

that the oxygen and sulfur atoms of *N*-benzoylthiourea and other *N*-acylthioureas have about equal basicities, but in spite of this fact protonation of oxygen requires much stronger acid than does protonation on sulfur. This results from the fact that $-H_A$ (which governs protonation on oxygen) increases with acid concentration more slowly than $-H_0'''$ (which governs protonation on sulfur). The fallacious but convenient method of comparing basicities by noting the concentration of sulfuric acid required for half-protonation would have indicated sulfur to be a much more basic center than oxygen. The importance of determining the acidity functions applicable to different classes of compounds is evident.

Experimental Section

Fisher reagent grade sulfuric acid and Fisher spectrograde methanol were used throughout. Sulfuric acid solutions were standardized by titration with BDH Chemicals' standard 0.1 *N* NaOH solution to Phenolphthalein end point. Melting points were taken on a hot stage microscope and are uncorrected. Analyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, Elsbach uber Engelskirchen, West Germany.

Materials. *N*-Acylthioureas were synthesized in high yields (60–80%) by the method of Douglas and Dains.¹⁹ All compounds

(19) I. B. Douglas and F. B. Dains, *J. Amer. Chem. Soc.*, **56**, 719, 1408 (1934).

were recrystallized from ethanol or ethanol-water. Table III lists melting points and analyses for new compounds.

Basicity Measurements. For solutions in acid concentrations up to 62%, a 0.500 ml aliquot of stock solution ($4-5 \times 10^{-3}$ *M*) of the *N*-acylthiourea was diluted to 75 ml with acid of the appropriate concentration, and the final concentration determined by titration of an aliquot. For solutions in acid concentrations above 62%, 0.500 ml of stock solution was added to a 25-ml volumetric flask and the methanol removed at reduced pressure. Acid (25 ml) of the appropriate concentration was added, and the flask shaken. Up to 10 min shaking was required in some cases, and completion of dissolution could be observed by shining a light through the solutions.

For pK_{BH^+} determinations, ultraviolet measurements were conducted at $25.0 \pm 0.1^\circ$ in 1-cm fused silica cells in a Unicam SP-800 spectrophotometer; for $pK_{BH_2^{2+}}$ determinations, the measurements were conducted at $33.0 \pm 1.0^\circ$. The spectral data in Table I were all recorded at $25.0 \pm 0.1^\circ$. The wavelengths of absorbance readings from which *pK* values were determined are listed in Table III. The *pK* values and slopes recorded in Table II were determined from a least-squares computer program for $\log I$ vs. H_0''' or H_A . The absorbance of *N*-acylthioureas in about 62% sulfuric acid was taken to be that of the monoprotonated form 2. The spectral changes occurring when acid concentration was further increased were due to further protonation plus a strong medium effect, similar to the changes already observed to accompany the protonation of amides,⁴ and the spectral data were treated in the manner already described⁴ to obtain the results recorded in Table II.

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Kinetic Studies of the Hydrolysis of *N*-Acylthioureas in Sulfuric Acid

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Abstract: *N*-Acylthioureas are hydrolyzed in sulfuric acid to the corresponding carboxylic acid and thiourea. In excess acid the pseudo-first-order rate constant increases with sulfuric acid concentration to a maximum in about 43% acid, then decreases to a minimum in about 72% acid, and then increases again. This behavior indicates a change from a bimolecular mechanism (A-2), involving water as a nucleophile in the rate-determining step, in 0–70% acid, to a unimolecular mechanism (A-1) involving an intermediate acyl cation in 70–100% acid. The change in mechanism is supported by changes in entropies of activation and in Hammett ρ values. An analytical expression for the entire rate profile over 0–100% acid is derived, and is used to show that an O-monoprotonated species is the most probable intermediate in the A-2 hydrolysis, and an N,S-diprotonated species in the A-1 hydrolysis.

The *N*-acylthiourea grouping is of interest because of its occurrence in thiopurines and thiopyrimidines, which are minor constituents of transfer ribonucleic acid.² We have shown recently that simple *N*-acylthioureas undergo successive mono- and diprotonation in aqueous sulfuric acid as the acid concentration is increased to 100%.³ For example, over the concentration range 36–60% acid *N*-acetylthiourea is protonated on sulfur ($pK_{BH^+} = 4.64$), the extent of protonation

being governed by the H_0''' value of the medium; and over the concentration range 65–95% it is protonated on the amide oxygen ($pK_{BH_2^{2+}} = -4.61$), the extent of diprotonation being governed by the H_A value of the medium. Subsequent to mono- or diprotonation there is a slow hydrolysis to acetic acid and thiourea.⁴ The mechanism of the hydrolysis of this and other *N*-acylthioureas has never been studied. In the present paper we report our studies on the kinetics of the hydrolysis of *N*-acetylthiourea, *N*-benzoylthiourea, and seven substituted *N*-benzoylthioureas. The kinetic data are best explained by assuming that, in addition to spectro-

(1) Holder of NRCC Studentships, 1968–1970.
 (2) M. N. Lipsett, *J. Biol. Chem.*, **240**, 3975 (1965); J. Carbon, H. David, and M. H. Studier, *Science*, **161**, 1146 (1968); L. Buczyuskyz, K. Biemann, and R. H. Hall, *ibid.*, **159**, 1481 (1968); S. Irie, Y. Inode, and F. Egami, *J. Biochem. (Tokyo)*, **63**, 274 (1968).
 (3) W. I. Congdon and J. T. Edward, *J. Amer. Chem. Soc.*, **94**, 6096 (1972).

