

Hydrolysis of Anilides

II.* Hydrolysis of Trifluoro- and Trichloroacetanilide by Hydroxyl Ions and by Some Other Catalysts

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The pK_a values of trifluoroacetanilide ($C_6H_5NHCOCF_3$) and trichloroacetanilide ($C_6H_5NHCOCCL_3$) have been determined and, using a pH-stat method, the compounds have been hydrolysed at 25°C in a constant ionic medium at hydroxyl ion concentrations ranging from 1 to about 10^{-6} M. The curves obtained when the observed pseudo first-order rate constants (k_{obs}) or their logarithms are plotted against hydroxyl ion concentrations or their logarithms (so-called pH-rate profiles) show a limiting value of k_{obs} at high pH values and the curves are of the same shape for both compounds. The mechanism of hydroxyl ion catalysis is discussed in some detail, and on the basis of comparisons of rate parameters of the two compounds, the hypothesis of dipolar anion formation preceding breakdown to products is discussed.

The rate of hydrolysis is strongly enhanced by the presence of very small concentrations of some species, such as the hydrogen carbonate and dihydrogen phosphate ions. It is shown that this effect can be interpreted as catalytic breakdown of an intermediate between substrate and hydroxyl ions. Hydroxyl ions also effect breakdown of the intermediate but are less efficient than the anions mentioned. From the equations derived, it is apparent that at a given pH all species acting in the breakdown of the intermediate alone, are expected to give the same limiting value of k_{obs} . At pH values smaller than pK_a this limiting value of the rate constant for both compounds is about 40 times larger than its value in the absence of such catalysts.

Anilides are generally very stable towards alkaline hydrolysis, but compounds containing strongly electron attracting groups in the acyclic part of the molecule are hydrolysed fairly rapidly. In an often cited paper, Biechler and Taft Jr.¹ reported on the alkaline hydrolysis of trifluoroacetanilide in water and in aqueous dioxane at 25.5°C and concentrations of hydroxyl ions ranging from 0.006 to 0.5 M. They found that the rate was not proportional

* Part I: see Ref. 9.

to the hydroxyl ion concentrations, and the relation between rate and pH was explained on the basis of ionization of trifluoroacetanilide at high pH-values and stability of the corresponding base towards alkaline hydrolysis. The kinetic data gave a pK_a value of 11.9. Bourne *et al.*² found that trifluoroacetanilide in aqueous alcoholic solution could be titrated against 0.1 M sodium hydroxide with an end point around pH 11–11.5, which shows that the compound has a pK_a value much smaller than 11.9. When the investigation here reported was partly completed, a paper by Mader³ appeared where he reports a pK_a of 9.5 at 25°C. He suggests a mechanism of hydroxyl ion catalysis which is principally accepted by us and discussed here in greater detail. The curve giving the relation between $\log k_{\text{obs}}$ and pH for trifluoroacetanilide (the pH-rate profile) obtained by Mader is at the higher hydroxyl ion concentrations in good agreement with that reported in this paper. At the lower hydroxyl ion concentrations, however, the agreement is less good. Mader obtained values for the rate parameters with the aid of computer analysis. It is shown that from the data now obtained, the parameters necessary for construction of a pH-rate profile can easily be evaluated without making use of computer analysis.

Except for the paper by Mader, catalysis by buffer species has, as far as we know, not been reported in anilide hydrolysis.* In his experiments, Mader used four different buffer systems, namely mono-, di-, and triethanolamine and morpholine. For the three ethanolamines, he found that at constant pH the relation between rate and buffer concentration was linear. With the morpholine buffers, the plot of rate against buffer concentration gave a somewhat curved line, the reason for which, however, was not discussed. The concentration range of the buffers used by him was much smaller than the range used by us.

At the start of this investigation, it was apparent to us that the interpretation of rate data for trifluoroacetanilide given by Biechler and Taft Jr. could not be correct. The purpose of the present study was primarily to elucidate the mechanism of hydroxyl ion catalysed hydrolysis of anilides with acidic properties. As the investigation progressed, it became apparent that some species other than hydroxyl ions are very effective catalysts. Since it was considered important to obtain information about these catalysts, a considerable part of this study is devoted to the effectiveness and mechanism of action of catalysts other than hydroxyl ions.

MATERIALS AND METHODS

Materials. The trifluoroacetanilide was prepared from trifluoroacetic acid and aniline;^{2,4} m.p. 86° (determined in an electrically heated metal block, using a calibrated Anschütz thermometer). Literature values vary between 86 and 90°C. Equiv. weight (determined by non-aqueous titration with 0.1 M tetrabutylammonium hydroxide, using pyridine as solvent and azo violet as indicator) 187.8, calc. 189.1. The trichloroacetanilide was prepared according to Votocek and Burda;⁵ m.p. 95–97°C (Ref. 5 gives 95–97°). Equiv.

* When this paper was ready for publication, the communication of Schowen, R. L. and Zuorick, G. M. (*Tetrahedron Letters* 43 (1965) 3839) about glycinate-catalysed hydrolysis of trifluoro-*N*-methyl-acetanilide came to our notice.

weight (non-aqueous titration) 238.1, calc. 238.5. The potassium chloride (reagent grade, Merck, Darmstadt) used for obtaining constant ionic strength, was for some experiments recrystallised twice from 0.1 M hydrochloric acid.

