{K_a + [\text{H}^+]} (k_4 [\text{N}] + k_5 [\text{N}]^2 + k_{\text{I}} [\text{I}] + k_{\text{NI}} [\text{N}] [\text{I}]) \quad (2)$$

In eqn. (2), [N] denotes concentration of hydroxylamine base, [I] concentration of imidazole base, and  $k_{\text{I}}$  is the previously determined constant for imidazole catalysis. At a given pH and at a hydroxylamine concentration which is large enough to give almost the limiting value of the cation catalysed alkaline hydrolysis, the first term in eqn. (2) is essentially constant and straight lines are to be expected when  $k_{\text{obs}}$  at a given concentration of hydroxylamine is plotted against concentration of imidazole. From the slope of such lines,  $k_{\text{NI}}$  is easily calculated. The value of  $k_{\text{NI}}$  used in the calculation of the lines in Fig. 7 is given in Table 1.

#### DISCUSSION

The large influence on rate caused by small concentrations of catalytic species, as shown particularly by the profiles in Figs. 1 and 4, further substantiates the theory of general acid catalysed breakdown of a substrate-hydroxyl ion complex. When the logarithm of the parameter  $k_3/k_{-1}$  of the ammonium type acids, studied in this and in the previous<sup>2</sup> investigation, is plotted against  $\log K_a$ , a straight line of slope 0.9 is obtained: this Brønsted plot is shown in Fig. 8. The hydrogen carbonate ion and the two phosphate ions are, however, more effective than amine cations of corresponding acid strength. The slope of a line on which these acids fall is, however, much smaller (0.55) than that for the ammonium cation acids. Therefore it is not so surprising that, as previously reported,<sup>1</sup> the catalytic effect of  $\text{H}_2\text{CO}_3$  is only slight,

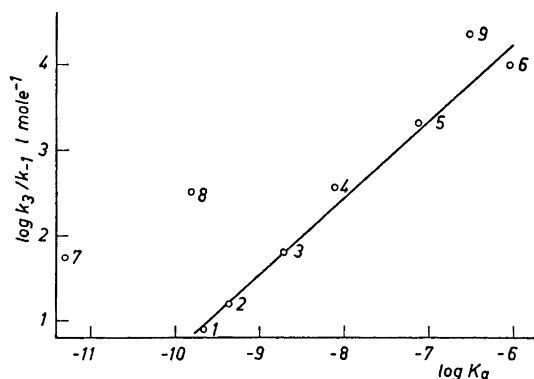


Fig. 8. Brønsted plot of  $\log(k_3/k_{-1})$  against  $\log K_a$ . Numbers 1–6 refer to the cations of the bases. 1 = monoethanolamine, 2 = ammonia, 3 = morpholine, 4 = hydrazine, 5 = imidazole, 6 = hydroxylamine, 7 =  $\text{HPO}_4^{2-}$ , 8 =  $\text{HCO}_3^-$ , 9 =  $\text{H}_2\text{PO}_4^-$ .

that the effect of  $\text{H}_3\text{PO}_4$  is found to be insignificant, and that the effect of hydronium ions is negligible at the pH values used in the experiments.

Most aminolyses of esters are correlated by the equation

$$k_{\text{obs}} = k_n[\text{N}] + k_{\text{gb}}[\text{N}]^2 + k_{\text{ga}}[\text{N}][\text{NH}^+] + k_{\text{OH}}[\text{N}][\text{OH}^-] \quad (3)$$

where  $k_{\text{obs}}$  is the pseudo first-order rate constant, N the amine base and  $\text{NH}^+$  the corresponding cation.<sup>8</sup> The constants for unassisted or water-assisted nucleophilic attack ( $k_n$  or  $k_4$  in the present paper), for self-assisted base catalysed nucleophilic attack ( $k_{\text{gb}}$  or  $k_5$ ), for the corresponding acid catalysed nucleophilic attack ( $k_{\text{ga}}$ ) and for hydroxyl ion catalysed attack ( $k_{\text{OH}}$ ) are of greatly differing importance for different substrates and nucleophiles. Often, one or several of the terms in eqn. (3) do not contribute to the value of  $k_{\text{obs}}$ . General catalysis is not important for esters with very good leaving groups, *e.g.* *p*-nitrophenylacetate,<sup>23</sup> but it is important for esters with somewhat poorer leaving groups, *e.g.* phenylacetate,<sup>3,24</sup> thiolactones and thioesters.<sup>11–15</sup> Of course, steric considerations are also of importance in discussing self-assisted general catalyses.

