

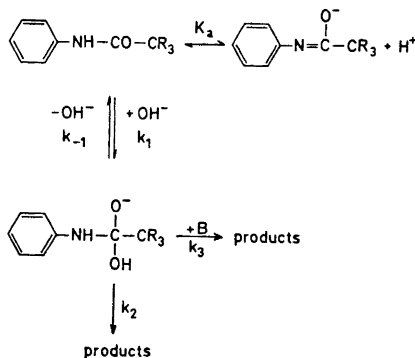
Hydrolysis of Anilides

XI. Kinetic Evidence for Extremely Unfavoured Product Formation from a Bulky Anilide-Hydroxide Ion Intermediate

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In previous papers from this laboratory the following reaction scheme for alkaline hydrolysis of anilides was presented.^{1,2}



Scheme 1.

B denotes hydroxide ions or weak acids. From this scheme, the following equation could be derived

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

k_{obs} being the pseudo first order rate constant at constant pH.

Values for the partitioning ratio k_2/k_{-1} of the order 0.003 were found at different temperatures in the alkaline hydrolysis of trimethylammonioacetanilide cation.^{3,4} Protonation of the anilide nitrogen is thought to precede product formation from the tetrahedral anilide-hydroxide ion intermediate and the very small value of k_2/k_{-1} was accounted as being due to steric hindrance of this process. It is well known that the local anaesthetic anilide lidocaine (diethylaminoacet-2',6'-dimethylanilide) is very stable towards hydrolysis, which is assumed to be due to the shielding effect

of the two *ortho* methyl groups.⁵ Also in that case, protonation of the anilide nitrogen of the tetrahedral intermediate might, however, be more hindered than the attack by hydroxide ion. In order to obtain information about the influence of two methyl groups in *ortho* positions on the steps in Scheme 1, the hydrolysis of the highly activated trifluoroacet-2',6'-dimethylanilide has now been studied.

Materials. The trifluoroacet-2',6'-dimethylanilide was prepared from 2,6-dimethylaniline and trifluoroacetic anhydride and recrystallized from aqueous ethanol; m.p. 90–92° (Ref. 6 gives 89–90°). In order to remove traces of protolytic impurities from the potassium chloride used (reagent grade), it was recrystallized from 0.1 M hydrochloric acid. All other chemicals were of reagent grade.

Determination of acidity constants. All determinations of equilibrium constants as well as the hydrolysis experiments were performed at $45 \pm 0.1^\circ\text{C}$ in an aqueous medium containing 20% (v/v) dimethyl sulfoxide and having an ionic strength of 1, obtained by addition of KCl. The stoichiometric $\text{p}K_w$ (= 13.64), the $\text{p}K_a$ of trifluoroacet-2',6'-dimethylanilide (= 9.40), and of HCO_3^- (= 9.94) were determined potentiometrically using a Radiometer pHM 4 as described previously for other solutions.^{1,7,8}

Hydrolysis experiments. All experiments were run at constant pH; for the smallest hydroxide ion concentrations in Fig. 1, the pH was held constant during hydrolysis by the addition of sodium hydroxide solution, either manually from an Agla microburette or automatically

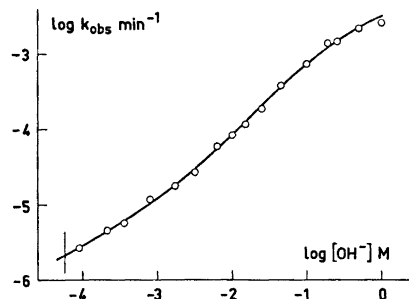


Fig. 1. Plot of $\log k_{\text{obs}}$ against $\log [\text{OH}^-]$. The curve is calculated from eqn. (1) using the following parameter values: $k_1 = 83 \text{ min}^{-1}$, $k_2/k_{-1} = 0.0008$, $k_{3,\text{OH}}/k_{-1} = 1.8 \text{ M}^{-1}$, $K_a = 4 \times 10^{-10}$ and $K_w = 2.3 \times 10^{-14}$. The bar denotes the value of $\log [\text{OH}^-]$ corresponding to the stoichiometric $\text{p}K_a$ -value of the anilide.

using a Radiometer TTT titrator and SBR titrigraph.^{1,9} The course of hydrolysis was followed by sampling and spectrophotometric determination of the 2,6-dimethylaniline at 280 nm in a phosphate buffer of pH 7.8. In that medium 2,6-dimethylaniline has a molar absorptivity of 1800 whereas that for the intact anilide is about 25.

