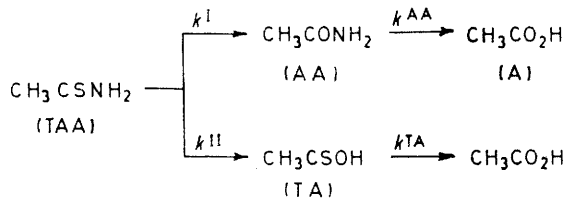
Kinetics of the Hydrolysis of Thioacetamide in Alkaline Solution

By **Oswald M. Peeters** and **Camiel J. De Ranter,*** Pharmacy Department, Katholieke Universiteit te Leuven, 3000 Leuven, Belgium

Kinetic studies of the hydroxide-catalysed hydrolysis of thioacetamide have shown that the reaction occurs by two parallel reaction paths. The rate constants of the overall reaction, the thioxo- and amino-group hydrolyses, have been determined in the temperature range 60—90° and the activation energies calculated. The relative importance of the two competitive reactions is influenced neither by temperature nor by variation in pH in the range 9.50—10.50. The mechanism of hydrolysis is discussed in the light of the mechanism proposed for amides.

THE hydrolysis of thioacetamide (TAA) can occur by two parallel reaction paths as represented in Scheme 1. In a previous paper we showed [1] that the acid-catalysed reaction proceeds predominantly by thioxo-group hydrolysis. Butler *et al.*[2] found in the hydroxide-catalysed



SCHEME 1

hydrolysis of TAA that amino-group hydrolysis prevails. Analytical difficulties restricted their quantitative experiments to a study of hydrolysis of the amino-group of TAA and of the hydrolysis of the evolved thioacetate (TA). From these hydrolysis rates an estimate was made of the rate of thioxo-group hydrolysis and also of the overall hydrolysis of TAA.

In the present study the individual reaction rates of thioxo- and amino-group hydrolysis of TAA, as well as the overall hydrolysis rate in sodium hydroxide solutions have been determined in the temperature range of 60—90° and at pH 9.50—10.50.

EXPERIMENTAL

Reagents.—All chemicals were AnalaR grade except thioacetic acid. This was purified by distillation and standardised potentiometrically with $AgNO_3$. Aqueous 0.01M-TAA solutions were prepared by weight. 1M-Sodium perchlorate solution was used to adjust the ionic strength. An NaOH solution (40 g l^{-1}) was used to control the pH to a predetermined value. The glass electrode was calibrated against 0.01M-disodium tetraborate solution. Buffers were sodium acetate–acetic acid (pH 4.7 and 5.7) and a sulphide antioxidant buffer [NaOH (20 g), ascorbic acid (18 g), and sodium salicylate (80 g) in H_2O (1 l)]. 5M-HCl was used to acidify TAA solutions for spectrophotometric determinations. Other solutions were 0.01M-lead perchlorate, 0.01M-EDTA, and 0.1M-silver nitrate.

Apparatus.—The reaction vessel was identical to that of ref. 1. The combined glass electrode was replaced by a Corning glass electrode and an Orion model 90-02 double junction reference electrode. A separate apparatus for removing hydrogen sulphide from the reaction samples consisted of a wash-bottle and four bubbling tubes. The first tube contained 10 ml of the pH 4.7 buffer, the second 5 ml of the reaction samples, and the fourth 25 ml of the sulphide antioxidant buffer. The third tube was a safety trap. The potentiometric titrations of TA and of sulphide were performed with a Tacussel Electronics autotitrator. The electrodes were an Orion model 94-16 specific sulphide ion electrode and an Orion model 90-02 double junction reference electrode. The absorption spectra were recorded on a Beckman model 25 spectrophotometer. For quantitative measurements a Shimadzu QV 50 spectrophotometer was used.

Procedure.—The experiments were performed at various temperatures (±0.5°). The TAA solution was stirred magnetically. Aeration of the solution with pure nitrogen prior to reaction removed dissolved oxygen; a stream of nitrogen was passed over the surface during the experiment to prevent reabsorption. The pH was adjusted to the predetermined value by the pH-stat mode of the autotitrator. Samples (6 ml) were taken at fixed intervals, transferred to test tubes, and placed in an ice-bath to quench the reaction. 5 ml of the sample was transferred to the second bubbling tube of the sulphide liberating apparatus. To test sulphide ion stability in the samples the sulphide concentration was followed with the specific sulphide ion electrode and showed a relative decrease of only 1% in 10 min. The whole transferring process required at most 4 min. A nitrogen stream pumped the pH 4.7 buffer from the first tube to the second where hydrogen sulphide was liberated and carried through the third to the fourth tube, where it was absorbed. Repeated tests showed that hydrogen sulphide was quantitatively forced through the bubbling tubes in a maximum of *ca.* 10 min and that it was completely retained by the collecting solution. The hydrolysis rates of TAA and TA at

[1] O. M. Peeters and C. J. De Ranter, *J.C.S. Perkin II*, 1974, 1832.

