Hydrolysis of Amides. Alkaline and General Acid Catalyzed Alkaline Hydrolysis of Some Substituted Acetamides and Benzamides

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Acetamide, trifluoroacetamide, trichloroacetamide, trimethylammonioacetamide cation, triethylammonioacetamide cation, benzamide, 4-nitrobenzamide, N,N-dimethyltrifluoroacetamide, N,N-diethyltrifluoroacetamide, N-cyclohexyltrifluoroacetamide, and N-benzyltrifluoroacetamide have been hydrolyzed at 25 °C or 45 °C in alkaline solution at ionic strength 1.

The pH-rate profiles show that the rate at high pH values is more than first-order in hydroxide ion concentration for the trialkylammonioacetamide cations, the benzamides, and the N-benzyltrifluoroacetamide, which can be interpreted as hydroxide ion catalyzed breakdown of a substrate-hydroxide ion intermediate. In accordance with a mechanism involving acid catalyzed breakdown of this intermediate to products, the rate of hydrolysis of these amides and of the N,N-diethyltrifluoroacetamide and the N-cyclohexyltrifluoroacetamide is enhanced by the presence of hydrogenphosphate or hydrogencarbonate ions. This makes it possible to determine the rate constants for the formation of the tetrahedral intermediates (k_1), and the ratios of the rate constants for the uncatalyzed breakdown of the intermediates to products and for their reversion to reactants (k_2/k_{-1}). The k_2/k_{-1} values are found to be largely independent of electronic effects in the acylic part but dependent on such effects from substituents in the amine part. The corresponding parameters (k_3/k_{-1}) for the hydroxide ion catalyzed breakdown of the intermediates have also been determined.

Many investigations have been carried out on the alkaline hydrolysis of aliphatic amides. Most of this work is summarized in the review of O'Connor[1] and in the work of DeWolfe and Newcomb.[2] The recent papers of Bolton and Jackson[3] and Yamana et al.[4] can also be mentioned, which deal with the effects of amide structure and temperature on the second order rate constant of the alkaline hydrolysis. The hydrolyses of, e.g., chloroacetamide,[5] trialkylammonioacetamide cations,[6] glycinamide,[7] and some N-substituted acetamides[4] showed at high pH values a dependence on hydroxide ion concentration larger than first order. The performed experiments did not, however, permit a detailed discussion of the mechanism. The mechanism of the hydrolysis of benzamide has earlier been investigated by measuring the hydrolysis rate and the oxygen exchange between carbonyl-^{18}O-labeled amide and water.[12,13]

In previous papers from this laboratory[8,9] rate equations have been derived from a mechanism (Scheme 1) shown to be applicable to the hydrolysis of anilides. As far as the mechanism refers to pure alkaline hydrolysis, it was also suggested by Mader[10] and Schowen et al.[11] The present investigation was undertaken to decide its validity in amide hydrolysis and when valid, to determine rate parameters corresponding to those already known for anilide hydrolysis.

MATERIALS AND METHODS

Materials. Benzamide, 4-nitrobenzamide, trifluoroacetamide, and trichloroacetamide of commercial grade were recrystallized from water. The acetamide was of reagent grade.

Trimethylammonioacetamide chloride was prepared from chloroacetamide and trimethylamine[14] and recrystallized from ethanol-ether;

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m.p. 192 – 194 °C (Ref. 14: 199 °C). The equiva-
lent weight was determined by argentometric
titration using 4,5-dichlorofluorescein as indica-
tor (found 153.9; calc. 152.6). Triethylammonio-
acetamide iodide was synthesized from diethyl-
aminoacetamide and ethyl iodide in acetone
solution (one week at room temperature) and
recrystallized from ethanol-ether; m.p. 150 –
152 °C (Ref. 6: 155 °C). Equiv. weight (argen-
tometric titration): 286.9; calc. 286.2. The di-
ethylaminoacetamide was prepared from chloro-
acetamide and diethylamine in ethanol-water
(24 h at room temperature); m.p. 74 – 75 °C
(Ref. 15: 76 °C). N,N-Dimethyltrifluoroacetam-
ide (Found: C 34.6; H 4.49; N 9.98. Calc.: C 34.1;
H 4.29; N 9.93) (b.p. 48 °C/16 mmHg; Ref. 16:
134.5 – 136.0 °C) and N,N-diethyltrifluoroacet-
amide (Found: C 42.5; H 5.89; N 8.06. Calc.:
C 42.6; H 5.96; N 8.28) (b.p. 60 °C/10 mmHg;
Ref. 17: 30 °C/2 mmHg) were prepared from the
ethyl ester of trifluoroacetic acid and the
appropriate amine.[16,17] N-Cyclohexyltrifluoro-
acetamide (m.p. 93 – 94 °C; Ref. 18: 94 – 95 °C)
and N-benzyltrifluoroacetamide (m.p. 72 – 75
°C; Ref. 18: 73.5 – 75 °C) were obtained from
trifluoroacetic anhydride and the appropriate
amine.[18]

