

Hydrolysis of Anilides

V. Alkaline Hydrolysis of the Trimethylammonioacetanilide and Trimethylammonioacet-*N*-methylanilide Cations and General Acid-Catalysed Alkaline Hydrolysis and Aminolysis of the Former. Kinetic Evidence for the Existence of More Than One Intermediate in the Hydrogen Carbonate Ion Catalysed Alkaline Hydrolysis

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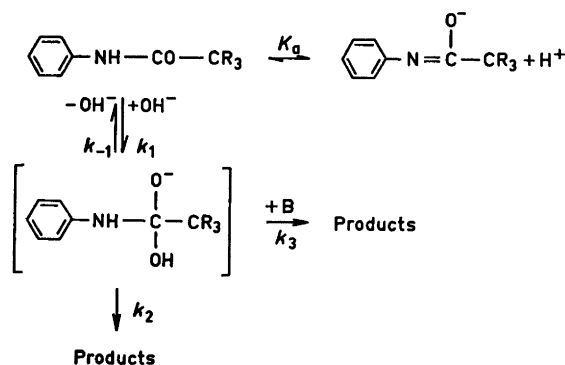
The so-called pH-rate profiles for the alkaline hydrolysis of the trimethylammonioacetanilide cation ($C_6H_5NHCOCH_2N^+(CH_3)_3=I$) and of the trimethylammonioacet-*N*-methylanilide cation ($C_6H_5N(CH_3)COCH_2N^+(CH_3)_3=II$) are given at 25°C and two different ionic strengths. The profiles explicitly indicate that I is an acid but not II. By photometric determination, the stoichiometric pK_a of I was found to have values of 11.95 and 12.32 at ionic strengths 1 and 3, resp., at 25°C. The velocities of the alkaline hydrolysis of I is in accordance with formation of a tetrahedral addition intermediate (the substrate-hydroxyl ion complex), which then breaks down to products either spontaneously or through the catalytic effect of hydroxyl ions (reaction scheme in the introduction). This mechanism is the most likely one also for II, even though it is not kinetically demonstrated in this case. The ratio of the rate constants for the uncatalysed breakdown to products and for return of the substrate-hydroxyl ion complex to reactants (k_2/k_{-1}) is determined for I and found to have the values of 0.0030 and 0.0026 at the ionic strengths 1 and 3, resp. This very small value of the ratio is interpreted as a result of chiefly steric effects.

Breakdown of the substrate-hydroxyl ion complex of I is much more sensitive to acid catalysis than to catalysis by hydroxyl ions, and at constant pH large concentrations of such catalysts can give limiting values of the pseudo first-order rate constant, *i.e.* formation of the substrate-hydroxyl ion complex becomes the rate determining step. These limiting rates are more than 300 times larger than the uncatalysed ones at the same pH. The catalytic effect of imidazolium ions, morpholinium ions, and the carbonic acid system is investigated. The catalytic parameter k_3/k_{-1} is, for the first two ions, pH independent but not for the hydrogen carbonate ion. The catalytic behaviour of the hydrogen carbonate ion over a broad pH range can be rationalised by assuming formation of a new intermediate through attack

of HCO_3^- on the substrate-hydroxyl ion complex and involvement of this intermediate in general base catalysed reactions, or as acid, in a protolytic equilibrium (see reaction schemes in the discussion).

The triethanolammonium cation has no catalytic effect, whereas the free base splits the amidic bond. The rate constant for this reaction is determined.

Brief surveys over the hydrolysis and aminolysis of anilides and related compounds were given in the previous papers in this series.¹⁻⁴ Trifluoro- and trichloroacetanilide were shown² to be acids with the stoichiometric $\text{p}K_a$ values 9.51 and 9.98 in a medium of 9.6 % (v/v) ethanol and ionic strength 1. The pH-rate profiles of these two anilides as well as the catalytic effect of weak acids indicated the existence of an intermediate formed between the unionised substrate and hydroxyl ions (the substrate-hydroxyl ion complex). From this intermediate, products are formed in a spontaneous reaction and in reactions catalysed by hydroxyl ions or by weak acids, principally according to the following scheme



Scheme 1.

where B denotes hydroxyl ion or weak acids. From this scheme the following equation could be derived

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

k_{obs} being the pseudo first-order rate constant at constant pH. With trifluoro- and trichloroacetanilide, which have strongly electron-withdrawing substituents in the acyclic part of the molecule, $[\text{H}^+]$ becomes negligible in comparison to K_a in strongly alkaline solutions, and when $k_{3,\text{OH}^-} [\text{OH}^-]$ in such solutions becomes much larger than $(k_{-1} + k_2)$, the value of k_{obs} becomes pH independent. With the two compounds mentioned, this situation was realised at approximately $[\text{OH}^-] = 0.1$. From the pH independent value of k_{obs} , the value of k_1 was directly obtained. The value of k_1 could also be calculated from the

limiting values of k_{obs} obtained at the larger concentrations of weak acid in experiments at constant pH and varying concentrations of acid catalyst. Generally, the value of k_3/k_{-1} increases with the increasing acidic strength of the catalyst, and for acids of the ammonium cation type the values of $\log(k_3/k_{-1})$ for trifluoroacetanilide were found to be a linear function of $\log K_a$ for the catalysts, the line having a slope of 0.9. At pH values where the hydroxyl ion catalysed breakdown of the intermediate is negligible, the limiting values of k_{obs} were, for both trifluoro- and trichloroacetanilide, 40 times larger than the uncatalysed ones, *i.e.* $k_2/k_{-1} = 0.025$.

Studies of the aminolysis of trifluoroacetanilide^{3,4} have shown that this reaction for some amines is merely first-order in amine, for others (amines with an unshared electron pair on the atom next to the nucleophilic centre) both first and second order in amine. Triethanolamine was shown to be an unexpectedly effective catalyst while its conjugate acid was without detectable catalytic effect on the breakdown of the substrate-hydroxyl ion complex. It is therefore easier to determine the rate constant for this base [k_4 in eqn. (4)] than for bases which also have a catalytically active conjugate acid.

In order to get more information about the general applicability of the reaction scheme referred to and about the variation of rate parameters with the nature of the substituents, anilides with other steric and electronic properties have been investigated or are under investigation in this laboratory. A report is made in this paper on the kinetics and mechanisms of two highly hindered quaternary compounds.

MATERIALS AND METHODS

Materials. Trimethylammonioacetanilide bromide was prepared by alkylation of dimethylaminoacetanilide with methyl bromide in acetone:^{5,6} m.p. 209–210°C (determined in an electrically heated metal block using a calibrated Anschütz thermometer). Ref. 7 gives m.p. 215°C. Equiv. weight (determined by argentometric titration using 4,5-dichlorofluorescein as indicator) 273.8, calc. 273.2. The dimethylaminoacetanilide was obtained by reacting 1-chloroacetanilide with dimethylamine (as a 33 % aqueous solution) in ethanol and recrystallising the chloride. 1-Chloroacetanilide was prepared from chloroacetylchloride and aniline.⁸ Trimethylammonioacet-*N*-methylanilide iodide was prepared in a corresponding manner using *N*-methylaniline instead of aniline and methyl iodide instead of methyl bromide. After recrystallisation from ethanol-ether a pale yellow product was obtained: m.p. 144–147°C. Equiv. weight (argentometrically) 336.5, calc. 334.2.