[2] E. A. Butler, D. G. Peters, and E. H. Swift, *Analyt. Chem.*, 1958, **30**, 1379.

room temperature and pH 4.7 are very small so that their contribution can be neglected. 20 ml of the sulphide-collecting solution was titrated potentiometrically against lead perchlorate which was standardised against EDTA solution at 70° at pH 5 (hexamethylenetetramine buffer), using Xylenol Orange as indicator. The solution from the second tube was transferred quantitatively to a 250 ml volumetric flask and diluted. 25 ml Of this solution was transferred into a 100 ml volumetric flask, 10 ml pH 5.7 buffer was added, and the mixture diluted to the mark. The absorbance resulting from both TAA and TA was measured at 245 nm. A further 25 ml of the solution was pipetted into a second 100 ml volumetric flask, 10 ml of 5M-HCl solution added, and the mixture diluted to 100 ml. The absorbance due to the TAA alone was measured at 261.5 nm.

RESULTS AND DISCUSSION

Spectra of TAA and TA.—The spectra of TAA and TA in pH 5.7 buffered solution and in 0.5M-HCl solution were recorded. The spectrum of TA in pH 5.7 buffered solution shows maxima at 245 and 225 nm, which are attributed respectively to thioacetate ion and to undissociated thioacetic acid.[3-5] The spectrum in 0.5M-HCl solution shows a single maximum at 220 nm due to undissociated TA. The calculated molar absorption coefficient of TA in pH 5.7 buffered solution at 245 nm is 8 755 l mol^{-1} cm^{-1}.

A change in pH has no significant effect on the spectrum of TAA. The molar absorption coefficients were calculated at 261.5, the maximum of the curve, and at

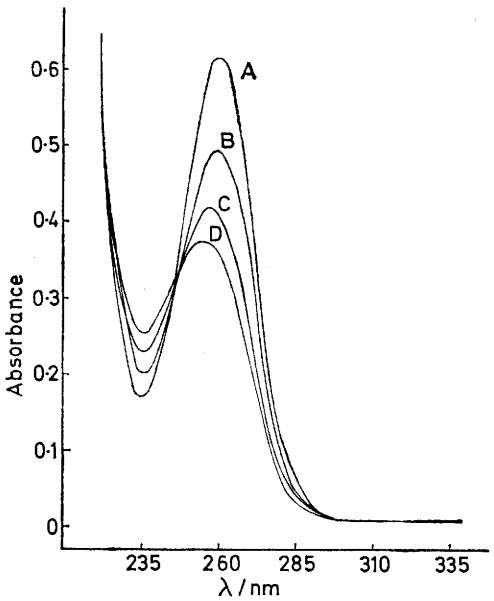


FIGURE 1 Absorption spectra of the diluted and pH 5.7 buffered sample solutions for the hydrolysis of 10^{-2}M-TAA at 80°, pH 10.00, and *I* 0.1. A, initial; B, after 20 min; C, after 40 min; D, after 60 min

245 nm. The values are respectively 11 727 and 4 820 l mol^{-1} cm^{-1}.

[3] J. Hipkin and D. P. N. Satchell, *Tetrahedron*, 1965, **21**, 835.
[4] M. Cefola, S. Peter, P. S. Gentile, and A. V. Celiano, *Talanta*, 1962, **9**, 537.

The absorption spectra of pH 5.7 buffered sample solutions, obtained from the hydrolysis of 10^{-2}M-TAA at 80°, pH 10.00, and *I* 0.1 are shown in Figure 1. The absorption maximum shifts gradually with time to 245