Even though many kinetic investigations regarding the reaction of amines with phenyl- and thioesters have appeared, especially during the last years, there are only a few dealing with the reaction of amines with acyl-activated or unactivated esters and amides. Weakly basic amines lacking the  $\alpha$ -effect, such as imidazole, do not react at all with substrates such as ethyl acetate,<sup>25</sup> and only slowly with substrates such as ethyl halogenoacetates<sup>25</sup> at room temperature. When amines lacking the  $\alpha$ -effect react with these types of substrates a first-order term is found.<sup>2,25</sup>

Relative to their base strengths, hydrazine and especially hydroxylamine, due to the  $\alpha$ -effect, react rapidly with phenyl- and thioesters, as shown by the values of  $k_n$  and often still more by the values of  $k_{\text{gb}}$  and  $k_{\text{ga}}$ . Hydroxylamine and hydrazine, however, also react with esters whose leaving groups

are poorer than those of phenyl- and thioesters, and also with amides. Kinetic investigations of these reactions are, however, very limited. Hydrazinolysis of ethyl acetate<sup>26</sup> is found to be first-order in hydrazine whereas the rate expression for hydroxylaminolysis of  $\gamma$ -butyro- and  $\delta$ -valerolactone contains one term which is second-order in hydroxylamine and one which is second-order in hydroxylamine and first-order in hydroxyl ion. Again, Jencks and Gilchrist<sup>22</sup> have shown that the reaction of formamide and acetamide with hydroxylamine proceeds through a tetrahedral intermediate, and according to the mechanisms postulated by them and commented upon by Fedor and Bruce<sup>14</sup> both the formation and the breakdown of the tetrahedral intermediate into reactants and products is catalysed by hydroxylammonium ions. When, as demonstrated by them, rate is plotted against pH at constant total hydroxylamine concentration, bell-shaped curves are obtained with a maximum around pH 6 (indicative of hydroxylammonium ion catalysis) and when rate is plotted against concentration of hydroxylamine at a given pH the slope of the curves first increases gradually but becomes essentially constant at higher concentrations (indicative of catalysis of an intermediate).

The rates now obtained in the hydroxylaminolysis and hydrazinolysis of trifluoroacetanilide do not obey any of the rate equations valid for the enumerated non-activated or acyl-activated substrates. Whereas the  $\alpha$ -effect is supposed to be the reason for the relatively high values of  $k_n$  (or  $k_4$ ) for hydroxylamine and hydrazine in reactions with many substrates with good leaving groups, it is not very apparent in the values of  $k_4$  in this investigation. Certainly hydroxylamine is the weakest of the amine bases used in this and in the previous investigation<sup>2</sup> but its  $k_4$ -value also is the smallest one and as has been mentioned, it is only some experiments at restricted conditions that definitely show the presence of a  $k_4$ -term in the rate expression. If a tetrahedral intermediate is formed by nucleophilic attack of hydroxylamine it seems reasonable to assume that without catalysis by other species this intermediate expels almost exclusively the good leaving group  $\text{NH}_2\text{OH}$  instead of the poor leaving group  $\text{C}_6\text{H}_5\text{NH}^-$  and thus reverts to reactants instead of going to products (see Fig. 9, dotted line). If the  $k_4$ -term in this case represents a hydroxylamine-assisted nucleophilic water attack then the value of  $k_4$  has to be very small, as hydroxylamine is a very weak base ( $\text{p}K_a = 6.05$ ). It should be mentioned that Jencks and Carriuolo<sup>25</sup> for ethyl halogenoacetates have found that product analysis and deuterium isotope effects indicate a shift from general base catalysis to nucleophilic attack at a  $\text{p}K_a$  value near 7–8. Their investigation

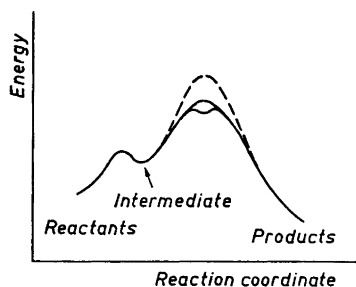


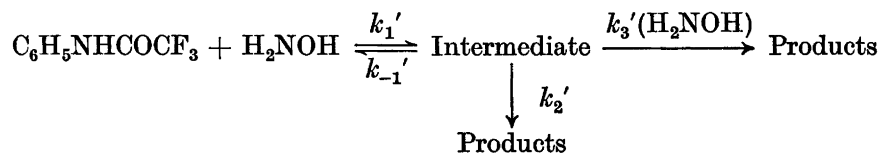
Fig. 9. Hypothetical plot of reaction coordinate versus energy, assuming formation of an intermediate of almost the same energy content as the activated complex formed before it. The activated complex preceding product formation, however, has a much higher energy content. The dotted line represents formation of the second activated complex without catalysis, and the full line with catalysis and with or without formation of a second intermediate.