(4) J. T. Edward, "The Chemistry of Organic Sulfur Compounds," Vol. II, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, 1966, p 295.

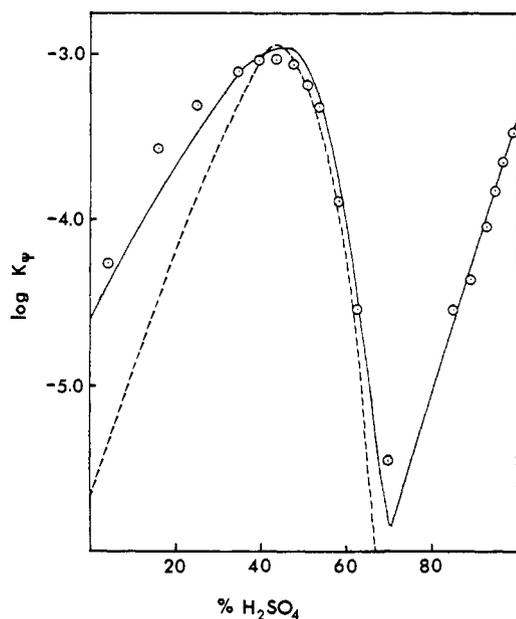


Figure 1. Rate-acidity dependence for the hydrolysis of *N*-acetylthiourea in aqueous acid at 49.3°. Points represent experimental k_p (in sec^{-1}), solid line, the theoretical curve derived from eq 11, and broken line, the theoretical curve derived from eq 6.

copically observable S-protonation and S,O-diprotonation,³ there is also a small amount of O-protonation and S,N-diprotonation.

The hydrolysis of *N*-acetylthioureas may be followed conveniently by ultraviolet spectroscopy. In the large excess of acid used, the reactions all show simple first-order kinetics. The pseudo-first-order rate constants (k_p) for the hydrolysis of *N*-acetylthiourea in 4–99% sulfuric acid at 49.3° are given in Table I and displayed

Table I. Experimental and Calculated Rates of Hydrolysis of *N*-Acetylthiourea in Sulfuric Acid at 49.3°

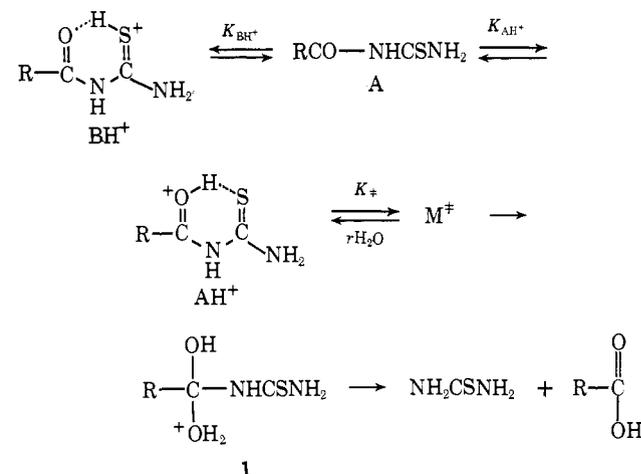
% (w/w) sulfuric acid	$10^4 k_p, \text{sec}^{-1}$ (exptl)	$10^4 k_p, \text{sec}^{-1}$ (calcd)
4.1	0.54 ± 0.01	
15.9	2.74 ± 0.03	1.30
25.2	4.94 ± 0.06	3.32
34.7	7.95 ± 0.09	7.20
39.6	9.10 ± 0.14	9.25
43.7	9.18 ± 0.12	10.60
47.2	8.48 ± 0.12	10.80
50.4	6.52 ± 0.18	8.60
53.4	4.74 ± 0.03	5.74
57.9	1.31 ± 0.01	1.89
62.4	0.29 ± 0.006	0.38
70.0	0.036 ± 0.01	0.14
84.9	0.29 ± 0.01	0.29
88.4	0.44 ± 0.02	0.40
92.2	1.09 ± 0.06	1.00
94.4	1.43 ± 0.02	1.58
96.4	2.23 ± 0.06	2.12
98.9	3.33 ± 0.09	

graphically in Figure 1. The rate increases with acid concentration up to a maximum in about 46% acid, decreases to a minimum in about 72% acid, and then increases again rapidly in the higher concentrations of acid. The rate-concentration profile closely resembles the profiles for the hydrolysis of esters of secondary al-

cohols, studied by Yates and McClelland,⁵ and analogy with these cases would suggest that hydrolysis occurs by two distinct mechanism: (i) in acid concentrations up to 72%, by an A-2 mechanism, in which one or more molecules of water add to the protonated *N*-acetylthiourea in the rate-determining step; and (ii) in acid concentrations above 72%, by an A-1 mechanism, in which the rate-determining step involves the rupture of one bond of mono- or diprotonated *N*-acetylthiourea without the intervention of water molecules.

This dichotomy of mechanism is supported by various lines of evidence reported below; furthermore, it will be shown that the most satisfactory variant of the possible A-2 mechanisms is that given in Scheme I.