All other chemicals used were of reagent
grade. In order to remove protolytic impurities
from the potassium chloride (reagent grade) it
was recrystallized from 0.1 M hydrochloric acid.

Hydrolysis experiments. The kinetic experi-
ments with trichloroacetamide and the trifluoro-
acetic acid derivatives were performed at 25 ±
0.05 °C. The other amides were hydrolyzed at
45 ± 0.1 °C. The concentration of the amides
varied between 0.002 and 0.04 M. The ionic
strength was 1, obtained by addition of potas-
sium chloride. Some experiments with benz-
amide were run at ionic strength 3. Water was
used as solvent except in the case of N-benzyl-
trifluoroacetamide and N-cyclohexyltrifluoro-
acetamide, when a solution of 9.6 v/v % ethanol
in water was used.

The experiments were performed as described
earlier.[8] The pH was maintained constant either
automatically with a Radiometer SBR titri-
graph combined with an SBU syringe burette
and a TTT titrator or manually with an Agla
microburette.[8] The rates of hydrolysis vary
considerably for the compounds. Thus, in some
experiments the hydrolysis was followed to
about 90 % completion, in others to less than
1 %. No loss of ammonia or amines due to
evaporation was noticed throughout the experi-
ments. The loss of chloride ions from trichloro-
acetamide has been shown to take place about
100 times slower than the hydrolysis.[5]

Hydrogenphosphate ions were used as cata-
lyzing species for the amides unsubstituted at
the amide nitrogen. Hydrogencarbonate ions
could not be employed for these amides because
they interfered in the assay method for am-
monia. For the N-substituted amides, however,
hydrogencarbonate ions were used.

The stoichiometric pK_w values have been
determined earlier and found to be 13.78 (25
°C, $\mu = 1$),[19] 13.92 (25 °C, 9.6 v/v % ethanol,
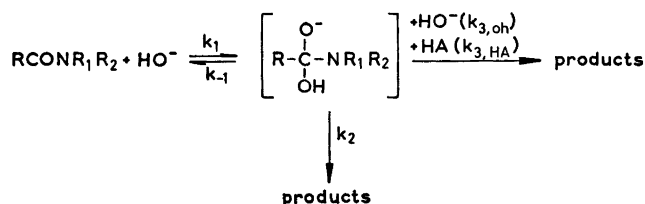$\mu = 1$)[8] and 13.16 (45 °C, $\mu = 1$).[20]

Assay. The ammonia formed in the hydrolysis
of the N-unsubstituted amides was determined
by a method – somewhat modified – used by
Kawamura.[21] It consists in oxidative condensa-
tion of aminopyrine and phenol in the presence
of potassium hexacyanoferrate(III) and am-
monium ions at pH 8. An aliquot of the hy-
drolysate at pH 8 was diluted to 15.00 ml with
1 M KCl. To this solution ($0.5 \times 10^{-4} – 4 \times 10^{-4}$
M in ammonium ions) 25.00 ml of a 0.1 M tris-
(hydroxymethyl)aminomethane buffer of pH 8.0
was added together with 4.00 ml of a solution
of 0.2 % phenol and 0.4 % aminopyrine and
3.00 ml of 5 % potassium hexacyanoferrate(III).
After exactly 30 min at room temperature the
solution was extracted with 10.00 ml of chloro-
form and the absorbance of the extract read at
455 nm in a 1 cm cell against a reagent blank.
The colour produced is stable for at least 1 h.
It is essential to have a fixed pH value and
ionic strength during the development of the
colour. The molar absorption coefficient was
1400. The rate constants (k_{obs} values) were
calculated from the slopes of the straight lines
obtained when plotting log [residual amide]
against time.

