

Hydrolysis of Anilides

X. Kinetics and Mechanisms for Acid and Alkaline Hydrolysis of Aminoacylanilides and Ammonioacylanilide Cations

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So-called pH-rate profiles are given in the range $[H^+] = 1$ to $[OH^-] = 1$ for hydrolysis at 95°C and ionic strength 1 of seven anilides, viz. $C_6H_5NHCO(CH_2)_nNHCH_3$, $C_6H_5NHCO(CH_2)_nN(CH_3)_2$ with $n = 2$ and 3, and $C_6H_5NHCO(CH_2)_nN^+(CH_3)_3Br^-$ with $n = 1 - 3$.

Product formation from an anilide cation-hydroxide ion intermediate is catalyzed by weak acids and at higher pH-values by hydroxide ions. For the four non-quaternary compounds studied, this intermediate, however, more easily goes to products than reverts to reactants, and therefore the catalytic effect is always small. For trimethylammoniobutyranilide and especially for trimethylammonioacetanilide cation, however, the intermediate more easily reverts to reactants than goes to products. Consequently, small concentrations of general acids are capable of giving large rate enhancements at constant pH for these cations and the superimposed hydroxide ion catalysis results for trimethylammonioacetanilide cation in an almost straight-line relationship between rate and pH up to $[OH^-] = 1$, in spite of a pK_a -value of 10.45 at 95°C ($pK_w = 12.02$ at 95°C).

The trimethylammoniopropionanilide cation undergoes a rapid hydroxide ion catalyzed elimination reaction, rendering calculation of hydrolysis constants impossible.

In the previous paper¹ a short review was presented of currently known mechanisms for hydroxide ion initiated anilide hydrolysis and, as far as is known, a hitherto unobserved mechanism, involving hydrogen ion catalyzed product formation from a substrate-hydroxide ion intermediate, was postulated. The anilides previously reported¹ are methylaminoacetanilide and dimethylaminoacetanilide. In order to get a more complete picture of the hydrolytic behaviour of aminoacylanilides, the hydrolysis of corresponding propion- and butyranilides, as well as the quaternary trimethylammonioacylanilide cations derived from acetic, propionic, and butyric acid, are now reported.

MATERIALS AND METHODS

Materials. The anilides were prepared according to general methods. From the appropriate ω -chloroacylchlorides and aniline, the compounds with $R = Cl$ in Table 1 were prepared,² and these ω -chloroacylanilides were then reacted with methylamine (33 % aqueous solution) or dimethylamine (40 % aqueous solution) in aqueous ethanol at room temperature. The hydrochlorides of the methyl- and dimethylaminoacylanilides were recrystallized from ethanol-ether. The quaternary compounds were prepared by alkylation of the dimethylaminoacylanilides with methyl bromide in acetone and were recrystallized from ethanol-ether. Trimethylammonioacetanilide bromide has previously been prepared by us.³ Melting points, determined in an electrically heated metal block, using calibrated Anschütz thermometers, and equivalent weights, determined by argentometric titration, using 4,5-dichlorofluorescein as indicator, are summarized in Table 1 for the ω -chloroacylanilides and the hydrolytically investigated anilides.

Table 1. Melting points and equivalent weights for anilides with the structural formula $C_6H_5NHC(O)(CH_2)_nR$.

<i>n</i>	R	M.p. °C,		Equiv. wt.	
		found	reported in lit.	found	calc.
1	Cl	130–132	134–135 ⁴		
2	»	116–117	119 ⁵		
3	»	69–71	68–70 ⁶		
2	NHCH ₃ HCl	171–172		216.0	214.7
3	»	168–169		227.3	228.7
2	N(CH ₃) ₂ HCl	195–196	197–199 ⁶	228.2	228.7
3	»	144–145		243.0	242.8
1	N ⁺ (CH ₃) ₃ Br ⁻	209–210	215 ⁷	273.8	273.2
2	»	ca. 190 (dec.)		288.2	287.2
3	»	181–182		301.6	301.2

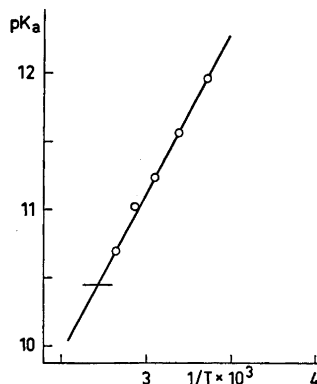
Acrylyl chloride was prepared from acrylic acid and benzoyl chloride:⁸ b.p. 74–76°C (Ref. 8: 72–74°C at 740 torr). Acrylanilide was prepared from acrylyl chloride and aniline:⁹ m.p. 104–105°C (Ref. 9: 104–105°C). The melting point, UV-, and IR-spectrum of the acrylanilide thus prepared agreed with those of the product isolated from the reaction between $C_6H_5NHC(O)CH_2CH_2N^+(CH_3)_3$ and OH^- .

All 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.¹⁰

Determination of acidity constants. The determination of the stoichiometric pK_w at 95°C and ionic strength 1 was described in the previous paper,¹ and the potentiometric method there described for determination of the pK_a of the aminoacetanilides was used also for the determination of the pK_a of the four methyl- and dimethylaminoacylanilides, presented in Table 2.

