

## Hydrolysis of Anilides

## IX.\* Rate-pH Profiles for the Hydrolysis of Two Substituted Aminoacetanilides. Kinetic Evidence for a Hydrogen Ion Catalyzed Breakdown of a Substrate-Hydroxide Ion Intermediate

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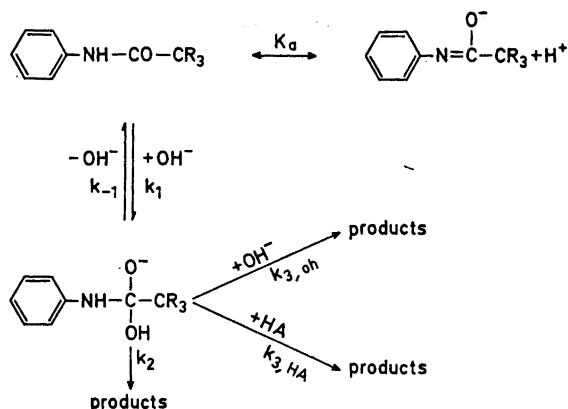
So-called rate-pH profiles are given in the range  $[H^+] = 1$  to  $[OH^-] = 1$  for the hydrolysis of methylaminoacetanilide and dimethylaminoacetanilide at 95°C and ionic strength 1. A rate equation containing conventional rate constants for the hydrolysis of a protolytic ester or amide is not in accord with the experimental rates in the broad pH range, where reaction between anilide cation and hydroxide ion is supposed to be the predominant one. A mechanism involving hydrogen ion catalyzed breakdown of an anilide cation-hydroxide ion intermediate is, however, entirely in accord with the kinetic data. This mechanism, given in Scheme 2, permits the calculation of  $k_1$ ,  $k_2/k_{-1}$  and  $k_{3,oh}/k_{-1}$ , and predicts limits for the rate enhancing effect of general acids when acting in the same way as  $H^+$  in the  $k_3$ -step. Rates in hydrolysis experiments, with phosphate ( $H_2PO_4^-$ ) ions present, are in good agreement with these predictions.

The rate-pH profile for the hydrolysis of an aminoacylanilide ( $\alpha$ -methylamino-2-methylpropionanilide) at elevated temperature (120°C) has previously been reported from this Laboratory.<sup>1</sup> In a series of papers, of which Ref. 2 is a survey, the effect of hydroxide ions, amines and general acids on the rate of aniline formation from some anilides has been studied. Scheme 1 and eqn. (1) were found to be applicable to non-protolytic anilides or anilides with a hydrolytically stable corresponding anionic base, e.g. trifluoroacetanilide.

$$k_{obs} = \frac{k_1 K_w}{K_a + [H^+]} \times \frac{k_2 + k_{3,oh}[OH^-] + k_{3,HA}[HA]}{k_{-1} + k_2 + k_{3,oh}[OH^-] + k_{3,HA}[HA]} \quad (1)$$

The parameters  $k_1$ ,  $k_2/k_{-1}$ ,  $k_{3,oh}/k_{-1}$  and  $k_{3,HA}/k_{-1}$  were determined for a number of anilides and weak acids. With  $HCO_3^-$  as catalyst, the general acid catalyzed pathway could for most anilides be shown to be more complicated than indicated in Scheme 1, giving a pH-dependent value of  $k_{3,HA}/k_{-1}$ .

\* Part VIII, see Ref. 2.



Scheme 1

The above-mentioned and previously investigated aminoacylanilide is a local anaesthetic and in order to gain more information about the hydrolysis of this important class of compounds, the two now actual aminoacylanilides were investigated. The hydrolysis of some other anilides is reported on in the subsequent paper.