Scheme I



One line of evidence comes from the modification of the Bunnett hydration parameter treatment⁶ introduced by Yates and coworkers.⁷ In applying this treatment in the present instance, we must take account of the fact that increasing acid concentration not only leads to protonation of *N*-acetylthiourea (A, R = Me) to give the reactive intermediate AH^+ , the amount formed being dependent on the protonation constant K_{AH^+} ⁸ and (we may assume) the H_A ($\equiv -\log h_A$) value¹⁰ of the acid solution, but it also (and more extensively) leads to protonation to give the unreactive species BH^+ , the amount formed being dependent on the protonation constant K_{BH^+} and the H_0''' ($\equiv -\log h_0'''$) value¹³ of the solution. The evidence already cited³ indicates that in 36–60% acid the formation of BH^+ is not accompanied by the formation of appreciable amounts

(5) K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, **89**, 2686 (1967).

(6) J. F. Bunnett, *ibid.*, **83**, 4956 (1961).

(7) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965); K. Yates and J. C. Riordan, *ibid.*, **43**, 2328 (1965).

(8) Protonated benzamide has a $\text{p}K_{\text{AH}^+}$ of -1.74 .⁷ The attachment of the electron-attracting $-\text{CS}-\text{NH}_2$ group to AH^+ would be expected to reduce $\text{p}K_{\text{AH}^+}$ to less than -4.0 ,⁹ in which case half-ionization would require acid stronger than 73% sulfuric acid.¹⁰ By contrast, half-protonation to give BH^+ occurs in 50% acid.³ The corresponding $\text{p}K_{\text{BH}^+}$ value for acetamide^{7,11,12} is less certain, but the spectroscopic evidence for *N*-acetylthiourea³ indicates that the formation of BH^+ is not attended by formation of appreciable quantities of AH^+ .

(9) G. Derald, Ph.D. Dissertation, McGill University, 1971.

(10) K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964); C. D. Johnson, A. R. Katritzky, and M. Shakir, *J. Chem. Soc. B*, 1235 (1967).

(11) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **40**, 966 (1962).

(12) A. R. Goldfarb, A. Mele, and M. Gutstein, *J. Amer. Chem. Soc.*, **77**, 6194 (1955).

(13) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

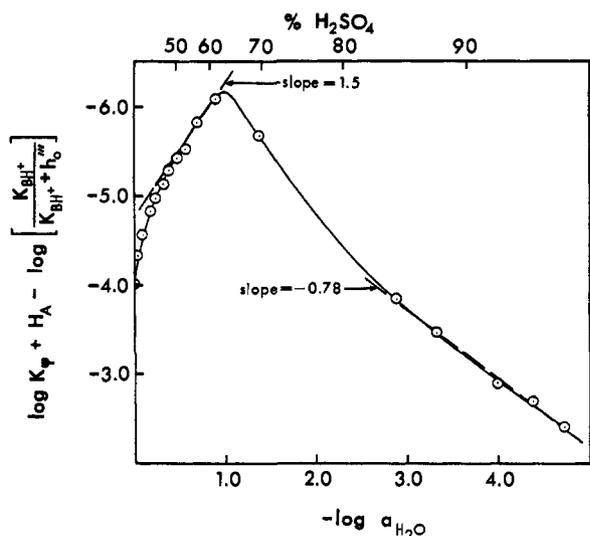


Figure 2. $\log k_\psi + H_A - \log \{K_{BH^+}/(h_0''' + K_{BH^+})\}$ vs. $-\log a_{H_2O}$ for *N*-acetylthiourea.

of AH^+ , and consequently application of the Brønsted equation to the situation outlined in Scheme I yields

$$\text{rate of reaction} = k_\psi([A] + [BH^+]) = \left(\frac{k_1 K_{\pm} [A] h_A a'_{H_2O} f_{AH^+}}{K_{AH^+} f_{\pm}} \right) \quad (1)$$

where k_1 is the rate constant for the slow reaction $AH^+ + rH_2O \rightarrow 1$; a_{H_2O} is the activity of water; the f 's are activity coefficients; and the other symbols can be understood by reference to Scheme I. Equation 1 may be rearranged to

$$k_\psi = \left(\frac{k_1 K_{\pm} h_A a'_{H_2O} f_{AH^+}}{K_{AH^+} f_{\pm}} \right) \left(\frac{[A]}{[A] + [BH^+]} \right) \quad (2)$$

from which may be derived

$$\log k_\psi + H_A - \log \left(\frac{K_{BH^+}}{h_0''' + K_{BH^+}} \right) = r \log a_{H_2O} + \log \left(\frac{k_1 K_{\pm} f_{AH^+}}{K_{AH^+} f_{\pm}} \right) \quad (3)$$

In Figure 2 is shown a plot of $(\log k_\psi + H_A - \log \{K_{BH^+}/(h_0''' + K_{BH^+})\})$ against $\log a_{H_2O}$.¹⁴ From 30 to 65% sulfuric acid the points lie close to a straight line of slope $r = 1.5$ and intercept $\log \{(k_1 K_{\pm} f_{AH^+})/(K_{AH^+} f_{\pm})\}$ equal to -0.6 . This can be interpreted as indicating that about two water molecules react with the protonated amide group of *N*-acetylthiourea to give the intermediate 1. Similar treatments have indicated that over the range 0–70% sulfuric acid, 2.1 molecules of water react with protonated ester molecules in the slow step of hydrolyses,⁶ and that over the range 0–55% acid about three molecules of water react in the slow step with protonated amide molecules.^{7,16} The curvature of a line drawn through the experimental points of Figure 2 can be interpreted as indicating that r decreases as the water activity of the acid solution de-

(14) Water activities measured at 25°¹⁵ were used in this plot, although the rates were measured at 49.3° (cf. ref 6).