The stoichiometric pK_a of trimethylammonioacetanilide cation at ionic strength 1 was determined photometrically at five temperatures between 25 and 81°C, and from these determinations, the value at 95°C, given in Table 2, was obtained by extrapolation (Fig. 1). The absorbancies at 242.5 nm, determined with a Zeiss PMQ II spectrophotometer with a thermostated cell-compartment, were used in the calculations, as described previously.³ For all solutions used in the absorbance measurements, $[OH^-]$ was known from the dilution, and after computation of the stoichiometric pK_w for the actual temperature,¹¹ values of $[H^+]$ necessary for the calculations could be obtained.

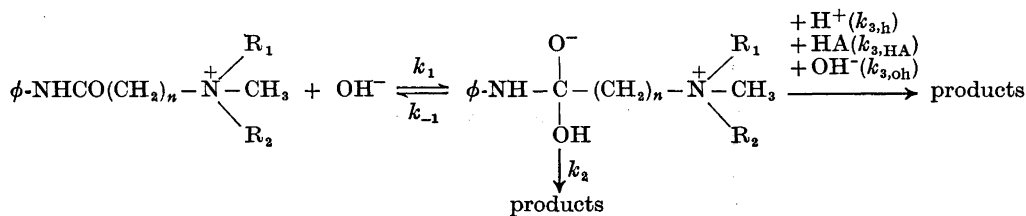
Fig. 1. Plot of the stoichiometric pK_a of trimethylammonioacetanilide cation at ionic strength 1 against $1/T$. The bar denotes the extrapolated value at 95°C.



Hydrolysis experiments. The hydrolysis experiments were performed at 95°C and ionic strength 1 as described in the previous paper,¹ and most of the withdrawn samples were analyzed by the method involving diazotization of the aniline formed, and coupling with *N*-(1-naphthyl)ethylenediamine.¹⁰ In some cases, the reaction has also been followed by UV-spectrophotometric determination of residual substrate in acid solution. The results obtained by these two methods were always in agreement with each other.

RATE EQUATIONS AND RESULTS

In the previous paper,¹ rate equations were derived for the hydrogen and hydroxide ion catalyzed hydrolysis of the acidic and basic forms of the aminoacylanilides. From the experimental rates, obtained with methylaminoacetanilide and dimethylaminoacetanilide as substrates, it was concluded that product formation from an anilide cation-hydroxide ion intermediate was catalyzed by hydrogen ions and by weak acids, according to Scheme 1. In this scheme, catalysis by OH^- in the k_3 -step is also included, although no such catalysis was observed in the paper referred to.



Scheme 1

For the substrates depicted in Scheme 1, n is 1–3, and R_1 and R_2 represent H and CH_3 . Assuming steady-state in the substrate-hydroxide ion intermediate, and using the same symbols as in the previous paper (k_{obs} = pseudo first order rate constant at constant pH, K_a = stoichiometric ionization constant of the substrate, K_w = stoichiometric ionization constant of water,

Table 2. Dissociation constants and rate parameters, experimentally determined and used in the construction of Figs. 2-7. Stoichiometric $pK_w = 12.02$ at 95°C and ionic strength 1.

Compound	pK_a	k_1/k_{-1} $\text{M}^{-1}\text{h}^{-1}$	k_1 $\text{M}^{-1}\text{h}^{-1}$	k_2/k_{-1}	$k_{\text{obs}} = \frac{k_1 k_2}{k_{-1} + k_2}$ $\text{M}^{-1}\text{h}^{-1}$	$k_{3,\text{oh}}/k_{-1}$ M^{-1}	$k_{\text{obs,b}}$ $\text{M}^{-1}\text{h}^{-1}$
$\phi\text{-NHCOCH}_2\text{NHCH}_3$	7.05	0.153	6260	0.17	925	9.7×10^4	2.27
$\phi\text{-NHCOCH}_2\text{N}(\text{CH}_3)_2$	6.66	0.067	4000	0.48	1300	9.9×10^4	0.44
$\phi\text{-NHCOCH}_2\text{N}^+(\text{CH}_3)_3$	10.45	0.034	4500	0.0033	15	0.145	
$\phi\text{-NHCO}(\text{CH}_2)_2\text{NHCH}_3$	8.15	0.88	1100	2.14	750	2100	1.30
$\phi\text{-NHCO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$	7.74	0.70	1700	1.34	975	425	1.40
$\phi\text{-NHCO}(\text{CH}_2)_2\text{N}^+(\text{CH}_3)_3$		0.85					
$\phi\text{-NHCO}(\text{CH}_2)_2\text{NHCH}_3$	8.64	2.25	300	1.40	110		8.00
$\phi\text{-NHCO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$	8.27	2.25	90	0.028	175	1830	1.00
$\phi\text{-NHCO}(\text{CH}_2)_2\text{N}^+(\text{CH}_3)_3$		2.40			2.45	0.018	

$k_{h,a}$ = second order rate constant for the reaction between the cationic form of the substrate and hydrogen ions, $k_{oh,b}$ = second order rate constant for the reaction between the basic form of the substrate and hydroxide ions), eqn. (1) is derived from Scheme 1.