did not, however, include compounds with  $\alpha$ -effect. Hydrazine is a considerably stronger base than hydroxylamine and the value of  $k_4$  is also larger. Compared with the values of  $k_4$  of some previously<sup>2</sup> used amines the value is, however, not especially high. Its value is about the same as for morpholine, which is a somewhat stronger base, but is smaller than the values for triethanolamine and tris(hydroxymethyl)aminomethane, which are bases of about the same strength as hydrazine. It can be mentioned that  $k_4$  for hydrazine in the breakdown of *p*-nitrophenylacetate and 2,2,2-trifluoroethyl thiolacetate is approximately 5000 times larger than  $k_4$  for tris(hydroxymethyl)aminomethane.<sup>15</sup> Summing up, it can be stated that no or only a small  $\alpha$ -effect is revealed in the values of  $k_4$  with trifluoroacetanilide as substrate and that a large  $\alpha$ -effect in a reaction first-order in ester or amide and first-order in nucleophile probably requires good leaving groups. However, extended investigations with different substrates and nucleophiles of this type are needed in order to enable more definite conclusions to be drawn regarding the relationship between structures and the  $\alpha$ -effect as shown in values of  $k_4$ .

The self-assisted base catalysed term is, at most concentrations and pH values, the predominant one in the hydroxylaminolysis of trifluoroacetanilide and at higher concentrations, the largest one also in the hydrazinolysis reaction. As already mentioned, the kinetics of hydroxylaminolysis of formamide<sup>21</sup> evidences the existence of a tetrahedral intermediate and hydroxylammonium ion catalysis of the breakdown of this intermediate. The rates now found for the breakdown of trifluoroacetanilide at very different pH values and concentrations of hydroxylamine and hydrazine do not prove the existence of a tetrahedral intermediate in this reaction. The pathway for the reaction second-order in amine, with for example, hydroxylamine can be simply formulated by



*i.e.*, the nucleophilic attack of  $\text{H}_2\text{NOH}$  is catalysed by another  $\text{H}_2\text{NOH}$  molecule. Of course, formation of an intermediate and not only of an activated complex may precede product formation in the above reaction scheme and if the breakdown of this intermediate to reactants as well as to products is catalysed by the same species, *e.g.* hydroxylammonium ions, the rate will still be second-order in hydroxylamine base and independent in these other species. If, in analogy with the catalysed alkaline hydrolysis, the reaction pathway is written as

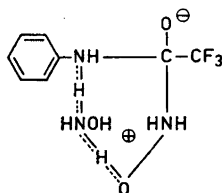


then the contribution to  $k_{\text{obs}}$  ( $k_{\text{obs}'}$ ) from the catalysed reaction is

$$k_{\text{obs}'} = \frac{k_1'k_3'[\text{H}_2\text{NOH}]^2}{k_{-1}' + k_2' + k_3'[\text{H}_2\text{NOH}]}$$

and the reaction will behave as second-order in hydroxylamine only if  $k_{-1}'$  ( $k_2'$  can be regarded as insignificant compared to  $k_{-1}'$ ) at all hydroxylamine concentrations is much larger than  $k_3'[\text{H}_2\text{NOH}]$ . In this very special case, the intermediate and the transition state preceding the formation of the intermediate may be very similar and have nearly the same energy content (see Fig. 9), whereas the transition state or states (if a new intermediate is formed) preceding the formation of products must have a much higher energy content, which, however, is smaller than that for the uncatalysed reaction. Thus interconversion between the intermediate and the first transition state (and reactants) will take place rapidly but product formation from this intermediate will take place slowly, relative to reversion to reactants, both for the catalysed and uncatalysed reaction. It is obvious that under these circumstances the mechanism for the catalysed reaction can be regarded as a base catalysed nucleophilic attack.

