

## Hydrolysis of Anilides

### III.\* Aminolysis and General Acid-Catalysed Alkaline Hydrolysis of Trifluoroacetanilide

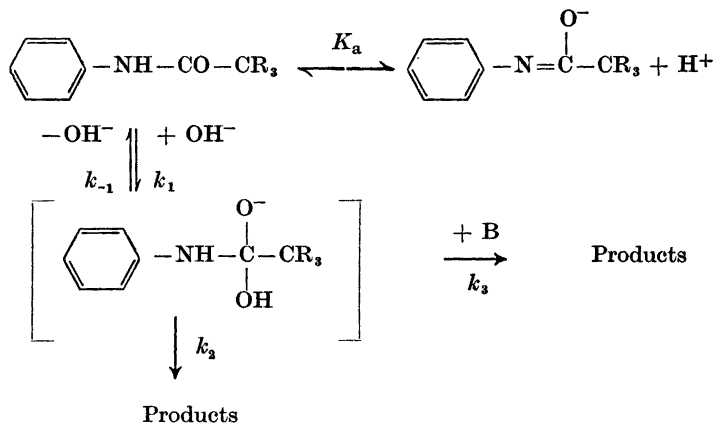
SVEN O. ERIKSSON and LOUISE BRATT

*Department of Chemistry, Kungl. Farmaceutiska Institutet, Stockholm, Sweden.*

Trifluoroacetanilide ( $C_6H_5NHCOCF_3$ ) is hydrolysed in the presence of the following buffer systems representing primary, secondary, and tertiary amines: ammonia, monoethanolamine, morpholine, imidazole, and triethanolamine. The catalytic effects are for each system determined at two or three different pH values under conditions of constant ionic strength and varying concentrations of catalytic species. The effect of some other catalysts of the amine type, *viz.* butylamine, pyrrolidine, pyrazole, and tris(hydroxymethyl)amino-methane,  $(HOCH_2)_3CNH_2$ , is investigated only superficially. A mechanism is proposed in which the cations of the amines act as general acids on the tetrahedral intermediate formed between substrate and hydroxyl ions, and the free bases act directly on the substrate as nucleophiles or *via* a water molecule as general bases. Values of the pseudo first order rate constants ( $k_{obs}$ ) calculated from an equation derived from this mechanistic pathway are in good agreement with the experimentally determined ones. The values of the catalytic constants of the general acids vary greatly and with the exception of the triethanolammonium ion, which is entirely inactive, the constants are well related to the dissociation constants of the acids. Also as a base, triethanolamine behaves exceptionally, but in this case as an unexpectedly effective catalyst. The mechanism of action of the amine bases is discussed and comparisons are made with recent findings and theories in the aminolysis of esters.

In a previous paper in this series dealing with the hydrolysis of trifluoro- and trichloroacetanilide<sup>1</sup> it was shown that breakdown to products of a tetrahedral intermediate formed in the reaction with hydroxyl ions, henceforth designated as substrate-hydroxyl ion complex, is catalysed not only by a second hydroxyl ion but also by species able to donate a proton to the intermediate. From the somewhat simplified mechanistic pathway given here

\* Part II: see Ref. 1.



the following equation could be derived

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

where  $k_{\text{obs}}$  is the pseudo first order rate constant. In the derivation of eqn. (1) it is assumed that only the acidic form of the anilides is reactive and that the steady state approximation can be applied to the intermediate in brackets. Jencks and Gilchrist<sup>2</sup> used a somewhat similar equation for calculation of rates in the hydroxylammonium ion catalysed formation of formohydroxamic acid from hydroxylamine and formamide, and recently Schowen and co-workers<sup>3,4</sup> have proposed a related equation for catalysis of the alkaline hydrolysis of trifluoro-N-methylacetanilide by a second hydroxyl ion. From eqn. (1) it is apparent that limiting values of  $k_{\text{obs}}$  will be obtained at constant pH when  $k_{3,i} [\text{B}_i] \gg k_{-1}$ . This was shown to be the case in the hydrolysis of trifluoro- and trichloroacetanilide<sup>1</sup> for rather small concentrations of  $\text{HCO}_3^-$ ,  $\text{H}_2\text{PO}_4^-$ , or  $\text{HPO}_4^{2-}$ , and the parameter values  $k_3/k_{-1}$  could be determined for these species as well as for hydroxyl ions. It was also briefly mentioned in the paper referred to above that the cations of some amines seemed to catalyse hydrolysis in the same way as the ampholytic anions enumerated. From the preliminary results obtained already at that time it was, however, apparent that values of  $k_{\text{obs}}$  much higher than the calculated limiting values could be obtained with at least some amine buffers. The pathway represented by eqn. (1) cannot therefore be the only one leading to formation of aniline in the presence of amines. In order to obtain more information about the action of amines and their corresponding acids in the splitting of an acyl-activated amide bond, catalytic parameters for some amine cations and amine bases have now been determined.