$$k_{obs} = \frac{1}{K_a + [H^+]} (k_{h,a}[H^+]^2 + k_1K_w \frac{k_2/k_{-1} + k_{3,h}[H^+]/k_{-1} + k_{3,HA}[HA]/k_{-1} + k_{3,oh}[OH^-]/k_{-1}}{1 + k_2/k_{-1} + k_{3,h}[H^+]/k_{-1} + k_{3,HA}[HA]/k_{-1} + k_{3,oh}[OH^-]/k_{-1}} + k_{oh,b}K_a[OH^-]) \quad (1)$$

Two requirements must be fulfilled for catalysis in the k_3 -step to be observable: (1) k_2/k_{-1} must not be too large, preferably $< \sim 2$; and (2) at least one of the catalytic parameters $k_{3,h}/k_{-1}$, $k_{3,HA}/k_{-1}$ or $k_{3,oh}/k_{-1}$ must be large enough to give a significant rate enhancement at some pH values, owing to catalysis in the k_3 -step.

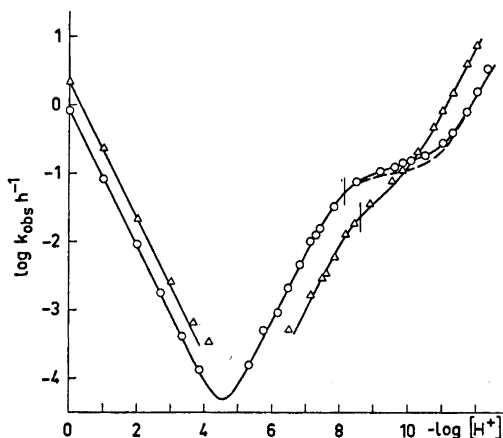


Fig. 2. Plot of $\log k_{obs}$ against $-\log[H^+]$ for methylaminopropionanilide (O) and methylaminobutyranilide (Δ) at 95°C and ionic strength 1. The fully drawn lines are calculated from eqn. (1) and parameter values given in Table 2, and the dashed curve from eqn. (2). The bars denote the values of $[H^+]$, corresponding to the stoichiometric pK_a values in Table 2.

Methylaminopropionanilide, dimethylaminopropionanilide and dimethylaminobutyranilide. The profiles for these compounds in Figs. 2 and 3, having a section consisting of a broken line, are constructed from eqn. (2).

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

In this equation, $k_{oh,a}$ is the second order rate constant for the reaction between the acidic form of the substrate and hydroxide ions, and is equal to $k_1k_2/(k_{-1} + k_2)$ in eqn. (1). Parameter values used in the calculations are summarized in Table 2. Values of $k_{h,a}$ and $k_{oh,b}$ are, as is apparent from Figs. 2

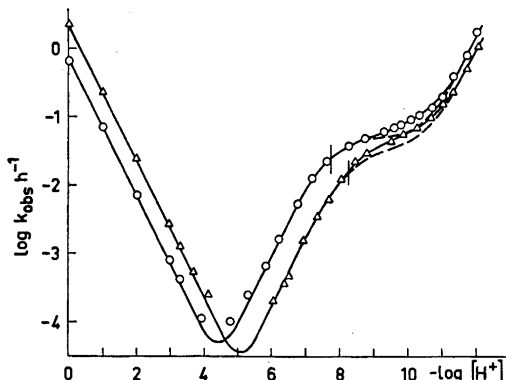


Fig. 3. Plot of $\log k_{\text{obs}}$ against $-\log [\text{H}^+]$ for dimethylaminopropionanilide (O) and dimethylaminobutyranilide (Δ). The fully drawn lines are calculated from eqn. (1) and parameter values given in Table 2, and the dashed curves from eqn. (2). The bars denote the values of $[\text{H}^+]$, corresponding to the stoichiometric $\text{p}K_a$ values in Table 2.

and 3, obtained from experiments in strongly acidic or alkaline solutions with direct proportionality between rate and concentration of hydrogen ions and hydroxide ions, resp. Values of $k_{\text{oh,a}}$ are obtained in the same way from experiments encompassing pH values ranging between that giving minimum rate and the value corresponding to the $\text{p}K_a$. A somewhat better, but not at all perfect, agreement between experimental values and those calculated from eqn. (2) in the $-\log [\text{OH}^-]$ range 8.5–11.5 would be obtained, if smaller values of K_a were used. The values of K_a are, however, determined with good accuracy, and therefore, a change of these values of the order of magnitude necessary to get a better agreement is unacceptable.

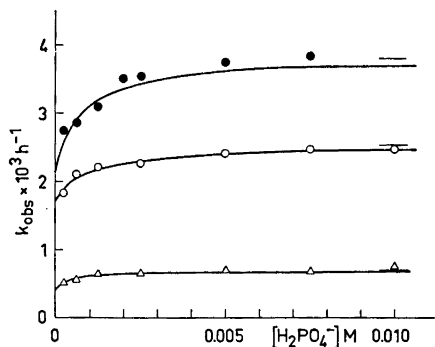
The fully-drawn curves are calculated from eqn. (1), using the parameter values of k_1 , k_2/k_{-1} , and $k_{3,\text{oh}}/k_{-1}$, given in Table 2, and setting $k_{3,\text{h}}/k_{-1} = 0$ (with no weak acids added $k_{3,\text{HA}}[\text{HA}]/k_{-1}$ is of course also zero). Even though the rate enhancement due to hydroxide ion catalysis in the k_3 -step is small, and k_1 , k_2/k_{-1} , and $k_{3,\text{oh}}/k_{-1}$ could not be determined with high precision, it is nevertheless obvious that the mechanism must be more complicated than that underlying eqn. (2), and that a mechanism involving hydroxide ion catalysis in the k_3 -step is in very good agreement with all the experimental results.