Hydrolysis experiments and determination of acidity constants. The kinetic experiments, as well as the determinations of the acidity constants and of the ionic product of water were performed at $25 \pm 0.05^\circ\text{C}$ in a medium of 9.6 % (v/v) ethanol and ionic strength 1 — obtained by addition of KCl. All the kinetic experiments were performed at constant pH and the concentration of the anilides was generally about 0.001 M. Because of the restricted solubility of trichloroacetanilide, concentrations down to about 0.6×10^{-4} M were used at the lowest pH values. The experiments at the higher pH values were performed in volumetric flasks in a thermostated bath. At hydroxyl ion concentrations smaller than about 0.01 M, a pH-stat method was used to maintain constant pH. The reaction vessel was equipped with a magnetic stirrer and a jacket through which water from an ultra-thermostat was circulated. In both cases, samples were withdrawn and analysed after appropriate intervals. A Radiometer model pHM 4 equipped with a glass and a saturated calomel electrode was used both in the pH-stat method and in the titrations described below. The electrodes were standardised with 0.05 M potassium biphthalate and 0.01 M borax⁶ before and after each experiment. In all the experiments, the pH readings for the standard solutions before and after an experiment agreed well and the difference between the pH values of the standard solutions was close to the theoretical one (departure as a rule less than 0.02 pH units). As soon as the pH changed by about 0.005 units, small amounts of sodium hydroxide solution were added by an Agla micro burette. Carbon dioxide was excluded by performing the experiments under nitrogen.

The relation between measured pH values and $[\text{OH}^-]$ and $[\text{H}^+]$ (concentration of hydroxyl and hydronium ions) was determined by measuring the pH of 100 ml of 1 M KCl in 9.6 % (v/v) ethanol upon addition of 1 M sodium hydroxide or hydrochloric acid solutions. An Agla micro burette was used in these titrations as well as in the determinations of the acidity constants of the anilides. For values of $[\text{OH}^-]$ or $[\text{H}^+]$ between approximately 5×10^{-4} and 2×10^{-2} M, plots of $\log [\text{OH}^-]$ or $\log [\text{H}^+]$ against pH were linear with slopes of 1 and -1 , respectively. By extrapolation, the relationship between $\log [\text{OH}^-]$ or $\log [\text{H}^+]$ and the measured pH is obtained over the whole pH scale. From the intersection of the lines the $\text{p}K_w$ value of 13.92 is obtained. This value is in good agreement with what could be expected from the value obtained by Harned and Hamer⁷ in 1 M KCl (13.77) and from the known influence of ethanol on the ionization product of water.⁸

Solutions of trifluoroacetanilide (0.0011 M) and trichloroacetanilide (0.0007 M) were titrated with 1 M sodium hydroxide. In a typical such titration of trifluoroacetanilide, pH readings after 13 different additions of titrant between 10 and 70 % of neutralisation gave the value of 9.51 ± 0.01 for the stoichiometric $\text{p}K_a$ and in a titration of trichloroacetanilide, 12 different additions between 15 and 60 % of neutralisation degrees gave the value of 9.98 ± 0.01 . The hydrolysis taking place during titration up to these degrees of neutralisations is negligible. The constants have also been determined photometrically using a Beckman photometer model DK with thermostated cell compartment. The agreement between the constants obtained by the two methods is good.

Assay. Two different methods — here called the *UV-method* and the *aniline-method* — have been used. In the *UV-method*, the withdrawn samples were added to a solution of hydrochloric acid in a volumetric flask and the volume adjusted by addition of water. The solutions to be measured were about 0.1 M with respect to hydronium ions. The absorbance (A) of these acid solutions was read in 1-cm cells at the maximum absorbance of the unhydrolysed anilides, viz. at $242.5 \text{ m}\mu$ with trifluoroacetanilide and at $248 \text{ m}\mu$ with trichloroacetanilide. At these wave-lengths, the absorbance of the products of hydrolysis at infinite time (A_∞) is almost negligible in acid solution. The pseudo first-order rate constants were calculated from the slopes of the straight lines obtained when $\log (A - A_\infty)$ was plotted against time. The UV-method was used at hydroxyl ion concentrations of about 0.005 M or higher. Using this method of analysis, the kinetic runs were followed for at least one half-life, and in most cases, for considerably longer periods. In the *aniline method* — used at hydroxyl ion concentrations smaller than about 0.005 M — the aniline formed is diazotised and coupled with *N*-(1-naphthyl)ethylenediamine. The procedure used by Eriksson and Omdal⁹ in determinations of 2-methylaniline was

adopted with some modifications. During addition of the different reagents, nitrogen was bubbled through the reaction mixture. Aniline couples easier than 2-methylaniline and the addition of acetate buffer could therefore be omitted. 10 min after the addition of *N*-(1-naphthyl)ethylenediamine solution, 1 M hydrochloric acid was added to give a total volume of 25, 50, or 100 ml. The absorbance was measured in 1 or 10 cm cells at 550 m μ , using a Beckman spectrophotometer model DU. A standard curve was made with freshly distilled aniline. The molar absorptivity is 47 900. From plots of the logarithm of residual anilide concentration or of aniline concentration (when the rate is very slow and the reaction followed only to about 4 % hydrolysis or less) against time, the pseudo first-order rate constants were calculated. The plots always gave straight lines. In all kinetic runs, six to fourteen samples were withdrawn and analysed.

