pinene from DPCB to produce an $RBH_2$, or its dimer, which then reacts with alkene to ultimately produce alcohol of opposite configuration. It thus appears possible to be able to prepare either configurational isomer of an alcohol, or any other derivative derivable from an alkylborane, from a single optical isomer of α-pinene by adjustment of the stoichiometry and mode of preparation of the asymmetric hydroboration reagent.

**Acknowledgment.** The authors wish to acknowledge Mr. Donald Schifferl for technical help in recording the $^{11}B$ nmr spectra.

# Mono- and Diprotonation of *N*-Acylthioureas in Aqueous Sulfuric Acid

**Wayne I. Congdon**[1] **and John T. Edward***

*Contribution from the Department of Chemistry, McGill University, Montreal 101, Canada.* *Received December 3, 1971*

**Abstract:** The basicities of *N*-acetylthiourea, *N*-benzoylthiourea, and eight substituted *N*-benzoylthioureas have been determined by a spectrophotometric method. Thiocarbonyl protonation takes place in 35–60% sulfuric acid and follows the $H_0'''$ value of the solution; the Hammett $\rho$ value for the protonation of meta- and para-substituted *N*-benzoylthioureas is $-0.42$. A second protonation, on the amide oxygen, takes place in 65–96% sulfuric acid, and follows the $H_A$ value of the solution; for this protonation $\rho$ is $-0.86$.

The protonation of amides (A) to their conjugate acids ($AH^+$) in aqueous sulfuric acid takes place on the carbonyl oxygen,[2,3] and the ionization ratio ($I \equiv [AH^+]/[A]$) is found to depend on the acidity of the solution as measured by the $H_A$ acidity function[4]

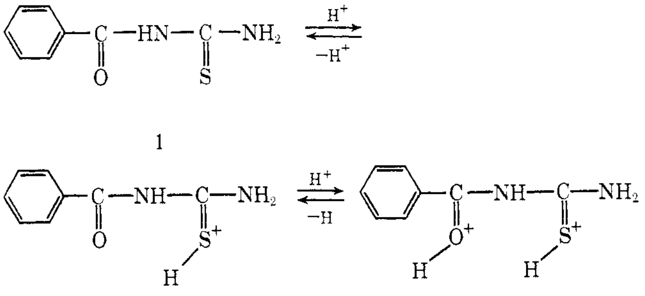
$$\log([AH^+]/[A]) = pK_{AH^+} - H_A \qquad (1)$$

where $K_{AH^+}$ ($\equiv$ −antilog $pK_{AH} = a_{H^+}a_H/a_{AH^+}$) is the thermodynamic dissociation constant of the conjugate acid. The conjugate acid of benzamide has a $pK_{AH^+}$ of $-1.74$, so that the amide is half-protonated in 35.2% sulfuric acid.[4] On the other hand, the protonation of N-substituted thioureas (B) occurs on the thiocarbonyl sulfur atom[2,5] and has been found[6,7] to follow the $H_0'''$ acidity function[8]

$$\log([BH^+]/[B]) = pK_{BH^+} - H_0''' \qquad (2)$$

*N*-Methylthiourea has a $pK_{BH^+}$ of $-1.75$, and is half-ionized in 22.6% sulfuric acid.[7] Thus it is almost identical in basicity with benzamide, although it is half-protonated in less concentrated acid because its protonation is governed by a different acidity function.

In *N*-benzoylthiourea (**1**) both amide and thiourea functions may be expected to have reduced basicities, and it becomes of interest to consider the question: will protonation take place first on the thiourea sulfur or on the benzoyl oxygen?[9] We show below that in this molecule both oxygen and sulfur sites have reduced but approximately equal basicities, but that because their protonation is governed by different acidity functions ($H_A$ and $H_0'''$), sulfur is protonated first to give the conjugate acid **2**, and then in stronger acid oxygen is protonated to give the conjugate acid **3**.



1

2

3

Evidence from which we conclude that the first protonation, occurring in 35–60% sulfuric acid, takes place on the thiourea thiocarbonyl (rather than on the amide carbonyl) consists of three experimental findings. First, the changes in the ultraviolet absorption (see Table I) are qualitatively very similar to those observed when *N*-methylthiourea is protonated in sulfuric acid, and different from those observed when benzamide is protonated. This comparison is shown in Figure 1. For both *N*-methylthiourea and *N*-benzoylthiourea the strong absorption band at longer wavelength is most

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[1] Holder of NRCC Studentship, 1968–1970.

[2] For a judicious survey of the early literature, see A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (*London*), 722 (1961); for important later references see R. J. Gillespie and J. Birchall, *Can. J. Chem.*, **41**, 148, 2642 (1963). M. Liler, *Chem. Commun.*, 115 (1971), while conceding that amides are predominantly O-protonated in concentrated acid solutions, argues that in dilute aqueous acids N-protonation becomes predominant because the N-protonated amide is more hydrated than the O-protonated amide. This last assertion lacks any experimental support; indeed, it would seem likely from the activity coefficient studies of Sweeting and Yates[3] to be the reverse of the truth.

[3] L. M. Sweeting and K. Yates, *Can. J. Chem.*, **44**, 2395 (1966).