From the profiles of the hydrolysis experiments given in Figs. 2 and 3, it is apparent that no hydrogen ion catalysis in the k_3 -step is observable. The difference in this respect from the acetyl derivatives reported on in the previous paper¹ will be treated in the Discussion.

In Fig. 4, some experiments in the presence of phosphate at a given pH value are graphically depicted. The curves were calculated from eqn. (1), using the values of k_1 and k_2/k_{-1} obtained from the profiles, and the value of $k_{3,\text{HA}}/k_{-1}$, given in the legend to Fig. 4. The small increase in rate, even in the presence of relatively large concentrations of these buffer species, is in

Fig. 4. Plot of k_{obs} against $[\text{H}_2\text{PO}_4^-]$ at $[\text{H}^+] = 10^{-8.89}$ ($[\text{H}_2\text{PO}_4^-]:[\text{HPO}_4^{2-}] = 1$). The lines are calculated from eqn. (1), using parameter values from Table 2 and values of $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1}$ given below. The bars denote limiting rates.

	$k_{3,\text{H}_2\text{PO}_4^-}/k_{-1} \text{ M}^{-1}$
● dimethylamino-propionanilide	3000
○ methylamino-propionanilide	3000
△ dimethylamino-butyranilide	7000



good agreement with the values of k_1 and k_2/k_{-1} used, and the form of the curves further supports the mechanism outlined in Scheme 1. Due to the small increases in rate and the experimental errors in k_{obs} , the reported values of $k_{3,\text{HA}}/k_{-1}$ must be regarded as very uncertain.

Methylaminobutyranilide. The profile in Fig. 2 is calculated from eqn. (2). The parameter values given in Table 1 and used in the construction are obtained from experiments performed in the three pH regions: strongly acidic ($[\text{H}^+] > 10^{-3}$), near neutral ($[\text{H}^+] \sim 10^{-7} - 10^{-8}$), and strongly alkaline ($[\text{H}^+] < 10^{-10.5}$). In the $[\text{H}^+]$ -region around $10^{-9} - 10^{-10}$, the experimental values are somewhat larger than the calculated ones, but the differences are considered as too small to justify the introduction of a hydroxide ion catalyzed k_3 -pathway in the calculations.

In the $[\text{H}^+]$ -region around $10^{-3.5} - 10^{-6.5}$, no experimental values are reported, and no calculated curve is drawn. The experimental rate values found in this region are larger than those calculated from eqn. (2). This phenomenon was tentatively thought to be ascribable to the presence of some impurity, from which aniline was liberated at a fast rate, as previously found for methylaminoacetanilide.¹ Repeated recrystallizations or isolation of the anilide after hydrolysis for some hours in the actual pH range have, however, not confirmed this hypothesis. The results obtained in the actual pH range are largely in agreement with a reaction between water and the acidic form of the substrate, or with its kinetic equivalent, *i.e.* reaction between free base and hydrogen ions. Such a reaction is of negligible significance for all the other substrates investigated in this study and in the previous paper. The reaction taking place in the actual range is catalyzed by the phosphate and imidazol systems. Due to the good pH-stability in the presence of these buffer species, the experiments can be followed for a long time, and the degree of hydrolysis can be determined both by the aniline method (diazotisation and coupling) and by UV-spectrophotometry (determination of residual anilide in acid solution at 242 nm). The methods have given commensurate results, and k_{obs} -values of the order $10^{-2.4} \text{ h}^{-1}$ are obtained at values of $[\text{H}^+]$ around $10^{-5.5}$.

Trimethylammonioacetanilide and trimethylammonio-butyranilide cation. Profiles of these compounds are given in Fig. 5. The alkaline hydrolysis and the general acid catalyzed alkaline hydrolysis of trimethylammonioacetanilide

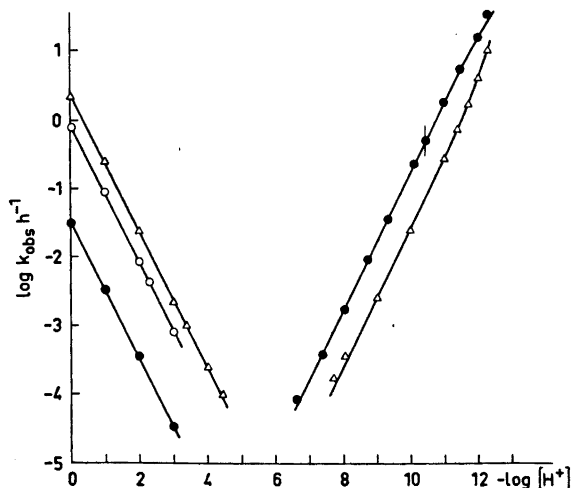


Fig. 5. Plot of $\log k_{\text{obs}}$ against $-\log [\text{H}^+]$ for trimethylammonioacetanilide cation (●), trimethylammoniopropionanilide cation (○), and trimethylammoniobutyranilide cation (△). The lines are calculated from eqn. (1) and parameter values given in Table 2. The bar denotes the value of $[\text{H}^+]$, corresponding to the stoichiometric pK_a value in Table 2.