#### MATERIALS AND METHODS

*Materials.* The trifluoroacetanilide was of the quality described previously.<sup>1</sup> The potassium chloride was of analytical grade and was recrystallised from 0.1 M hydrochloric acid. Triethanolammonium chloride was recrystallised from water. All chemicals used

as catalysts were either of analytical grade or of the best commercially available grade. The determinations of their acidity constants have in all cases shown a high degree of purity. Buffers of ammonia and triethanolamine were prepared from their hydrochlorides by the addition of standardised potassium hydroxide solution, and of the other amines, by the addition of standardised hydrochloric acid to solutions of the free bases. Some concentrated buffers of triethanolamine were prepared from reagent grade triethanolamine and from the recrystallised hydrochloride.

*Determination of acidity constants.* 50 ml of approximately 0.02 M solutions of ammonia, monoethanolamine, morpholine, imidazole, and triethanolammonium chloride were titrated with 1 M sodium hydroxide solution or 1 M hydrochloric acid at  $25 \pm 0.05^\circ\text{C}$  in a medium of 9.6 % (v/v) ethanol and ionic strength 1, as previously described for the  $pK_a$  determination of trifluoroacetanilide and trichloroacetanilide.<sup>1</sup> Knowing the relation between measured pH and  $[\text{H}^+]$  and  $[\text{OH}^-]$ <sup>1</sup> stoichiometric  $pK_a$  values were calculated for at least 15 additions between approximately 10 % and 90 % neutralisation. The largest deviation from the values given in Table 1 has for all five compounds been about 0.01  $pK_a$  unit.

*Hydrolysis experiments and assay.* The previously described<sup>1</sup> pH-stat method was used also in this investigation. After having adjusted and measured the pH of solutions of good buffer capacity, these solutions could be removed from the special reaction vessel (containing the electrodes) to a volumetric flask placed in a thermostated bath. Generally, the quotients [acid]/[base] of the catalysts reported in Figs. 1–4 were obtained by setting and keeping the pH at a fixed value. At some of the largest concentrations of catalytic species, however, the quotients were determined from the known concentrations of acidic and basic forms. In these cases, a deviation of a few hundredths of a pH unit from the pH value at smaller concentrations of catalyst has sometimes been noticed.

The two previously described assay methods<sup>1</sup> — determination of residual anilide in acidified solutions by UV-spectrophotometry at  $242.5\text{ m}\mu$  or determination of aniline by diazotisation and coupling — were used also in this investigation. For all five catalysts, both methods have been used — the diazotisation method being preferable at slow rates and the UV-method at faster rates.

Using a Beckman photometer model DK-2, absorbance curves have been run after periods of not less than 8 half-lives. With all catalysts investigated in detail such curves were identical with the curves obtained with freshly distilled aniline in neutral or alkaline medium.

## RESULTS

All the catalytic species used gave at high amine concentrations values of  $k_{\text{obs}}$  larger than the limiting values calculated by means of eqn. (1). If it is assumed that the rate equation for formation of aniline (or breakdown of substrate) also contains a term which is first order with respect to both unionised substrate and amine base (N) having the rate constant  $k_4$ , eqn. (2) is obtained:

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

In Figs. 1–4, experimentally determined values of  $k_{\text{obs}}$  are plotted against concentrations of catalytic species. At small pH values, the scale used in Figs. 1 and 2 cannot demonstrate the effect of small concentrations of catalyst, especially with imidazole. Therefore, values of  $k_{\text{obs}}$  at very small concentrations of imidazole at the three acidities used and of morpholine and ammonia at the smallest pH value used for these compounds have been plotted against concentration of catalyst in Fig. 3. At these concentrations, the acidic form of the catalysts is responsible for almost all rate enhancement. Figs. 1 and 2