Formation of fluoride and chloride ions. Fluoride and chloride ions might also be formed during hydrolysis of the amide bond. If these ions are formed in appreciable amounts simultaneously with aniline, the rate of aniline formation might be influenced, especially after long reaction times. Therefore, in order to assess the rate at which these ions are formed, they were determined in partly and in completely hydrolysed solutions. *Fluoride ions* were estimated spectrophotometrically according to the method of Icken and Blank,¹⁰ which is based on the bleaching of a thorium-alizarin lake by fluoride ions. With the experimental conditions used, hydrolysis of about 0.2 % of the fluorine is easily detected. No fluoride ions could be detected after complete hydrolysis of the amide bond at hydroxyl ion concentrations of 0.01 and 0.001 M. After acidification with nitric acid, *chloride ions* were determined electrometrically, using a Radiometer pHM 4 and the following cell:

Ag, AgCl; solution to be examined; K₂SO₄ (sat); Hg₂SO₄, Hg.

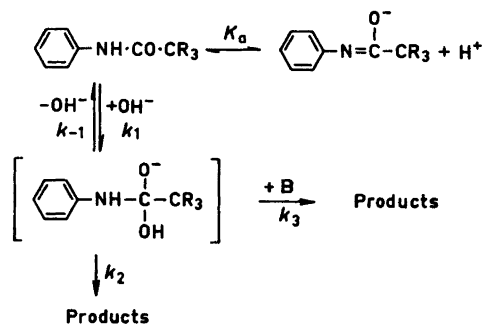
Emf-determinations of solutions containing known amounts of hydrochloric acid instead of trichloroacetanilide gave differences in emf close to the theoretical ones in the concentration range 10⁻⁴ to 10⁻² M. By using an experimental curve relating the concentration of chloride ions to emf, concentrations down to about 10⁻⁵ M could be roughly estimated. Some determinations were made on partly and on completely hydrolysed solutions with hydroxyl ion concentrations of 0.1, 0.01, and 0.001 M. These determinations showed that chloride ions were formed more rapidly from the ionised trichloroacetanilide than from trichloroacetate ions and that the concentration of chloride ions was small compared to the concentration of aniline both in partly and in almost completely hydrolysed solutions at the higher concentrations of hydroxyl ions. At the lowest hydroxyl ion concentration, however, the concentrations of chloride ions were not negligible in comparison to those of aniline.

In all hydrolysis experiments with trichloroacetanilide, the solutions after being made alkaline assume a distinct odour of phenylisocyanide. This odour appears almost immediately in the strongly alkaline solutions and after some time in the most weakly alkaline solutions. Alkaline solutions containing aniline and sodium trichloroacetate (0.001 M with respect to both components) do not develop this odour even after a long time.

The mechanism of phenylisocyanide and chloride ion formation has not been investigated in detail but the conceivable influence of ionization of chlorine and of phenylisocyanide formation on the rate of aniline formation at low hydroxyl ion concentrations will be touched upon in the discussion.

RATE EQUATIONS AND RESULTS OF HYDROLYSIS EXPERIMENTS

The following reaction scheme explains the rate data obtained in pure hydroxyl ion catalysed hydrolysis and in hydrolysis catalysed by species giving a limiting value of the pseudo first-order rate constant k_{obs} at constant pH.



Assuming that the basic form of the anilide does not react, and applying the steady state approximation to the intermediate in brackets, henceforth called the intermediate, the following equation is derived:

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

Generally, B is hydroxyl ions or any other species catalysing the breakdown of the intermediate. If more than one species B is operating in the breakdown of the intermediate, $k_{3,i}[\text{B}_i]$ in eqn. (1) has to be replaced by $\sum k_{3,i}[\text{B}_i]$. This is the case when, in addition to another catalyst operating in the breakdown process, the concentration of hydroxyl ions is large enough to cause a significant part of the hydrolytic reaction to proceed *via* k_3 .

Figs. 1, 4, and 5 show that both compounds reach a limiting value of k_{obs} at high concentrations of B. When k_{obs} does not increase with further increase in the concentration of B, the whole reaction goes *via* k_3 , as shown by the dotted curves in Figs. 1 and 4. The value of $k_{3,i}[\text{B}_i]$ is then much larger than $(k_{-1} + k_2)$ and eqn. (1) can be simplified to

$$k_{\text{obs}} = \frac{k_1 K_w}{K_a + [\text{H}^+]} \quad (2)$$

This equation shows that at limiting values of k_{obs} , the rate determining step is formation of the intermediate and that k_1 is obtained from these values of k_{obs} . If B is hydroxyl ions, $[\text{H}^+]$ according to Fig. 1 is small compared to K_a and eqn. (2) can then be written as

$$k_{\text{obs}} = k_1 K_w / K_a \quad (3)$$

At the lowest hydroxyl ion concentrations used in the experiments and with no catalytic species other than OH^- present, the rate tends to become proportional to $[\text{OH}^-]$. This being the case, k_2 must be much larger than $k_{3,\text{OH}^-}[\text{OH}^-]$ and eqn. (1) can then be written as

$$k_{\text{obs}} = \frac{k_1 K_w}{K_a + [\text{H}^+]} \times \frac{k_2}{k_{-1} + k_2} \quad (4)$$

or, if K_a is negligible compared to $[\text{H}^+]$,

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{OH}^-]}{k_{-1} + k_2} \quad (5)$$

With k_1 known, the quotient $k_2/(k_{-1} + k_2)$ or k_2/k_{-1} can now be obtained from the experimental values at those small concentrations of hydroxyl ions, where rate is proportional, or almost so, to $[\text{OH}^-]$.

