Hydrolysis of Anilides. XII. Alkaline and General Acid Catalyzed Alkaline Hydrolysis of Two *ortho*-Substituted Trifluoroacetanilides

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Rate-pH-profiles are given for the alkaline hydrolysis of trifluoroacet-2,4-dimethylanilide and trifluoroacet-2,6-dimethyl-3-nitroanilide at 45 °C and ionic strength 1 in an aqueous medium containing 20 v/v % dimethyl sulfoxide. The pK_a values of these anilides have been determined in the same medium.

The rate constants for the formation of the tetrahedral amide-hydroxide ion intermediates (k_1) are given as well as the ratios of the rate constants for the uncatalyzed breakdown (k_2) of the intermediates and for the reversion to reactants (k_{-1}). A very low k_2/k_{-1} value (0.00060) is found for the trifluoroacet-2,6-dimethyl-3-nitroanilide. The corresponding ratios for the hydroxide ion $(k_{3,oh}/k_{-1})$ and for the hydrogen-carbonate ion $(k_{3,HCO_3}{}^-/k_{-1})$ catalyzed product formation from the intermediates have also been determined.

To obtain information on the effect of dimethyl sulfoxide on the rate constants, trifluoroacetanilide was hydrolyzed at 25 °C in an aqueous alkaline medium of ionic strength 1 containing 5 or 20 v/v % dimethyl sulfoxide. Some increase with increasing dimethyl sulfoxide contents was found in the k_1 values while the k_2/k_{-1} ratios were almost unchanged.

In the previous work in this series [1] a sterically highly hindered amide, trifluoroacet-2,6-dimethylanilide, was studied and an extremely low ratio (0.0008) of k_2/k_{-1} (cf. Scheme 1) was found. To get more information concerning the basis for low k_2/k_{-1} values two other *ortho*-substituted anilides have now been studied, one of them with an electron-attracting ring substituent (NO_2). The NO_2-group decreases pK_a and increases k_1 and $k_{3,oh}/k_{-1}$, factors profitable for obtaining high accuracy in the calculation of rate parameters. The experiments were run in

20 v/v % dimethyl sulfoxide solution, and in order to learn how the DMSO content affects the rate constants, the previously studied [2] trifluoroacetanilide has been hydrolyzed at two different DMSO concentrations.

MATERIALS AND METHODS

Materials. The trifluoroacet-2,4-dimethylanilide was prepared from 2,4-dimethylaniline and trifluoroacetic anhydride and recrystallized from aqueous ethanol; m.p. 93 – 94 °C (Ref. 3 gives 91 °C).

The trifluoroacet-2,6-dimethyl-3-nitroanilide, obtained by nitration of trifluoroacet-2,6-dimethylanilide with mixed acid, had melting point 108 – 110 °C and analysis gave: C 46.2, H 3.39, N 10.9. (Calc. C 45.8, H 3.46; N 10.7). To determine the site of nitration, the anilide was hydrolyzed in 1 M hydrochloric acid and the substituted aniline was isolated. It consisted of yellow crystals with m.p. 80 – 81 °C. Ref. 4 gives m.p. 81 – 82 °C for 2,6-dimethyl-3-nitroaniline while 2,6-dimethyl-4-nitroaniline melts at 158 – 160 °C.

The trifluoroacetanilide was of the quality used earlier by Eriksson and Holst.[2] All other chemicals were of reagent grade. In order to remove protolytic impurities from the potassium chloride, it was recrystallized from 0.1 M hydrochloric acid.

Hydrolysis experiments. The experiments with the ring-substituted anilides were run at 45 ± 0.1 °C in an aqueous solution containing 20 v/v % dimethyl sulfoxide and having an ionic strength of 1, obtained by addition of potassium chloride. The trifluoroacetanilide was hydrolyzed at 25 ± 0.05 °C and ionic strength 1 in solutions of 5 and 20 v/v % dimethyl sulfoxide in water. The concentration of the anilides varied between 5×10^{-4} and 0.01 M. The experiments were run at constant pH as described

previously.[1] Carbon dioxide was excluded when hydrolyzing at the lowest pH values by performing the experiments under nitrogen.

The stoichiometric pK_a and pK_w values were determined potentiometrically in the same way as described earlier [3,5] and are given in Table 1. Hydrogencarbonate ions were used as catalyzing species for the ring-substituted anilides.