All other chemicals used were of reagent grade or the commercially best available grade. In order to remove traces of protolytic impurities from the potassium chloride (reagent grade) it was recrystallised from 0.1 M hydrochloric acid.

Hydrolysis experiments. The kinetic experiments were performed at $25 \pm 0.05^\circ\text{C}$ in an aqueous medium of constant ionic strength, obtained by addition of KCl. The pH-stat method previously described² was used in experiments where hydrochloric acid or sodium hydroxide solution had to be added to keep the pH constant, *e.g.* in experiments with pure alkaline hydrolysis at hydroxyl ion concentrations smaller than about 0.01 M and in experiments with hydrogen carbonate catalysis at low pH values. At the smallest pH values used in the experiments with the carbonic acid system, CO_2 was used instead of hydrochloric acid to restore the pH when it slowly rose during an experiment. For the strongly alkaline solutions and for most solutions where buffers were used as catalysts, the pH remained almost constant for a long time and the solutions to be studied could therefore be kept in volumetric flasks in a thermostated water-bath.

In the case of I, most of the withdrawn samples were analysed by the previously described aniline method (diazotisation and coupling with *N*-(1-naphthyl)ethylenediamine).² Using this method of analysis, the hydrolyses were mostly followed as far as decomposition of only a small part of the substrate — in an extreme case to less than 0.01 % hydrolysis. In some experiments at high hydroxyl ion concentrations, remaining anilide was determined at 243 nm after acidification (the UV-method).² Using this method of analysis, the experiments were mostly followed for several half-lives. In the case of II, the rate of hydrolysis was followed by measuring the increase in absorbance at 287 nm in alkaline or neutral solution. At this wave-length, *N*-methylaniline has a maximum absorbance whereas the anilide does not absorb. At the smaller hydroxyl ion concentrations, samples were withdrawn at appropriate intervals and the absorbance measured at 287 nm. At the highest hydroxyl ion concentrations, one of the following two assay methods were used: the solution to be examined was placed immediately after being prepared in a 1 cm cell in a thermostated cell-compartment of a Beckman spectrophotometer model DK-2 and the increase in absorbance at 287 nm was recorded as a function of time. Alternatively, samples were withdrawn from a solution in a volumetric flask and added to a solution of phosphoric or citric acid, thus giving a buffer where hydrolysis takes place very slowly. The absorbance of these solutions was then measured at 287 nm. In each hydrolysis experiment, at least six samples were withdrawn and analysed and k_{obs} was evaluated graphically as previously described.³ For all reported values of k_{obs} , the experimental values accommodated a straight line very well.

Determination of acidity constants. The relation at 25°C between measured pH values and $[\text{H}^+]$ and $[\text{OH}^-]$ (molar concentrations of hydrogen and hydroxyl ions) in 1 M and 3 M KCl was determined as described previously for a medium consisting of 9.6 % ethanol.² From the intersection of the lines obtained when $\log[\text{H}^+]$ and $\log[\text{OH}^-]$ were plotted against pH, the stoichiometric $\text{p}K_w$ values of 13.78 ($\mu=1$) and 14.13 ($\mu=3$) were obtained. From data given in a paper by Harned and Hamer,⁹ $\text{p}K_w$ can be calculated to have the values 13.78 and 14.06 at $\mu=1$ and $\mu=3$, respectively.

Using a Beckman DK-2 spectrophotometer with a thermostated cell-compartment, the UV absorbances were recorded at 25°C and various hydroxyl ion concentrations for solutions of the two anilides. Compound II absorbed only at wavelengths smaller than about 240 nm and did not reveal any change in absorption characteristics with concentration of hydroxyl ions in the range examined (up to about 0.2 M). These spectra were not run on the iodide of II, as the iodide ion itself absorbs in UV. This ion was therefore removed as AgI from an aqueous solution of the iodide of II, and the excess of silver ions was then precipitated as AgCl. Aliquots of the stock solution thus obtained were added to sodium hydroxide solutions of different concentrations and the UV spectra recorded.

In Fig. 1, absorbance as a function of wavelength is given for I at different concentrations of hydroxyl ions at the ionic strength 1. In Fig. 2, the quotient C/A , where C = total concentration of anilide and A = absorbance in 1 cm cell at 242.5 nm, is plotted against $[\text{H}^+](C \cdot \epsilon_a - A)/A$. From the slope, $-1/(K_a \cdot \epsilon_b)$, of this line, K_a is obtained. ϵ_a and ϵ_b denote molar absorptivity of the acidic and basic forms and are obtained from acid (or neutral) and, at zero time, strongly alkaline solutions, resp. ϵ_b is also obtained from the ordinate intercept. The value of K_a at the ionic strength 3 was determined in the same way and the line from which K_a is calculated is given in Fig. 2.

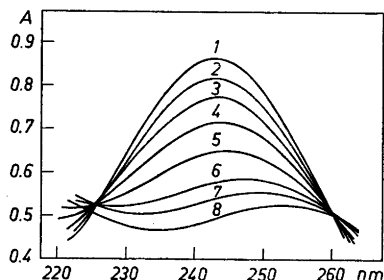


Fig. 1. Absorption curves in 1 cm cell of 8.2×10^{-4} M solution of I at $\mu=1$ and different $[\text{OH}^-]$. 1) 10^{-7} and $10^{-11.78}$, 2) 0.0019, 3) 0.0047, 4) 0.0100, 5) 0.0200, 6) 0.0500, 7) 0.100, 8) 0.500.

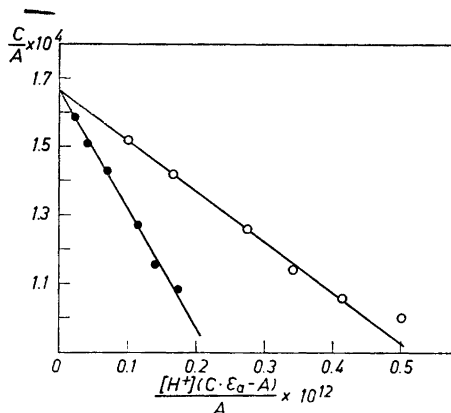


Fig. 2. Plot of C/A (C = total concentration of I, A = absorption at 242.5 nm in 1 cm cell) against $[H^+](C \cdot \epsilon_a - A)/A$ for evaluating K_a at $\mu=1$ (O) and $\mu=3$ (●).

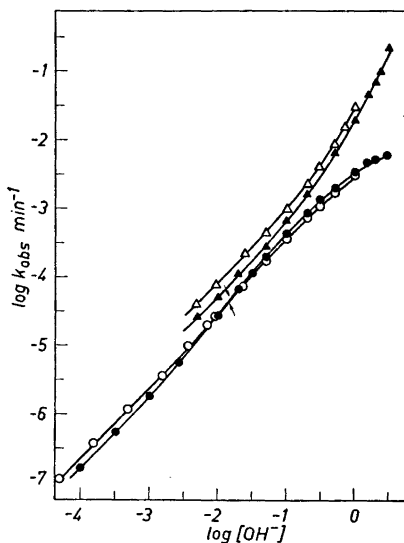


Fig. 3. Plot of $\log k_{obs}$ against $\log [OH^-]$. The lines are calculated from eqn. (1) and parameter values in Table 1. Experimentally determined values for I at $\mu=1$ (O), at $\mu=3$ (●) and for II at $\mu=1$ (Δ) and at $\mu=3.2$ (\blacktriangle). The arrows denote the values of $[OH^-]$ corresponding to the stoichiometric pK_a value of I at the two ionic strengths.