From Figs. 1, 4, and 5 the concentration of B at half the limiting values of k_{obs} is obtained with rather good accuracy. In the case of pure hydroxyl ion catalysis, $[\text{H}^+]$ is negligible compared to K_a at this value of k_{obs} , and therefore the following expression is valid both when B is hydroxyl ions (Fig. 1) and when B is a catalyst used at constant pH (Figs. 4 and 5).

$$k_{-1} - k_2 = k_{3,i}[\text{B}_i] \quad (6)$$

Of course, curves of the type shown in Figs. 2 and 3 can also be used to estimate the relation between $(k_{-1} - k_2)$ and $k_{3,i}$.

Knowing the values of k_2/k_{-1} and of $k_{3,i}/(k_{-1} - k_2)$ the quotients $k_2/(k_{-1} + k_2 + k_{3,i}[\text{B}_i])$ and $k_{3,i}[\text{B}_i]/(k_{-1} + k_2 + k_{3,i}[\text{B}_i])$ in eqn. (1) can be calculated at any concentration of B, and all the parameters necessary for constructing profiles relating the value of k_{obs} to the concentration of catalytic species are known. Knowing the value of k_2/k_{-1} , the values of $k_{3,i}/k_{-1}$, which are given in Tables 1 and 2, are easily calculated from eqn. (6).

The rate equation proposed by Mader also contains a constant for the water-catalysed reaction. His rate profile indicates that this reaction is responsible for half the rate at the hydroxyl ion concentration of 10^{-6} M and the computer analysis gave the value of $3.04 \times 10^{-5} \text{ min}^{-1}$ for the rate constant. We have determined k_{obs} in solutions acidified with hydrochloric acid to give hydrogen ion concentrations of 10^{-4} , 10^{-3} , and 10^{-2} M. The medium was the same as that used in all the determinations of rate constants; the aniline formed was determined after appropriate intervals and the reactions were followed for several weeks. Owing to the very small degradations, the pH-constancy was good. The following values for k_{obs} were obtained:

trifluoroacetanilide;	$6.2 \times 10^{-7} \text{ min}^{-1}$ at $[\text{H}^+] = 10^{-3}$ and 10^{-4}
	$17 \times 10^{-7} \text{ min}^{-1}$ at $[\text{H}^+] = 10^{-2}$
trichloroacetanilide;	$0.8 \times 10^{-7} \text{ min}^{-1}$ at $[\text{H}^+] = 10^{-3}$ and 10^{-4}
	$1.8 \times 10^{-7} \text{ min}^{-1}$ at $[\text{H}^+] = 10^{-2}$

That the rate is the same at hydronium ion concentrations of 10^{-3} and 10^{-4} M and that it is much larger than the hydroxyl ion catalysed rate, strongly indicates that all hydrolysis taking place at these hydronium ion concentrations is water-catalysed and that the constants therefore are the pseudo monomolecular rate constants for water catalysis.

At the smallest concentrations of hydroxyl ions in Fig. 1, the values of the rate constants first obtained could not be repeated some months later. The smaller the hydroxyl ion concentrations were, the larger were the relative deviations. Potentiometric examination (titration with hydrochloric acid and with sodium hydroxide solution) of the potassium chloride used, revealed that different batches contained different amounts of impurities consuming

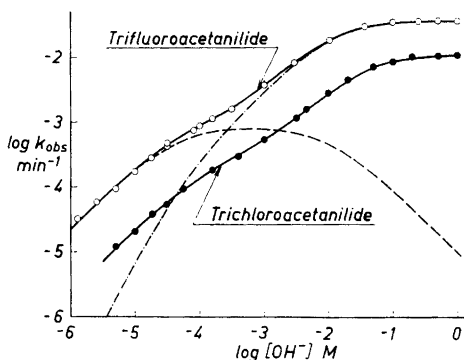


Fig. 1. Plot of $\log k_{\text{obs}}$ against $\log [\text{OH}^-]$. The full lines are calculated from eqn. (1) and parameter values in Table I. For trifluoroacetanilide the dotted lines show the contribution to k_{obs} from the reaction proceeding via k_2 (---) and via k_3 (-·-·-·). Experimentally determined values for trifluoroacetanilide (○), and for trichloroacetanilide (●).

hydrogen ions. After recrystallisation twice from 0.1 M hydrochloric acid and washing the crystals with ethanol, protolytic impurities could not be detected by potentiometric titration. Using this recrystallised potassium chloride, smaller values of the rate constants were obtained, which were also reproducible. Mader apparently obtained too large values for k_{obs} at small concentrations of hydroxyl ions. One of the reasons might have been impurities in the potassium chloride. In order to get the experimental values to fit a calculated curve, the computer analysis gave him a large value of the constant for water-catalysis and a value of K_a that was twice as large as the photometrically determined value.

In Fig. 1, $\log k_{\text{obs}}$ is plotted against $\log [\text{OH}^-]$ for trifluoro- and trichloroacetanilide. The curves are calculated from eqn. (1) and the parameter values used are presented in Table I. Most of the experimental values of k_{obs} deviate by less than 5% (0.02 log units in k_{obs}) from the calculated ones and only exceptionally is the deviation as large as about 10% (0.04 log units in k_{obs}). For trifluoroacetanilide, the dotted lines show the contribution to k_{obs} from the reaction proceeding via k_2 and k_3 . From these lines it is apparent that at half the limiting value of k_{obs} only about 2.5% of the hydrolysis proceeds via k_2 . Also in the case of trichloroacetanilide, about 2.5% of the hydrolysis goes via k_2 at half the limiting value of k_{obs} .