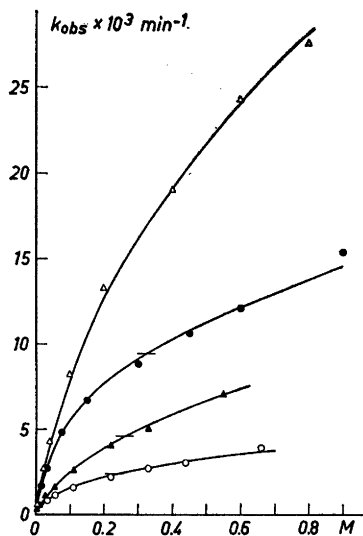


Fig. 1. Plot of  $k_{\text{obs}}$  against total concentration of ammonia and monoethanolamine. The lines are calculated from eqn. (2) and parameter values given in Table 1. The bars denote the limiting values of  $k_{\text{obs}}$  calculated from eqn. (1). Catalysis by ammonia at ratio  $[\text{base}]/[\text{acid}] = 0.1$  ( $[\text{OH}^-] = 10^{-5.56}$ )  $\circ$ , at ratio 0.5 ( $[\text{OH}^-] = 10^{-4.86}$ )  $\bullet$ , by monoethanolamine at ratio  $[\text{base}]/[\text{acid}] = 0.102$  ( $[\text{OH}^-] = 10^{-5.25}$ )  $\blacktriangle$ , at ratio 0.912 ( $[\text{OH}^-] = 10^{-4.30}$ )  $\triangle$ .

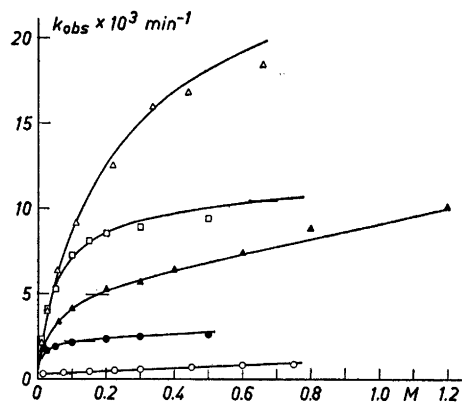


Fig. 2. Plot of  $k_{\text{obs}}$  against total concentration of imidazole and morpholine. The lines are calculated from eqn. (2) and parameter values given in Table 1. The bars denote the limiting values of  $k_{\text{obs}}$  calculated from eqn. (1). Catalysis by imidazole at ratio  $[\text{base}]/[\text{acid}] = 2$  ( $[\text{OH}^-] = 10^{-6.60}$ )  $\circ$ , at ratio 15.9 ( $[\text{OH}^-] = 10^{-6.60}$ )  $\bullet$ , at ratio 100 ( $[\text{OH}^-] = 10^{-4.80}$ )  $\square$ , by morpholine at ratio  $[\text{base}]/[\text{acid}] = 1$  ( $[\text{OH}^-] = 10^{-6.21}$ )  $\blacktriangle$ , at ratio 10 ( $[\text{OH}^-] = 10^{-4.21}$ )  $\triangle$ .

show that at high concentrations of catalyst the relationship between  $k_{\text{obs}}$  and concentration of catalyst is described by a straight or only weakly curved line. From the slope of these lines values of  $k_4$  are approximately estimated. When the contribution to  $k_{\text{obs}}$  from the  $k_4$ -term is thus approximately known, the value of  $k_3/k_{-1}$  can be estimated as previously shown.<sup>1</sup> Values of  $k_4$  and  $k_3/k_{-1}$  giving the best fit to the experimental values of  $k_{\text{obs}}$  are then easily obtained by a few successive approximations. From the values of  $k_{\text{obs}}$  plotted in Fig. 4 it is apparent that  $k_{\text{obs}}$  up to rather high concentrations of triethanolamine is a function of the concentration of free amine only and that the triethanolammonium ion has no catalytic effect ( $k_3 = 0$ ). The deviation of the experimental values from the straight lines at high amine concentrations in Fig. 4 will be commented upon in the discussion.