#### MATERIALS AND METHODS

*Materials.* The two anilides were obtained by reacting 1-chloroacetanilide (prepared from 1-chloroacetylchloride and aniline<sup>3</sup>) with methylamine (33 % aqueous solution) or dimethylamine (40 % aqueous solution) in aqueous ethanol at room temperature. The hydrochlorides were recrystallized from ethanol-ether, and their equivalent weights determined by argentometric titration, using 4,5-dichlorofluorescein as indicator; melting points were taken in an electrically heated metal block, using a calibrated Anschütz thermometer. Methylaminoacetanilide hydrochloride: m.p. 229–231°C, equiv. wt. 200.7 (calc. 200.7); dimethylaminoacetanilide hydrochloride: m.p. 162–163°C, equiv. wt. 214.3 (calc. 214.7). The hydrolytic experiments at pH-values where the rate is very small ( $k_{\text{obs}} < 10^{-3} \text{h}^{-1}$ ) revealed that the methylaminoacetanilide contained traces of a compound, liberating aniline much more rapidly than did methylaminoacetanilide. This impurity, which could not be removed by repeated recrystallizations, was completely eliminated by digesting an aqueous solution of approximately pH 3 at 95°C for some hours, and then isolating the methylaminoacetanilide hydrochloride.

All the other chemicals used were of reagent grade or of the commercially best available grade. In order to remove traces of protolytic impurities from the potassium chloride (reagent grade), it was recrystallized from 0.1 M hydrochloric acid.<sup>4</sup>

*Determination of acidity constants.* Using a Radiometer pHM 4, equipped with a glass and a calomel electrode, values of the electromotive force  $E$  of actual solutions were measured at 95°C. The electrodes were standardized before and after the measurements against 0.05 M potassium hydrogen phthalate (pH = 4.227 at 95°C) and 0.01 M borax (pH = 8.833 at 95°C),<sup>5</sup> and the pH of a given solution was obtained from the equation

$$\text{pH} = \text{pH}_s + \frac{(E_s - E) 4.606}{E_d}$$

where  $\text{pH}_s$  and  $E_s$  are the values for one of the standard solutions, and  $E_d$  the positive difference in  $E$  between the two standard solutions. In all standardizations,  $E_d/4.606$  was very close to the theoretical value of 0.07305 V. As described previously,<sup>4</sup> values of pH after various additions of 1 M HCl or 1 M NaOH from an Agla microburette to 1 M

KCl in a double-walled thermostated vessel give straight lines with slope  $-1$  and  $1$ , resp., when plotted against  $\log [H^+]$  or  $\log [OH^-]$  (brackets denote concentrations). These lines are used when transforming pH to  $\log [H^+]$  or  $\log [OH^-]$ , and from their intersection, a stoichiometric  $pK_a$ -value of 12.02 is obtained. This value is in good agreement with the value 12.04, which can be calculated from the equations and constants given by Harned and Owen.<sup>6</sup>

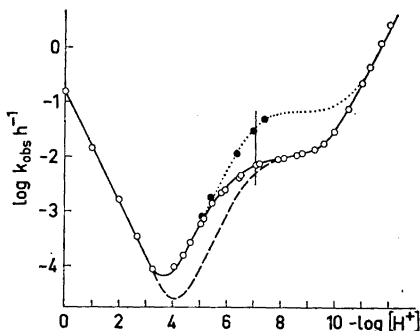
The stoichiometric  $pK_a$  of methyl- and dimethylaminoacetanilide was determined by titrating 100 ml of approximately 0.005 M solutions of their hydrochlorides in 1 M KCl with 1 M NaOH. From pH values after about 8 additions, corresponding to approximately 10–80 % neutralization, the  $pK_a$  has been calculated. The values have as a rule deviated by less than 0.02 units from the mean values reported in Table 1.

The  $pK_a$  of  $H_2PO_4^-$  at 95°C and ionic strength 1 was determined from measurements of the hydrogen ion concentrations of solutions with the quotient  $[H_2PO_4^-]:[HPO_4^{2-}] = 10$  and 1, and a total concentration of phosphate of 0.005–0.1. The  $pK_a$  value  $6.39 \pm 0.02$  was obtained.