In the experiments with hydrogen carbonate or mono- and dihydrogen phosphate ions, presented in Figs. 2–5, these species at half the limiting

Table I. Dissociation constants and rate parameters experimentally determined and used in the construction of Fig. 1.

Compound	$\text{p}K_a$	k_1 l mole ⁻¹ min ⁻¹	k_2/k_{-1}	$k_{3,\text{OH}^-}/k_{-1}$ l mole ⁻¹
Trifluoroacetanilide	9.51	930	0.025	93
Trichloroacetanilide	9.98	93	0.025	34

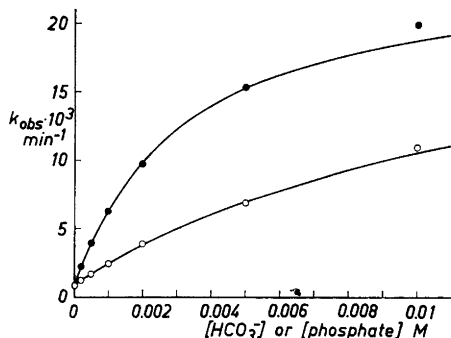


Fig. 2. Plot of k_{obs} for trifluoroacetanilide against $[\text{HCO}_3^-]$ and total concentration of phosphate. The lines are calculated from eqn. (1) and parameter values in Tables 1 and 2. Catalysis by HCO_3^- at $[\text{OH}^-] = 10^{-4.09}$ M (●), and by phosphate at $[\text{OH}^-] = 10^{-4.00}$ M (○).

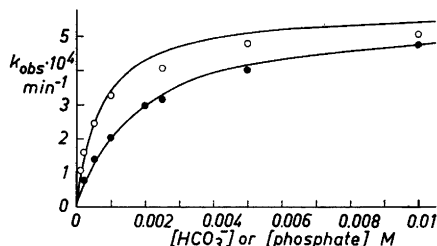


Fig. 3. Plot of k_{obs} for trifluoroacetanilide against $[\text{HCO}_3^-]$ and total concentration of phosphate. The lines are calculated from eqn. (1) and parameter values in Tables 1 and 2. Catalysis at $[\text{OH}^-] = 10^{-6.20}$ M by HCO_3^- (●), and by phosphate (○).

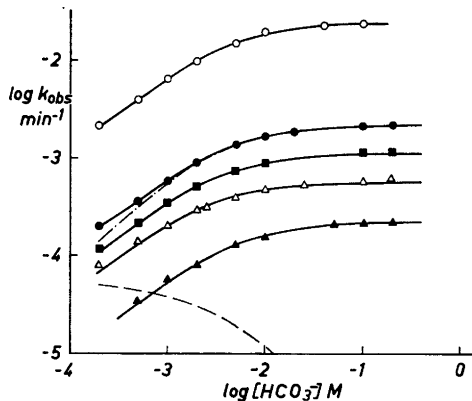


Fig. 4. Plot of $\log k_{\text{obs}}$ against $\log [\text{HCO}_3^-]$. The lines are calculated from eqn. (1) and parameter values in Tables 1 and 2. For trifluoroacetanilide at $[\text{OH}^-] = 10^{-5.6}$ the dotted lines show the contribution to k_{obs} from the reaction proceeding via k_2 (---) and via k_3 (-.-.-). Catalysis by HCO_3^- at $[\text{OH}^-] = 10^{-5.60}$ for trichloroacetanilide (▲), and for trifluoroacetanilide at $[\text{OH}^-] = 10^{-6.20}$ (△), $10^{-5.90}$ (■), $10^{-5.60}$ (●), $10^{-4.09}$ (○).

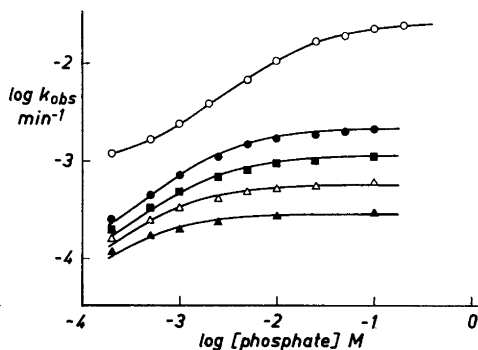


Fig. 5. Plot of $\log k_{\text{obs}}$ for trifluoroacetanilide against \log of total concentration of phosphate. The lines are calculated from eqn. (1) and parameter values in Tables 1 and 2. Catalysis by phosphate at $[\text{OH}^-] = 10^{-6.50}$ (▲), $10^{-6.20}$ (△), $10^{-5.90}$ (■), $10^{-5.60}$ (●), and $10^{-4.00}$ (○).

value of k_{obs} catalyse about 97.5 % of the hydrolysis — as exemplified in Fig. 4 for hydrogen carbonate catalyses of trifluoroacetanilide at $[\text{OH}^-] = 10^{-5.60}$ M. The deviations of the experimental values in Figs. 2–5 from the calculated ones are mainly of the same magnitude as just discussed for Fig. 1.