In the calculation of the curves in Figs. 1–4 the values of  $k_3/k_{-1}$  and of  $k_4$  given in Table 1 have been used. With the exception of triethanolamine at the above-mentioned high concentrations, the agreement between experimental values and calculated curves is good, the deviations being only excep-

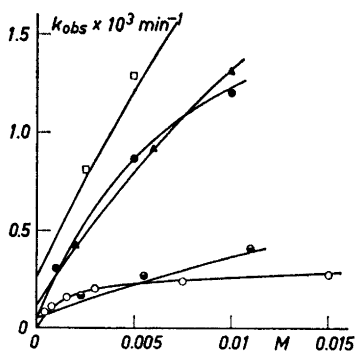


Fig. 3. Plot of  $k_{obs}$  against total concentration of imidazole, morpholine and ammonia. The lines are calculated from eqn. (2) and parameter values given in Table 1. Catalysis by imidazole at ratio [base]/[acid] = 2 ( $[OH^-] = 10^{-6.50}$ )  $\circ$ , at ratio 15.9 ( $[OH^-] = 10^{-5.60}$ )  $\bullet$ , at ratio 100 ( $[OH^-] = 10^{-4.80}$ )  $\square$ , by morpholine at ratio [base]/[acid] = 1 ( $[OH^-] = 10^{-5.21}$ )  $\blacktriangle$ , by ammonia at ratio [base]/[acid] = 0.1 ( $[OH^-] = 10^{-5.56}$ )  $\ominus$ .

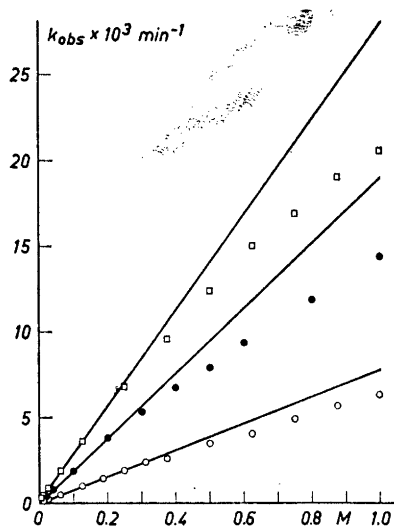


Fig. 4. Plot of  $k_{obs}$  against total concentration of triethanolamine. The lines are calculated from eqn. (2) and parameter values given in Table 1. Catalysis at ratio [base]/[acid] = 0.25 ( $[OH^-] = 10^{-6.50}$ )  $\circ$ , at ratio 1 ( $[OH^-] = 10^{-5.90}$ )  $\bullet$ , at ratio 4 ( $[OH^-] = 10^{-5.30}$ )  $\square$ .

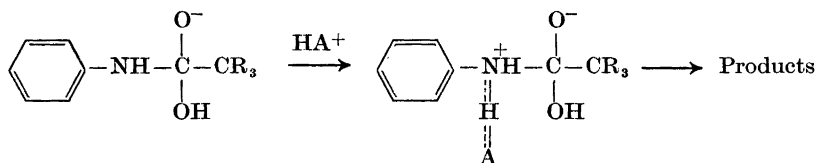
Table 1. Dissociation constants and rate parameters experimentally determined and used in the construction of Figs. 1–4 together with the previously<sup>1</sup> determined dissociation constants and rate parameters:  $pK_w = 13.92$ ,  $pK_a$ , trifluoroacetanilide = 9.51,  $k_1 = 930$   $l\ mole^{-1}min^{-1}$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

Catalytic compound	$pK_a$	$k_3/k_{-1}$ $l\ mole^{-1}$	$k_4 \times 10^3$ $l\ mole^{-1} min^{-1}$
Monoethanolamine	9.66	8	75
Ammonia	9.36	16	27
Morpholine	8.71	65	10
Triethanolamine	8.02	0	39
Imidazole	7.12	2100	1.4

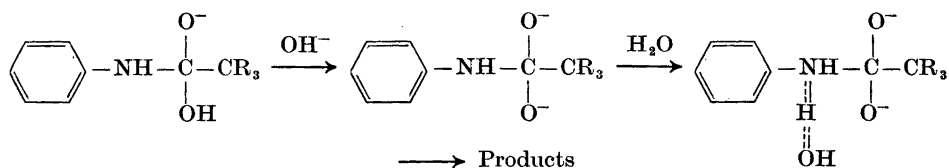
tionally as large as 10 %. With increasing concentration of buffer species, new medium effects might be expected to arise. There is, however, in Figs. 1 and 2 no clear indication of especially large relative deviations from calculated values at the highest concentrations of catalytic species. Some experiments with the catalysts here enumerated and with some other presumptive catalysts mentioned in the synopsis will be briefly dealt with in the discussion.