The determination of the stoichiometric K_{a,HCO_3^-} and K_a values for the three amines used as catalysts in this investigation were performed at 25°C and ionic strength 1, and for HCO_3^- and imidazole also at ionic strength 3, as previously described for these species in a medium containing ethanol.^{2,3}

RESULTS

Hydroxyl ion catalysed hydrolysis of I. In Fig. 3, the so-called pH-rate profile for the alkaline hydrolysis is given at two ionic strengths. Up to a hydroxyl ion concentration of 1 M, the profiles are almost straight lines of slope 1. However, a more complicated mechanism than simple first-order hydroxyl ion catalysis must be operating in the more alkaline solutions, since the substrate is an acid with pK_a around 12 and it is not likely that the base would be hydrolysed at the same rate as the acid. A more careful inspection of the two profiles of I in Fig. 3 shows that they are straight lines of slope 1 only in the region where the hydroxyl ion concentrations are smaller than 10^{-3} M. At hydroxyl ion concentrations larger than 10^{-3} M there is first a region where k_{obs} increases somewhat more rapidly than the hydroxyl ion concentration and then, at the highest hydroxyl ion concentrations, the reverse is true.

Table 1. Dissociation constants and rate parameters experimentally determined, and used in the construction of Fig. 3. Stoichiometric $pK_w=13.78$ ($\mu=1$) and 14.13 ($\mu=3$).

Compound	μ	pK_a	k_1 $M^{-1}min^{-1}$	k_2/k_{-1}	$k_{3,OH^-}/k_{-1}$ M^{-1}	$\frac{k_1k_2}{k_{-1}+k_2}$ $M^{-1}min^{-1}$	$k_{3,OH^-}/k_2$ M^{-1}
I	1	11.95	0.74	0.0030	0.37	0.0022	123
I	3	12.32	0.62	0.0026	0.53	0.0016	204
II	1	—	—	—	—	0.0083	2.5
II	3.2	—	—	—	—	0.0051	3

These facts agree with the mechanism already mentioned leading to eqn. (1). In the case of trifluoro- and trichloroacetanilide, a limiting value of k_{obs} was obtained at high hydroxyl ion concentrations and from that value k_1 could be directly obtained. The two profiles of I in Fig. 3 do not reach a limiting value of k_{obs} even though it is obvious that the profile at the larger ionic strength is approaching such a value. Evaluating k_1 from profiles like those in Fig. 3 is of course more difficult and the uncertainty in the numerical value obtained is greater than when it can be calculated from limiting rates. The experiments with imidazolium ion and especially with hydrogen carbonate ion catalysis at small pH values give, however, at constant pH profiles which considerably facilitate the estimation of the value of k_1 . Using values of k_1 which deviate at the most by 15 % from those given in Table 1 and corresponding variations in k_2/k_{-1} and k_3/k_{-1} , a set of rate parameters were tried in the calculation of the profiles. The parameters finally chosen and used in the calculation of the profiles are those given in Table 1. The deviation of the experimental values from the calculated ones is generally very small and always less than 10 %. When a value of k_1 to be used in all the calculations is fixed, k_2/k_{-1} is directly obtained from the values of k_{obs} at the smallest hydroxyl ion concentrations, where the rate is directly proportional to $[OH^-]$, and thus $k_{3,OH^-} [OH^-]$ is negligible compared to k_2 . That value of $k_{3,OH^-}/k_{-1}$ is then used which, as a whole, gives the best agreement between the experimental and calculated values at the higher hydroxyl ion concentrations. Values of $k_{3,OH^-}/k_{-1}$ differing from those in Table 1 by 10 % definitely give less good fit to the experimental values.

The two profiles in Fig. 3 intersect at $[OH^-]=10^{-2}$. The differences between the parameter values at the two different ionic strengths are quite reasonable. Thus k_1 is expected to decrease with increasing ionic strength (reaction between species with different charges) and k_3 is expected to increase with increasing ionic strength as the negative charge of the substrate-hydroxyl ion complex is certainly closer to the reaction centre than is the positive charge of the quaternary nitrogen (k_{-1} is assumed to be essentially constant). At the largest hydroxyl ion concentrations, the ionic medium no longer consists mainly of KCl and new medium effects might be expected to arise. This is, however, not very apparent from the profiles in Fig. 3. In cases with high hydroxyl ion concentrations, both NaOH and KOH were used in the experiments. The

k_{obs} values obtained do, however, solely depend upon the concentration of hydroxyl ions.

Hydroxyl ion catalysed hydrolysis of II. The profiles of II in Fig. 3 refer to the ionic strengths 1 and 3.2. These profiles show no tendency of approaching a limiting value of k_{obs} at high hydroxyl ion concentrations and therefore give no indications of acidic properties for this anilide. For pure hydroxyl ion catalysis of nonprotolytic compounds, eqn. (1) can be written in the form

$$k_{\text{obs}} = k_1 [\text{OH}^-] \frac{k_2 + k_{3,\text{OH}^-}[\text{OH}^-]}{k_{-1} + k_2 + k_{3,\text{OH}^-}[\text{OH}^-]} \quad (2)$$

When eqn. (2) is valid and it is possible to get such hydroxyl ion concentrations that $k_{3,\text{OH}^-}[\text{OH}^-]$ becomes much larger than $(k_{-1} + k_2)$, it is apparent that the profile at such high hydroxyl ion concentrations will approach a straight line of slope 1, enabling k_1 to be obtained with good accuracy from such a line. The profiles, however, show that this method for obtaining k_1 cannot be used in the case in question. Some preliminary experiments with hydrogen carbonate ion catalysis have shown that the catalytic effect here is much smaller than it is for I and the value of k_{obs} at constant pH does not seem to tend to a limit, hence also this method fails to give the value of k_1 . The slope of the two curves in Fig. 3 is 1 at the smallest hydroxyl ion concentrations and then increases continually with increasing concentration of hydroxyl ions. This shows that the term $k_{3,\text{OH}^-}[\text{OH}^-]$ is negligible compared to k_2 at the smallest hydroxyl ion concentrations and indicates that it is negligible compared to k_{-1} at all hydroxyl ion concentrations in Fig. 3. If this last premise is true, eqn. (2) can be written in the form

$$k_{\text{obs}} = \frac{k_1 k_2}{k_{-1} + k_2} ([\text{OH}^-] + \frac{k_{3,\text{OH}^-}}{k_2} [\text{OH}^-]^2) \quad (3)$$

This equation has been used in the calculation of the two profiles, and the parameter values used are given in Table 1. Eqn. (3) is of the same form as the eqn. $k_{\text{obs}} = k_1[\text{OH}^-] + k_{\text{II}}[\text{OH}^-]^2$ which was found to be valid by Biechler and Taft¹⁰ and by Bruylant and coworkers^{11,12} in the alkaline hydrolysis of some *N*-methylanilides and some amides, respectively. The rate of hydrolysis of II and of I seems to be influenced in the same way by changes in the ionic

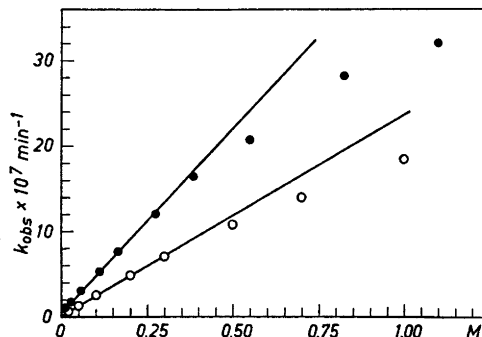


Fig. 4. Plot of k_{obs} against total concentration of triethanolamine. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 2. Catalysis at ratio [base]:[acid]=1 ($[\text{OH}^-]=10^{-5.70}$) O, at ratio 10 ($[\text{OH}^-]=10^{-4.70}$) ●.

