Acylation. Part XXXVIII.[1] Kinetics and Mechanism of Hydrogen Ion Catalysed Hydrolysis of Thiobenzamide

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Catalysed hydrolysis of thiobenzamide in moderately concentrated aqueous mineral acid leads initially to both benzamide and thiobenzoic acid, the former constituting *ca.* 25% of the product at 8·5M-HCl and 60°. The subsequent hydrolysis of thiobenzoic acid is relatively very rapid, but that of benzamide is *ca.* 3-fold slower than that of thiobenzamide under the same conditions. The general kinetic features of the thiobenzamide hydrolysis are otherwise similar to those found for benzamide and other *O*-amides, the rate passing through a maximum value as the catalyst concentration is increased. For thiobenzamide we find E_a 19·4 kcal mol^{-1} and $\Delta S^\ddagger$ -21 cal mol^{-1} K^{-1}. The pK_a is $-2{\cdot}38$ at 25°. The mechanism of hydrolysis is discussed in the light of mechanisms possible for *O*-amides. A carbonyl addition mechanism is required to produce benzamide and can alone explain all the facts. A contribution from a synchronous mechanism is not, however, excluded.

PREVIOUS work on the hydrogen ion catalysed hydrolysis of thioamides is scant. In principle such hydrolysis can lead initially either to the thioacid or to the *O*-amide [reactions (1)]. The only simple *S*-amide to have been the subject of previous kinetic work is thioacetamide. Three studies exist. Two [2,3] assumed that acetamide is the only organic product; the third [4] provided no evidence either for or against acetamide, but produced

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[1] Part XXXVII, D. P. N. Satchell and V. F. Shvets, *J.C.S. Perkin II*, 1973, 995.

[2] S. Washizuka, *Bunseki Kagaku*, 1961, **10**, 580.

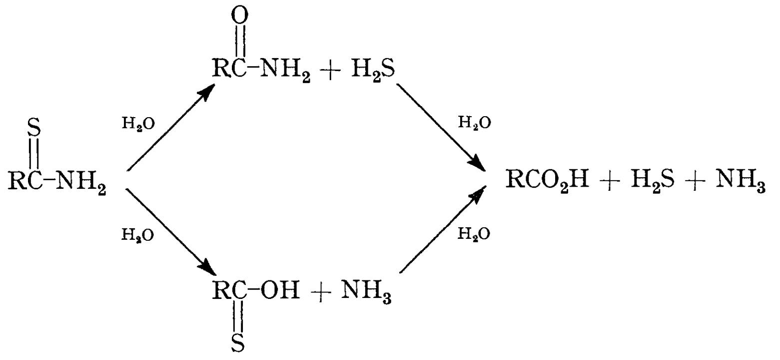
[3] E. H. Swift and E. A. Butler, *Analyt. Chem.*, 1956, **28**, 146.

[4] D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, 1957, **79**, 2684.

some spectroscopic evidence that an unknown amount of thioacid was formed. Leaving aside the unknown product distribution, the reported[4] kinetic behaviour resembles that found for the *O*-analogue, except that the rate maximum occurs at a higher catalyst concentration. We report now on thiobenzamide.

EXPERIMENTAL

Materials.—Thiobenzamide (Eastman Kodak) was recrystallised from ethanol–water and from benzene. It had m.p. 115—116°. Benzamide and benzoic acid were recrystallised B.D.H. reagents with m.p.s 129 and 120°, respectively. Thiobenzoic acid was a previous sample.[5] Hydrochloric and perchloric acids and ethanol were the B.D.H. AnalaR reagents.



$$RC(=S)NH_2 \xrightarrow{H_2O} RC(=O)NH_2 + H_2S \xrightarrow{H_2O} RCO_2H + H_2S + NH_3$$
$$RC(=S)NH_2 \xrightarrow{H_2O} RC(=S)OH + NH_3 \xrightarrow{H_2O} RCO_2H + H_2S + NH_3$$

(1)