## DISCUSSION

*Catalysis by acids.* In the previous paper in this series<sup>1</sup> the catalytic parameter  $k_3/k_{-1}$  for  $\text{HCO}_3^-$ ,  $\text{H}_2\text{PO}_4^-$ , and  $\text{HPO}_4^{2-}$  was determined and as an explanation of the catalytic efficiency of these ions the hypothesis was advanced that breakdown to products of the tetrahedral intermediate might be especially enhanced in the presence of catalysts able to donate and accept a proton simultaneously. Mechanisms with phosphate species and hydrogen carbonate ions acting as bifunctional catalysts have also been proposed for aniline formation from N-phenyliminotetrahydrofuran and 4-hydroxybutyranilide and for some other reactions discussed in papers by Cunningham and Schmir.<sup>5,6</sup> The results now obtained, however, show that also cationic acids of the amine type can be very effective catalysts in the hydrolysis of trifluoroacetanilide. These cations cannot donate and accept a proton in a concerted mechanism and therefore are supposed to act only as general acids, principally according to the reaction scheme



General acid catalysis of reactions involving carbonyl compounds has been reviewed by Bender<sup>7</sup> and of carbonyl addition reactions by Jencks<sup>8</sup> and no detailed discussion will be made at this point regarding the pathway from the tetrahedral intermediate to products. The reaction scheme above, however, does not necessarily imply that the zwitter ion is a real intermediate or that products are formed directly from this zwitter ion. As has been shown previously, also the strongly basic hydroxyl ion can catalyse breakdown *via*  $k_3$ . The reaction path might then be depicted as follows



An intermediate of the type shown in the last formulation may most reasonably be regarded as only a fleeting intermediate (transition state) and might

precede product formation also in general acid catalysis of the breakdown of the substrate-hydroxyl ion complex.

With the exception of triethanolammonium ion, the amine cations now investigated have given values of  $k_3/k_{-1}$  which, when plotted against  $K_a$  (a Brønsted plot), fall fairly well on a straight line with a slope of approximately 1. A few experiments with butylamine and pyrrolidine at a pH value where they are present almost completely as cations have shown that these species have only a very small catalytic activity. For butylamine, with a  $pK_a$  value of approximately 10.8 in the medium used in this investigation,  $k_3/k_{-1} < 2$ , and for pyrrolidine, with  $pK_a$  of approximately 11.4,  $k_3/k_{-1} < 1$ . That triethanolammonium ion with  $pK_a = 8.02$  has no observable catalytic effect certainly depends upon steric difficulties to donate a proton to the anilide nitrogen. Comparison of molecular models of triethanolammonium ion and the cation of tris(hydroxymethyl)aminomethane ( $pK_a = 8.25$ ) clearly shows that the amino hydrogens in the latter are much more approachable for the anilide nitrogen than the amino hydrogen of the former. Some experiments with tris(hydroxymethyl)aminomethane have also shown that in the breakdown of the substrate-hydroxyl ion complex catalysed by its cation,  $k_3/k_{-1}$  has a value of approximately 50 l mole<sup>-1</sup>. When compared with the values in Table 1 this value is somewhat smaller than would be expected from its  $pK_a$  value which might indicate some steric hindrance in the delivering of a proton to the anilide nitrogen.

The previously determined values of  $k_3/k_{-1}$  for phosphate species and hydrogen carbonate ions are higher than for amines with corresponding  $K_a$  values. Brønsted relationships are, however, only expected to hold for acids of the same type and it cannot be concluded from the values of  $k_3/k_{-1}$  that phosphate species and hydrogen carbonate ions act in an other way than acids of the amine cation type. Pyrazole, which could be expected to accept and donate a proton in a concerted mechanism, has in some experiments been shown to have a very small catalytic activity.

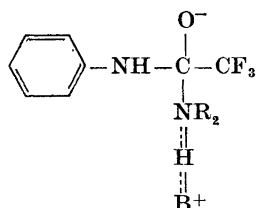
The profiles in Figs. 1 and 2 more or less indicate a change in the rate determining step around the limiting value of  $k_{obs}$ . The concept of general acid catalysis of the breakdown of the substrate-hydroxyl ion complex seems to be unique but is strongly supported by the good agreement between this interpretation and the experimental values. Catalysis of the breakdown of the substrate-hydroxyl ion complex will be more important and easier to detect the smaller the quotient  $k_3/k_{-1}$  is. Some as yet unpublished hydrolysis data of anilides with substituents in the acyclic part of the molecule having no, or only small, electronattracting power show that this kind of general acid catalysis is not restricted to compounds containing strongly electron-attracting substituents.