**Hydrolysis experiments.** Most of the hydrolysis experiments were performed in the double-walled thermostated vessel, used in the potentiometric determination of acidity constants. The vessel was equipped with a closely-fitting cover, containing holes to accommodate the electrodes and the Agla microburette for addition of alkali or acid, and to permit sampling. Model experiments have shown that loss of aniline and water due to evaporation is negligible during the length of time a hydrolysis experiment is proceeding (only exceptionally exceeding 1 h). In some cases, with solutions of good buffer capacity, the experiments were conducted in volumetric flasks in a thermostated oil-bath, and then often followed over longer times (sometimes several half-lives). When needed, the pH was adjusted in advance. All hydrolysis experiments were performed at 95°C and ionic strength 1, obtained by addition of KCl. The withdrawn samples were analyzed by the previously described aniline method, involving diazotisation of the aniline formed, and coupling with *N*-(1-naphthyl)ethylenediamine.<sup>4</sup> The pseudo first-order rate constants were, as previously described,<sup>4</sup> evaluated graphically by plotting against time either the concentration of aniline, when less than 4 % of the anilide is hydrolyzed, or otherwise the logarithm of the concentration of the substrate. At least six samples were withdrawn and analyzed in a given hydrolysis experiment.

## RATE EQUATIONS AND RESULTS

**Log  $k_{obs} - \log [H^+]$  profiles.** In Figs. 1 and 2, values of  $\log k_{obs}$ , the pseudo first-order rate constant at constant pH, are plotted against  $-\log [H^+]$ . For a protolytic compound with both the acidic (a) and basic (b) form hydrolyzable, and with the rates first-order in reacting species, eqn. (2) defines the three second-order rate constants  $k_{n,a}$ ,  $k_{oh,a}$  and  $k_{oh,b}$ .



*Fig. 1.* Plot of  $\log k_{obs}$  against  $-\log [H^+]$  for methylaminoacetanilide at 95°C and ionic strength 1. The fully drawn line is calculated from eqn. (5) and parameter values given in Table 1, the dashed curve (---) from eqn. (3) with  $k_{oh,a} = k_1 k_2 / (k_{-1} + k_2)$ , and the dotted curve (···) from eqn. (3) with  $k_{oh,a} = k_1$ . The bar denotes the value of  $[H^+]$ , corresponding to the stoichiometric  $pK_a$  value in Table 1. Experimentally determined values in absence of catalysts other than solvolytic ones (O), and in presence of phosphate (●). Concentrations of  $H_2PO_4^-$  ( $pK_a = 6.39$ ) are: 0.025 at  $[H^+] = 10^{-5.99}$  and  $10^{-6.39}$ ; 0.020 at  $[H^+] = 10^{-6.39}$ ,  $10^{-6.99}$  and  $10^{-7.39}$ .