The hydrolysis of trifluoroacetamide was also
followed by UV measurements. The absorbance
of the amide in 0.1 M hydrochloric acid was
measured at 230 nm, where the absorbances of
the hydrolysis products are small. The rate
constants were obtained as described by Eriks-
son and Holst.[8] The results were in accordance
with those obtained by ammonia determination.
The UV method was also used for N-benzyltri-
fluoroacetamide and N-cyclohexyltrifluoroacet-
amide, the absorbances being measured at 228
nm and 225 nm, respectively.

To determine the dimethylamine and diethyl-
amine formed by hydrolysis of the N,N-dialkyl-
substituted amides, a method described by
Dahlgren[22] was used. The amines were chlo-
rinated at pH 8.1 and 25 °C with hypochlorite
(solution containing 9.5×10^{-3} % active chlorine)
and the excess hypochlorite was destroyed by
nitrite. The chloroamines then oxidized iodide
ions in a starch-potassium iodide reagent and
the colour produced was measured at 580 nm.
The molar absorption coefficient in the case
of dimethylamine was 31 000 and of diethyl-
amine 29 000. Some experiments at high pH
values with N,N-dimethyl- and N,N-diethyltri-
fluoroacetamide were followed by UV measure-
ments at 230 nm as described above, giving
results agreeing with those obtained by amine
determination.

RATE EQUATIONS AND RESULTS

The reaction scheme proposed for the alkaline
hydrolysis of anilides [8,9] is found to be applicable

$$RCONR_1R_2 + HO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\begin{array}{c} O^- \\ | \\ R-C-NR_1R_2 \\ | \\ OH \end{array} \right] \overset{+HO^- (k_{3,oh})}{\underset{+HA\ (k_{3,HA})}{\xrightarrow{\hspace{2cm}}}} products$$

$$\downarrow k_2$$

$$products$$

Scheme 1.

also here, *cf.* Scheme 1.

HA denotes weak acids. From the scheme, the following equation is derived, where k_{obs} is a pseudo first-order rate constant at constant pH.

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

Acetamide, trifluoroacetamide, and trichloroacetamide. As can be seen in Figs. 1 and 2, the pH-rate profiles for these compounds are straight lines with slope 1 in the pH-range used. Hence, no $k_{3,oh}$-step was found, and eqn. (1) simplifies to

$$k_{obs} = \frac{k_1 k_2 [HO^-]}{k_{-1} + k_2} = k_{oh}[HO^-] \quad (2)$$

The rate enhancing effect of hydrogencarbonate and hydrogenphosphate ions was also too small to permit an estimation of k_1 and k_2/k_{-1}.

Trimethylammonioacetamide and triethylammonioacetamide cations, benzamide, and 4-nitrobenzamide. According to Fig. 2, a more than first order dependence on hydroxide ion concentration is found at high pH values. With benzamide some experiments have been run at ionic strength 3 in order to be able to use high hydroxide ion concentrations to confirm the deviation from slope 1. For pure hydroxide ion catalysis eqn. (1) can be written in the form

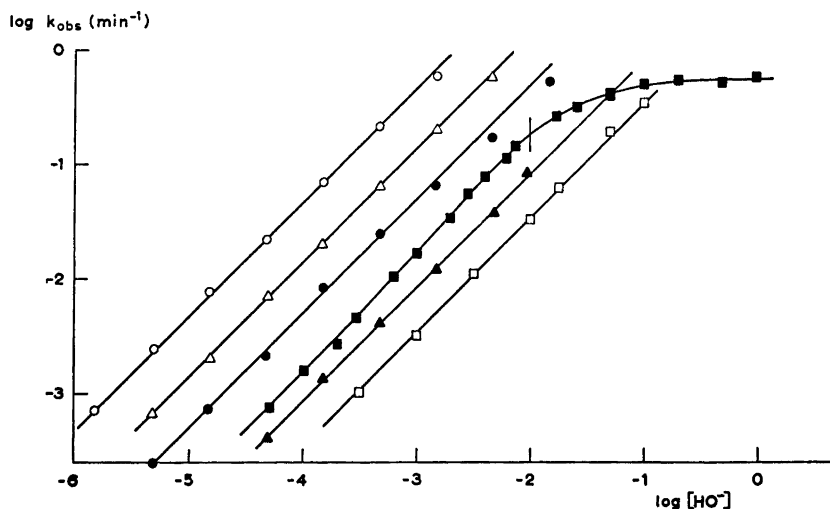$$k_{obs} = k_1[HO^-] \times \frac{k_2 + k_{3,oh}[HO^-]}{k_{-1} + k_2 + k_{3,oh}[HO^-]} \quad (3)$$