*Catalysis by bases.* In the concentration range given in Figs. 1–2 and at least at the small and medium concentrations given in Fig. 4, the amine bases give aniline in a reaction that seems to be first order both in unionised substrate and in amine base. Amine catalysed formation of hydrolytic products has been thoroughly investigated in some cases of ester hydrolysis,<sup>7,9–18</sup> but apart from reactions of acylimidazoles and related compounds<sup>7,19</sup> only little has been reported about amine catalysed product formation in the case of amides.

From the investigations of ester hydrolysis it is apparent that esters with a good leaving group in the alcoholic part, such as phenyl and thiol esters, are sensitive to nucleophilic catalysis (attack on carbonyl carbon) by amine bases with the intermediate formation of the acylated amine.<sup>7,9,11,13</sup> These reactions are sometimes catalysed by a second molecule of amine or by an other base acting as a general base (attack on hydrogen).<sup>7,10,15,18</sup> Esters activated in the acyclic part but with a poorer leaving group in the alcoholic part, *e.g.* ethyl esters, are supposed to be subject to general base catalysis with a water molecule acting as the nucleophile when the catalysing amine is a weak base, *e.g.* imidazole. When the amine is a stronger base, at least part of the catalysis is a nucleophilic reaction.<sup>11,13</sup> Even when the amine acts as a nucleophile the reaction can be subject to general base catalysis, *e.g.* by hydroxyl ions.<sup>13</sup> These acyl-activated esters are, however, mostly less sensitive to amine catalysed hydrolysis than phenyl and thiol esters are.

In the present investigation, no experiments have been made to differentiate between nucleophilic and general basic action of amine bases. Direct confirmation of nucleophilic catalysis by following the concentration of the amide possibly formed or by its characterisation might be difficult when, as often seems to be the case, the amide is hydrolysed much more rapidly than the anilide.

Also in the case of imidazole, which, of the amines investigated, has by far the smallest value of  $k_4$ , the effect of the base on the rate of aniline formation at the smallest pH value is large enough to convince that it is not solely a medium effect. The comparatively small value of  $k_4$  for imidazole can be taken as an indication of general basic rather than nucleophilic action. In nucleophilic reactions, *e.g.* in the catalytic hydrolysis of *p*-nitrophenyl acetate, imidazole is a more effective catalyst than ammonia,<sup>9</sup> whereas in the breakdown of ethyl halogenoacetates<sup>11</sup> ammonia is much more effective than imidazole which is supposed to act as a general base in this case. A linear relationship between base strength and catalytic efficiency is expected to hold much better for general basic catalysis than for nucleophilic catalysis. The relation between values of  $k_4$  and base strength alone does not, however, with any certainty differentiate between nucleophilic and general basic action. When it can be shown that the rate equation contains a term that is second order in amine, a mechanism implying nucleophilic attack of one mole of amine ( $\text{NHR}_2$ ) with a second mole of amine acting as general base ( $\text{B}$ ) is strongly supported. An analogous case is when the reaction is first order in amine and first order in an other base ( $\text{B}$ ), *e.g.* hydroxyl ions. For such reactions an activated complex of the form



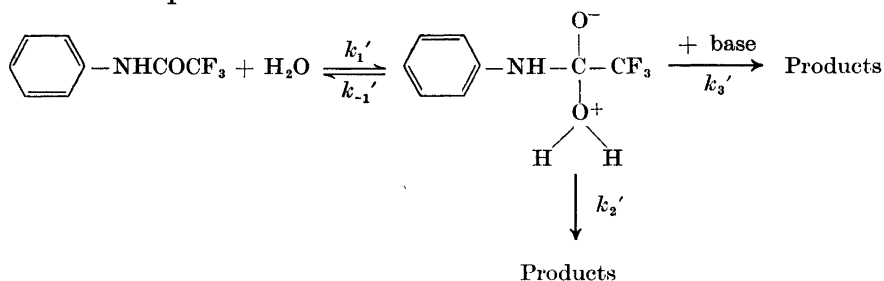


can be written. Amines without an ionisable hydrogen, *e.g.* triethanolamine, cannot, when they function as nucleophiles, be subject to this sort of general base catalysis. In the concentration ranges shown in Figs. 1 and 2, no significant dependence on amine concentration higher than first order is observed. Even though the existence of such a dependence can be said to demonstrate nucleophilic attack of the amine, the lack of it does not disprove this mode of action. A subsequent paper will deal with the kinetics of the reaction of trifluoroacetanilide with hydroxylamine and hydrazine, where the rate equation does contain terms second order in the concentration of amine base.