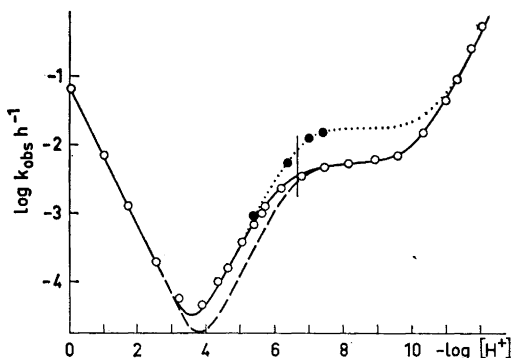


Fig. 2. Plot of  $\log k_{\text{obs}}$  against  $-\log [\text{H}^+]$  for dimethylaminoacetanilide at  $95^\circ\text{C}$  and ionic strength 1. The fully drawn line is calculated from eqn. (5) and parameter values given in Table 1, the dashed curve (---) from eqn. (3) with  $k_{\text{oh,a}} = k_1 k_2 / (k_{-1} + k_2)$ , and the dotted curve (···) from eqn. (3) with  $k_{\text{oh,a}} = k_1$ . The bar denotes the value of  $[\text{H}^+]$  corresponding to the stoichiometric  $\text{p}K_{\text{a}}$  value in Table 1. Experimentally determined values in absence of catalysts other than solvolytic ones (O), and in presence of phosphate (●). Concentrations of  $\text{H}_2\text{PO}_4^-$  ( $\text{p}K_{\text{a}} = 6.39$ ) are: 0.025 at  $[\text{H}^+] = 10^{-5.39}$ ; 0.020 at  $[\text{H}^+] = 10^{-6.39}$ ,  $10^{-6.99}$  and  $10^{-7.39}$ .

$$-d[\text{c}]/dt = k_{\text{obs}}[\text{c}] = k_{\text{h,a}}[\text{a}][\text{H}^+] + k_{\text{oh,a}}[\text{a}][\text{OH}^-] + k_{\text{oh,b}}[\text{b}][\text{OH}^-] \quad (2)$$

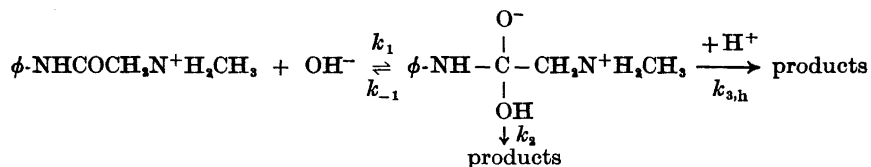
Introducing the ionization constant of the substrate,  $K_{\text{a}}$ , and of water,  $K_{\text{w}}$ , eqn. (2) can be written in the form of eqn. (3):

$$k_{\text{obs}} = \frac{1}{K_{\text{a}} + [\text{H}^+]} (k_{\text{h,a}}[\text{H}^+]^2 + k_{\text{oh,a}}K_{\text{w}} + k_{\text{oh,b}}K_{\text{a}}[\text{OH}^-]) \quad (3)$$

In eqns. (2) and (3), three further hydrolytic reactions could be included: reaction between free base and water, between the acidic form and water, and between free base and hydrogen ions. The first of these is kinetically indistinguishable from reaction between the acidic form and hydroxide ion, which reaction is assumed to take place to a much larger extent than that between base and water. The second and third reactions, which are kinetically indistinguishable, should, if of any significance, lead to a constant value of  $k_{\text{obs}}$  around  $[\text{H}^+] = 10^{-4}$  in Figs. 1 and 2. This not being the case, also these two reactions are not taken into further account. In strongly acid solution with  $[\text{H}^+] > 10^{-3}$ , the second and third terms in eqns. (1) and (2) are negligible, and  $k_{\text{h,a}}$  is obtained from experiments in the  $-\log [\text{H}^+]$  range 0–3. In the same way,  $k_{\text{oh,b}}$  is obtained from experiments at the largest hydroxide ion concentrations in Figs. 1 and 2: at least up to hydroxide ion concentrations of 1 M, this reaction is first-order in  $[\text{OH}^-]$ .

The second term in eqns. (1) and (2) is expected to be the predominant one around the  $\text{p}K_{\text{a}}$  value of the substrate. In fact, according to Figs. 1 and 2, this hydroxide ion initiated breakdown of the acidic form of the anilides is the predominant reaction over a range of more than 5 pH-units. Figs. 1 and 2 show, however, that the experimentally determined rates of hydrolysis and those calculated from eqn. (3) – dotted lines based on a  $k_{\text{oh,a}}$  value, de-