Assay. The hydrolyses were followed by determining the anilines by diazotisation and coupling with N-(1-naphthyl)ethylenediamine as described earlier.[2] The 2,4-dimethylaniline couples very slowly and the previously used method had to be modified. Thus the coupling reaction was allowed to proceed during 72 h in a refrigerator and the coloured product was measured at 560 nm. The molar absorption coefficient of about 30 000 varied somewhat from time to time. Thus reference samples were always run concurrently. The coupled product of diazotized 2,6-dimethyl-3-nitroaniline has a molar absorption coefficient of 38 100 at 500 nm.

RATE EQUATIONS AND RESULTS

The results are consistent with the reactions in Scheme 1, where B denotes hydroxide or hydrogencarbonate ions (substituents in the aromatic ring are omitted). Using the steady-state approximation, eqn. (1) can be derived, where k_{obs} is the pseudo first-order rate constant at constant pH.

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

When $(k_{-1} + k_2)$ is negligible compared to $k_{3,i}[B_i]$, the equation simplifies to

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

Thus, under these presumptions, k_{obs} reaches a limiting value from which k_1 can be obtained. According to Figs. 1 and 2 the experiments in alkaline medium could be used for the calculation of k_1. For trifluoroacet-2,4-dimethylanilide the experiments with hydrogencarbonate ion catalysis could also be used for this purpose (*cf.*
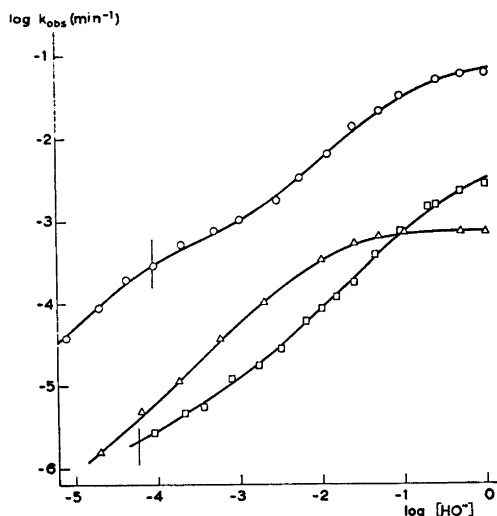

Fig. 1. Plot of log k_{obs} against log [HO⁻] for trifluoroacet-2,4-dimethylanilide ○, trifluoroacet-2,6-dimethyl-3-nitroanilide △, and trifluoroacet-2,6-dimethylanilide (from Ref. 1) □ at 45 °C in a 20 v/v % DMSO solution of ionic strength 1. The fully drawn lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of log [HO⁻] corresponding to the stoichiometric pK_a values in Table 1.

Fig. 3). With k_1 known, k_2/k_{-1} and $k_{3,oh}/k_{-1}$ were calculated as described previously using a Hewlett-Packard 9810A model 10 calculator.[1] The values giving the best fit to experimental data are given in Table 1 and were used when calculating the curves in Figs. 1 and 2.

The curves in Fig. 4 for hydrogencarbonate ion catalysis of the nitro compound almost coincide. The experiments were run at pH values above the pK_a, and from eqn. (1) it is apparent that graphs of k_{obs} as a function of $[HCO_3^-]$ will be pH-independent when $K_a \gg [H^+]$ and $k_{3,HCO_3^-}/k_{-1}$ is a real constant. No approach to a limiting rate was reached and so
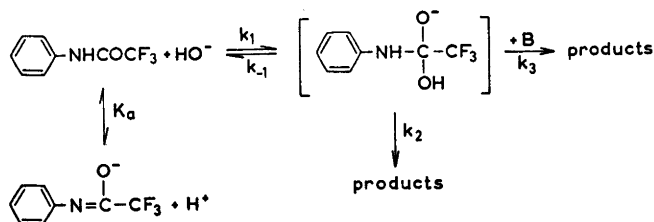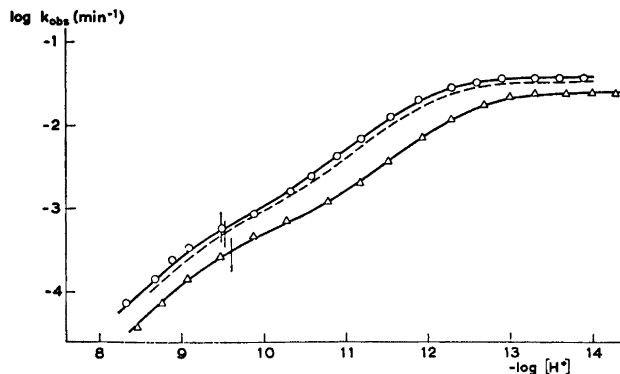
Scheme 1.