From Fig. 4 it is apparent that the increase in rate is retarded at high concentrations of the triethanolamine system in comparison to the rate increase at smaller concentrations. If triethanolamine acts as a general base and water is the nucleophile there might be at least two reasons for this retardation.

1. The stoichiometric concentration of water decreases perceptibly at high concentrations of this buffer system with its rather high molecular weight. Water certainly is also tied up by the triethanolamine molecules with their three hydroxyl groups, making the concentration of »free» water smaller than the stoichiometric one.

2. If the simplified reaction scheme



is applicable where the zwitter-ionic intermediate is in a steady state concentration, the experimental values will deviate from the straight lines in Fig. 4 as soon as  $k_3'[\text{base}]$  is not negligible compared to  $k_{-1}'$ , and the deviations will be greater the larger the value of  $k_{\text{obs}}$  is. Fig. 4 indicates that the value of  $k_{\text{obs}}$  at the highest concentration of triethanolamine at the ratio 4 of  $[\text{base}]/[\text{acid}]$  approaches a limiting value. This indication is more pronounced in some experiments at the still higher concentrations given below.

Total molar concentration of triethanolamine	$[\text{base}]/[\text{acid}] = 4$	$k_{\text{obs}} \times 10^3 \text{ min}^{-1}$ $[\text{base}]/[\text{acid}] = 1$
1.25	23.8	16.9
1.50	26.1	19.2
1.75	28.3	21.3
2.00	29.0	22.7

The decrease in water concentration caused by increased triethanolamine concentration decreases the rate of formation of the zwitter-ionic intermediate and what the limiting value of  $k_{\text{obs}}$  would be at constant water concentration according to the mechanism written above cannot be determined with any certainty. If this limiting value of  $k_{\text{obs}}$  were known, the parameters  $k_1'$ ,  $k_2'/k_{-1}'$  and  $k_3'/k_{-1}'$  could be calculated because the value of  $k_{\text{obs}}$  for the water-catalysed reaction when no catalysing base is present is known ( $= 6.2 \times 10^{-7} \text{ min}^{-1}$ ).<sup>1</sup> At all events, if the reaction scheme written above represents the main path, the value of  $k_2'/k_{-1}'$  will be very small (of the magnitude  $10^{-5}$ ) and deviations from a straight line will only be observed with effective catalysts in large concentrations. General basic catalysis according to the reaction mechanism written would be strongly supported if a catalyst could be found which gives a limiting value of  $k_{\text{obs}}$  or which at least causes  $k_{\text{obs}}$  to approach such a value at a rather small concentration of catalyst. Assuming that triethanolamine acts as a general base, such a catalyst must at the same time be approximately as weak a base as triethanolamine and have a value of  $k_4$  considerably larger than that for this compound. The previously mentioned tris(hydroxymethyl)aminomethane is a weak base ( $\text{p}K_{\text{a}} = 8.25$ ) but its  $k_4$  value (approximately  $23 \times 10^{-3} \text{ l mole}^{-1} \text{ min}^{-1}$ ) is smaller than that for triethanolamine and the deviations shown by the latter have not been observed in experiments performed with large concentrations of this compound.

Even though the deviation of the  $k_{\text{obs}}$ -values from the straight lines in Fig. 4 support general basic rather than nucleophilic catalysis of triethanolamine, they do not definitely prove it. With triethanolamine as nucleophile and water promoting formation of products from the activated complex, experimental values like those in Fig. 4 might also be obtained. Still another mechanistic pathway is that a previously formed complex between water and triethanolamine is the nucleophile; the experimental values might then deviate from the straight lines in Fig. 4 because at high concentrations only part of the triethanolamine is present as this active complex. Such a mechanism can be characterised as nucleophilic catalysis by water and general basic catalysis by triethanolamine. Molecular models indicate that sterically it should be much easier for triethanolamine to attack a water-hydrogen than a carbonyl-carbon.