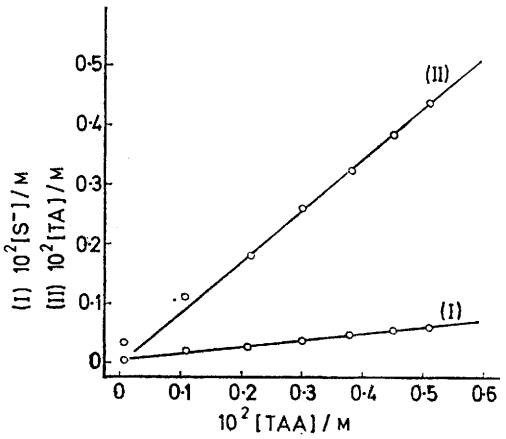


FIGURE 2 Hydrolysis of 10^{-2}M-TAA at 80°, pH 10.00, and *I* 0.1. Sulphide concentration (I) and TA concentration (II) as a function of the hydrolysed TAA concentration

nm, at which wavelength thioacetate ion absorbs. The same shift was observed by Rosenthal and Taylor.[6]

The spectra of the acidified solutions from the hydrolysis of TAA at the above mentioned conditions are all symmetrical and show maximal absorption at 261.5 nm. This indicates that the thioacetate ion present is completely converted into undissociated thioacetic acid which does not absorb significantly at that wavelength.

Hydrolysis of TAA at pH 10.00, 80°, *and* I 0.1.—A series of experiments with 10^{-2}M-TAA solutions was performed under these conditions in order to obtain a reasonable rate of hydrolysis. A plot of the concentrations of TAA, TA, and sulphide (hydrogen sulphide plus its dissociation products) against time shows typical curves for parallel first-order reactions. The TAA concentration was calculated from the absorbance at 261.5 nm of the acidified sample solutions. The TA concentration was calculated from the difference in absorbance at 245 nm between the measured absorbance for the pH 5.7 buffered solutions and the absorbance calculated for the TAA present. The sulphide concentration was determined by potentiometric titration.

Determination of k^{TAA}. A plot of the logarithm of the TAA concentration *versus* time is linear. The straight line through the experimental points, which are the means of five independent experiments, was obtained by regression analysis. Its slope gives the rate constant, $k^{TAA} = 11.96 \times 10^{-3}$ min^{-1} (standard deviation *s* 0.075×10^{-3} min^{-1}).

Determination of k^{I}. The sulphide concentration is linearly related to the TAA hydrolysed, which is shown in Figure 2-(I). The slope of the straight line is equal to the

[5] Y. Hirabayashi and T. Mazume, *Bull. Chem. Soc. Japan*, 1965, **38**, 171.
[6] D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, 1957, **79**, 2684.

ratio [7] k^{I} : k^{TAA} from which the calculated k^{I} value is 1.32×10^{-3} min^{-1} (s 0.029×10^{-3} min^{-1}). The ratio gives directly the relative importance of thioxo hydrolysis, which in this case contributes 11.0%.

To check this linear relationship a similar experiment was performed in which the sulphide produced was measured directly in the reaction vessel using the specific sulphide ion electrode. The response time of the electrode is fast enough to follow the hydrolysis reaction.[8,9] A plot of the measured potential against the logarithm of the TAA hydrolysed gives a straight line with a slope of 34.2 mV (s 0.52 mV) which agrees very well with the theoretical value of the $2\ 303RT/nf$ coefficient.

A rate constant could not be obtained from the potential measurements because the calculation of sulphide smaller than the obtained k^{TAA}. This difference can result from oxidation of sulphide in the reaction vessel [10] or from the uncertainty * in the molar absorption coefficient of TA. Nevertheless from the results it is evident that the hydrolysis of TAA in sodium hydroxide solutions occur by two parallel reaction paths.

Effect of Ionic Strength on Hydrolysis at pH 10.00 *and* 80°.—No measurable effect upon the hydrolysis rate resulted from variation of the ionic strength from 0.002 5 to 0.4. The mean result of 17 experiments is k^{TAA} 12.7 $\times$ 10^{-3} min^{-1} (s 0.24 $\times$ 10^{-3} min^{-1}).

Effect of pH *on Hydrolysis at* 80° *and* I 0.1.—The hydrolysis was studied in the pH range 9.50—10.50 and the rate constants are given in Table 1. Plots of log k *versus* pH give straight lines. The slopes of these lines

TABLE 1

Effect of pH on the first-order rate constants and on the relative importance of the two reaction paths of the hydrolysis of TAA

pH	$10^{3}k^{TAA}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{3}k^{I}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{3}k^{II}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{2}k^{I}$: k^{TAA} (%)	$10^{2}k^{II}$: k^{TAA} (%)
9.50	3.62	0.097	0.51	0.022	2.86	0.094	14.2	79
9.75	7.77	0.089	1.01	0.029	5.82	0.12	13.0	75
10.00	11.96	0.075	1.32	0.029	9.49	0.19	11.0	79
10.25	24.0	0.50	2.52	0.070	19.9	0.43	10.5	83
10.50	36.2	0.85	3.54	0.16	29.6	1.47	9.8	82