Kinetic Arrangements.—Thiobenzamide is only slightly soluble in water and reaction mixtures therefore always contained 2% v/v ethanol to assist dissolution. Stock solutions of thiobenzamide were made up in ethanol and reactions initiated by the addition of a small aliquot portion of the stock solution to a large excess of aqueous acid of known (1—10M) composition. Normally $[PhCSNH_2]_{initial} \simeq 10^{-4}$M. Reactions mixtures were contained in stoppered flasks immersed in a thermostat bath controlled to $\pm 0{\cdot}1°$. The hydrolysis was studied at three temperatures, but most experiments were conducted at 50°. It was evident, in the light of previous work[6] with thiobenzoic acid, that if this substance was formed as a hydrolysis product it would itself be relatively very rapidly hydrolysed under the conditions necessary for convenient hydrolysis of thiobenzamide. On the other hand, the other possible product, benzamide, is reported[7,8] to hydrolyse rather more slowly than the rate now found for its *S*-analogue under the same conditions. The detectable products during thiobenzamide hydrolysis are therefore benzoic acid and benzamide. In dilute aqueous acid thiobenzamide has absorption maxima at 290 and 250 nm. As the acid concentration is increased these maxima are converted into a single maximum, at 275 nm, with approximately twice as large an extinction coefficient (ε 15,100). We followed the disappearance of thiobenzamide at 290 nm. Both benzoic acid and benzamide absorb only slightly in this region. Aliquot portions of a reaction mixture were withdrawn at appropriate intervals and their optical densities determined using a Unicam SP 800 spectrophotometer and quartz cells of 1 cm path length. In all runs the loss of thiobenzamide was an accurately first-order process over 2—3 half-lives. The observed rate constants (k_{obs}; Table) were reproducible to within $\pm 10\%$.

Basicity of Thiobenzamide.—Amides, both the *O*- and *S*-analogues, are extensively protonated in concentrated aqueous acid, but few pK_a values for *S*-amides are known.[9] We have measured the pK_a value for thiobenzamide at 25°. Suitable mixtures were made up as in the kinetic experiments, containing a fixed concentration (10^{-4}M) of thiobenzamide dissolved in aqueous hydrochloric acid of various known concentrations. For each mixture the spectrum was recorded between 350 and 200 nm. The pK_a value was calculated by standard methods[9] from the spectral changes noted above. The absorption at 275 nm is due to the *S*-protonated amide[9] and an isosbestic point occurs at 295 nm. The plot of log ($[BH^+]/[B]$) against H_0 has a slope 0·92 and gives pK_a $-2{\cdot}38$. The plot against H_A has a slope of 0·67. Our results are therefore in agreement with Janssen's[10] who found that the protonation of certain other *S*-amides was reflected better by H_0 than by H_A.

Products.—As explained above, hydrolysis *via* the thioacid will lead to benzoic acid as the detectable product, whilst hydrolysis *via* benzamide will also lead to some benzoic acid, the actual amount depending upon the time elapsing before the thiobenzamide hydrolysis is quenched. For a given temperature and acid concentration the rate of loss of benzamide can be calculated from existing data;[7,8] comparison with our present results for thiobenzamide showed us that the most favourable conditions for detecting benzamide, if indeed it was formed, would be to allow the thiobenzamide hydrolysis to proceed for *ca.* 2—3 half-lives at *ca.* 8·5M-HCl. These favourable conditions would result, on work-up, in a three-component mixture of thiobenzamide, benzamide, and benzoic acid which, if analysable for benzamide, would permit a calculation of the total benzamide formed *via* our knowledge of its rate of hydrolysis. (To allow the thiobenzamide hydrolysis to run to effective completion seriously decreases the chance of detecting any benzamide and also the accuracy of the calculation of the total formed.) Preparative scale experiments along the above lines, which also simulated as far as possible the

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[5] D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc.* (*B*), 1970, 1306.

[6] J. Hipkin and D. P. N. Satchell, *Tetrahedron*, 1965, **21**, 835.

[7] B. S. Rabinovitch and C. A. Winkler, *Canad. J. Res.*, 1942, **20B**, 73.

[8] C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J.C.S. Perkin II*, 1972, 1869.

[9] R. B. Homer and C. O. Johnson, in 'The Chemistry of Amides,' ed. J. Zabricky, Interscience, London, 1970.

[10] M. J. Janssen, *Rec. Trav. chim.*, 1963, **82**, 1197.

concentration conditions of the kinetic experiments, were conducted at 60°. The reaction mixture was quenched by cooling and by careful neutralisation with sodium carbonate. The organic material was separated by repeated extraction with ether. (The quantitative effectiveness of the extraction procedure was independently checked.) Evaporation of the ether led to a solid which was analysed by g.l.c. on Carbowax 20M with stilbene as an internal standard, using a Perkin-Elmer F11 gas chromatograph. The i.r. spectrum of the solid was also examined. The results showed that the hydrolysis takes place *via* both the benzamide and the thioacid routes, and that the former accounts for 25 ± 3% of the overall reaction. Microanalysis of the solid for C, H, S, and N was also compatible with this result.