Hydrogen carbonate and hydrogen phosphates are very effective catalysts. Fig. 2 illustrates the effect of small concentrations of these species at relatively high concentrations of hydroxyl ions, and Fig. 3 at a smaller one. A comparison of these plots also shows that in the pH-range used, the relative enhancement of the hydroxyl ion catalysed rate in the case of hydrogen carbonate is almost constant for a given concentration of catalyst, whereas the effect of phosphate strongly increases when the ratio $[\text{H}_2\text{PO}_4^-]/[\text{HPO}_4^{2-}]$ is increased with decreasing pH. In Figs. 4 and 5, $\log k_{\text{obs}}$ is plotted against $\log [\text{HCO}_3^-]$ or \log [phosphate] for the experiments with hydrogen carbonate and phosphate ions as catalysts. The limiting values of k_{obs} are calculated from eqn. (2), and $k_{3,i}/k_{-1}$ is estimated from half the limiting values of k_{obs} in these plots. Using the values of $k_{3,i}/k_{-1}$ given in Table 2, the curves in Figs. 2–5 are calculated from eqn. (1).

The $\text{p}K_a$ values of hydrogen carbonate and dihydrogen phosphate in a medium containing 9.6 % ethanol and of ionic strength 1 were determined from measurements of hydrogen ion concentrations of solutions with equal concentrations of hydrogen carbonate and carbonate or dihydrogen phosphate and hydrogen phosphate ions. The following values were obtained from pH measurements at total concentrations of acid and its conjugate base ranging from 0.1 to 0.002 M: $\text{p}K_{a,\text{HCO}_3^-} = 9.81 \pm 0.03$, $\text{p}K_{a,\text{H}_2\text{PO}_4^-} = 6.52 \pm 0.03$. The highest concentration of hydroxyl ions used in experiments with hydrogen carbonate corresponds to equal concentrations of hydrogen carbonate and carbonate ions and the value of $k_{3,\text{HCO}_3^-}/k_{-1}$ obtained in this experiment is not higher than the values at smaller hydroxyl ion concentrations, thus indicating that carbonate ions are not operating in the breakdown of the

Table 2. Rate parameters experimentally determined and used in the construction of Figs. 2–6. The calcd. values of $k_{3,B}/k_{-1}$ are obtained from eqn. (7) using the following parameter values: $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1} = 2.3 \times 10^4$, $k_{3,\text{HPO}_4^{2-}}/k_{-1} = 55$ and $K_{a,\text{H}_2\text{PO}_4^-} = 10^{-6.52}$.

Compound	Catalytic species B	$\log [\text{OH}^-]$	$\log (k_{3,B}/k_{-1})$ 1 mole ⁻¹	$\log (k_{3,B}/k_{-1})$ calc. 1 mole ⁻¹
Trifluoroacetanilide	HCO_3^-	-6.20	2.71	
»	»	-5.90	2.61	
»	»	-5.60	2.53	
»	»	-4.09	2.51	
Trichloroacetanilide	»	-5.60	2.43	
Trifluoroacetanilide	H_2PO_4^- and HPO_4^{2-}	-6.50	3.43	3.42
»	»	-6.20	3.16	3.15
»	»	-5.90	2.85	2.88
»	»	-5.60	2.66	2.62
»	»	-4.00	1.81	1.81

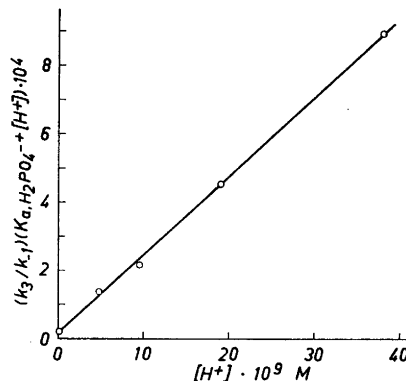


Fig. 6. Plot of $(k_3/k_{-1})(K_a, \text{H}_2\text{PO}_4^- + [\text{H}^+])$ against $[\text{H}^+]$ for evaluating $k_{3, \text{H}_2\text{PO}_4^-}/k_{-1}$.

intermediate. In the case of phosphate catalysis, the value of k_3/k_{-1} increases considerably with decreasing concentration of hydroxyl ions. If $k_{3, \text{H}_2\text{PO}_4^-}/k_{-1}$ and $k_{3, \text{HPO}_4^{2-}}/k_{-1}$ are the catalytic constants for the two species respectively, and if the phosphate is present only as H_2PO_4^- and HPO_4^{2-} , the following equation is valid

$$\frac{k_3}{k_{-1}} = \frac{k_{3, \text{H}_2\text{PO}_4^-}}{k_{-1}} \times \frac{[\text{H}^+]}{K_a + [\text{H}^+]} + \frac{k_{3, \text{HPO}_4^{2-}}}{k_{-1}} \times \frac{K_a}{K_a + [\text{H}^+]} \quad (7)$$

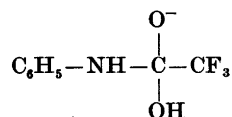
where k_3/k_{-1} is the experimentally determined catalytic parameter at different concentrations of hydroxyl ions and K_a is the acidity constant of H_2PO_4^- . Eqn. (7) can be written as

$$\frac{k_3}{k_{-1}} (K_a + [\text{H}^+]) = \frac{k_{3, \text{H}_2\text{PO}_4^-}}{k_{-1}} \cdot [\text{H}^+] + \frac{k_{3, \text{HPO}_4^{2-}}}{k_{-1}} \cdot K_a$$

In Fig. 6, $(k_3/k_{-1})(K_a + [\text{H}^+])$ is plotted against $[\text{H}^+]$. From the slope of this line, the value of $2.3 \times 10^4 \text{ l mole}^{-1}$ is obtained for $k_{3, \text{H}_2\text{PO}_4^-}/k_{-1}$. At $[\text{OH}^-] = 10^{-4}$, most of the catalytic effect is brought about by HPO_4^{2-} and the value of 54 l mole^{-1} for the parameter $k_{3, \text{HPO}_4^{2-}}/k_{-1}$ reported in Table 2 is calculated from eqn. (7) and from the experimental value of k_3/k_{-1} when $[\text{OH}^-] = 10^{-4} \text{ M}$.