TABLE 2

Effect of temperature on the first-order rate constants and on the relative importance of the two reaction paths of the hydrolysis of TAA

T/°C	$10^{3}k^{TAA}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{3}k^{I}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{3}k^{II}$/ min^{-1}	$10^{3}s$/ min^{-1}	$10^{2}k^{I}$: k^{TAA} (%)	$10^{2}k^{II}$: k^{TAA} (%)
60	0.74	0.019	0.08	0.011	0.60	0.016	11.0	81
70	4.12	0.013	0.43	0.019	3.42	0.017	10.5	83
80	11.96	0.075	1.32	0.029	9.49	0.19	11.0	79
90	39.6	0.55	4.8	0.64	33.5	0.56	12.0	85

(hydrogen sulphide plus its dissociation products) is complicated by the uncertainties in reference electrode potential, in standard electrode potential, and in the dissociation constants of hydrogen sulphide at the temperature used. Calibration curves at the working temperature with known total sulphide concentration could solve this problem.

Determination of k^{II}. If the hydrolysis of TA is slow compared with its formation, as would be expected from the results of Cefola *et al.*[4] and of Butler *et al.*,[2] a linear relation must exist between the TA formed and the TAA hydrolysed. The results are shown in Figure 2(II) where the slope of the straight line is k^{II} : k^{TAA}, from which k^{II} 9.49 $\times$ 10^{-3} min^{-1} (s 0.19 $\times$ 10^{-3} min^{-1}) was calculated. The relative importance of amino hydrolysis, calculated from the k^{II} : k^{TAA} ratio, is 79% of the overall TAA hydrolysis.

Since the two competitive reactions are first-order and if these are the only reactions $k^{TAA} = k^{I} + k^{II}$. The sum of the measured k^{I} and k^{II}, however, is *ca.* 10% are 0.99 (s 0.057) for the overall TAA hydrolysis, 0.84 (s 0.064) for thioxo-group hydrolysis, and 1.03 (s 0.053) for amino-group hydrolysis. These results revealed that these three hydrolysis reactions were inversely first-order with respect to hydronium ion activity and consequently first-order with respect to hydroxide ion activity.

The second-order rate constants are obtained from a plot of the first-order rate constants *versus* a_{OH^-}, for which the equilibrium constant [11] $10^{-12.598}$ for water at 80° was used. The calculated values from the slopes are k^{TAA} 4.55 (s 0.30), k_2^{I} 0.42 (s 0.038), and k_2^{II} 3.77 l mol^{-1} min^{-1} (s 0.28 l mol^{-1} min^{-1}).

In Table 1 the k^{I} : k^{TAA} and k^{II} : k^{TAA} ratios at different pH are summarised and from these results it is clear that pH has no significant effect on the relative importance of the reaction paths.

The results of the acid- and hydroxide-catalysed hydrolysis of TAA, plotted in a log k^{TAA} *versus* pH diagram, gives by extrapolation the isocatalytic point between pH 5 and 6.

* Due to the titration method used for the standardisation of TA the molar absorption coefficient could only be evaluated with a mean error of *ca.* 6%.

[7] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' Wiley, New York–London, 1961, p. 161.

[8] T. M. Hseu and G. A. Rechnitz, *Analyt. Chem.*, 1968, **40**, 1054.

[9] T. S. Light and J. L. Swartz, *Analyt. Letters*, 1958, **1(13)**, 825.

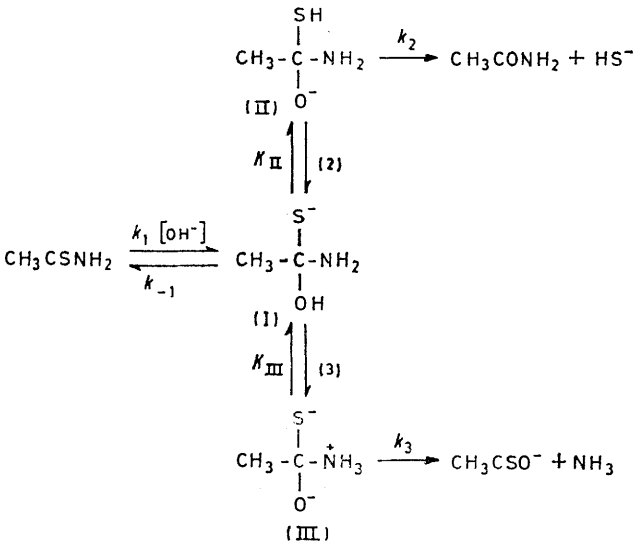
[10] D. G. Peters and A. Salajegheg, *Analyt. Chem.*, 1966, **38**, 1824.