terminated from rates in the  $[H^+]$  range  $10^{-4.5} - 10^{-5.5}$ , and dashed lines on a  $k_{oh,a}$  value from rates in the  $[H^+]$  range  $10^{-7.5} - 10^{-9}$  — deviate much from each other in a given pH-range. The dotted curves show much larger rates than the experimental ones in a broad pH range, and in order to conform to the experimental results, the value of  $k_{oh,a}$  used in the calculations must therefore be based on a mechanism, leading to a decrease in rate over a broad pH range. Such mechanisms will be considered in the discussion. The dashed curves, on the other hand, give much smaller rates than the experimental ones in a broad pH range. These values of  $k_{oh,a}$  therefore necessitate a mechanism leading to increase of rate in a broad pH range. Such a mechanism would involve hydrogen ion catalyzed breakdown of a substrate-hydroxide ion intermediate, shown in Scheme 2, the substrate being the acidic form of methylaminoacetanilide. From this scheme, a pH-dependent expression for  $k_{oh,a}$  ( $k'_{oh,a}$ ) is derived under assumption of steady state of the substrate-hydroxide ion intermediate.



Scheme 2

$$k'_{oh,a} = k_1 \frac{k_2 + k_{3,h}[H^+]}{k_{-1} + k_2 + k_{3,h}[H^+]} \quad (4)$$

Substituting the pH-dependent expression in eqn. (4) for  $k_{oh,a}$  in eqn. (3), eqn. (5) is obtained, which is in accord with all experimental values of  $k_{obs}$  in the absence of non-solvolytic catalysts.

$$k_{obs} = \frac{1}{K_a + [H^+]} (k_{h,a}[H^+]^2 + k_1 K_w \frac{k_2/k_{-1} + k_{3,h}[H^+]/k_{-1}}{1 + k_2/k_{-1} + k_{3,h}[H^+]/k_{-1}} + k_{oh,b} K_a [OH^-]) \quad (5)$$

Assuming that eqn. (5) is applicable,  $k_1$  can be estimated from  $k_{obs}$  values in the  $[H^+]$  region  $10^{-4} - 10^{-5.5}$ . In that pH region, the slope is close to 1, thus limiting  $H^+$ -catalysis obtained in the  $k_3$ -step ( $k'_{oh,a} = k_1$ ). In the  $[H^+]$  region  $10^{-7.5} - 10^{-9}$ , the quotient  $k_{3,h}[H^+]/k_{-1}$  can be assumed to be small compared to  $k_2/k_{-1}$ , and with  $k_1$  known,  $k_2/k_{-1}$  can be estimated from the  $k_{obs}$  values in that region [ $k'_{oh,a} = k_1 k_2 / (k_{-1} + k_2)$ ]. From the intermediate  $[H^+]$  range  $10^{-5.5} - 10^{-7}$ ,  $k_{3,h}/k_{-1}$  is calculated. After some preliminary calculations, the values of  $k_1$ ,  $k_2/k_{-1}$  and  $k_{3,h}/k_{-1}$ , given in Table 1, were found to give the best fit to the experimental values, and were consequently used in the calculation of the profiles.

*Catalysis by weak acids.* Weak acids have previously<sup>2</sup> been shown to catalyze breakdown of the substrate-hydroxide ion intermediate in the same way as hydrogen ions do, according to Scheme 2. In these experiments with weak acids as catalysts, the  $[H^+]$ -values were, however, at the most about  $10^{-7}$  M, and under these conditions, no hydrogen ion catalysis was observed with any

Table 1. Dissociation constants and rate parameters experimentally determined and used in the construction of Figs. 1–2. Stoichiometric  $pK_w = 12.02$  at  $95^\circ\text{C}$  and ionic strength 1.