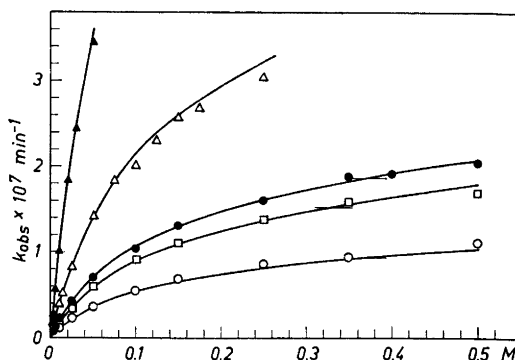


Fig. 5. Plot of k_{obs} against concentration of imidazolium ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 2. The bars denote the values of $k_1[\text{OH}^-]$ [=the limiting values of k_{obs} calculated from eqn. (1)].

	$-\log [\text{OH}^-]$	[acid]:[base] for imidazole	μ
○	6.90	2	1
□	6.61	1	3
●	6.60	1	1
△	6.30	0.5	1
▲	5.90	0.2	1

strength. Sodium hydroxide solution was used as the alkalisng agent in all these experiments.

The reaction of triethanolamine with I. In Fig. 4, results at two different pH values are given. It is apparent that only the basic form of triethanolamine is active and that the relationship between rate and concentration of triethanolamine deviates from a straight line at high triethanolamine concentrations, *i.e.* the liberation of aniline from I in the presence of triethanolamine follows the same pattern as from trifluoroacetanilide.³ For the amines investigated in the present study, the following equation was used to calculate rates

$$k_{\text{obs}} = \frac{k_1 K_w}{K_a + [\text{H}^+]} \times \frac{k_2 + \sum k_{3,i} [\text{B}_i]}{k_{-1} + k_2 + \sum k_{3,i} [\text{B}_i]} + \frac{k_4 [\text{H}^+] [\text{N}]}{K_a + [\text{H}^+]} \quad (4)$$

where [N] is the concentration of amine base. When k_3 is zero, as it is for the triethanolammonium ion, k_4 is obtained from the slope of the straight lines at small triethanolamine concentrations.

Breakdown of I in imidazole and morpholine buffers. In Figs. 5 and 6, the profiles of k_{obs} against catalyst concentration are presented for imidazole buffers at 9 different pH values. One of the profiles in Fig. 5 refers to the ionic strength 3, all the others to the ionic strength 1. In Fig. 7, corresponding profiles for morpholine buffers are given for 3 different pH values and ionic strength 1. The ratio [acid]:[base] of the catalyst varies for imidazole from 2 to 0.01 and for morpholine from 10 to 0.1. All the profiles are calculated by eqn. (4) and the parameter values given in Tables 1 and 2.

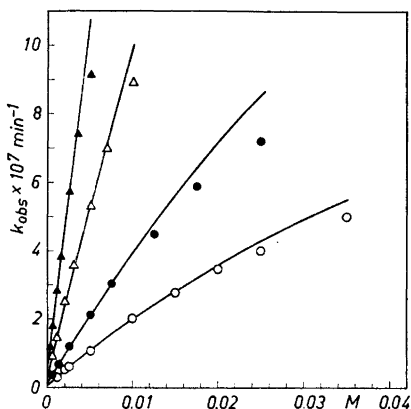


Fig. 6. Plot of k_{obs} against concentration of imidazolium ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 2. $\mu=1$ in all experiments.

	$-\log [\text{OH}^-]$	[acid]:[base] for imidazole
○	5.60	0.1
●	5.30	0.05
△	4.90	0.02
▲	4.60	0.01

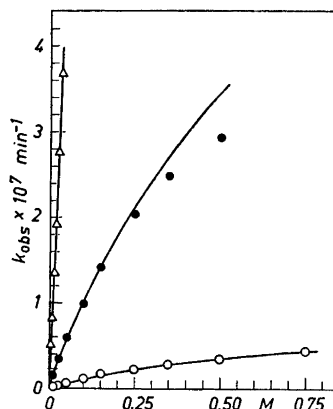


Fig. 7. Plot of k_{obs} against concentration of morpholinium ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 2. The bar on the ordinate denotes the uncatalysed value of k_{obs} at the largest concentration of hydroxyl ions. $\mu=1$ in all experiments.

	$-\log [\text{OH}^-]$	[acid]:[base] for morpholine
○	5.99	10
●	4.99	1
△	3.99	0.1

The relation between the k_4 values for triethanolaminolysis of trifluoroacetanilide³ and I is $0.039/(48 \times 10^{-7})=8100$. Assuming the same quotients for the k_4 values in the imidazole and morpholine reactions and using the k_4 values for trifluoroacetanilide given in a previous paper,³ the values $k_{4,\text{imidazole}}=1.7 \times 10^{-7}$ and $k_{4,\text{morpholine}}=12 \times 10^{-7}$ are obtained for I. The profiles at the two largest ratios [acid]:[base] in Fig. 5 indicate the presence of a k_4 -term in the rate expression and also enable the constant to be roughly estimated. The value given in Table 2 and used in the final calculations is somewhat smaller than 1.7×10^{-7} but of that order of magnitude. At the

Table 2. Dissociation constants and rate parameters experimentally determined, and used in the construction of Figs. 4–7.

Catalytic compound	μ	$\text{p}K_{\text{a}}$	k_3/k_{-1} M^{-1}	$k_4 \times 10^7$ $\text{M}^{-1}\text{min}^{-1}$
Triethanolamine	1	8.08	0	48
Imidazole	1	7.18	11	1.0
»	3	7.52	11	1.0
Morpholine	1	8.79	1.4	7

largest ratios of [acid]:[base] in Fig. 5 and the largest catalyst concentration, the k_4 -term contributes at the most to about 25 % of the calculated value of k_{obs} . In most experiments in Figs. 5 and 6, the contribution to k_{obs} from the k_4 -term is, however, smaller than or of the order of 5 %. For morpholine, k_3/k_{-1} is much smaller than for imidazole and limiting rates cannot be approached, and neither can k_4 be determined with any certainty. The value of k_4 used in the final calculations is related to the corresponding constant for trifluoroacetanilide in the same way as the constants for imidazole are related to the two substrates. The contribution to the calculated k_{obs} -values in Fig. 7 from a k_4 -term is at most 10 %.

The experimental values of k_{obs} are somewhat smaller than the calculated ones at the higher pH values and the higher concentrations of amine base in Figs. 5–7. In these experiments, calculated and actual pH values agreed very well, but this, of course, does not disprove that new medium effects are introduced with increasing concentrations of imidazole and morpholine base. In the experiments at the smallest pH values and largest concentrations of the amine cations, the measured pH values were somewhat smaller than the calculated ones. The deviations were at most about 0.07 pH units in Fig. 5 and 0.04 pH units in Fig. 7. In most experiments, however, the deviations were negligible. These solutions with a pH deviating from the calculated one have a large buffer capacity and their pH values have not been corrected. The experiments with equal concentration of imidazole and imidazolium ion at the ionic strength 3 have shown that the deviations of the observed pH values from the calculated ones are about the same as at the ionic strength 1.