Fig. 2. Plot of log k_{obs} against $-\log$ [H$^+$] for trifluoroacetanilide at 25 °C and ionic strength 1 in 5 v/v % (O) and 20 v/v % (△) DMSO solution. The dashed curve is for 9.6 v/v % ethanol solution and taken from Ref. 2. The fully drawn lines are calculated from eqn. (1) and parameter values given in Table 1. The bars denote the values of $-\log$ [H$^+$] corresponding to the stoichiometric pK_a values in Table 1.
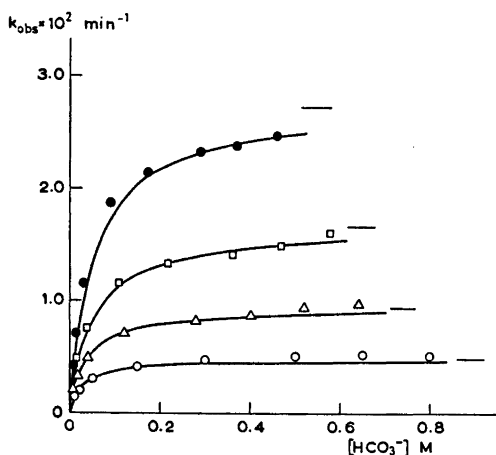

Fig. 3. Plot of k_{obs} against concentration of hydrogencarbonate ions for trifluoroacet-2,4-dimethylanilide at 45 °C and ionic strength 1 in 20 v/v % DMSO solution. The curves are calculated from eqn. (1) and parameter values given in Table 1 and $k_{3,HCO_3}-/k_{-1}$ values given below. The bars denote limiting values of k_{obs}.

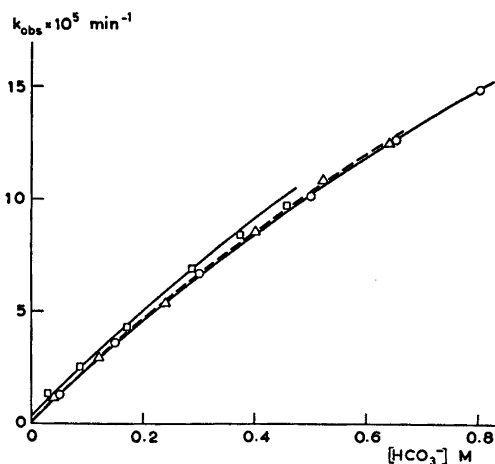| [H$^+$]	[HCO$_3^-$]/[CO$_3^{2-}$]	$k_{3,HCO_3}-/k_{-1}$M^{-1}
O $10^{-8.43}$	32	35
△ $10^{-8.74}$	16	30
☐ $10^{-9.04}$	8	20
● $10^{-9.34}$	4	20

Fig. 4. Plot of k_{obs} against concentration of hydrogencarbonate ions for trifluoroacet-2,6-dimethyl-3-nitroanilide at 45 °C and ionic strength 1 in 20 v/v % DMSO solution. The curves are calculated from eqn. (1) and parameter values given in Table 1 and $k_{3,HCO_3}-/k_{-1}$ values given below.

[H$^+$]	[HCO$_3^-$]/[CO$_3^{-2}$]	$k_{3,HCO_3}-/k_{-1}$M^{-1}
O $10^{-8.43}$	32	0.39
△ $10^{-8.74}$	16	0.35 dashed curve)
☐ $10^{-9.34}$	4	0.34

the experiments could not be used for the calculation of k_1. $k_{3,HCO_3^-}/k_{-1}$ values given in the text to Figs. 3 and 4 are obtained from the experiments shown in these figures and are used together with parameter values in Table 1 when calculating the theoretical curves from eqn. (1).