(15) W. F. Glauque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *J. Amer. Chem. Soc.*, **82**, 69 (1960).

(16) R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 4273 (1963).

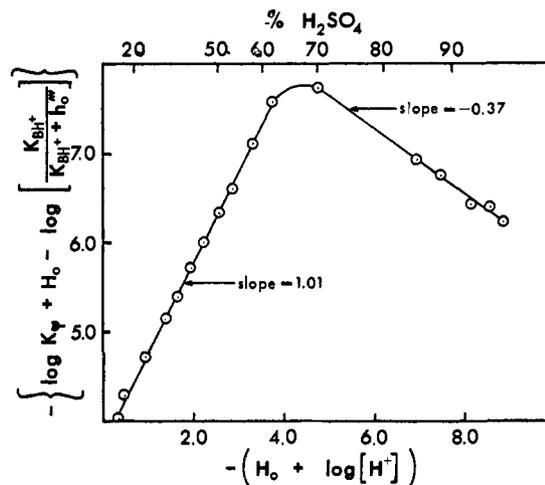


Figure 3. $\log k_\psi + H_0 - \log \{K_{BH^+}/(K_{BH^+} + h_0''')\}$ vs. $-(H_0 + \log [H^+])$ for *N*-acetylthiourea.

creases,¹¹ or that the ratio (f_{AH^+}/f_{\pm}) is not completely invariant with acid concentration or both. However, considering the Bunnett–Yates plot solely as an empirical criterion of reaction mechanism, the experimental curve of Figure 2 indicates an A-2 mechanism of hydrolysis up to 72% sulfuric acid, and then an abrupt change (shown by a change of slope to -0.78) to an A-1 mechanism.

Bunnett and Olsen¹⁷ have found that plots of $(\log k_\psi + H_0)$ against $(H_0 + \log [H^+])$ (rather than against $\log a_{H_2O}$, as in the original Bunnett treatment⁶) are generally linear, and that the slopes Φ are useful empirical criteria of reaction type. For example, Φ for A-2 hydrolyses of amides is generally about $+0.6$, while for A-1 hydrolyses it is lower and may be negative. The Bunnett–Olsen plot of the results for *N*-acetylthiourea, shown in Figure 3, has satisfactory linearity over the region 0–65% sulfuric acid; Φ (1.01) is large, but not unprecedented, for A-2 hydrolyses.¹⁷ Again, the indication of a change in mechanism when the acid concentration exceeds 72% is unmistakable as Φ changes sign (to -0.37).

Another line of evidence indicating a change from an A-2 to an A-1 mechanism comes from measurements of the entropy of activation (ΔS^\ddagger). Acid-catalyzed ester and amide hydrolyses proceeding by an A-1 mechanism have ΔS^\ddagger of about 0 to $+10$ eu, while those proceeding by an A-2 mechanism have ΔS^\ddagger of -15 to -30 eu.^{18–21} Plots of $\log k_\psi$ vs. $1/T$ for *N*-acetylthiourea in 25.2, 57.9, and 96.9% sulfuric acid are linear, and yield ΔS^\ddagger values of -26 , -21 , and -11 eu, respectively, in these concentrations of acid (Table II). The entropy of activation in the first two acid concentrations, which are on each side of the concentration for maximal rate (Figure 1), indicate an A-2 mechanism with essentially no competing A-1 component. The

(17) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 4273 (1963).

(18) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(19) M. L. Bender, H. Ladenheim, and M. C. Chen, *J. Amer. Chem. Soc.*, **83**, 123 (1961); M. L. Bender and M. C. Chen, *ibid.*, **85**, 30, 37 (1963).

(20) M. Fuller and W. M. Schubert, *ibid.*, **85**, 108 (1963); D. P. Weeks, A. Grodshi, and R. Fanucci, *ibid.*, **90**, 1458 (1968); D. P. Weeks and G. W. Zuorick, *ibid.*, **91**, 477 (1969).

(21) J. A. Duffy and J. A. Leisten, *J. Chem. Soc.*, 853 (1960).