All the calculated profiles in Figs. 5–7 presume that $[\text{OH}^-]$ and activity coefficients for the reacting species are the same over the whole profile. The relatively small but systematic deviations shown at the higher pH values for solutions with large concentrations of free imidazole and morpholine are therefore not surprising, and do not disprove the mechanism leading to eqn. (4).

Breakdown of I in buffers of the carbonic acid system. The experimental values of k_{obs} and the calculated curves are given in Figs. 8–10 for 12 pH values at the ionic strength 1, and in Figs. 8 and 9 also for 2 pH values at the ionic strength 3. The ratio $[\text{HCO}_3^-]/[\text{CO}_3^{2-}]$ varies at the lower ionic strength from 115 to 0.06. From the profiles in Figs. 8 and 9 it is apparent that the experiments at the largest concentrations of HCO_3^- give values of k_{obs} which, when plotted against $[\text{HCO}_3^-]$, form almost straight lines with a slope that increases with increasing pH and which is greater than it should be according to eqn. (1) using any reasonable values of k_1 , k_2/k_{-1} , and k_3/k_{-1} . This indicates the presence of a k_4 -term, with carbonate ion acting as a nucleophile. If it is assumed that the slopes at large concentrations of catalyst in Fig. 8 are mainly due to the k_4 -term, k_1 can be obtained from these profiles with fairly good accuracy.

All the profiles in Figs. 8–10 are calculated by eqn. (4) and the parameter values given in Table 3. As seen from Table 3, the value of k_3/k_{-1} used in the calculations is pH dependent. At small pH values and small concentrations of HCO_3^- , the contribution to k_{obs} from the k_4 -term is small, e.g. for the profiles in Fig. 8 less than 5 % for all values with $[\text{HCO}_3^-] \leq 0.1$. At the largest concentrations of HCO_3^- in Fig. 8, the contribution to k_{obs} from the k_4 -term is

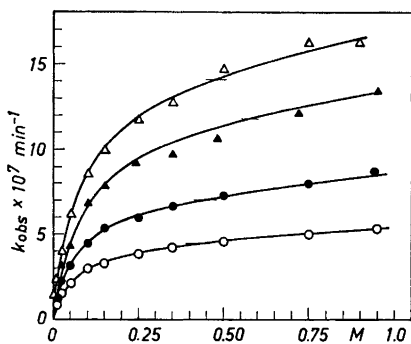


Fig. 8. Plot of k_{obs} against concentration of hydrogen carbonate ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 3. The bars denote the values of $k_1[\text{OH}^-]$.

	$-\log [\text{OH}^-]$	$[\text{HCO}_3^-]:[\text{CO}_3^{2-}]$	μ
○	6.22	115	1
●	6.02	72	1
△	5.72	36	1
▲	5.72	23	3

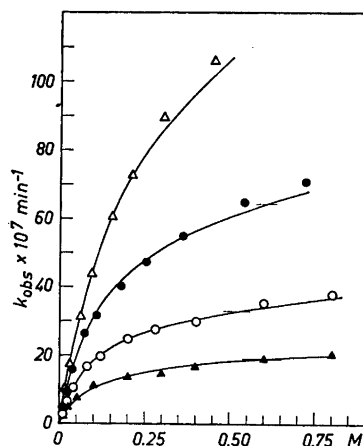


Fig. 9. Plot of k_{obs} against concentration of hydrogen carbonate ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 3. The bars denote the values of $k_1[\text{OH}^-]$.

	$-\log [\text{OH}^-]$	$[\text{HCO}_3^-]:[\text{CO}_3^{2-}]$	μ
▲	5.51	14	3
○	5.35	15.5	1
●	5.06	8	1
△	4.78	4.2	1

approximately 20 % and at the highest pH values (Fig. 10), where the limiting value of the HCO_3^- -catalysed reaction is not approached, it is in most experiments around 10 %.

Especially at the smaller pH values and at the largest concentrations of HCO_3^- , the use of eqn. (4) with a k_4 -term leads to a better agreement between the experimental values and calculated ones than is possible with eqn. (1),

Table 3. Values of k_3/k_{-1} used in the construction of Figs. 8–10. $k_4/\text{CO}_3^{2-} = 14 \times 10^{-6} \text{ M}^{-1}\text{min}^{-1}$ ($\mu=1$) and $6 \times 10^{-6} \text{ M}^{-1}\text{min}^{-1}$ ($\mu=3$). Stoichiometric $\text{p}K_{\text{a,HCO}_3^-} = 9.62$ ($\mu=1$) and 9.77 ($\mu=3$).

μ	$-\log [\text{OH}^-]$	$\frac{[\text{HCO}_3^-]}{[\text{CO}_3^{2-}]}$	k_3/k_{-1} M^{-1}	μ	$-\log [\text{OH}^-]$	$\frac{[\text{HCO}_3^-]}{[\text{CO}_3^{2-}]}$	k_3/k_{-1} M^{-1}
1	6.22	115	17	1	4.78	4.2	5.5
1	6.02	72	16	1	4.47	2.1	4.0
1	5.72	36	14	1	4.18	1.05	3.2
3	5.72	23	12	1	3.87	0.51	2.8
3	5.51	14	11	1	3.56	0.25	2.5
1	5.35	15.5	11.5	1	3.26	0.125	2.4
1	5.06	8	8.5	1	2.97	0.064	2.4

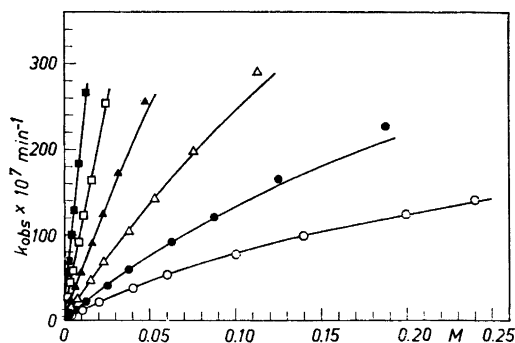


Fig. 10. Plot of k_{obs} against concentration of hydrogen carbonate ion. The lines are calculated from eqn. (4) and parameter values given in Tables 1 and 3. The bars on the ordinate denote the uncatalysed values of k_{obs} at the three largest concentrations of the hydroxyl ions. $\mu=1$ in all experiments.

	$-\log [\text{OH}^-]$	$[\text{HCO}_3^-]:[\text{CO}_3^{2-}]$
○	4.47	2.1
●	4.18	1.05
△	3.87	0.51
▲	3.56	0.25
□	3.26	0.125
■	2.97	0.064

which does not contain this term. It must, however, be emphasized that the experiments which most strongly suggest the presence of a k_4 -term are those where the ionic medium mainly consists of ionic species other than K^+ and Cl^- ; hence it cannot be excluded that the k_4 -term might be, at least partly, a result of the introduction of new medium effects at high catalyst concentrations. For the profiles in Figs. 8 and 9 at the ionic strength 3, at least two thirds of the ionic strength is given by potassium chloride. These profiles, however, are of the same general shape as those at ionic strength 1, even though the value of k_4 is considerably smaller at $\mu=3$ than at $\mu=1$. The agreement between the calculated and the actual pH values at different concentrations of NaHCO_3 — Na_2CO_3 -buffers is very good at the ionic strength 1 but, as noted especially at pH values higher than those in Figs. 8 and 9, somewhat less good at the ionic strength 3 (pH decreases with increasing concentration of buffer species).