cation has previously been investigated by us at 25°C.³ Its hydrolysis has now been investigated also at 95°C and over a broader pH-range, in order to get parameter values for comparison with the other investigated substrates. Both anilides show hydroxide ion, but not hydrogen ion, catalysis in the k_3 -step. There is, however, a pH-region in Fig. 5, where, owing to experimental difficulties at these very small rates, no experiments were performed in unbuffered solutions, but where H^+ -catalysis in the k_3 -step might exist. The two profiles can be calculated from eqn. (1). However, in the case of trimethylammonioacetanilide cation, eqn. (1) simplifies to eqn. (3), as the zwitterionic base seems to be stable to hydrolysis, and in the case of trimethylammoniobutyranilide cation, it simplifies to eqn. (4), as this compound lacks protolytic properties.

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

$$k_{\text{obs}} = k_{\text{h,a}}[\text{H}^+] + k_1[\text{OH}^-] \frac{k_2/k_{-1} + k_{3,\text{oh}}[\text{OH}^-]/k_{-1}}{1 + k_2/k_{-1} + k_{3,\text{oh}}[\text{OH}^-]/k_{-1}} \quad (4)$$

With K_a known, k_1 , k_2/k_{-1} , and $k_{3,\text{oh}}/k_{-1}$ for trimethylammonioacetanilide cation are obtained from the profile in Fig. 5, as described previously.³ For trimethylammoniobutyranilide cation, the k_3 -pathway is of importance only at the largest hydroxide ion concentrations in Fig. 5, and none of the parameters k_1 , k_2/k_{-1} , and $k_{3,\text{oh}}/k_{-1}$ can be directly obtained from the profile. From experiments with general acid catalysis, described below, k_1 and k_2/k_{-1} can, however, be evaluated, and knowing these parameters, $k_{3,\text{oh}}/k_{-1}$ is obtained

from experiments at the largest hydroxide ion concentrations. Both substrates are hydrolyzed also in 2 M NaOH. Doubling the ionic strength has apparently only small effect on the hydrolysis rate of trimethylammonioacetanilide cation, as is evident from the profiles and parameter values at 25°C.³ An increase in ionic strength can be assumed to affect the rate parameters of both substrates in the same manner, *i.e.* it will cause a decrease of k_1 and an increase of $k_{3,\text{oh}}/k_{-1}$, giving a rather small total effect on the rate. In the case of trimethylammonio-butyranilide cation, rates were determined in 1 M NaOH at ionic strengths 1 and 2 (by addition of KCl). The rate was somewhat larger at the smaller ionic strength, and therefore the value in 2 M NaOH is certainly not too high, due to an ionic strength effect.

Fig. 6 shows the catalytic effect of imidazolium ion on the rate of the alkaline hydrolysis of trimethylammonioacetanilide cation. At the pH-values used in these experiment, hydrogen ion catalyzed hydrolysis is negligible, $[\text{H}^+] \gg K_a$, and $k_2/k_{-1} \gg k_{3,\text{oh}}[\text{OH}^-]/k_{-1}$, thus the simple eqn. (5) can be used for the calculations:

$$k_{\text{obs}} = k_1[\text{OH}^-] \frac{k_2/k_{-1} + k_{3,\text{HA}}[\text{HA}]/k_{-1}}{1 + k_2/k_{-1} + k_{3,\text{HA}}[\text{HA}]/k_{-1}} \quad (5)$$

Especially the rates at the lower pH value in Fig. 6 are valuable in the evaluation of k_1 and k_2/k_{-1} . The same values of these constants are of course used for the calculations of the curves in Figs. 5 and 6. Even though limiting values of k_{obs} are not obtained, and the fit of experimental values to calculated ones is not faultless — the experimental error might be of the order of 10 %, and

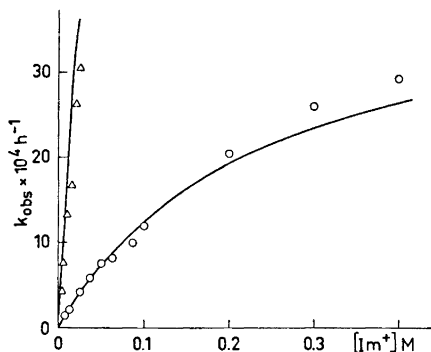


Fig. 6. Plot of k_{obs} for trimethylammonioacetanilide cation against concentration of imidazolium ion (Im^+). The lines are calculated from eqn. (5), using parameter values given in Table 2, and with $k_{3,\text{Im}^+}/k_{-1} = 4.0 \text{ M}^{-1}$. Catalysis at ratio [acid]:[base] = 1 ($[\text{H}^+] = 10^{-6.00}$) O, at ratio 0.1 ($[\text{H}^+] = 10^{-7.00}$) Δ . The limiting value of k_{obs} at $[\text{H}^+] = 10^{-6.00}$ is $43 \times 10^{-4} \text{ h}^{-1}$.