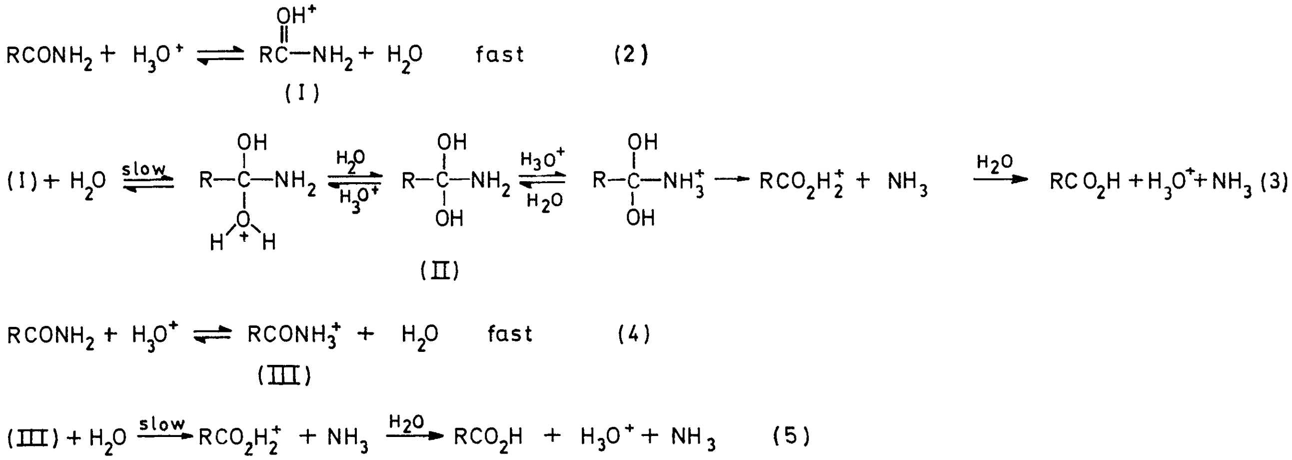
DISCUSSION

The catalysed hydrolysis of *O*-amides in moderately concentrated aqueous acid has been often studied kinetically.[11] The general features of the reaction are established but its mechanism is still debated. Two schemes, (2)—(3) and (4)—(5), are compatible with the existing evidence, the most significant piece of which is the apparent absence of carbonyl oxygen exchange concurrent with hydrolysis.[12] This result is readily explained by the synchronous displacement scheme, (4)—(5). For the carbonyl addition scheme it is necessary to assume that the (catalysed) loss of OH from (II) is negligible (say 10^2—10^3-fold slower) compared with the rate of the corresponding loss of NH_2. This is indeed likely in view of the relative basicities of alcohols and amines. Scheme (2)—(3) is often preferred to (4)—(5) since it is generally agreed that *O*-amides protonate principally on the carbonyl group.[9,13] However, the expected [14] great reactivity of (III) could well counterbalance the unfavourable ratio [(III)]:[(I)]. Both schemes are also compatible with the other especially characteristic feature of the hydrolysis: the fact that k_{obs} passes through a maximum value as $[H_3O^+]$ increases. This phenomenon is attributable [15] to the opposing effects of the increasingly complete protonation of the amide and the fall in water activity as $[H_3O^+]$ rises. Since the ratio [(III)]:[(I)] will be (approximately) independent of $[H_3O^+]$ both routes remain viable explanations.[11]

Hydrolysis of thiobenzamide in aqueous mineral acid

$[PhCSNH_2]_0 \simeq 10^{-4}$M; k_{obs} = observed first-order rate constant

(i) Hydrochloric acid						
(a) At 37 °						
[HCl]/M	5·83	7·00	8·17	9·33		
$10^2k_{obs}/h^{-1}$	3·80	3·60	3·20	2·10		
(b) At 50°						
[HCl]/M	1·16	2·33	2·92	4·09	5·25	5·83
$10^2k_{obs}/h^{-1}$	1·23	3·16	4·51	8·10	11·0	12·8
[HCl]/M	7·00	8·17	9·33	10·5		
$10^2k_{obs}/h^{-1}$	12·1	10·1	7·07	1·29		
(c) At 60°						
[HCl]/M	3·05	4·10	5·10	5·60	5·83	6·10
$10^2k_{obs}/h^{-1}$	7·5	14·9	19·9	24·5	29·9	37·4
[HCl]/M	7·10	8·20	9·33			
$10^2k_{obs}/h^{-1}$	36·6	33·6	18·1			
(ii) Perchloric acid at 50°						
$[HClO_4]$/M	1·18	2·37	3·55	4·74	5·92	7·10
$10^2k_{obs}/h^{-1}$	0·844	2·20	3·60	6·00	4·72	1·99
$[HClO_4]$/M	8·29	9·47				
$10^2k_{obs}/h^{-1}$	0·680	~0·10				