DISCUSSION

Acidic properties. UV-spectrophotometry and the kinetic experiments have not revealed acidic properties of II at the hydroxyl ion concentrations used in the experiments, hence it is concluded that it is the hydrogen atom bound to the anilide nitrogen that is dissociated in I.

Pure alkaline hydrolysis. From Fig. 3 it is apparent that II hydrolyses more rapidly than I in strongly alkaline solution. Also in weakly alkaline solution, where dissociation of I as an acid or product formation *via* k_3 is

unimportant, Fig. 3 and the values of $k_1k_2/(k_{-1}+k_2)$ in Table 1 show that II hydrolyses somewhat more rapidly than I. There seems to be no reason for supposing that k_1 should be larger for II than for I but assuming a reaction between H_2O and the anilide nitrogen in the k_2 -step,^{2,13} k_2/k_{-1} can, from electronic considerations, be expected to be larger for II than for I. Thus the experimental data indicate that k_2/k_{-1} is increased more than k_1 is decreased by *N*-methylation. This really is the case when constants for trifluoroacetanilide and *N*-methyltrifluoroacetanilide are compared. Values of k_1 and k_2/k_{-1} for trifluoroacetanilide² and the corresponding constants for *N*-methyltrifluoroacetanilide, which can be calculated from constants given by Schowen *et al.*¹⁴ show that the ratio of the k_1 -values is 1.4 and of the k_2/k_{-1} -values 0.2.

The value of $k_{3,OH^-}/k_2$ for I is much larger than for II. This certainly depends partly on a smaller value of $k_{3,OH^-}/k_{-1}$ for II than for I and partly on a larger value of k_2/k_{-1} for II than for I.

In the case of benzoate ester hydrolysis, Bender *et al.*¹⁵ have proposed that the increased steric strain in the tetrahedral intermediate by bulky groups would favour hydrolysis over exchange, *i.e.* increase k_2/k_{-1} . In the case of anilide hydrolysis, however, the proposed proton transfers in the intermediate preceding breakdown to products^{2,13} certainly are hindered by bulky groups, and it seems reasonable to assume that the steric strain in highly hindered intermediates is most easily relieved by return to reactants and that bulky groups therefore decrease the value of k_2/k_{-1} . In agreement with this, k_2/k_{-1} is much smaller for I than for trifluoro- and trichloroacetanilide.² The views now presented probably are applicable to amide hydrolysis on the whole. If the proton shifts between the oxygen atoms of the substrate-hydroxyl ion complex of I are much faster than the breakdown to either reactants or products, almost complete oxygen exchange in the substrate will take place before significant hydrolysis has occurred as soon as the reaction *via* k_2 is not overshadowed by reaction *via* k_3 . As discussed previously^{2,3} the k_{3,OH^-} -step certainly involves primarily abstraction of a proton from the OH-group of the intermediate — in a general base or equilibrium process — and this process is of course strongly favoured by electron-attracting groups in the acyclic part. It is therefore expected that the value of $k_{3,OH^-}/k_{-1}$ as well as of K_a will decrease rapidly with decreasing electron-attracting power of the substituents, which is corroborated by a comparison of the corresponding constants for trifluoro- and trichloroacetanilide. Of course, steric factors might also influence the value of $k_{3,OH^-}/k_{-1}$. Values of k_1 , k_2/k_{-1} and $k_{3,OH^-}/k_{-1}$ will be more thoroughly discussed when data for more anilides, including anilides without electron-attracting substituents in the acyclic part, have been accumulated. Such investigations are now in progress and will be reported on elsewhere.^{16,17}

Imidazolium and morpholinium ion catalysis. The rate parameters k_3/k_{-1} for hydrolysis of I in the presence of these catalysts are much smaller than those for hydrolysis of trifluoroacetanilide.³ The values of k_3/k_{-1} for acid catalysts seem to be influenced by the bulky groups in the acyclic part of the substrate in the same way as the value of k_2/k_{-1} is. Also, decreased steric accessibility of the acid hydrogen of a bulky catalyst may lower the value of k_3/k_{-1} . The very bulky triethanolammonium ion has catalytic effect neither on trifluoroacetanilide nor on I, whereas k_3/k_{-1} with the imidazolium ion is almost 200 times

larger for trifluoroacetanilide than for I and with morpholinium ion almost 50 times larger; k_2/k_{-1} is about 10 times larger.^{2,3} Even though the values of k_3/k_{-1} are much smaller for I than for trifluoroacetanilide, the increase of the uncatalysed rate *via* k_3 that can be obtained in the presence of large concentration of catalyst is determined by the value of k_{-1}/k_3 , hence the uncatalysed rate is increased by a factor of 40 in the case of trifluoroacetanilide and by a factor of more than 300 in the case of I.

Catalysis by the carbonic acid system. The values of k_3/k_{-1} in Table 3 show that, contrary to the case of catalysis by imidazolium and morpholinium ions, this quotient in the case of catalysis by the carbonic acid system is not constant but decreases with increasing pH. At least one explanation for the decrease of the values might be that H_2CO_3 is a more efficient catalyst than HCO_3^- . In order to evaluate the constants $k_{3,\text{H}_2\text{CO}_3}/k_{-1}$ and $k_{3,\text{HCO}_3^-}/k_{-1}$, the experimentally determined values of k_3/k_{-1} at different pH values can be treated as shown previously for the phosphate catalysed hydrolysis of trifluoroacetanilide,² *i.e.* by plotting $(k_3/k_{-1})(K_{a,\text{H}_2\text{CO}_3} + [\text{H}^+])$ against $[\text{H}^+]$ a straight line should be obtained and $k_{3,\text{H}_2\text{CO}_3}/k_{-1}$ should be derivable from the intercept and $k_{3,\text{HCO}_3^-}/k_{-1}$ from the slope of such a line. The constant for the expression $[\text{H}^+][\text{HCO}_3^-]/([\text{H}_2\text{CO}_3] + [\text{CO}_2])$ is reported to have the value of 1.14×10^{-6} in 1 M NaCl at 25°C, and for the expression $[\text{H}^+][\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]$ it is about 400 times larger (Ref. 18, p. 760 and 693), hence $[\text{H}^+]$ is negligible compared to $K_{a,\text{H}_2\text{CO}_3}$ at all the pH values investigated and k_3/k_{-1} can be directly plotted against $[\text{H}^+]$, which is done in Fig. 11. The values in Fig. 11 show, however, that a straight line is not obtained at all. It is seen that at the highest concentrations of H^+ , where a possible contribution to k_3/k_{-1} from catalysis by H_2CO_3 should be greatest, the values of k_3/k_{-1} increase only very slowly. The largest values of k_3/k_{-1} in Fig. 11 may be considered to lie on a straight line of small slope, the extension of which would intercept the ordinate around 14: this would then be the value of $k_{3,\text{HCO}_3^-}/k_{-1}$. Alternatively, the continually decreasing slope of a line connecting experimental values in Fig. 11 can indicate ap-