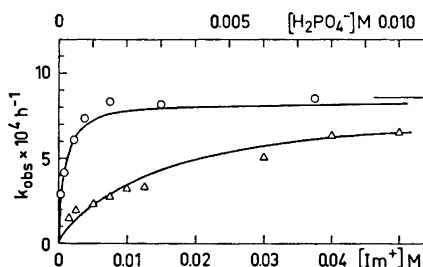


Fig. 7. Plot of k_{obs} for trimethylammonio-butyranilide cation against $[\text{H}_2\text{PO}_4^-]$ at $[\text{H}^+] = 10^{-6.99}$ ($[\text{H}_2\text{PO}_4^-]:[\text{HPO}_4^{2-}] = 0.25$) O, and against concentration of imidazolium ion (Im^+) at $[\text{H}^+] = 10^{-7.00}$ ([acid]:[base] = 0.1) Δ . The lines are calculated from eqn. (5), using parameter values given in Table 2, and with $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1} = 6000 \text{ M}^{-1}$, and $k_{3,\text{Im}^+}/k_{-1} = 65 \text{ M}^{-1}$. The bar denotes the limiting value of k_{obs} at $[\text{H}^+] = 10^{-7.00}$.

medium effects cannot be entirely ignored — the rates at the lower pH in Fig. 5 and the applicability of the same constants, both at the larger and at the smaller pH value, definitely support the mechanism underlying eqn. (5). Some experiments were also performed in the presence of phosphate. These experiments, which are not presented in graphic form here, give a value of $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1}$, which is only about one hundredth of that for trimethylammoniumbutyranilide cation (Fig. 7). Large concentrations of phosphate must therefore be used, in order to approach the limiting rate, and the influence on activity coefficients from phosphate species is then clearly noticeable; a value of $k_{3,\text{H}_2\text{PO}_4^-}/k_{-1}$, calculated from experiments in the presence of small concentrations of phosphate species, will give calculated rate values larger than the experimental ones at large concentrations of phosphate.

In Fig. 7, two curves calculated from eqn. (5) are given for the general acid catalyzed alkaline hydrolysis of trimethylammoniumbutyranilide cation: one for catalysis by phosphate, the other by imidazolium ion. From these experiments, the values of k_1 and k_2/k_{-1} , used in the construction of the profile in Fig. 5, are obtained.

Trimethylammonio-propionanilide cation. For this compound, Fig. 5 gives rates of hydrolysis only in acidic solution. The experiments have been followed both by UV-spectrophotometry at 240 nm (absorption maximum of the quaternary compound) and by the aniline method (diazotisation and coupling of the aniline formed). In neutral or alkaline solution, the quaternary compound undergoes a rapid hydroxide ion catalyzed elimination reaction, forming acrylanilide. This reaction is easily followed spectrophotometrically. At the absorption maximum of the quaternary compound at 240 nm, the absorbance of acrylanilide is about half of that of the former, and at the absorption maximum of acrylanilide at 265 nm, the absorption of the trimethylammonio-propionanilide cation is less than one fourth of that of acrylanilide. The second order rate constant for the elimination at 25°C and ionic strength 1 has been determined to $105 \text{ M}^{-1} \text{ min}^{-1}$ ($6300 \text{ M}^{-1} \text{ h}^{-1}$) from experiments in the $[\text{OH}^-]$ -range $10^{-2.7} - 10^{-4.3}$. This value corresponds to elimination rates at 25°C in alkaline solution, which are 10^3 times faster than the hydrolyses rates of trimethylammonioacetanilide and trimethylammoniumbutyranilide cation (taken as an average) at 95°C, hence it seems hardly possible to determine rate constants for the alkaline hydrolysis of trimethylammonio-propionanilide cation.

DISCUSSION

In addition to the parameter values of the seven anilides studied in this paper, values of methylamino- and dimethylaminoacetanilide from the previous paper¹ will be discussed. Parameter values for these nine compounds are summarized in Table 2.

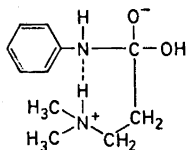
$k_{h,a}$. From Table 2 it is apparent that there is almost no difference in $k_{h,a}$ for the three butyric acid derivatives ($2.3 \text{ M}^{-1} \text{ h}^{-1}$) or for the three propionic acid derivatives, whose $k_{h,a}$ values, however, are about three times smaller ($0.8 \text{ M}^{-1} \text{ h}^{-1}$). For the three acetic acid derivatives, $k_{h,a}$ is still smaller (0.15 ; 0.067 ; $0.034 \text{ M}^{-1} \text{ h}^{-1}$), and decreases when the amino group, which here is close to the reaction center, becomes more bulky.

k_1 . The values of k_1 , the second order rate constant for formation of an intermediate between the cationic form of the anilides and hydroxide ion, indicate that steric factors are of small importance, and that the values are largely a function of the number of CH_2 -groups between the carbonyl carbon and the electron-withdrawing positively charged nitrogen. For the acetyl derivatives, the values are around $5000 \text{ M}^{-1} \text{ h}^{-1}$, for the propionyl derivatives around $1400 \text{ M}^{-1} \text{ h}^{-1}$, and for the butyryl derivatives around $200 \text{ M}^{-1} \text{ h}^{-1}$.

k_2/k_{-1} . When discussing factors influencing the k_2/k_{-1} parameter, it must be borne in mind that this ratio is determined by reactions undergone by the activated complex, having a tetrahedral carbon atom bound to the anilide nitrogen. The steric requirements for this tetrahedral carbon might, as is easily visualized by Stuart models, be rather different from those of the carbonyl carbon of the substrate.