$$\mathrm{RCONH_2 + H_3O^+ \rightleftharpoons \underset{(I)}{R\overset{\overset{OH^+}{\|}}{C}{-}NH_2} + H_2O} \quad \text{fast} \quad (2)$$

$$\mathrm{(I) + H_2O \underset{}{\overset{slow}{\rightleftharpoons}} R{-}\overset{\overset{OH}{|}}{\underset{\underset{H\ \overset{+}{O}\ H}{|}}{C}}{-}NH_2 \underset{H_3O^+}{\overset{H_2O}{\rightleftharpoons}} \underset{(II)}{R{-}\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{C}}{-}NH_2} \underset{H_2O}{\overset{H_3O^+}{\rightleftharpoons}} R{-}\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{C}}{-}NH_3^+ \longrightarrow RCO_2H_2^+ + NH_3 \xrightarrow{H_2O} RCO_2H + H_3O^+ + NH_3} \quad (3)$$

$$\mathrm{RCONH_2 + H_3O^+ \rightleftharpoons \underset{(III)}{RCONH_3^+} + H_2O} \quad \text{fast} \quad (4)$$

$$\mathrm{(III) + H_2O \xrightarrow{slow} RCO_2H_2^+ + NH_3 \xrightarrow{H_2O} RCO_2H + H_3O^+ + NH_3} \quad (5)$$

Consider now how our present results for thiobenzamide compare with the *O*-amide pattern. (i) k_{obs} passes through a maximum as $[H_3O^+]$ rises (Figure). This maximum occurs at *ca.* 6·5M in hydrochloric acid and at *ca.* 5·0M in perchloric acid. For benzamide (pK_a —1·50) [9] the corresponding maxima occur at *ca.* 4·0M and at *ca.* 3·5M, respectively. The occurrence of the maximum at a higher acidity for thiobenzamide is compatible, assuming the explanation of the maximum given

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[11] B. C. Challis and J. A. Challis, ref. 9, ch. 13.

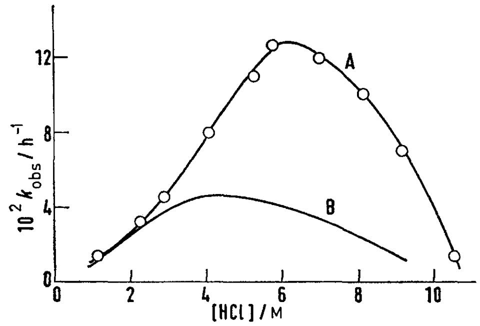
[12] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835.

[13] A. E. Fersht, *J. Amer. Chem. Soc.*, 1971, **93**, 3504.

[14] C. R. Smith and K. Yates, *Canad. J. Chem.*, 1972, **50**, 771.

[15] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2000.

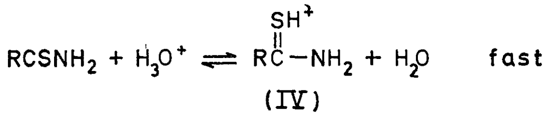
above, with the lower basicity of this compound (see Experimental section). (ii) The results in the Table lead to E_a 19·4 kcal mol^{-1} and $\Delta S^{\ddagger} = -21$ cal mol^{-1} K^{-1}.



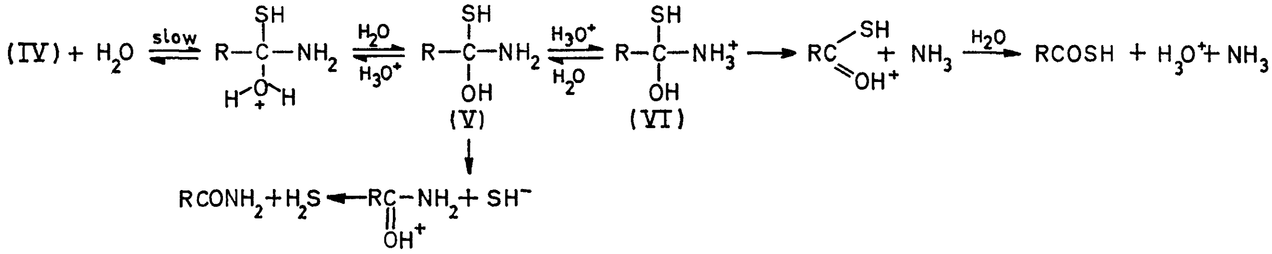
Hydrolysis of A, thiobenzamide and B, benzamide in aqueous hydrochloric acid at 50° (calculated from data in refs. 7 and 8)