DISCUSSION

The k_1 values in Table 1 for the ring-substituted anilides follow the expected pattern, i.e. ortho-substitution with methyl groups decreases k_1 and an electron-attracting nitro group in a position other than ortho increases the constant. This increase is about seven times, which is somewhat less than the thirteenfold increase found when N-methyltrifluoroacetanilide is m-nitro-substituted.[6] The low ratios of k_2/k_{-1} for the ring-substituted anilides may undoubtedly be related to highly hindered proton transfers in the tetrahedral intermediates. Electron-releasing ring substituents, such as CH_3, in meta or para position, have been shown to increase the value of k_2/k_{-1}, the effect, however, being rather small.[6] The values reported here for the 2,6-substituted compounds seem to be by far the lowest hitherto found in amide hydrolysis.

The steric hindrance also decreases the $k_{3,oh}/k_{-1}$ and $k_{3,HCO_3^-}/k_{-1}$ ratios. In accordance with results obtained recently for p-nitrotrifluoroacetanilide,[7,8] the $k_{3,oh}/k_{-1}$ value is also here found to be significantly increased by a nitro substituent. The larger dependence on nitro-substitution of $k_{3,oh}/k_{-1}$ than of k_2/k_{-1} was interpreted by Pollack and Dumsha[7] to signify that, contrary to the mechanism of the k_2-step,

a negative charge is formed on the amide nitrogen in the transition state of the $k_{3,oh}$-step for the nitro-substituted anilide. According to them, the mechanism with a negatively charged leaving aniline group then should be specific for anilides with strongly electron-attracting groups in the ring.

The $k_{3,HCO_3^-}/k_{-1}$ ratios increased slightly with increasing concentration of hydrogen ions as has been noticed earlier and discussed for other compounds.[1,9]

According to Table 1, the k_1 value of trifluoroacetanilide increases somewhat with increasing concentration of dimethyl sulfoxide. This was expected because of the desolvation of hydroxide ions in DMSO-water mixtures. The same effect has been found earlier for the second-order rate constants for the alkaline hydrolyses of, e.g., ethyl acetate[10] and aliphatic dicarboxylic esters.[11] Gani and Viout[12] found that second order rate constants for the alkaline hydrolyses of p-chlorophenoxyacetamide and acetamide decreased with increasing concentration of DMSO. In the present work an increase of the second-order rate constant of the alkaline hydrolysis (k_{oh}) is, however, found, when the DMSO concentration is increased, this being due to the increase of k_1, while the ratio k_2/k_{-1} remains almost constant. It is hard to draw any general conclusions from this as only two mixtures were investigated, both with rather small concentrations of DMSO. Our main purpose with these experiments was to establish how the used concentrations of DMSO influence the values of k_2/k_{-1}. The results seem to permit the conclusion that the influence is small.

Table 1. Experimentally determined dissociation constants and rate parameters used in the construction of Figs. 1–4. The solvent was 20 v/v % DMSO unless otherwise noted and the ionic strength was 1. $pK_w = 14.27$ (25 °C) and 13.64 (45 °C).

	Temp. °C	pK_a	$k_{oh}{}^a$ M^{-1} min^{-1}	k_1 M^{-1} min^{-1}	k_2/k_{-1}	$k_{3,oh}/k_{-1}$ M^{-1}
Trifluoroacet-2,6-dimethylanilide [b]	45	9.40	0.0660	83	0.00080	1.8
Trifluoroacet-2,6-dimethyl-3-nitroanilide	45	7.77	0.340	570	0.00060	80
Trifluoroacet-2,4-dimethylanilide	45	9.59	5.91	850	0.0070	7.3
Trifluoroacetanilide	25	9.60	29.3	1200	0.024	85
Trifluoroacetanilide [c]	25	9.47	25.6	1050	0.025	100
Trifluoroacetanilide [d]	25	9.51	22.7	930	0.025	93

^{a} $k_{oh} = k_1 k_2/(k_{-1} + k_2)$. ^{b} The values are taken from Ref. 1. ^{c} In 5 v/v % DMSO ($pK_w = 13.88$). ^{d} In 9.6 v/v % ethanol ($pK_w = 13.92$) (from Ref. 2).

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