Compound	$pK_a$	$k_{h,a}$ $\text{M}^{-1}\text{h}^{-1}$	$k_1$ $\text{M}^{-1}\text{h}^{-1}$	$k_2/k_{-1}$	$\frac{k_1 k_2}{k_{-1} + k_2}$ $\text{M}^{-1}\text{h}^{-1}$	$k_{3,h}/k_{-1}$ $\text{M}^{-1}$	$k_{\text{oh,b}}$ $\text{M}^{-1}\text{h}^{-1}$
Methylaminoacetanilide	7.05	0.153	6260	0.17	925	$9.7 \times 10^5$	2.27
Dimethylaminoacetanilide	6.66	0.067	4000	0.48	1300	$9.9 \times 10^5$	0.44

certainty, and neither was any such catalysis calculated for. Furthermore, a comparison between the fully drawn lines with hydrogen ion catalysis and the dashed ones without in Figs. 1 and 2 shows that this catalysis is small or negligible at  $[\text{H}^+] < 10^{-7.5}$ . If the mechanism underlying eqn. (5) is correct, then no catalyst acting in the same way as  $\text{H}^+$  in Scheme 2 should be able to raise  $k_{\text{obs}}$  above the dotted lines in Figs. 1 and 2. It was therefore considered interesting to examine the effect of a weak acid on the hydrolysis rate. Dihydrogen phosphate ion, which has been used previously and found very effective,<sup>2,4</sup> was selected for these experiments. With general acids (HA), acting in the same way as  $\text{H}^+$  in Scheme 2,  $k_{\text{obs}}$  should be calculable from eqn. (6).

$$k_{\text{obs}} = \frac{1}{K_a + [\text{H}^+]} (k_{h,a}[\text{H}^+]^2 + k_1 K_w \frac{k_2/k_{-1} + k_{3,h}[\text{H}^+]/k_{-1} + k_{3,HA}[\text{HA}]/k_{-1}}{1 + k_2/k_{-1} + k_{3,h}[\text{H}^+]/k_{-1} + k_{3,HA}[\text{HA}]/k_{-1}}) + k_{\text{oh,b}} K_a [\text{OH}^-] \quad (6)$$

In Fig. 3,  $k_{\text{obs}}$  is plotted against  $[\text{H}_2\text{PO}_4^-]$  at three pH values for methylaminoacetanilide, and at two for dimethylaminoacetanilide. The lines are calculated from eqn. (6). The values of  $k_{\text{obs}}$  at the largest concentration of  $\text{H}_2\text{PO}_4^-$  at each of these pH values are also plotted in Figs. 1 and 2, where, in addition, a few values of  $k_{\text{obs}}$ , obtained in the presence of phosphate at larger values of  $[\text{H}^+]$  than those used in Fig. 3, are also plotted.

## DISCUSSION

As already mentioned, reaction between anilide cation and hydroxide ion is not kinetically distinguishable from reaction between free base and water, nor is hydrogen ion catalyzed breakdown of a base-water intermediate distinguishable from the mechanism outlined in Scheme 2, which shows  $\text{H}^+$ -catalyzed breakdown of a cation-hydroxide ion intermediate. It can easily be shown that if reaction between base and water is predominant in the actual pH range, the value of the uncatalyzed pseudo first-order rate constant is  $[k_1 k_2 / (k_{-1} + k_2)] (K_w / K_a)$ . For methylaminoacetanilide, this expression has the value of  $9.9 \times 10^{-3} \text{h}^{-1}$ , and for dimethylaminoacetanilide,  $5.7 \times 10^{-3} \text{h}^{-1}$ . These

values are only 230 and 77 times smaller, resp., than those of  $k_{\text{oh,b}}$ , and as it seems unlikely that  $\text{H}_2\text{O}$  should be such a comparatively strong nucleophile in this reaction, reaction between anilide cation and hydroxide ion is definitely favoured as the predominant one in the  $-\log[\text{H}^+]$  range 4–9.