The value of k_2/k_{-1} for trimethylammonioacetanilide cation is very small, and only insignificantly larger at 95°C than previously found at 25°C (0.0030).³ The small value at this lower temperature was ascribed to the high degree of steric strain in the bulky substrate-hydroxide ion complex. This strain is unquestionably much more facily relieved by reversion to reactants than by breakdown to products, because this latter process is thought to be preceded by a hindered hydrogen bonding to the anilide nitrogen.¹² For trimethylammoniobutyranilide cation, the value of k_2/k_{-1} is about ten times larger than for trimethylammonioacetanilide cation, and about the same as at 25°C for some previously investigated anilides, *viz.* trifluoro- and trichloroacetanilide (both 0.025)¹⁰ and monofluoroacetanilide (0.021).¹³ In the anilide-hydroxide ion intermediates of these compounds, the electron-withdrawing effect of the substituents naturally decreases the basicity of the anilide nitrogen and, with it, also its tendency to hydrogen bonding.¹⁴ The values of k_2/k_{-1} for these intermediates also are smaller than that for acetanilide (0.084).¹⁵ The difference in basicity of the anilide nitrogen in acetanilide and trimethylammoniobutyranilide cation cannot be large. The intermediate of the latter can, however, have conformations, effectively blocking hydrogen bonding to the anilide nitrogen.

For the methylamino- and dimethylaminoacetanilide cations, the values of k_2/k_{-1} are larger than for the currently discussed anilides, in spite of the comparatively low basicity of the anilide nitrogen, resulting from the electron-attracting character of the positively charged ammonium nitrogen. Still larger values of k_2/k_{-1} are obtained for the corresponding propionic and butyric acid derivatives, for which compounds an intermediate with intramolecular hydrogen bonding, as shown for dimethylammoniopropionanilide cation, seems reasonable.



Such an intermediate can directly give two good leaving groups, and a large value of k_2/k_{-1} is consequently to be expected. Intramolecular donation from an ammonium hydrogen atom to the anilide nitrogen might to some extent take place also in the intermediate of the acetyl derivatives, and be the reason for their rather large k_2/k_{-1} values.

$k_{\text{oh,a}}$. The values of $k_{\text{oh,a}}$ ($=k_1k_2/(k_{-1}+k_2)$) in Table 2 show that cations with an ionizable hydrogen are hydrolyzed by hydroxide ions much more rapidly than the corresponding trimethylammonium cations. As the difference in k_1 between these forms is small or negligible, almost all the differences in rates originate from the mode of partitioning of the tetrahedral intermediate.

$k_{3,h}/k_{-1}$. At pH-values where the anilides with a protolytic amino group are mainly present in the acidic form, and hydroxide ion initiated hydrolysis of these forms is the predominant reaction; the difference in rate between the two aminoacetanilides and the trimethylammonio derivative is even larger than is apparent from the values of $k_{\text{oh,a}}$. This is due to the H^+ -catalyzed k_3 -pathway. This pathway, which was also discussed in the previous paper,¹ is not apparent from the profiles of the other anilides now investigated. As already mentioned, and as is apparent from Fig. 5, rates are not determined for the quaternary compounds in the pH-range, where this form of catalysis might possibly exist. At all events, even if it occurs, the value of $k_{3,h}/k_{-1}$ must, at least for trimethylammonioacetanilide cation, be much smaller than for the other two acetyl derivatives. When compared with the profiles for methylamino- and dimethylaminoacetanilide, those for the corresponding propionyl and butyryl derivatives have their minima in k_{obs} displaced towards higher pH-values. This displacement, and the high values of k_2/k_{-1} , largely reduce the possibilities to detect an H^+ -catalyzed k_3 -pathway. Even values of $k_{3,h}/k_{-1}$ of the order 10^6 M^{-1} , as found for the acetyl derivatives, will hardly be revealed from the profiles at $[\text{H}^+]$ values smaller than 10^{-6} . With the minima in rate at $[\text{H}^+]$ values of $10^{-4.5} - 10^{-5}$, only a small pH-range is available for detection of even large values of $k_{3,h}/k_{-1}$. In that $[\text{H}^+]$ -range, the rates are small and the experimental difficulties exceptionally large, making the probable error in the rate constants as large as 10–20%. (With k_{obs} having a value as low as 10^{-4} h^{-1} , it will take about 2 h to obtain an absorbance of 0.5 in 10 cm cells, when hydrolyzing a 1% anilide solution.) For dimethylamino-propionanilide cation with experimentally determined rates around $[\text{H}^+] = 10^{-5}$, a better fit of the k_{obs} -values to the calculated curve would have been obtained if H^+ -catalysis in the k_3 -step had been taken into account.