Table II. Temperature Dependence of the Rate of Acid-Catalyzed Hydrolysis of *N*-Acetylthiourea (A) and of *N*-Benzoylthiourea (B)

Reaction	Temp, °C	$10^4 k_{\psi}$, sec ⁻¹	log <i>A</i> , sec ⁻¹	ΔS^{\ddagger} , eu	E_a , kcal/mol
A in 25.2% acid	40.0	2.21 ± 0.09	7.57 ± 0.2	-26 ± 2	16 ± 2
	49.3	4.94 ± 0.06			
	68.6	20.80 ± 1.10			
	73.6	26.40 ± 0.70			
A in 57.9% acid	40.0	0.52 ± 0.01	8.64 ± 0.27	-21 ± 2	19 ± 3
	49.3	1.31 ± 0.01			
	68.6	7.06 ± 0.18			
A in 96.9% acid	58.6	5.44 ± 0.07	10.80 ± 0.07	-11 ± 1	21 ± 1
	68.9	14.20 ± 0.05			
	80.4	40.10 ± 1.20			
	80.4	40.10 ± 1.20			
B in 39.6% acid	49.1	0.39 ± 0.03	9.60 ± 0.33	-17 ± 2	21 ± 2
	68.6	2.25 ± 0.12			
	79.9	6.60 ± 0.163			

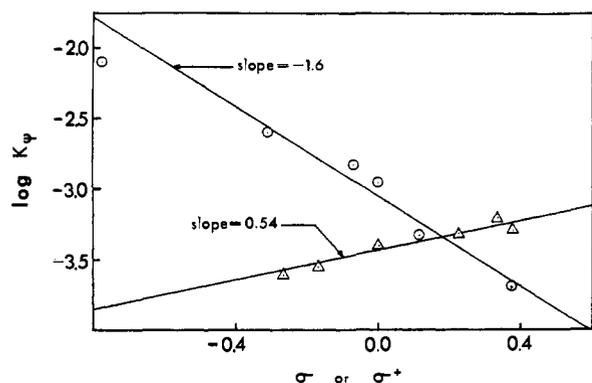


Figure 4. (A) Log k_{ψ} vs. σ for substituted *N*-benzoylthioureas in 28.3% sulfuric acid at 85.0° (Δ). (B) Log k_{ψ} vs. σ^+ for substituted *N*-benzoylthioureas in 96.9% sulfuric acid at 58.6° (\circ).

large change in ΔS^{\ddagger} in 96.9% sulfuric acid is consistent with a change to an A-1 mechanism; the value is more negative than expected, but this aberration is explained below.

The ΔS^{\ddagger} for the hydrolysis of *N*-benzoylthiourea in 39.6% acid (Table II) also is indicative of an A-2 mechanism in this concentration.

A third line of evidence for a change from an A-2 to an A-1 mechanism comes from the Hammett ρ values for the hydrolysis of meta- and para-substituted *N*-benzoylthioureas.²² The rates of A-1 hydrolyses of methyl 4-substituted 2,6-dimethylbenzoates, substituted benzamides, and substituted benzoyl chlorides follow σ^+ , and have ρ_{ov} values near -3 , because of the large effect of electron-releasing groups in stabilizing the intermediate acylium ion.¹⁹ On the other hand, the rates of A-2 hydrolyses follow σ , and have ρ_{ov} close to zero, because of the opposing effects of substituents on the preequilibrium protonation and on the subsequent rate-determining attack of water.²⁴ For example, the small ρ_{ov} (0.12) for the hydrolysis of substituted benzamides is made up of two components almost equal but opposite in sign: ρ_1 for the protonation step (-0.92 , ref 7)

(22) The rate of hydrolysis of the *p*-methoxy compound in 96.9% sulfuric acid falls below that predicted by the $\rho\sigma^+$ relationship. This deviation may be explained by hydrogen bonding of methoxyl with sulfuric acid with consequent increase in σ^- . Using the correction suggested by Stewart and Yates²³ of $+0.16$, giving $\sigma^+ = -0.618$, log k_{ψ} of *N*-*p*-methoxybenzoylthiourea fits nicely on the straight line of Figure 4.

(23) R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, **80**, 6355 (1958).

(24) J. A. Leisten, *J. Chem. Soc.*, 765 (1959); J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, **38**, 1518, 2271 (1960).

and ρ_2 for the attack of water on the protonated benzamide ($+1.05$, ref 24).

$$\rho_{ov} = \rho_1 + \rho_2 \quad (4)$$

In attempting to estimate ρ_{ov} for the hydrolysis of *N*-benzoylthioureas according to Scheme I, we must take account of a third effect, that of an electron-releasing group in encouraging the diversion of A into the pool of inactive cation BH^+ ($\rho_3 = -0.42$, ref 3). If it is assumed that ρ_1 for the step $A + H^+ \rightleftharpoons AH^+$ and ρ_2 for the step $AH^+ + rH_2O \rightarrow$ products have the same values as the corresponding ρ_1 and ρ_2 for the hydrolysis of substituted benzamides, then ρ_{ov}' , given by

$$\rho_{ov}' = \rho_1 + \rho_2 - \rho_3 \quad (5)$$

is calculated as $+0.56$, extremely close to the experimental ρ_{ov} of $+0.54$ found from plots of log k_{ψ} against σ for six substituted *N*-benzoylthioureas in 28.3% sulfuric acid (Table III and Figure 4). This result sup-

Table III. Pseudo-First-Order Rate Constants (k_{ψ} , in sec⁻¹) for the Hydrolysis of Substituted *N*-Benzoylthioureas in Two Concentrations of Sulfuric Acid