These values are similar to those obtained for benzamide[7,8] and other *O*-amides.[11] The value of $\Delta S^{\ddagger}$ suggests that a molecule of water is included in the transition state, in agreement with schemes (2)—(3) and (4)—(5). (iii) The values of k_{obs} for thiobenzamide are always comparable with, and, over most of the acidity range, *ca.* three-fold greater than, those for benzamide under the same conditions (Figure). Comparison of the existing data for thioacetamide[4] and acetamide[16,17] also reveals that the *S*-amide is the more reactive. (iv) The fact (see Experimental section) that, under conditions of extensive substrate protonation, *ca.* 25% of the initial product of the thiobenzamide hydrolysis is benzamide means that a scheme like (4)—(5) cannot alone underlie the reaction. Circumstances (i)—(iv) are, however, compatible with scheme (6)—(7), analogous to (2)—(3), if we accept certain additional provisos. These are (a) that, when R = Ph, the attack of H_2O on (IV) is *ca.* three-fold faster than its attack on (I), and (b) that the (uncatalysed) loss of SH^- from (V) (the catalysed loss will be very slight since the SH group will be much more difficult to protonate than the NH_2 group) is *ca.* three-fold slower than the catalysed loss of NH_2.

Proviso (a) is reasonable in view of the electron-attracting powers of sulphur relative to oxygen. Proviso (b) appears, at first sight, to be unlikely since H_2S is a much[18] (*ca.* 250-fold) stronger acid in water than is NH_4^+, and SH^- will therefore be a much better leaving group than NH_3. However, under the experimental conditions (1—10M acid) (V) will probably be converted largely into (VI) from which loss of SH^- will be more difficult. Hence proviso (b) could effectively be satisfied.



$$\mathrm{RCSNH_2 + H_3O^+ \rightleftharpoons \underset{(IV)}{R\overset{\overset{\textstyle SH^+}{\|}}{C}-NH_2} + H_2O} \quad \text{fast} \qquad (6)$$



$$(\mathrm{IV}) + \mathrm{H_2O} \overset{\text{slow}}{\rightleftharpoons} \mathrm{R-\overset{SH}{\underset{H-\overset{+}{O}-H}{C}}-NH_2} \overset{\mathrm{H_2O}}{\underset{\mathrm{H_3O^+}}{\rightleftharpoons}} \underset{(\mathrm{V})}{\mathrm{R-\overset{SH}{\underset{OH}{C}}-NH_2}} \overset{\mathrm{H_3O^+}}{\underset{\mathrm{H_2O}}{\rightleftharpoons}} \underset{(\mathrm{VI})}{\mathrm{R-\overset{SH}{\underset{OH}{C}}-NH_3^+}} \longrightarrow \mathrm{RC\overset{SH}{\underset{OH^+}{\lessgtr}}} + \mathrm{NH_3} \xrightarrow{\mathrm{H_2O}} \mathrm{RCOSH + H_3O^+ + NH_3} \quad (7)$$

$$(\mathrm{V}) \downarrow \qquad \mathrm{RCONH_2 + H_2S \longleftarrow R\underset{\underset{\textstyle OH^+}{\|}}{C}-NH_2 + SH^-}$$

If proviso (b) were, in fact, not satisfied, and (V) were to decompose largely *via* loss of SH^-, then a concurrent process similar to scheme (4)—(5) would be needed to account for the production of thioacid. Some authors have favoured concurrent addition and synchronous schemes for *O*-amide hydrolysis,[12] but the evidence is not yet convincing.[8] What our study shows is that carbonyl addition is certainly required in part for the *S*-amide and could explain all the facts.

[4/184 *Received, 30th January, 1974*]

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[16] V. K. Krieble and K. A. Holst, *J. Amer. Chem. Soc.*, 1938, **60**, 2976.

[17] T. W. J. Taylor, *J. Chem. Soc.*, 1930, 2741.

[18] R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, p. 92.