A discussion regarding the structure of the complex transforming to products in the catalysed reaction must be very speculative. That one molecule of hydroxylamine (or hydrazine) acts as a nucleophile is unquestionable but regarding the direct action of the other, different possibilities are open. It seems quite reasonable to assume that the very weak base hydroxylamine requires the assistance of a second molecule to expel the poor leaving group  $\text{C}_6\text{H}_5\text{NH}^-$ . Attack by a second molecule of base on a hydrogen of the nucleophile will facilitate the expulsion of hydroxamic acid or hydrazide, and hydrogen bonding to the anilide nitrogen will facilitate the expulsion of the aniline part of the molecule. As discussed by Bruice and Fedor<sup>13</sup> for hydroxylaminolysis of thiol esters, these two routes for assisted mechanisms can be combined in a concerted mechanism with an intermediate (or activated complex) that can be depicted by



None, one, or both of the hydroxyl groups might be directly involved in the formation and breaking of bonds in the complex; corresponding structures can be discussed also in the hydrazinolysis reaction. Breakdown of the hypothetical complex into products will give hydroxamic acid as a primary reaction product. In the reaction of hydroxylamine with esters, it has been shown that *O*-acylhydroxylamine sometimes is the major initial product.<sup>27</sup> This is probably not the case in the reaction with amides and anilides<sup>22</sup> and as all experiments have been followed by the determination of remaining anilide or formed aniline the rates obtained are not influenced by the nature of the initial products from the acyclic part.

The choice of imidazole as a potential catalyst in the hydroxylamine reaction was dictated mainly by two reasons: it is a base of suitable strength for these experiments and from a previous investigation<sup>2</sup> it is known that the rate-enhancing effect of imidazole itself is very small. It has been found that imidazole catalyses the hydroxylamine reaction with tyrosine ethyl ester and *N*-acetyltyrosine ethyl ester.<sup>28</sup> Similarly, imidazole as well as the imidazolium ion catalyses hydrazinolysis of thiolactones and thioesters.<sup>13</sup> Also the rate of formohydroxamic acid formation from formamide is somewhat increased in imidazole buffer but the rate dependence was not investigated in detail.<sup>22</sup> From the experiments graphically presented in Fig. 7, it is apparent that imidazole can replace one of the hydroxylamine molecules in the rate term second-order in these species. Imidazole is a stronger base ( $pK_a = 7.12$ ) than hydroxylamine, hence it is not so surprising that  $k_{NI}$  is somewhat larger than  $k_5$  for the reaction second-order in hydroxylamine. Anderson<sup>28</sup> and Jencks and Gilchrist<sup>22</sup> have followed the reactions by determining the hydroxamic acid formed. The reaction found by them must therefore be an imidazole catalysed nucleophilic attack of hydroxylamine. It is well known that the affinity of hydroxylamine to carbonyl carbon in many cases is large<sup>23</sup> in comparison to its basicity, so it seems very reasonable to assume that the main reaction leading to the  $k_{NI}$ -term involves hydroxylamine as nucleophile and imidazole as general base — thus indicating a high tendency to nucleophilic attack of hydroxylamine and stressing the importance of assistance in order to get products from the attack.

Imidazole catalysis has also in a few experiments been studied in the hydrazinolysis reaction. Imidazole seems to act in the same way in this case but the value of  $k_{NI}$  is smaller (approximately  $18 \times 10^{-3} \text{ M}^{-2} \text{ min}^{-1}$ ) than in the corresponding hydroxylaminolysis reaction. Hydrazine is a stronger base than imidazole and the value of  $k_5$  in the hydrazinolysis reaction is also larger than the value of  $k_{NI}$ .

The hydroxylaminolysis reaction has also in some experiments been studied in the presence of morpholine buffer and hydrogen carbonate ions. From the experiments with morpholine buffers it is apparent that the reaction is influenced by morpholine base in the same way as by imidazole. Morpholine is a stronger base than imidazole ( $pK_a$  values 8.71 and 7.12, resp.) and its catalytic constant is also somewhat larger (approximately  $105 \times 10^{-3} \text{ M}^{-2} \text{ min}^{-1}$ ). No enhancing effect is noted for the hydroxylaminolysis reaction in the presence of the very weak base hydrogen carbonate.

There seems to be no doubt that the amine cationic acids catalyse the breakdown of a substrate-hydroxyl ion complex but the kinetic experiments reveal no other influence on the rate. The hydroxylaminolysis of formamide and acetamide is catalysed by hydroxylammonium ions<sup>22</sup> and many general base catalysed ester aminolysis reactions are also general acid catalysed. The absence of kinetically demonstrable acid catalysis in the aminolysis reactions of trifluoroacetanilide is probably ascribable to the strong electron-withdrawing effect of the trifluoro group. Some preliminary experiments with hydroxylaminolysis of acetanilide have shown that this reaction is catalysed by hydroxylammonium ions.

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