Substituent	28.3% H ₂ SO ₄ ^a	96.9% H ₂ SO ₄ ^b
<i>p</i> -Methoxy	2.63 ± 0.09	79.70 ± 4.80
<i>p</i> -Methyl	2.89 ± 0.24	25.30 ± 1.30
<i>o</i> -Methyl		47.50 ± 2.40
<i>m</i> -Methyl		14.80 ± 1.30
(None)	4.02 ± 0.30	11.10 ± 0.30
<i>p</i> -Chloro	4.83 ± 0.30	4.75 ± 0.02
<i>m</i> -Fluoro	6.31 ± 0.60	
<i>m</i> -Chloro	5.15 ± 0.24	2.03 ± 0.04

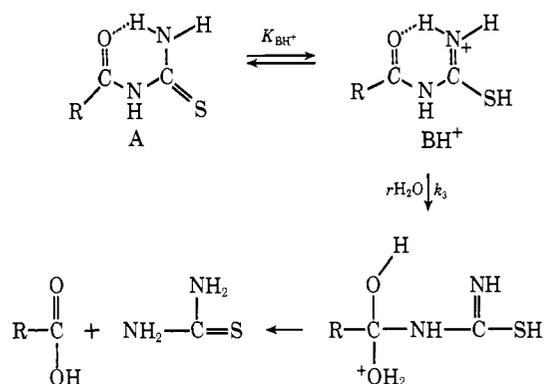
^a Measurements made at 85.0°. ^b Measurements made at 58.6°.

ports the A-2 mechanism of Scheme I, but is also compatible with other possible A-2 mechanisms, such as that involving BH^+ rather than AH^+ as an intermediate, shown in Scheme II. Such a mechanism would require $\rho_4 \approx 1.0$ for the step $BH^+ + rH_2O \rightarrow$ products, a reasonable value (*cf.* ρ for $AH^+ + rH_2O \rightarrow$ products). However, this mechanism is less successful than that of Scheme I in accounting for the rate-concentration profile of the reaction.²⁵ The theoretical curve of eq 2, based on Scheme I, fits the experimental points con-

(25) A third possible A-2 mechanism would involve attack of water on the *N*-protonated intermediate, $RCONH_2^+CSNH_2$. It would seem impossible at the moment to distinguish between this possibility and that of Scheme I (*cf.* analogous case of acid hydrolysis of amides²⁶).

(26) C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. Ind. (London)*, 1835 (1967).

Scheme II



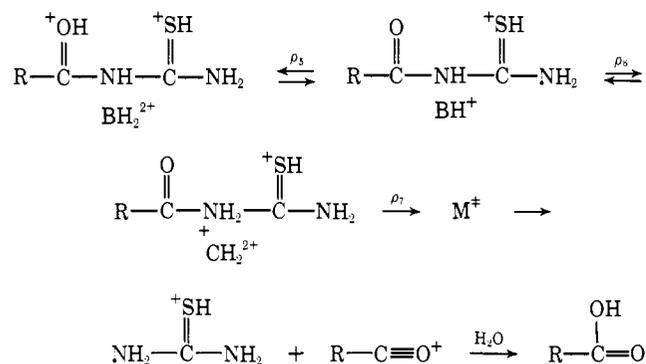
siderably better in the dilute region (where the rate is sensitive to the acidity function chosen) than does the curve based on eq 6, which is derived by application of

$$k_{\psi} = \left(\frac{k_3 f_{\text{BH}^+}}{f_{\pm}} \right) \left(\frac{h_0''' }{h_0''' + K_{\text{BH}^+}} \right) a_{\text{H}_2\text{O}}^r \quad (6)$$

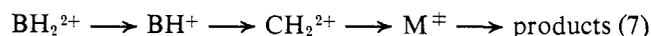
the Brønsted equation to the kinetic situation depicted in Scheme II. Bunnett-Yates plots of $(\log k_{\psi} + \log \{h_0'''/h_0''' + K_{\text{BH}^+}\})$ against $\log a_{\text{H}_2\text{O}}$ give a value of 4.5 for r , which has been used in calculating the theoretical curve based on eq 6 shown in Figure 1; the use of lower values of r increases further the divergence of the theoretical curve from the experimental points.

The change from an A-2 to an A-1 mechanism when hydrolysis is carried out in 96.9% sulfuric acid is shown by the fact that $\log k_{\psi}$ now follows σ^+ rather than σ , and that ρ_{ov} has changed from +0.54 to -1.60. The negative sign of ρ_{ov} is expected for an A-1 reaction. A more detailed analysis indicates, as a plausible mechanism for the hydrolysis in concentrated acid, that shown in Scheme III. In this concentration of acid

Scheme III



diprotonation to BH_2^{2+} is essentially complete, and so the overall reaction is



In such a case

$$\rho_{\text{ov}} = \rho_6 + \rho_7 - \rho_5 \quad (8)$$

Since $\rho_5 = -0.86$,³ this would indicate that $\rho_6 + \rho_7 = -2.46$, about the same value as ρ_{ov} for the A-1 hydrolysis of benzamides,²¹ which also proceeds by N-protonation followed by cleavage to give the acylium ion.