Results. From the so-called pH-rate profile in Fig. 1, it is apparent that k_{obs} is approaching a limiting value at the largest hydroxide ion concentrations. The limit is reached when $k_{3,\text{oh}}[\text{OH}^-]/k_{-1} \gg (1 + k_2/k_{-1})$, *i.e.* when the second fraction expression in eqn. (1) becomes 1. Then k_1 is obtained directly from the limiting value of k_{obs} in a profile. Even though this situation is not reached in Fig. 1, the shape of the profile nevertheless permits a rough estimation of k_1 . From the k_{obs} -value at the smallest hydroxide ion concentration in Fig. 1, a maximum value of k_2/k_{-1} is easily calculated for a given value of k_1 . With k_1 and k_2/k_{-1} roughly known, $k_{3,\text{oh}}/k_{-1}$ can be estimated, preferably from experiments in the $[\text{OH}^-]$ -range of 10^{-1} – 10^{-2} . For 13 different values of k_1 in the range 50–100 $\text{M}^{-1} \text{min}^{-1}$ a series of calculations for different combinations of k_2/k_{-1} and $k_{3,\text{oh}}/k_{-1}$ have been performed using a program adapted to a Hewlett-Packard 9810A model 10 calculator. The values giving the best fit to the experimental ones are those finally used in the calculation of the curve in Fig. 1. In Fig. 2, profiles for hydrogen carbonate ion catalysis are given at four

different pH values. The values of $k_{3,\text{HCO}_3^-}/k_{-1}$ show a slight decrease with increasing pH. This might, as discussed in previous papers on anilide hydrolysis, be due to the existence of more than one intermediate on the reaction path.²

Discussion. At hydroxide ion concentrations larger than approximately 10^{-2} the slope of the profile in Fig. 1 decreases continually with increasing hydroxide ion concentrations, thus indicating that the anionic form of the anilide is stable towards alkaline hydrolysis in the investigated pH-range. It is of interest to compare rate parameters for trifluoroacetanilide and the compound now investigated. Unfortunately, the rate constants for trifluoroacetanilide were determined at a different temperature (25°C instead of 45°C) and in a somewhat different medium (9.6% (v/v) ethanol instead of 20% (v/v) dimethyl sulfoxide). Temperature has, however, been found to have only a small influence on k_2/k_{-1} and $k_{3,\text{i}}/k_{-1}$.^{3,4,10} Both ethanol and dimethyl sulfoxide certainly diminish the quotient k_2/k_{-1} somewhat.^{11,12} Its value in a pure aqueous medium is, however, probably less than twice the value in the discussed media. The actual solvent effects on k_1 are probably less than those on k_2/k_{-1} . The effect of dimethyl sulfoxide on the rate constants in hydrolysis of anilides is subject to further investigation. Trifluoroacetanilide has at 25°C a k_1 -value of 930 $\text{M}^{-1} \text{min}^{-1}$.¹ If the temperature dependence is about the same as for *N*-methyltrifluoroacetanilide¹³ the value at 45° should be around 2000 $\text{M}^{-1} \text{min}^{-1}$, *i.e.* somewhat more than 20 times larger than for the 2',6'-dimethyl derivative – a value corresponding well to the ratio of the rate constants for alkaline hydrolysis of the *N*-phenylcarbamic acid ester $\text{C}_6\text{H}_5\text{NHCOOC}_2\text{H}_4\text{N}(\text{C}_2\text{H}_5)_2$ and its 2',6'-dimethyl derivative.¹⁴ In the hydrolysis of esters, k_2/k_{-1} is generally large and the overall rate constants therefore do not deviate too much from the values of k_1 . The comparison consequently shows that two *ortho* methyl groups influence the formation of a tetrahedral substrate-hydroxide ion intermediate to about the same extent in anilides and *N*-phenylcarbamic acid esters. The much larger ratio in the rates of hydrolysis for the two anilides than for the carbamic acid esters is therefore essentially due to the extremely small value of k_2/k_{-1} for the trifluoroacet-2',6'-dimethylanilide and is explained on the basis of a sterically highly hindered reac-

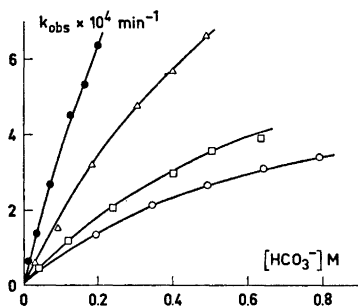


Fig. 2. Plot of k_{obs} against concentration of hydrogen carbonate ion. The curves are calculated from eqn. (1) and parameter values given in the text to Fig. 1 and the following values of $k_{3,\text{HCO}_3^-}/k_{-1}$: $-\log [\text{H}^+]$, $k_{3,\text{HCO}_3^-}/k_{-1}$: ○ 8.59, 1.4; □ 8.77, 1.25; △ 9.17, 1.2; ● 9.94, 1.0.