Fig. 1. Plot of log k_{obs} against log [HO$^-$] for trifluoroacetamide $\bigcirc$, trichloroacetamide $\bullet$, *N,N*-dimethyltrifluoroacetamide $\triangle$, *N,N*-diethyltrifluoroacetamide $\blacktriangle$, *N*-cyclohexyltrifluoroacetamide $\square$, and *N*-benzyltrifluoroacetamide $\blacksquare$ at 25 °C, $\mu = 1$. For the last two compounds the medium consisted of 9.6 v/v % ethanol. The fully drawn lines are calculated from eqns. (2) or (5) and parameter values given in Table 1. The bar denotes the value of [HO$^-$] corresponding to the $pK_a = 11.92$ for *N*-benzyltrifluoroacetamide.

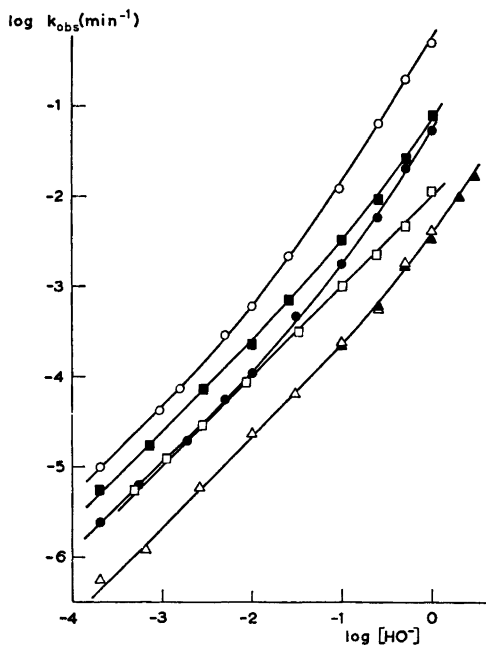Fig. 2. Plot of log k_{obs} against log [HO⁻] for acetamide □, trimethylammonioacetamide cation ○, triethylammonioacetamide cation ●, benzamide △, and 4-nitrobenzamide ■ at 45 °C, $\mu = 1$ and benzamide ▲ at 45 °C, $\mu = 3$. The fully drawn lines are calculated from eqns. (2) or (3) and parameter values given in Table 1.

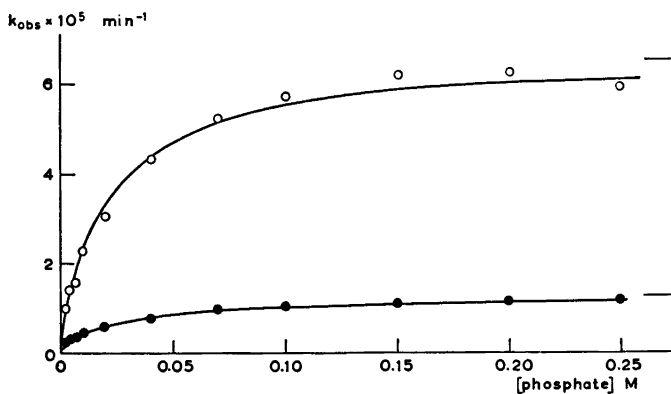Figs. 3 and 4 show some experiments in the presence of hydrogen phosphate ions. $k_{3,oh}[HO⁻]$

in eqn. (1) is negligible at the pH values used and thus the following equation is valid

$$k_{obs} = k_1[HO⁻] \times \frac{k_2 + k_{3,phosph}[\text{phosphate}]}{k_{-1} + k_2 + k_{3,phosph}[\text{phosphate}]} \quad (4)$$

From the limiting rates, k_1 can be determined with fairly good accuracy, $(k_{-1} + k_2)$ being negligible compared with $k_{3,phosph}$ [phosphate]. With k_1 known, k_2/k_{-1} is obtained from the experiments at low pH values in Fig. 2, where $k_{3,oh}[HO⁻] \ll k_2$, $k_{3,oh}/k_{-1}$ is obtained from the experiments at the largest values of [HO⁻].