The mechanism of Scheme III would also explain the low ΔS^{\ddagger} (-11 eu) observed for hydrolysis of *N*-acetylthiourea in 96.9% sulfuric acid, mentioned above. The

value of ΔS^{\ddagger} of -1.8 to +14.2 eu observed for A-1 acid-catalyzed ester hydrolyses¹⁸ would suggest a ΔS^{\ddagger} value of 0-10 eu for the steps $\text{BH}^+ \rightarrow \text{products}$; however, in the present reaction we must take account of the additional stage $\text{BH}_2^{2+} \rightarrow \text{BH}^+$. It is difficult to estimate with confidence ΔS° for this stage because of lack of information on ionization processes in sulfuric acid, but if the solvation changes are similar to those accompanying ionization processes in water, a ΔS° of -10 to -20 eu would be reasonable.²⁷ The addition of the ΔS° and ΔS^{\ddagger} terms could then lead to the overall ΔS^{\ddagger} of -11 eu observed.

In 70-100% sulfuric acid, the stoichiometric concentration of *N*-acetylthiourea is made up almost completely of BH^+ and BH_2^{2+} in varying proportions, and so application of the Brønsted equation to the kinetic situation of Scheme III leads to

$$\text{rate} = k_{\psi}([\text{BH}^+] + [\text{BH}_2^{2+}]) = k_2[\text{CH}_2^{2+}]f_{\text{CH}_2^{2+}}/f_{\pm} \quad (9)$$

where k_2 is the rate constant for the reaction $\text{CH}_2^{2+} \rightarrow \text{products}$. It is known³ that $[\text{BH}_2^{2+}]/[\text{BH}^+] = h_{\text{A}}/K_{\text{BH}_2^{2+}}$, and if it is assumed that $[\text{CH}_2^{2+}]/[\text{BH}^+] = h_0/K_{\text{CH}_2^{2+}}$,²⁸ it can be shown that eq 9 leads to

$$k_{\psi} = \left(\frac{k_2 K_{\text{BH}_2^{2+}} f_{\text{CH}_2^{2+}}}{K_{\text{CH}_2^{2+}} f_{\pm}} \right) \left(\frac{h_0}{K_{\text{BH}_2^{2+}} + h_{\text{A}}} \right) \quad (10)$$

A plot of $\log k_{\psi}$ vs. $\{-H_0 - \log(K_{\text{BH}_2^{2+}} + h_{\text{A}})\}$ gives a straight line of unit slope over the range 84.9-96.4% sulfuric acid, as required by eq 10 if the activity coefficient ratio ($f_{\text{CH}_2^{2+}}/f_{\pm}$) is invariant with acid concentration. The intercept gives $\log \{(k_2 K_{\text{BH}_2^{2+}} f_{\text{CH}_2^{2+}})/(K_{\text{CH}_2^{2+}} f_{\pm})\}$ equal to -7.47. Combining eq 2 and 10 gives

$$k_{\psi} = \left(\frac{k_1 K_{\pm} h_{\text{A}} a_{\text{H}_2\text{O}}^r f_{\text{AH}^+}}{K_{\text{AH}^+} f_{\pm}} \right) \left(\frac{K_{\text{BH}^+}}{h_0''' + K_{\text{BH}^+}} \right) + \left(\frac{k_2 K_{\text{BH}_2^{2+}} f_{\text{CH}_2^{2+}}}{K_{\text{CH}_2^{2+}} f_{\pm}} \right) \left(\frac{h_0}{h_{\text{A}} + K_{\text{BH}_2^{2+}}} \right)$$

and this equation covers fairly well the variation of rate with acid concentration from 0 to 100% sulfuric acid, as shown in Table I and Figure 1.

Finally it should be noted that *N*-*o*-methylbenzoylthiourea would be expected to show a very different rate-concentration profile from that displayed in Figure 1. In 28.3% acid, the rate was too slow to be measurable, as might be expected for an A-2 mechanism subject to steric hindrance; on the other hand, in 96.9% acid the rate was 90% greater than that of the *p*-methyl isomer, as would be expected for an A-1 mechanism subject to steric acceleration. For *o*-toluoyl-*p*-nitroanilide Duffy and Leisten²¹ found an even greater (28-fold) enhancement of rate over that of the *p*-methyl isomer in the A-1 acid-catalyzed region.

(27) This can be considered only an educated guess. K. N. Bascombe and R. P. Bell, *Discuss. Faraday Soc.*, **24**, 158 (1957), estimate that the protonation of a Hammett primary amine indicator is accompanied by the liberation of four water molecules. This would indicate $\Delta S^{\circ} \approx +20$ eu for this reaction if one accepts Schaleger and Long's estimate¹⁸ of +5 eu for each molecule of water liberated in an ionization reaction. There is evidence that the protonation of an amide is accompanied by the liberation of smaller amounts of water,^{10,11} so that a ΔS° of about +15 eu for $\text{BH}^+ + \text{H}^+ \rightarrow \text{BH}_2^{2+}$ would be reasonable.

(28) It might be expected that the protonation of BH^+ to give CH_2^{2+} would be governed by an acidity function applying to secondary amines; however, in 80-100% sulfuric acid the slopes of H_0 and H_0''' against per cent acid are roughly parallel, and so it seems likely that the ionization of CH_2^{2+} will follow H_0 fairly closely.

Experimental Section

The physical properties of all compounds used in this study were previously reported.³ Most rate measurements were made with a Unicam SP-800 recording uv spectrophotometer at 6-, 20-, and 60-min single-wavelength time scans (or by using a scale expander and slave recorder), with the sample in a 1-cm fused silica cell with a Teflon stopper in a controlled-temperature ($\pm 0.1^\circ$) cell block. For very slow rates the reaction was carried out in a 50-ml flask immersed in a constant-temperature bath. Aliquots (3 ml) were removed periodically, quenched by cooling, and measured for ultraviolet absorbance.