tion preceding breakdown to products, *viz.* protonation of the anilide nitrogen ($k_2/k_{-1} = 0.025$ for trifluoroacetanilide and 0.0008 for the 2',6'-dimethyl derivative). The small values of $k_{3,oh}/k_{-1}$ and $k_{3,HCO_3^-}/k_{-1}$ also reflect a high degree of steric hindrance in reactions between the tetrahedral intermediate and other species; the value of 1.8 M^{-1} for $k_{3,oh}/k_{-1}$ is to be compared with 93 M^{-1} for trifluoroacetanilide, and corresponding values for $k_{3,HCO_3^-}/k_{-1}$ are 1 and 300 M^{-1} . Due to the small value of k_2/k_{-1} , the effect of HCO_3^- on the rate is large despite the small value of the catalytic constant, thus for the lowest curve and highest concentration of HCO_3^- in Fig. 2 the rate is increased more than 600 times.

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1. Eriksson, S. O. and Holst, C. *Acta Chem. Scand.* **20** (1966) 1892.
2. Eriksson, S. O. *Acta Pharm. Suecica* **6** (1969) 139.
3. Eriksson, S. O., Meresaar, U. and Wahlberg, U. *Acta Chem. Scand.* **22** (1968) 2773.
4. Eriksson, S. O. and Meresaar, U. *Acta Chem. Scand.* **25** (1971) 2697.
5. Bullock, K. and Grundy, J. J. *Pharm. Pharmacol.* **7** (1955) 755.
6. Pailer, M. and Hubsch, W. J. *Monatsh. Chem.* **97** (1966) 1541.
7. Eriksson, S. O. and Regårdh, C. G. *Acta Pharm. Suecica* **6** (1968) 457.
8. Eriksson, S. O. and Meresaar, U. *Acta Chem. Scand.* **25** (1971) 2688.
9. Eriksson, S. O. *Acta Pharm. Suecica* **6** (1969) 321.
10. Bender, M. L., Ginger, R. D. and Unik, J. P. *J. Am. Chem. Soc.* **80** (1958) 1044.
11. Eriksson, S. O. *Acta Pharm. Suecica* **6** (1969) 121.
12. Gani, V. and Viout, P. C. R. H. *Acad. Sci. Ser. C* **274** (1972) 1746.
13. Schowen, R. L., Jayaraman, H. and Kershner, L. J. *J. Am. Chem. Soc.* **88** (1966) 3373.
14. Christensson, I. *Acta Chem. Scand.* **18** (1964) 904.

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Structural and Magnetic Properties of CrP

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In view of the interesting cooperative magnetic phenomena which have been disclosed for MnP^{1-4} and the isostructural phases FeP ,⁵ $\text{MnP}_{1-x}\text{As}_x$,^{6,7} CrAs ,⁸⁻¹⁰ $\text{Cr}_{1-x}\text{Mn}_x\text{As}$,¹¹ MnAs ,¹² and FeAs ,¹³ and the trends in these data, it seemed of interest to explore closer the magnetic properties of CrP. However, the sparse nuclear magnetic resonance and magnetic susceptibility data¹⁴ already at hand indicate that magnetic ordering may be absent in CrP down to 4.2 K. The results of a parallel study on VAs¹⁵ appear to suggest a similar conclusion.

Experimental. Samples were made by heating weighed quantities of the elements (99 % Cr crystal powder and 99.999 % red P from Koch-Light Laboratories) in evacuated, sealed quartz tubes. The samples were maintained for one week at 650°C, crushed, subjected to two further annealings at 850°C with intermediate crushings, and finally cooled to room temperature over a period of three days.

The experimental details concerning the X-ray and neutron diffraction, density, magnetic susceptibility, and diffuse reflectance measurements have been presented in previous communications.^{9,13,15}

Results. The composition of the CrP phase, which has no appreciable range of homogeneity, was determined to be $\text{CrP}_{1.00 \pm 0.03}$ by application of the disappearing phase principle to Guinier photographic data. Further support for the stoichiometric 1:1 composition is obtained from the pycnometrically measured density of 5.46 g cm^{-3} .

The results (Table 1) derived by least squares profile refinements of the powder neutron diffraction data taken at 17, 81, and 293 K show that the MnP type crystal structure of CrP remains virtually unchanged below room temperature. In view of the experience gained from our preceding neutron diffraction studies^{9,13,15} of isostructural compounds all calculations were