Compounds substituted at the amide nitrogen. The pH-rate profiles in Fig. 1 for the *N*-substituted amides are straight lines except for *N*-benzyltrifluoroacetamide, where a small curvature upwards can be noticed at [HO⁻] = $2.5 \times 10^{-3} - 2.5 \times 10^{-2}$ M. This depends on hydroxide ion catalysis in the k_3-step. At still higher hydroxide ion concentrations, k_{obs} reaches a limiting value, indicating the existence of a pK_a value for this amide. Assuming that the amide anion is stable to hydrolysis, it can be shown that the following equation is valid, as has earlier been found for anilides.[8,19]

$$k_{obs} = \frac{k_1 K_w}{K_a + [H^+]} \times \frac{k_2 + k_{3,oh}[HO⁻]}{k_{-1} + k_2 + k_{3,oh}[HO⁻]} \quad (5)$$

At high pH values, where $k_{3,oh}[HO⁻] \gg (k_{-1} + k_2)$ and $K_a \gg [H^+]$, the equation simplifies to

$$k_{obs} = k_1 K_w / K_a \quad (6)$$

Fig. 3. Plot of k_{obs} against total concentration of phosphate at 45 °C, $\mu = 1$ for trimethylammonioacetamide cation ○ and triethylammonioacetamide cation ● at [H⁺] = $10^{-8.96}$. The lines are calculated from eqn. (4) with parameter values given in Table 1 and the following $k_{3,phosph}/k_{-1}$ values: ○ 50 M⁻¹, ● 45 M⁻¹. The bars denote limiting values of k_{obs}.
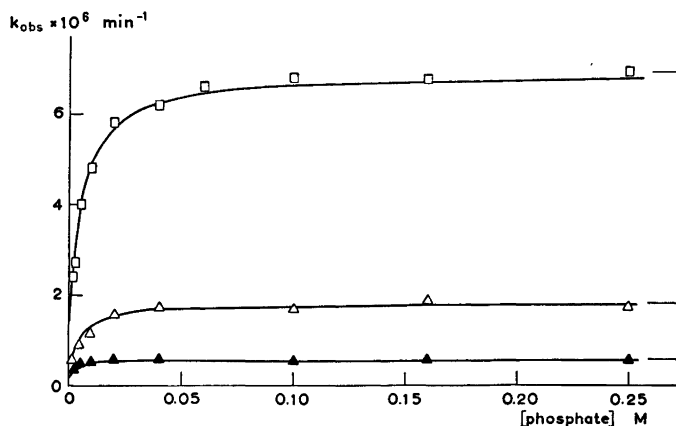
Fig. 4. Plot of k_{obs} against total concentration of phosphate at 45 °C, $\mu = 1$ for 4-nitrobenzamide ☐ and benzamide ▲ at $[H^+] = 10^{-8.96}$ and for benzamide at $[H^+] = 10^{-9.46}$ △. The lines are calculated from eqn. (4) with parameter values given in Table 1 and the following $k_{3,phosph}/k_{-1}$ values: ☐ 220 M^{-1}, △ 250 M^{-1}, and ▲ 700 M^{-1}. The bars denote limiting values of k_{obs}.

thus giving a constant value of k_{obs}.