From the above discussion it is apparent that of the anilides presented in Table 2, only the first two are suitable for detection of H^+ -catalysis in the k_3 -step and determination of $k_{3,h}/k_{-1}$, and that the corresponding propionyl and butyryl derivatives might have values of $k_{3,h}/k_{-1}$ of the same order as the acetyl derivatives, even if this is not clearly demonstrable from the profiles.

$k_{3,\text{oh}}/k_{-1}$. The value of $k_{3,\text{oh}}/k_{-1}$ for trimethylammonioacetanilide cation at 95°C in Table 2 is of the same order as at 25°C (0.37).³ Even though the value is small, the existence of the OH^- -catalyzed k_3 -pathway has a very large effect on the shape of the profile in Fig. 5. Thus, at infinite hydroxide ion concentration, the limiting value of k_{obs} , which is easily calculated from eqn. (3), is raised from 0.39 to 121 h^{-1} . As expected, OH^- -catalysis in the k_3 -step is less

important for trimethylammoniobutyranilide cation, but nevertheless, the effect is large enough to be clearly demonstrated at the largest hydroxide ion concentrations in Fig. 5.

The $k_{3,oh}/k_{-1}$ values for the acidic forms of the aminopropionyl and aminobutyryl derivatives, given in Table 2, are higher than previously found for anilides at 25°C, but of the same order as values for barbituric acids at 25°C.^{12,16,17} As discussed previously by Bender and Thomas,¹⁴ catalysis according to Scheme 1, with OH⁻ acting as a general base, cannot be differentiated from a combination of an equilibrium reaction (action of the substrate-hydroxide ion intermediate as an acid) and a rate process. Especially when regarding the $k_{3,oh}$ -step as a combination of a protolytic equilibrium and a rate process, it seems logical that the discussed intramolecular hydrogen bonding in the intermediates of these substrates, in which also an oxygen bound to the tetrahedral carbon might be involved instead of the anilide nitrogen, will increase the value of that equilibrium constant, and consequently also of $k_{3,oh}$. That no value is given for methylaminobutyranilide cation does not necessarily mean that it is small. As already pointed out, there are some indications in the profile of an OH⁻-catalyzed k_3 -step, but since k_2/k_{-1} has not been evaluated, no evaluation of $k_{3,oh}/k_{-1}$ is possible. No values of $k_{3,oh}/k_{-1}$ are given for the two aminoacetanilides in Table 2. From their profiles given in the previous paper,¹ it is apparent that values of the order reported for the corresponding propionyl and butyryl derivatives should have been revealed by the k_{obs} -values in the [H⁺]-region 10⁻⁸–10⁻¹⁰.⁵ The limit for detection of an OH⁻-catalyzed k_3 -pathway seems for these substrates to lie around a value of 100 M⁻¹ for $k_{3,oh}/k_{-1}$. The current discussion illustrates the great influence of the shape of a pH-rate profile on the possibilities to detect pathways and determine rate parameters. Thus the value 0.145 of $k_{3,oh}/k_{-1}$ M⁻¹ has a very large effect on the shape of the profile of trimethylammonioacetanilide cation, whereas a value of approximately 100 M⁻¹ should not be revealed from the profiles of methylamino- and dimethylaminoacetanilide.

$k_{oh,b}$. From both steric and electronic considerations, the values of $k_{oh,b}$ can be expected to be larger for a methylamino than for a dimethylamino derivative, the difference, however, being small when the length of the carbon chain between the carbonyl and amino groups is increased. This reasoning is largely valid for the acetyl and propionyl derivatives, whereas in the case of the butyranilides, the difference is large due to the unexpectedly high value for the methylamino derivative. A possible reason might be that an increased susceptibility to nucleophilic attack on the carbonyl carbon, owing to hydrogen bonding between the carbonyl oxygen and the amino hydrogen, is more pronounced in this substrate than in the corresponding propionyl derivative. Such an increased susceptibility due to hydrogen bonding also in the cationic form might explain a special reactivity towards water as nucleophile, leading to unexpectedly high values of k_{obs} in the [H⁺]-range 10⁻⁴–10⁻⁶.⁵

Up to [OH⁻]=1 there is no clear indication of an OH⁻-catalyzed k_3 -pathway for these uncharged anilides. Such a pathway is, however, supposed to exist and might at lower temperatures be noticed at smaller hydroxide concentrations.

$k_{3,HA}/k_{-1}$. Values of $k_{3,HA}/k_{-1}$ are given for $H_2PO_4^-$ and imidazolium ion in the legends to Figs. 4, 6, and 7. The experiments reported were performed mainly in order to evaluate k_1 and k_2/k_{-1} , or to obtain additional data for calculating these parameters; not much effort has been devoted to obtaining values of $k_{3,HA}/k_{-1}$ as accurate as possible. The only directly comparable values at 25°C and 95°C are for trimethylammonioacetanilide cation as substrate, and for imidazolium ion as catalyst, with $k_{3,HA}/k_{-1} = 11$ at 25°C, and 4 at 95°C. Comparisons of the values now obtained with those at 25°C for other substrates¹² seem, however, to permit the prediction that $k_{3,HA}/k_{-1}$ generally decreases with temperature.

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