*Some other considerations regarding the pathway to products.* The anilide ion ( $\text{C}_6\text{H}_5\text{NH}^-$ ) is certainly a very poor leaving group and rate data obtained in this and in the preceding paper strongly suggest that attack on the anilide nitrogen by general acids enhance the breakdown of the substrate-hydroxyl ion complex. Irrespective of the mode of action of amine catalysts, such protonation of the anilide nitrogen might be expected to enhance aniline formation also in the case of catalysis by free amines. In no case, however, has a significant kinetic dependence on the concentration of acids been found for the amine reaction. With ammonia, monoethanolamine, and triethanolamine, which have cations with small or no catalytic activity, experiments have been performed in the presence of rather large concentrations of hydrogen carbonate or imidazolium ions. These ions, which are very effective in catalysing breakdown of the substrate-hydroxyl ion complex seem, however, not to affect the

rate of the amine reaction. There might be more than one reason for the failure to demonstrate general acid catalysis in these reactions. Both the absence of a negative net charge and the presence of a more or less bulky amine molecule in the activated complex certainly make it much less accessible for catalysis by acids than the substrate-hydroxyl ion complex.

In the series imidazole, morpholine, ammonia, and monoethanolamine, the value of  $k_4$  increases with increasing base strength. Triethanolamine, however, has a much higher value of  $k_4$  than would be expected from its base strength. Whereas the bulky groups completely inhibit the activity of the cation as a general acid catalyst the same groups seem to assist in its action as a basic catalyst. It should be mentioned that tris(hydroxymethyl)amino-methane, which, like triethanolamine, is more effective in the breakdown of trifluoroacetanilide than would be expected from its base strength, catalyses the hydrolysis of ethyl dichloroacetate<sup>11</sup> and of *p*-nitrophenyl acetate.<sup>9</sup> The primarily formed reaction product in the former case is the amide but in the latter case, it seems to be an ester, *i.e.* one of the oxygen atoms is acting as a nucleophile. It is tempting to assume that this compound and triethanolamine act poly-functionally in the breakdown of trifluoroacetanilide.

*Acknowledgements.* We wish to thank Dr. Allan Ågren for his interest in this work, and to acknowledge the skilful technical assistance given by Miss Susi Burkhart.

#### REFERENCES

1. Eriksson, S. O. and Holst, C. *Acta Chem. Scand.* **20** (1966) 1892.
2. Jencks, W. P. and Gilchrist, M. J. *Am. Chem. Soc.* **86** (1964) 5616.
3. Schowen, R. L., Jayaraman, H. and Kershner, L. *J. Am. Chem. Soc.* **88** (1966) 3373.
4. Schowen, R. L., Jayaraman, H., Kershner, L. and Zuorick, G. W. *J. Am. Chem. Soc.* **88** (1966) 4008.
5. Cunningham, B. A. and Schmir, G. L. *J. Am. Chem. Soc.* **88** (1966) 551.
6. Cunningham, B. A. and Schmir, G. L. *J. Am. Chem. Soc.* **89** (1967) 917.
7. Bender, M. L. *Chem. Rev.* **60** (1960) 53.
8. Jencks, W. P. In Cohen, S. G., Streitwieser, Jr. and Taft, R. W. *Progress in Physical Organic Chemistry*, Interscience, New York 1964, Vol. 2.
9. Jencks, W. P. and Carriuolo, J. *J. Am. Chem. Soc.* **82** (1960) 1778.
10. Bruice, T. C. and Mayahi, M. F. *J. Am. Chem. Soc.* **82** (1960) 3067.
11. Jencks, W. P. and Carriuolo, J. *J. Am. Chem. Soc.* **83** (1961) 1743.
12. Bruice, T. C. and Benkovic, S. J. *J. Am. Chem. Soc.* **86** (1964) 418.
13. Kirsch, J. F. and Jencks, W. P. *J. Am. Chem. Soc.* **86** (1964) 833, 837.
14. Johnson, S. L. *J. Am. Chem. Soc.* **86** (1964) 3819.
15. Bruice, T. C. and Fedor, L. R. *J. Am. Chem. Soc.* **86** (1964) 4886.
16. Bruice, T. C. and Willis, R. G. *J. Am. Chem. Soc.* **87** (1965) 531.
17. Fedor, L. R. and Bruice, T. C. *J. Am. Chem. Soc.* **87** (1965) 4138.
18. Jencks, W. P. and Gilchrist, M. J. *Am. Chem. Soc.* **88** (1966) 104.
19. Jencks, W. P. and Carriuolo, J. *J. Biol. Chem.* **234** (1959) 1272, 1280.

Received April 5, 1967.