The experiments with hydrogencarbonate ions showed no catalytic effect for N,N-dimethyltrifluoroacetamide. Thus for this amide only $k_{oh} = k_1 k_2/(k_{-1} + k_2)$ could be calculated. The k_1 values for the other N-substituted compounds were obtained from the experiments with hydrogencarbonate ions (Figs. 5 – 7) at low pH values

Fig. 5. Plot of k_{obs} against concentration of hydrogencarbonate ions at 25 °C, $\mu = 1$ for N,N-diethyltrifluoroacetamide at $[H^+] = 10^{-8.36}$ ($[HCO_3^-]/[CO_3^{2-}] = 18$) ○ and at $[H^+] = 10^{-8.72}$ ($[HCO_3^-]/[CO_3^{2-}] = 8$) △. The curves are calculated from eqn. (1) with parameter values given in Table 1 and the following $k_{3,HCO_3^-}/k_1$ values: ○ 45 M^{-1} and △ 40 M^{-1}. The bars denote limiting values of k_{obs}.

as described above for hydrogenphosphate catalysis. With k_{oh} and k_1 known, k_2/k_{-1} is calculated using eqn. (2) and $k_{3,HCO_3^-}/k_{-1}$ from the experiments in Figs. 5 – 7 using eqn. (1), $k_{3,oh}[HO^-]$ being negligible. The stoichiometric pK_a value of 11.92 for N-benzyltrifluoroacetamide is obtained from eqn. (6) using the limiting value of k_{obs} at the highest hydroxide ion concentrations.
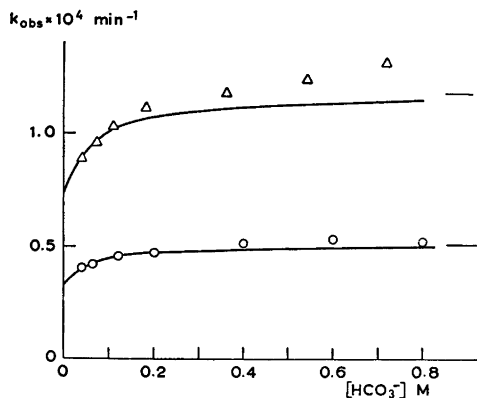
DISCUSSION

Pure alkaline hydrolysis. In anilide hydrolysis the breakdown of the substrate-hydroxide ion complex to products is thought to be preceded by a proton transfer to the anilide nitrogen.[9,23] In a recent work by Kershner and Schowen [24] on the hydrolysis of N-methylanilides it is suggested that the breakdown of the tetrahedral intermediate proceeds along two different rate-determining pathways, one involving proton transfer from catalyst to nitrogen giving an ammonium intermediate and the other involving C-N-bond cleavage to give a hydrogen-bonded anilide ion intermediate. The former is favoured by poor leaving groups (pK_b of the corresponding aniline < 9) and the latter by good leaving groups (pK_b of the corresponding aniline > 9). If this is true also for other amides, the compounds studied in this work require a proton transfer to the amide nitrogen before
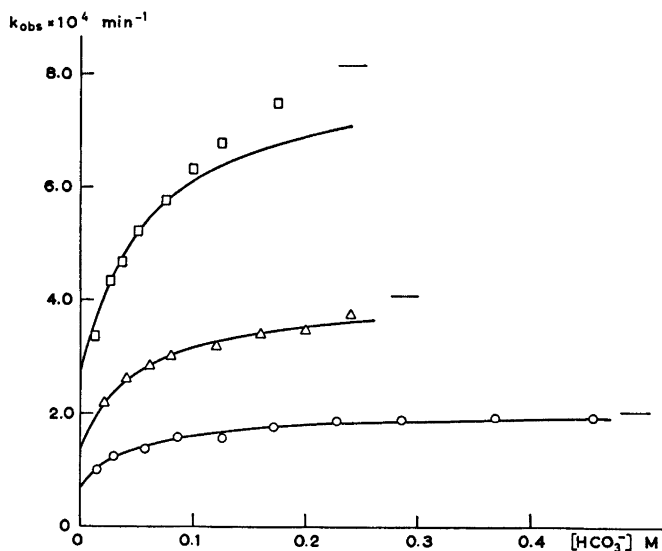
Fig. 6. Plot of k_{obs} against concentration of hydrogencarbonate ions at 25 °C, $\mu = 1$ in 9.6 v/v % ethanol for *N*-cyclohexyltrifluoroacetamide. The curves are calculated from eqn. (1) and parameter values given in Table 1. Values of $k_{3,HCO_3}-/k_{-1}$ are given below. The bars denote limiting values of k_{obs}.