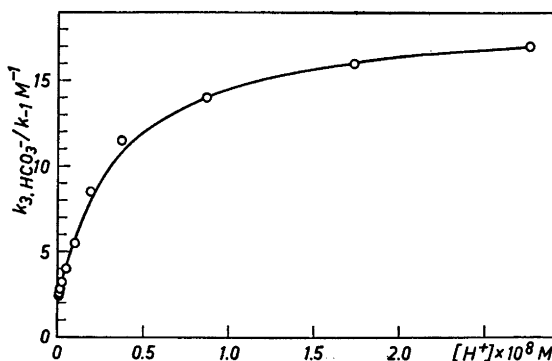
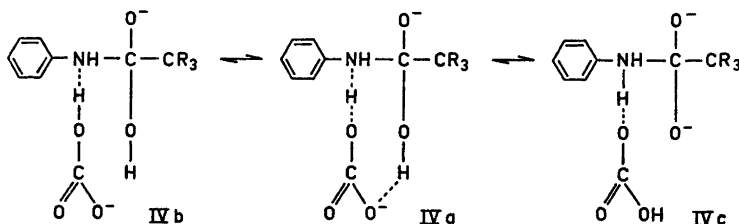
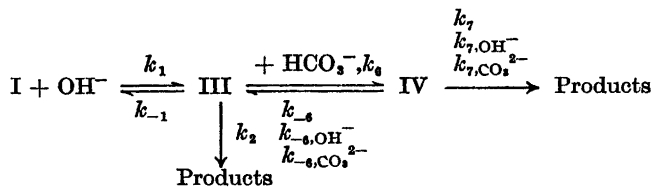


Fig. 11. Plot of $k_{3,\text{HCO}_3^-}/k_{-1}$ against $[\text{H}^+]$. All values are taken from Table 3 ($[\text{H}^+] = 1.66 \times 10^{-14}/[\text{OH}^-]$) and refer to $\mu = 1$. The line is calculated from eqn. (10) with $a = 19c$, $b = 2.4d = 5.28 \times 10^6c$, $d = 2.2 \times 10^6c$.

proach to a limiting value of $k_{3,\text{HCO}_3^-}/k_{-1}$ only slightly in excess of the value of 17, which is obtained at the largest concentration of hydrogen ions. Thus the contribution to k_3/k_{-1} from H_2CO_3 -catalysis in the pH range investigated is small or negligible even at the highest values of $[\text{H}^+]$ and the pH dependence of k_3/k_{-1} at all the smaller values of $[\text{H}^+]$ cannot be explained from pH independent values of $k_{3,\text{HCO}_3^-}/k_{-1}$ and $k_{3,\text{H}_2\text{CO}_3}/k_{-1}$. This fact might at first seem to contradict the mechanism leading to eqns. (1) and (4). On the other hand, profiles calculated from eqn. (4) at all pH values in Figs. 8–10 agree very well with the experimental values. These profiles are founded on values of k_1 and k_2/k_{-1} used in all calculations and it is hard to visualise a basically different mechanism leading to the profiles obtained. The pH dependence of $k_{3,\text{HCO}_3^-}/k_{-1}$ seems to be most reasonably rationalised by considering the formation of products *via* k_3 in greater detail. Hitherto, the pathway for the acid catalysed formation of products from the substrate-hydroxyl ion complex has been denoted only by the rate constant k_3 and it has not been discussed if a new intermediate [IV in scheme 2] or intermediates are formed on the path from the substrate-hydroxyl ion complex to products. Intermediate IV might be represented by the formal structures IVa–IVc.



Just as hydroxyl ions are supposed to act on the hydroxyl group of the substrate-hydroxyl ion complex [III in scheme 2] and thus catalyse formation of products, hydroxyl ion and carbonate ion might be expected to act on the same group in IVb and thus promote formation of products. These bases might, however, also attack a hydrogen bound to the anilide nitrogen (preferably of IVa) thus giving a poor leaving group and promoting the reverse reaction from IV to III. The pathways discussed are, together with the spontaneous or water-promoted breakdown of IV to III or products, depicted in scheme 2, where I represents the unionised substrate and k_1 , k_{-1} , and k_2 symbolise the same rates as in scheme 1 and eqns. (1) and (4).



Scheme 2.

Reaction between III and OH^- is not included in scheme 2. If scheme 2 covers the pathways leading to hydrolysis, the disappearance of IV at small concentrations of OH^- and CO_3^{2-} is expected to occur predominantly in the uncatalysed reactions with the rate constants k_{-6} and k_7 . At larger pH values, the disappearance of IV in one or both directions might also be brought about by hydroxyl ions and, if hydroxyl ions are effective, the weaker base CO_3^{2-} might also possibly be a catalyst for these reactions. It seems therefore reasonable to attribute the disappearance of IV according to scheme 2 to the following three main factors (a, b, and c). The equations obtained when the steady state approximation is applied to III and to (III+IV) can all be written in the same form as eqn. (1) but with k_3 replaced by the expressions discussed below:

a) Only k_{-6} and k_7 are of importance in the disappearance of IV. On these presumptions, eqn. (5) is valid for the above mentioned relation.

$$k_3 = k_6 k_7 / (k_{-6} + k_7) \quad (5)$$

From eqn. (5) it is apparent that this mechanism requires a pH independent value of k_3/k_{-1} and it may apply to all cases with a constant value of k_3/k_{-1} but not to the HCO_3^- -catalysed hydrolysis of I.

b) In addition to k_{-6} and k_7 one or both of the OH^- -catalysed reactions represented by k_{-6,OH^-} and k_{7,OH^-} are of importance in the disappearance of IV. The postulate that k_{-6,OH^-} is negligible but k_{7,OH^-} is important obviously cannot lead to a diminished value of the overall constant k_3 with increasing pH and is therefore not discussed further.

The postulate that k_{7,OH^-} is negligible but k_{-6,OH^-} is important gives

$$k_3 = \frac{k_6 k_7}{k_{-6} + k_7 + k_{-6,\text{OH}^-} [\text{OH}^-]} \quad (6)$$

According to eqn. (6), k_3 decreases with increasing pH and will approach zero at large concentrations of OH^- . Table 3 and Fig. 11, however, show that k_3/k_{-1} does not approach zero but the value of 2.4, hence also this mechanism is rejected.

The postulate that both k_{-6,OH^-} and k_{7,OH^-} are of importance gives

$$k_3 = k_6 \frac{k_7 + k_{7,\text{OH}^-} [\text{OH}^-]}{k_{-6} + k_7 + (k_{-6,\text{OH}^-} + k_{7,\text{OH}^-}) [\text{OH}^-]} \quad (7)$$

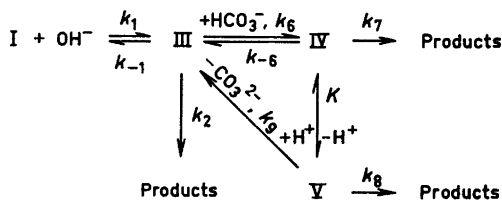
With $[\text{OH}^-]$ small, eqn. (7) becomes identical with eqn. (5) and with $[\text{OH}^-]$ large, eqn. (7) simplifies to $k_3 = k_6 k_{7,\text{OH}^-} / (k_{-6,\text{OH}^-} + k_{7,\text{OH}^-})$, i.e. according to eqn. (7) the value of k_3 , and hence also of k_3/k_{-1} , is constant at small pH values, then varies with pH in a given pH range and finally becomes constant again at large pH values. It is apparent that eqn. (7) at least qualitatively is compatible with the values of k_3/k_{-1} in Table 3 and Fig. 11. Eqn. (7) will be discussed again together with an other proposed mechanism later in this paper.

c) In addition to the reactions under a) and b) one or both of the CO_3^{2-} -catalysed reactions represented by $k_{-6,\text{CO}_3^{2-}}$ and $k_{7,\text{CO}_3^{2-}}$ should be taken into account. Assuming both of these constants to be significant, eqn. (8) is obtained.

$$k_3 = k_6 \frac{k_7 + k_{7,\text{OH}^-}[\text{OH}^-] + k_{7,\text{CO}_3^{2-}}[\text{CO}_3^{2-}]}{k_{-6} + k_7 + (k_{-6,\text{OH}^-} + k_{7,\text{OH}^-})[\text{OH}^-] + (k_{-6,\text{CO}_3^{2-}} + k_{7,\text{CO}_3^{2-}})[\text{CO}_3^{2-}]} \quad (8)$$

With one of the constants for carbonate ion catalysis equal to zero, eqn. (8) still contains one or two terms for carbonate ion catalysis and it is apparent that, with one or both of the CO_3^{2-} -catalysed reactions being important, k_3 will vary not only with pH but also with concentration of catalyst. All the profiles in Figs. 8–10 are, however, constructed with a given value of k_3/k_{-1} at a given pH and, as the deviations of the experimental values from these profiles are small, it is concluded that carbonate ion catalysis according to scheme 2 is negligible.