In dilute solution rates could be conveniently followed by absorbance (A) measurements at about 280 nm for most compounds, but in concentrated acid the wavelength for maximal absorbance change was highly dependent upon the type of acyl substituent; in general, measurements were taken at wavelengths near 230 nm and/or near 300 nm. It was found that k_{ψ} was invariant with substrate concentration over the range of 5×10^{-5} – 2×10^{-2} M, and k_{ψ} obtained from rates of product formation was shown to equal k_{ψ} obtained from rates of substrate disappearance. Products were shown to be stable under the reaction conditions, since after seven-ten half-lives in every case the isosbestic points of spectral curves were still sharply defined. Rates were followed for at least two half-lives, and infinity values were taken after six-ten half-lives. The final spectrum in all cases was identical with the spectrum of

thiourea and the carboxylic acid in the appropriate concentration of sulfuric acid. For slower reactions Guggenheim's method²⁹ was used to obtain the rate. All calculations were done by an IBM-360 computer and a least-squares program for $\log(A_t - A_{\infty})$ vs. time was used throughout. In nearly every case correlation coefficients of better than 0.998 for eight points were obtained.

For very fast reactions, for which a sampling technique was not possible, 3 ml of acid was placed in a stoppered cell, which was left to reach thermal equilibrium in the cell block for a minimum of 10 min. Methanolic stock solution (8–10 μ l) of the *N*-acylthiourea was then injected into the solution, which was shaken and placed back into the thermostated cell block; spectra were recorded after a 3- to 10-min reequilibration. For kinetic runs carried out in a thermostated 50-ml flask, 50 ml of acid was placed in the flask and left for a minimum of 15 min to reach thermal equilibrium. A 10- μ l sample of stock solution of *N*-acylthiourea was then injected by use of a Hamilton syringe with a Chaney adaptor, the solution was well shaken, and after 0.5 hr back in the bath, the initial aliquot was taken.

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(29) K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill, New York, N. Y., 1965, p 14.

Hydrolysis of Coordinated Nitriles to Carboxamide Complexes of Pentaamminecobalt(III)

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Abstract: It has been found that benzonitrile and 3- and 4-cyanophenol coordinated to pentaamminecobalt(III) are hydrolyzed in alkaline solution to the corresponding nitrogen-bonded carboxamido product. The kinetics of the reaction has been studied and found to be first order in hydroxide ion concentration, with rate constant ($M^{-1} \text{sec}^{-1}$, 25.6°), ΔH^\ddagger (kcal mol⁻¹), and ΔS^\ddagger (cal mol⁻¹ deg⁻¹), for benzonitrile, 18.8, 16.6, 2.7, for 3-cyanophenol, 3.57, 15.1, -5.5, and for 4-cyanophenol, 0.18, 16.3, -7.4, respectively. The product of the hydrolysis is converted in acid solution to $(\text{NH}_3)_5\text{CoNH}_2\text{COC}_6\text{H}_5$ and the pK_a of the latter has been determined to be 1.65 at 25° in 1 M LiClO_4 .

It has been observed previously^{1,2} that metal ions can catalyze the hydrolysis of nitriles to the corresponding carboxamide. During work to extend previous studies³ on nitrogen-bonded carboxamide complexes of pentaamminecobalt(III) it was observed that coordinated nitriles in this system are easily hydrolyzed to the desired N-bonded carboxamide product. The kinetics of this process and the characterization of the benzamide product are described here.

The kinetics have been studied in order to provide further insight into the mechanism for the catalyzed hydrolyses in the more labile copper(II)² and nickel(II) systems. In the latter systems there is the possibility that a coordinated hydroxide ion is actually attacking the nitrile, although arguments against this possibility

have been made by Breslow, *et al.*¹ With pentaamminecobalt(III) no coordinated groups can be reacting and attack by free hydroxide ion must be involved. The reaction with nickel(II) seems unusual in that the rate enhancement is primarily associated with a ΔS^\ddagger effect, and it is of interest to determine if this is also true for $(\text{NH}_3)_5\text{Co}^{3+}$.

Experimental Section

All the nitrile complexes can be prepared by the same general procedure. A mixture of aquopentaamminecobalt(III) perchlorate (5 g), a fivefold molar excess of the nitrile, and 2–3 g of molecular sieve, and 50 ml of trimethyl phosphate was heated on a steam bath at 70–80° until the solution turned yellow-brown (1–2 hr). The molecular sieve was removed by filtration and the filtrate treated with *sec*-butyl alcohol (~800 ml) to precipitate the crude product. This product may be purified by recrystallization of the perchlorate salt from aqueous solution or by ion exchange chromatography on Rexyn-102H weak acid cation exchange resin. In the latter method the eluting agent was aqueous sodium chloride and the procedure described previously³ was used to isolate the product. The properties reported here all refer to ion-exchanged materials.

The N-bonded benzamide complex was prepared from the benzonitrile complex by dissolving the latter in a minimum amount of

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(3) R. J. Balahura and R. B. Jordan, *J. Amer. Chem. Soc.*, **92**, 1533 (1970).