[11] T. Ackermann, *Z. Electrochem.*, 1958, **62**, 411.

Effect of Temperature on Hydrolysis at pH 10.00 *and* I 0.1.—Hydrolysis reactions were carried out from 60 to 90° and the results are collected in Table 2. The values of the equilibrium constant for water at the different temperatures, as given by Ackermann,[11] were used in calculating second-order rate constants.

From a plot of log k_2 against T^{-1} the energies of activation were obtained. They are 20 (*s* 1.6) for the overall TAA hydrolysis, 20 (*s* 1.2) for thioxo hydrolysis, and 20 kcal mol^{-1} (*s* 1.7 kcal mol^{-1}) for amino hydrolysis.

From the activation energies and from the values of columns 8 and 9 in Table 2 it appears that the temperature has no significant effect on the relative importance of the parallel reaction paths.



SCHEME 2

The second-order rate constant for amino-group hydrolysis of TAA at 90° obtained by Butler *et al.*[2] (5 l mol^{-1} min^{-1}) is *ca.* 40% smaller than the experimental value obtained in this study (8.8 l mol^{-1} min^{-1}). The difference results mainly from their distillation technique used. Their estimates for the overall hydrolysis (6—7 l mol^{-1} min^{-1}) and thioxo-group hydrolysis (1—2 l mol^{-1} min^{-1}) show consequently the same relative difference with our experimental results (10.4 and 1.2 l mol^{-1} min^{-1}).

Mechanism of Hydrolysis.—The mechanism proposed by Seydel[12] for the alkaline hydrolysis of 2-ethylpyridine-4-thiocarboxamide implies the occurrence of the thiolimide form of the thioamide. This is very questionable because several studies[13] show that thioamides exist almost exclusively in the thionamide form.

The mechanism depicted in Scheme 2 was deduced in analogy with the mechanism proposed for the alkaline hydrolysis of amides.[14] The rate equation obtained shows nucleophilic attack of hydroxide ion on the thiocarbonyl carbon. The tetrahedral intermediate (I) is in equilibrium with forms (II) and (III) owing to a proton transfer, which probably occurs by means of a water molecule. The dipolar ion (III) reacts to give thioacetate ion by C–N bond cleavage and acetamide results from (II) by C–S fission. Subsequent hydrolyses of thioacetate[4] and acetamide[15] are slow (k_2^{TA} 4.4 × 10^{-3} l mol^{-1} min^{-1} at 80°; k_2^{AA} 6.78 × 10^{-2} l mol^{-1} min^{-1} at 75°) compared with TAA hydrolysis (k_2^{TAA} 4.76 l mol^{-1} min^{-1} at 80°). These substances can therefore be regarded as products rather than as intermediates. The ratio of these products shows that 80% of the hydrolysed TAA reacts *via* the dipolar ion (III). Since HS^- is a better leaving group than NH_3 (H_2S is a much stronger acid in water than NH_4^+), the greater relative importance of the route *via* (III) must result from a favourable position of equilibrium 3.

The independence of the product ratio of pH and temperature indicates that the pH has no influence on the equilibria between the tetrahedral intermediates and that both processes are equally responsive to changes in temperature.

From our results it is impossible to determine which step is rate limiting. In a study of the buffer-catalysed alkaline hydrolysis of 2,2,2-trifluoroacetanilide[16,17] the rate-limiting step was assumed to be the conversion of the initial addition intermediate into the dipolar ion intermediate. If this suggestion holds for the thioamides, the rate-limiting step in the hydrolysis of TAA would be the proton transfer between the tetrahedral intermediates.

[5/1885 *Received*, 29*th September*, 1975]

[12] J. Seydel, *Tetrahedron Letters*, 1966, 1145.
[13] W. Walter and J. Voss, in 'The Chemistry of Amides,' ed. J. Zabicky, Interscience, London, 1970, p. 434.
[14] B. C. Challis and J. A. Challis, ref. 13, p. 816.
[15] A. Bruylants and F. Kezdy, *Rec. Chem. Progr.*, 1960, **21**, 213.
[16] S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892.
[17] S. O. Eriksson and L. Bratt, *Acta Chem. Scand.*, 1967, **21**, 1812.