In scheme 2, the hydroxyl ion is assumed to act as a general base in catalysing the disappearance of IV. Scheme 3, on the other hand, assumes that IV is in equilibrium with its conjugate base V and that III and products are formed from these intermediates in uncatalysed reactions.



Scheme 3.

Applying the steady state approximation to III and to (III+IV+V), an equation is derived which can be written in the same form as eqn. (1) but with k_3 substituted by its equivalent in eqn. (9), where K_b is the base constant of V.

$$k_3 = k_6 \frac{k_7 + k_8[\text{OH}^-]/K_b}{k_{-6} + k_7 + (k_8 + k_9)[\text{OH}^-]/K_b} \quad (9)$$

Eqns. (9) and (7) are equivalent ($k_{7,\text{OH}^-} = k_8/K_b$ and $k_{-6,\text{OH}^-} = k_9/K_b$), hence the mechanism in scheme 2 leading to eqn. (7) and the mechanism in scheme 3 are kinetically indistinguishable.

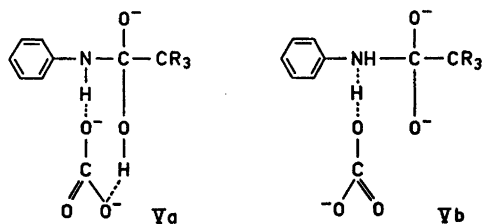
Eqns. (7) and (9) can be written in the form

$$k_3/k_{-1} = \frac{a + b [\text{OH}^-]}{c + d [\text{OH}^-]} \quad (10)$$

where $a = k_6 k_7$, $b = k_6 k_7 / K_b$ (or $b = k_8 k_6 / K_b$), $c = k_{-1}(k_{-6} + k_7)$, and $d = k_{-1}(k_{-6,\text{OH}^-} + k_{7,\text{OH}^-})$ [or $d = k_{-1}(k_8 + k_9)/K_b$]. At the highest values of $[\text{OH}^-]$, a limiting value of 2.4 is obtained for k_3/k_{-1} , which gives $b = 2.4d$. As has already been pointed out, k_3/k_{-1} at the largest values of $[\text{H}^+]$ in Fig. 11 can be interpreted either as approaching a limit whose value is only somewhat larger than 17 or as lying on a line of small slope which intersects the ordinate at around 14. Both these interpretations give an approximate value of a/c and permit a to be expressed in terms of c . Eqn. (10) will then contain only the two constants

c and d and curves of k_3/k_{-1} as a function of $[\text{OH}^-]$ (or of $[\text{H}^+]$ as in Fig. 11) for different relations between c and d can be calculated. Such calculations show that better agreement between the experimental and calculated values is obtained when a/c is somewhat larger than 17 than when it is about 14 and when catalysis by H_2CO_3 is also taken into account. It is therefore concluded that catalysis by H_2CO_3 is of no account in the pH range investigated. After trying different values for the ratios a/c and d/c , the quotients $a/c=19$ and $d/c=2.2 \times 10^5$ were finally chosen as those giving the best fit to the experimental values and were therefore used in the calculation of the curve in Fig. 11. At no pH value in Fig. 11 do the values of $k_{3,\text{HCO}_3^-}/k_{-1}$ used in the construction of Figs. 8–10 deviate from those calculated with eqn. (10) by as much as 10 %.

In nucleophilic attacks at the carbonyl carbon of esters and amides, kinetic evidence for mechanisms involving intermediates in acid-base equilibrium have been obtained in the hydroxylaminolysis and methoxylaminolysis of thioesters¹⁹ and in the hydrolysis of penicillins brought about by monochatecholate ion.²⁰ In these cases there is, however, a primarily formed intermediate that is involved in an acid-base equilibrium, whereas scheme 3 presumes that a second intermediate on the reaction path is involved in an acid-base equilibrium. Supposing that scheme 3 represents a pathway in the hydrogen carbonate ion catalysed breakdown of I, the formal structures Va and Vb seem to be the most likely ones for V.



The removal of CO_3^{2-} from Va leads directly to III, whereas removal of CO_3^{2-} from Vb leads to a structure with two good leaving groups and therefore preference is given for product formation from Vb. As displacement of the equilibrium between IV and V towards V leads to a diminished value of the overall constant k_3 , it is assumed that V exists predominantly in the form of Va. Formal structures like IVa and Va can not be formed in imidazolium and morpholinium ion catalysis and as removal of a proton from the anilide nitrogen in IV is expected to occur more easily from IVa than from IVb and IVc the postulated existence of IVa can explain that k_3/k_{-1} is pH dependent in hydrogen carbonate ion catalysis but not in imidazolium and morpholinium ion catalysis. Even though cyclic intermediates like IVa and Va support the kinetics obtained in the hydrogen carbonate ion catalysed reaction, they do not differentiate between general base catalysis as in scheme 2 and an equilibrium process as in scheme 3. The existence of both pH independent and pH dependent k_3 -catalysts indicates that at least one of them forms part of an intermediate and does not solely donate a proton. Some preliminary experiments

with phosphate species present as catalysts have shown that k_3/k_{-1} in this case is pH dependent also at high pH values, where, in analogy with the effect on trifluoroacetanilide,² HPO_4^{2-} is expected to be responsible for all or almost all of the catalytic effect. These observations show that the same mechanism probably is operating in phosphate as in hydrogen carbonate ion catalysis. Good profiles of k_{obs} against catalyst concentration according to eqn. (1) or (4) are, however, not obtained over a broad concentration range of catalyst, which probably is due to very large changes in activity coefficients when a considerable part of KCl is replaced by phosphate species (Ref. 18, p. 731–734).

In the hydrogen carbonate ion catalysed alkaline hydrolysis of trifluoroacetanilide, k_3/k_{-1} varied only slightly with pH and was almost the same (330) at the two largest concentrations of hydroxyl ions ($10^{-5.60}$ M and $10^{-4.09}$ M).² IV must in the case of trifluoroacetanilide be a stronger acid than in the case of I and the value of 330 for k_3/k_{-1} might be the limiting value with all product formation going *via* V. As already discussed, k_3/k_{-1} for imidazolium and morpholinium ion catalysis is 200 times and 50 times larger, respectively, for trifluoroacetanilide than for I, hence it seems at least as reasonable to compare the value 330 with the limiting value of k_3/k_{-1} for I in strongly alkaline solution (2.4) as with the limiting value in weakly alkaline solution (19).

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