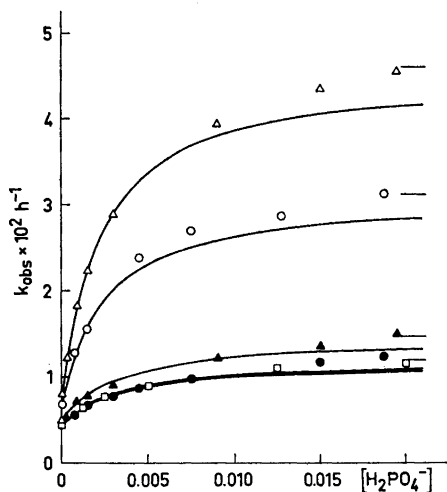
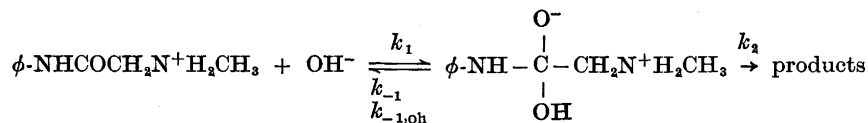


Fig. 3. Plot of  $k_{\text{obs}}$  against  $[\text{H}_2\text{PO}_4^-]$ . The lines are calculated from eqn. (6), using parameter values given in Table 1 and with  $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1} = 500 \text{ M}^{-1}$  for methylaminoacetanilide and  $450 \text{ M}^{-1}$  for dimethylaminoacetanilide. The bars denote limiting rates at a given value of  $[\text{H}^+]$ .

Anilide	$-\log [\text{H}^+]$	$[\text{H}_2\text{PO}_4^-]/[\text{HPO}_4^{2-}]$
□ Methylaminoacetanilide	6.39	1
○ Methylaminoacetanilide	6.99	0.25
△ Methylaminoacetanilide	7.39	0.10
● Dimethylaminoacetanilide (the lowest curve)	6.99	0.25
▲ Dimethylaminoacetanilide	7.39	0.10

The mechanism given in Scheme 2 has been previously discussed by Fedor and Bruce in the hydrolysis of ethyl trifluorothiolacetate.<sup>7</sup> The pH-rate profile was admittedly in accord with the above mechanism, yet it nevertheless had to be rejected, because it gave a value of  $k_1$  greater than what was feasible for a diffusion controlled process. The two protolytic anilides here investigated are much less sensitive to hydrolysis than is ethyl trifluorothiolacetate, and give profiles differing in shape at large values of  $[\text{H}^+]$  from that of this ester. All the experimentally determined rates currently found are in good agreement with the mechanism in Scheme 2, and the parameter values in Table 1 seem to be reasonable. The values of  $k_2/k_{-1}$  are thus of the same order of magnitude as those of acetanilide and some *p*-substituted acetanilides, as determined by Bender and Thomas,<sup>8</sup> utilizing hydrolytic and oxygen-exchange data. Good agreement with the value for acetanilide was later obtained by one of the present authors, using a purely kinetic method.<sup>9</sup> As far as is known,  $k_{3,\text{h}}/k_{-1}$  has never previously been determined for a hydroxide ion catalyzed hydrolysis, and, consequently, neither has  $k_2/k_{-1}$  previously been determined from a pH-rate profile, utilizing hydrogen ion catalyzed breakdown of a substrate-hydroxide ion intermediate.

Mechanisms involving hydroxide ion catalyzed reversion of an intermediate to reactants (with the rate constant  $k_{-1,\text{oh}}$ ) might be expected to give similar equations as those derived for formation of hydrogen ion catalyzed products from the same intermediate. Such a mechanism is that outlined in Scheme 3.



Scheme 3

For this mechanism, the pH-dependent expression for  $k_{\text{oh,a}}$  ( $k''_{\text{oh,a}}$ ) has the form

$$k''_{\text{oh,a}} = k_1 \frac{k_2}{k_{-1} + k_2 + k_{-1,\text{oh}}[\text{OH}^-]} \quad (7)$$

*i.e.*,  $k''_{\text{oh,a}}$  goes from  $k_1 k_2 / (k_{-1} + k_2)$  at small values of  $[\text{OH}^-]$  to a limiting value of zero at large values of  $[\text{OH}^-]$ , which cannot be in accord with the experimental results. The same pH-dependence as expressed in eqn. (7) is obtained when reaction between anilide cation and hydroxide ion is replaced by reaction between free base and water.