	$[H^+]$	$[HCO_3^-]/[CO_3^{2-}]$	$k_{3,HCO_3}-/k_{-1}$ M^{-1}
O	$10^{-9.21}$	4:1	32
△	$10^{-9.51}$	2:1	29
□	$10^{-9.81}$	1:1	25

product formation from the intermediate. The ease of this transfer and hence the k_2/k_{-1} ratio seems to be insensitive to inductive effects of acyl substituents but decreased by steric hindrance.[8,25,26]

No or a very small general acid catalytic effect was found for the hydrolyses of acetamide, trifluoroacetamide, trichloroacetamide, and *N,N*-dimethyltrifluoroacetamide, indicating a high value of the partitioning ratio k_2/k_{-1}. This is to be expected, because the steric hindrance for the proton transfer to the amide nitrogen is small. For these compounds, only the second order rate constant for the alkaline hydrolysis (*cf.* k_{oh} in Table 1) could be determined. As k_2/k_{-1} is large, k_1 is approximately equal to k_{oh} according to eqn. (2), and the value increases as expected with increasing electron-attracting power of the substituents. The value for trichloroacetamide is almost in accordance with that obtained by Kezdy and Bruylants[5] (46.8 M^{-1} min^{-1}), who followed the hydrolysis with UV measurements. Yamana *et al.*[4] found that the alkaline hydrolysis

of acetamide was more than first-order in hydroxide ion concentration at high pH values. We, however, have not been able to confirm this.

The k_1 values, given in Table 1, for the benzamides and trialkylammonioacetamide cations are reasonable, considering the influence of steric and inductive effects on the formation of the intermediate. Bender *et al.*[12] have determined k_1 for benzamide to 1.15×10^{-2} M^{-1} min^{-1} at 40.7 °C (this work 0.92×10^{-2} M^{-1} min^{-1} at 45 °C) from hydrolysis rate measurements together with oxygen exchange data. Their k_2/k_{-1} ratio was 0.263 (this work 0.30). The ratios k_2/k_{-1} for the two benzamides are almost the same, showing no influence from the different inductive effects of the acyl parts, which confirms the earlier results with anilides.[8] The values are larger than that for acetanilide (0.084 at 25 °C),[27] probably due to the larger basicity of the amide nitrogen compared with the anilide nitrogen and less steric hindrance, both being favourable for the proton transfer to nitrogen. For the trialkylammonioacetamide cations the k_2/k_{-1} ratios are

Table 1. Experimentally determined rate parameters, used in the construction of Figs. 1 — 7. The solvent was water except for the last two compounds, where 9.6 v/v % ethanol in water was used. The ionic strength was 1.

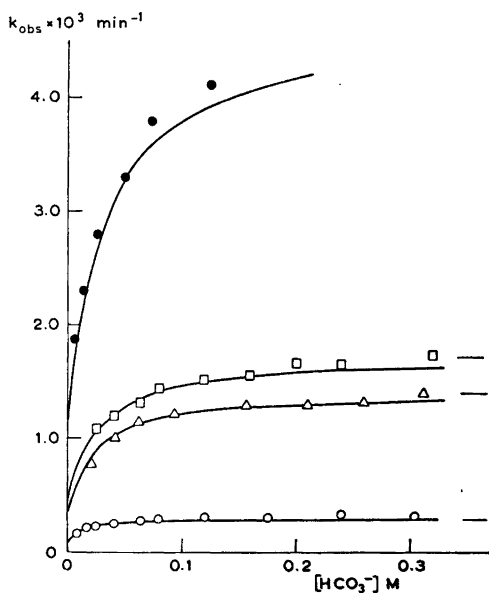| Compound	Temp. °C	$k_{oh}{}^{a}$ M^{-1} min^{-1}	k_1 M^{-1} min^{-1}	k_2/k_{-1}	$k_{3,oh}/k^{-1}$ M^{-1}
CH_3CONH_2	45	0.0100			
CF_3CONH_2	25	470			
CCl_3CONH_2	25	50.5			
$(CH_3)_3N^+CH_2CONH_2$	45	0.0470	1.05	0.047	1.00
$(C_2H_5)_3N^+CH_2CONH_2$	45	0.0110	0.20	0.059	0.34
$PhCONH_2$	45	0.00212	0.0092	0.30	0.50
$4\text{-}NO_2\text{-}Ph\text{-}CONH_2$	45	0.0240	0.11	0.28	1.30
$CF_3CON(CH_3)_2$	25	140			
$CF_3CON(C_2H_5)_2$	25	8.60	13.5	1.75	
$CF_3CONH\text{-}C_6H_{10}$	25	3.50	10.5	0.50	
$CF_3CONHCH_2\text{-}Ph$	25	15.0	60	0.33	130