DISCUSSION

In his reaction scheme, Mader postulated formation of the intermediate



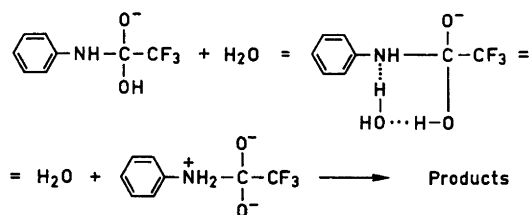
through hydration of the anion of trifluoroacetanilide, and he also discussed its potential formation through ionization of hydrated trifluoroacetanilide. These two pathways by which the intermediate may arise are, however,

kinetically indistinguishable from its formation *via* k_1 . Using the parameter values of Table 1, the second order rate constant for alkaline hydrolysis of undissociated trifluoroacetanilide is calculated from the expression $k_1 k_2 / (k_{-1} + k_2)$, giving a value of 23 l mole⁻¹ min⁻¹. According to Biechler and Taft Jr., this constant for trifluoro-*N*-methylacetanilide at 25.5°C and ionic strength 0.6 has the value of 147 l mole⁻¹ min⁻¹. This compound cannot give an intermediate through hydration of a conjugate base. For the ions C₆H₅NHCOCH₂N⁺(CH₃)₃ and C₆H₅N(CH₃)COCH₂N⁺(CH₃)₃, the corresponding constants are 0.0022 (determined in this laboratory) and 0.0073 l mole⁻¹ min⁻¹ (Ref. 1), resp., whilst for acetanilide and *N*-methylacetanilide at approximately 100°C, Davis¹¹ found the values of 0.053 and 0.064 l mole⁻¹ min⁻¹, resp. Compared with these two pairs of constants and with the constant for *N*-methyltrifluoroacetanilide, the constant for trifluoroacetanilide is not unexpectedly high and its value at least does not indicate significant formation of the intermediate through hydration of the anion.

The second order rate constant for *N*-methyltrifluoroacetanilide is of the order to be expected from polar and steric substituent constants.^{1,12} If significant formation of the intermediate had taken place through hydration and ionization of this compound or of the acidic form of trifluoroacetanilide, abnormally high values of the rate constants should have been obtained. This not being the case is an indication that hydration of the carbonyl group is not an important step in the hydrolytic breakdown.¹³

From parameter values in Table 1, the second order rate constant for undissociated trichloroacetanilide is found to have the value of 2.3 l mole⁻¹ min⁻¹, which is one tenth of that for trifluoroacetanilide. A comparison of the parameter values in Table 1 shows that the larger value for the trifluoro derivative is to be attributed entirely to differences in k_1 , because k_2/k_{-1} has the same value for both compounds. In their investigation on the alkaline hydrolysis of acetanilide and its *p*-chloro, *p*-methyl, and *p*-methoxy derivatives, Bender and Thomas¹⁴ discussed some different pathways for the breakdown of the intermediate. The process favoured by them involves formation of a dipolar anion before breakdown to products. This hypothesis will be further discussed in connection with the proposed mechanisms for the action of catalytic species in the breakdown of the intermediate.

The processes leading to products from the intermediate *via* k_2 might according to Bender and Thomas be depicted by



The dipolar anion rapidly breaks down to the stable fragments aniline and trifluoroacetate ion. Formation of the intermediate is, of course, facilitated by electron-attracting groups, and the difference in k_1 of the two compounds is therefore expected. From isotopic exchange studies, Bender and Thomas found that exchange was favoured over hydrolysis by electron-attracting groups in the *para* position, that is k_2/k_{-1} decreases with the electron-attracting power of the substituents in the benzene nucleus. They also found that the effect of substituents on the rate of hydrolysis was very small, because the influence on k_1 was counteracted by the influence on k_2/k_{-1} . According to Bender and Thomas, the equilibrium position of dipolar anion formation essentially depends on the basicity of the nitrogen atom of the anilide and therefore the ratio k_2/k_{-1} increases with the electron-donating power of the substituents in the benzene nucleus. However, the facility with which dipolar anions are formed also must be influenced by the ability of the hydroxyl group of the intermediate to donate a proton. For the two compounds investigated by us, the ratio k_2/k_{-1} is the same and smaller than for any of the compounds investigated by Bender and Thomas. In contrast to substituents in the nucleus, substituents in the acyclic part certainly affect the electron density in the hydroxyl group of the intermediate as much as at the nitrogen atom and therefore the same value of k_2/k_{-1} for the trifluoro and trichloro compound does not oppose the theory of dipolar anion formation before breakdown to products.