The inapplicable mechanism in Scheme 3 gives no clue to the catalytic action of weak acids, whereas it seems logical that they should act in the same way as  $\text{H}^+$  in the  $k_3$ -step in Scheme 2. In fact, the experiments in the presence of phosphate ions lend much further support to the mechanism in Scheme 2, because all the experimental rates in Fig. 3 are close to the curves calculated from eqn. (6) with values of  $k_1$  and  $k_2/k_{-1}$  determined from the rate-pH profiles. Even at the smallest value of  $[\text{H}^+]$  ( $10^{-7.39}$ ), the rates approach, but do not exceed the limiting rates represented by the dotted curves in Figs. 1 and 2. These limiting rates are obtained when  $k_1$  becomes rate determining and all product-formation takes place *via*  $k_3$ .

With the substrates trimethylammonioacetanilide cation,<sup>10</sup> monofluoroacetanilide,<sup>11</sup> and acetanilide,<sup>9</sup> the parameter  $k_{3,\text{HCO}_3^-}/k_{-1}$  was shown to be pH-dependent, in agreement with the hydroxide ion catalyzed breakdown of a substrate-hydroxide ion-hydrogen carbonate ion intermediate or in accord with the functioning of this intermediate as an acid. This pH-dependence, which is presumably possible also with  $\text{H}_2\text{PO}_4^-$  as catalyst, was only weakly manifested in the  $\text{HCO}_3^-$ -catalyzed breakdown of the trifluoroacetanilide-hydroxide ion intermediate, and not observed at all in the corresponding phosphate catalysis with a large catalytic effect of  $\text{H}_2\text{PO}_4^-$  and a small one of  $\text{HPO}_4^{2-}$ .<sup>4</sup> A pH-independent value of  $k_{3,\text{HA}}/k_{-1}$  does not necessarily mean that hydroxide ion catalyzed product-formation from a complex intermediate does not occur, or that this intermediate does not function as an acid, but might well be the result of product-formation mainly *via* this hydroxide ion catalysis, or mainly from the basic form of the substrate-hydroxide ion-weak acid intermediate at all the pH values used.<sup>2</sup>

Too much emphasis must not be given to the fact that a pH-independent value of  $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1}$  has been used in the calculation of the curves in Fig. 3. A somewhat decreasing value of  $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1}$  with increasing pH in combination with a small but not negligible value of  $k_{3,\text{HPO}_4^{2-}}/k_{-1}$  might, for such a small pH range as that used in Fig. 3, also lead to an approximately constant value of the catalytic parameter. In fact, some experiments in the presence of



phosphate at values of  $[H^+] < 10^{-7.39}$  gave rates somewhat larger than those calculated from the parameter value of  $k_{3,H_2PO_4^-}/k_{-1}$ , given in the legend to Fig. 3, thus indicating some catalytic effect also of  $HPO_4^{2-}$ .

The values of  $k_{3,H_2PO_4^-}/k_{-1}$  for the two anilide cations are much smaller than that for trifluoroacetanilide (23 000 at 25°C).<sup>4</sup> Values of this parameter may decrease with temperature, and they certainly depend on the steric nature of the substrate.<sup>3,10</sup> Imidazolium ion, which is often a good catalyst in the breakdown of substrate-hydroxide ion intermediates,<sup>2</sup> has also been used in some experiments. It is obvious that this acid (stoichiometric  $pK_a = 6.0$  at 95°C, and ionic strength = 1) catalyzes in the same way as  $H_2PO_4^-$ . The catalytic constant is, however, rather small ( $k_3/k_{-1} < 30$ ), and limiting rates are not approached with moderate catalyst concentrations at pH values where a great rate enhancement should be possible.

In a subsequent paper, the other rate constants in Table 1 are discussed, together with the same constants for the hydrolysis of some closely related anilides.<sup>13</sup>

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