^{a} $k_{oh} = k_1k_2/(k_{-1} + k_2)$.

Fig. 7. Plot of k_{obs} against concentration of hydrogencarbonate ions at 25 °C, $\mu = 1$ in 9.6 v/v % ethanol for *N*-benzyltrifluoroacetamide. The curves are calculated from eqn. (1) and parameter values given in Table 1. Values of $k_{3,HCO_3}/k_{-1}$ are given below. The bars denote limiting values of k_{obs}.

	[H$^+$]	[HCO$_3^-$]/[CO$_3^{-2}$]	$k_{3,HCO_3}/k_{-1}$ M^{-1}
O	$10^{-8.61}$	16:1	120
△	$10^{-9.21}$	4:1	60
□	$10^{-9.38}$	8:3	50
●	$10^{-9.81}$	1:1	40

smaller, the acyl substituents being bulkier than in the benzamides.

According to Taft-type steric parameters [4,28] and Stuart molecule models, the *N,N*-diethyltrifluoroacetamide ought to be more sterically hindered at the carbonyl group than the cyclohexyl compound, which in turn should be more hindered than the amide with a benzyl substituent. Comparing molecule models of the tetrahedral intermediates with regard to the hindrance at the nitrogen, the differences seem to be smaller. Despite the larger steric hindrance and the somewhat larger electron-releasing power of the diethyl compound compared with the cyclohexyl one, the k_1 value is higher for the former. The latter amide is hydrolyzed in 9.6 v/v % ethanol solution and some decrease of k_1 can be expected, as has been noticed before for acetanilide (0.0047 and 0.0039 M^{-1} min^{-1}, resp.).[27] The decrease here is almost equally as large. Thus it seems that the k_1 values in water solution are about the same. The differences between the k_2/k_{-1} values of these amides substituted at the amide nitrogen might be explained as due to the different nitrogen electron availabilities, which will influence the protonation before breakdown to products. k_2/k_{-1} for trifluoroacetanilide [8] is twenty times lower than that for *N*-cyclohexyltrifluoroacetamide (0.025 and 0.50, resp.) and eight times lower than the value for *N*-methyltrifluoroacetanilide (0.205).[24] Some increase in k_2/k_{-1} values has also been found for *N*-methyltri-

fluoroacetanilides with electron-donating ring substituents.[24] The electron-attracting power of the substituents is reflected in the $k_{3,oh}/k_{-1}$ values, as has been found previously for, $e.g.$, trifluoroacetanilide and trichloroacetanilide ($k_{3,oh}/k_{-1}$ = 93 and 34 M^{-1}, resp.).[8]

Catalysis by weak acids. The experiments with hydrogenphosphate and hydrogencarbonate ions have been run mainly to enable the k_1 values to be calculated. Only the experiments giving limiting rates with hydrogenphosphate ions are given in Figs. 3 and 4. Some preliminary experiments not reaching limiting rates were run at $[H^+] = 10^{-9}$.[46] also for the other amides in the figures beside benzamide and showed that $k_{3,phosph}/k_{-1}$ decreased with decreasing concentration of hydrogen ions. The same tendency is noticed in Figs. 5 − 7, where hydrogencarbonate ions were used as catalyst. An explanation might be the existence of more than one intermediate as suggested for the hydrogencarbonate ion catalysis of anilides.[9,19] At high pH values and high concentrations of the carbonate system the calculated curves in Figs. 5 − 7 deviate somewhat from the experimental results. This might be due to carbonate ion acting as a nucleophile or catalyzing the water attack on the amide when forming the tetrahedral intermediate, as described earlier.[19,29]

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