For both compounds, $k_{3,\text{OH}^-}/k_{-1}$ is much larger than k_2/k_{-1} . If k_2 is expressed as a second order rate constant for the reaction between intermediate and water, it is easily shown that hydroxyl ions are about 2×10^5 (trifluoroacetanilide) and 7×10^4 (trichloroacetanilide) times more effective than water molecules in the breakdown of the intermediate. These ratios are larger than those obtained by Biechler and Taft Jr. for *N*-methyltrifluoroacetanilide (about 10^4) and some other substituted *N*-methylacetanilides. On the whole, their data also show that the attack of the second hydroxyl ion is strongly promoted by increasing electron-attracting power of the substituents.

Solutions of trichloroacetanilide completely hydrolysed at hydroxyl ion concentrations of 0.1, 0.01, and 0.001 M all gave UV-spectra identical, or almost so, with the spectrum of aniline. The UV-spectra of aniline and phenylisocyanide in ethanol are rather different.¹⁵ Isocyanides are regarded as stable in alkaline solution and hydrolysable in acid solution. Since, however, quantitative data are lacking, it cannot be entirely excluded that some of the phenylisocyanide formed might have been hydrolysed to aniline also in alkaline solutions. In the hydrolysis experiments at small hydroxyl ion concentrations, the aniline was assayed by the method involving acidification followed immediately by diazotisation (reaction time 3 min). After the diazotisation, isocyanide apparently remained in the reaction mixture, as evidenced by its characteristic odour. With a long time-interval between acidification and diazotisation, the odour disappeared without, however, a measurable increase in the aniline content being observed. If the amounts of aniline formed from phenylisocyanide are not negligible in comparison to the amounts of aniline primarily formed, the values of k_{obs} will not correspond to pure anilide hydrolysis. Chloride ions might be formed without formation of phenylisocyanide but it is hard

to visualise a mechanism for formation of phenylisocyanide without simultaneous formation of chloride ions. Therefore, it can be concluded from the determinations of chloride ion that at high concentrations of hydroxyl ions the rate of formation of phenylisocyanide is negligible compared to the rate of formation of aniline. No such conclusion can be drawn regarding the rates at small hydroxyl ion concentrations. At small hydroxyl ion concentrations, the values of k_{obs} have always been calculated from initial rates and therefore it can be assumed that products other than phenylisocyanide formed simultaneously with chloride ions do not significantly affect the determined rates of aniline formation. The facts discussed above together with the good agreement of the experimental values with the theoretically calculated pH-profile, and the uniformity of the profiles of the two compounds indicate that also at small concentrations of hydroxyl ions most of the aniline is formed *via* direct hydrolysis of the amide bond.

The postulated mechanism with the catalytic species acting in the breakdown of the intermediate only, explains all the results obtained with hydrogen carbonate and phosphate ions. Formation of a complex between the anilides and the catalytic species would also lead to a hydrolytic behaviour of the kind actually obtained if the complex were hydrolysed much more rapidly than the free anilide; the limiting rate should then correspond to complete complex formation. Using four different concentrations of trifluoroacetanilide (0.513×10^{-3} , 1.026×10^{-3} , 2.056×10^{-3} , and 4.466×10^{-3} M), the same hydroxyl ion concentration ($10^{-5.6}$ M) and the same hydrogen carbonate concentration (0.001 M) in all the experiments, the rate constants k_{obs} were determined. In order of increasing anilide concentration, the following values were obtained: 6.08×10^{-4} , 6.00×10^{-4} , 6.25×10^{-4} , and 5.91×10^{-4} min^{-1} . These values show no trend depending on substrate concentration. If complex formation were responsible for the hydrolytic behaviour found, small concentrations of anilide in this case should have given a comparatively larger complex concentration and larger values of k_{obs} . This not being the case, complex formation between substrate and catalytic species must be excluded as an explanation for the results obtained.

If an intermediate were formed in a reaction between anilide and hydrogen carbonate or phosphate ions and products were formed from this intermediate in a reaction with hydroxyl ions, there would be no reason for obtaining a limiting value of k_{obs} . Therefore, also this mechanism can be excluded. Generally, it is not likely that hydrogen carbonate and dihydrogen phosphate ions should act as strong nucleophilic catalysts, whereas carbonate and hydrogen phosphate ions should have no or a smaller catalytic effect.

The values of $k_{3,i}/k_{-1}$ in Table 2 show that hydrogen carbonate and particularly dihydrogen phosphate ions are much more effective than hydroxyl ions in the breakdown of the intermediate. A few preliminary and as yet unpublished hydrolysis experiments with trifluoroacetanilide and some other potential catalysts have been carried out and will be briefly discussed, because the results of these experiments assist in elucidating the proposed mechanism of hydrogen carbonate and phosphate catalysis. The catalytic effect of the hydrazinium ion $\text{H}_3\text{N}^+-\text{NH}_2$ seems to be of the same order of magnitude as that of the hydrogen carbonate ion, whereas acetate and citrate ions show

phosphate ion is a much stronger acid than the hydrogen phosphate ion also might be of importance.

Acknowledgements. We wish to thank Dr. Allan Ågren for his interest in this work, and to acknowledge the skilful technical assistance given by Mrs. Berit Jansson and Miss Susi Burkhart. Professor Richard Dahlbom read the manuscript and gave some valuable comments on it. A grant from *Anslaget för ograduerade forskares vetenskapliga verksamhet vid Kungliga Farmaceutiska Institutet* to one of us (S.O.E.) is gratefully acknowledged.

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Received March 30, 1966.