[4] K. Yates, J. B. Stevens, and A. R. Katritzky, *ibid.*, **42**, 1957 (1964); K. Yates and J. B. Stevens, *ibid.*, **43**, 529 (1965); C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc. B*, 1235 (1967).

[5] I. C. Wang, Ph.D. Dissertation, McGill University, 1963.

[6] L. Lantos, Ph.D. Dissertation, McGill University, 1966; J. T. Edward and J. K. Liu, *Can. J. Chem.*, **47**, 1117 (1969).

[7] G. Derdall, Ph.D. Dissertation, McGill University, 1971.

[8] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, **86**, 2671 (1964).

[9] Protonation on nitrogen may be assumed to take place to a negligible extent for reasons discussed in ref 2. The experimental work described in the present paper can be interpreted without the necessity of invoking any appreciable N-protonation.

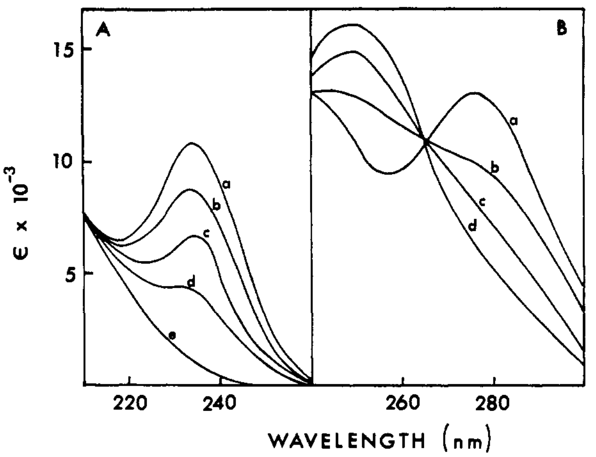

Figure 1. (A) Ultraviolet spectra of *N*-methylthiourea (ref 6) in a, 0.0%; b, 15.9%; c, 21.3%; d, 27.1%; and e, 66.4% sulfuric acid. (B) Ultraviolet spectra of *N*-benzoylthiourea in a, 0.0%; b, 47.0%; c, 52.7%; and d, 62.4% sulfuric acid.

Table I. Absorption Spectra of *N*-Acylthioureas

| Acyl group | $\lambda_B$, nm | $10^{-3}$ $\epsilon_B$ | $\lambda_{BH^+}$, nm | $10^{-3}$ $\epsilon_{BH^+}$ | $\lambda_{BH_2^{2+}}$, nm | $10^{-3}$ $\epsilon_{BH_2^{2+}}$ |
|---|---|---|---|---|---|---|
| Acetyl | 265 | 12.7 | 225 | 10.4 | 232 | 9.2 |
| | | | | | 218 | 9.7 |
| Benzoyl | 275 | 13.0 | 252 | 16.2 | 267 | 13.2 |
| | 239 | 13.3 | | | | |
| *p*-Methoxybenzoyl | 285 | 23.6 | 300 | 17.2 | 298 | 14.1 |
| | 216 | 17.2 | 225 | 16.5 | 225 | 14.2 |
| *m*-Chlorobenzoyl | 278 | 11.5 | 252 | 18.0 | 258 | 16.8 |
| | 239 | 12.0 | | | | |
| *p*-Chlorobenzoyl | 275 | 15.6 | 266 | 17.6 | 284 | 16.1 |
| | 248 | 16.6 | | | | |
| *m*-Fluorobenzoyl | 278 | 12.4 | 248 | 18.0 | 254 | 15.1 |
| | 237 | 13.4 | | | | |
| *p*-Methylbenzoyl | 275 | 16.9 | 271 | 15.0 | 291 | 15.5 |
| | 260 | 15.5 | | | | |
| *m*-Methylbenzoyl | 274 | 14.8 | 258 | 14.9 | 277 | 13.5 |
| | 243 | 14.3 | | | | |
| *o*-Methylbenzoyl | 274 | 14.4 | 233 | 13.1 | 264 | 8.8 |
| | | | 250[a] | 11.6 | 236 | 10.8 |
| *p*-Nitrobenzoyl | 266 | 17.9 | 264 | 18.4 | | |

[a] Shoulder.

probably due to a π → π* transition and undergoes a blue shift as the acid strength is increased.[10] Good isosbestic points for the spectral curves in different concentrations of acid are observed; this behavior is general for *N*-acylthioureas and thioureas,[5,6] and indicates a simple equilibrium involving B and BH$^+$. Second, the ionization ratios, determined by the conventional spectrophotometric method,[11] are found to follow $H_0'''$ (eq 2) and not $H_A$ (eq 1). This is shown for *N*-benzoylthiourea in Figure 2, where the slope of the straight line obtained by plotting log ([BH$^+$]/[B]) *vs.* $H_0'''$ lies close to unity, as required by eq 2; a similar plot against $H_A$ has a slope of 2.2. The slopes and the p$K_{BH^+}$ values obtained by application of eq 2 to the spectral data for *N*-benzoylthiourea and six meta- and para-substituted *N*-benzoylthioureas are given in Table II. A plot of these p$K_{BH^+}$ values *vs.* σ yields the straight line shown in Figure 3, the slope (Hammett ρ value) of which equals −0.42 (correlation coefficient 0.961). This ρ value is

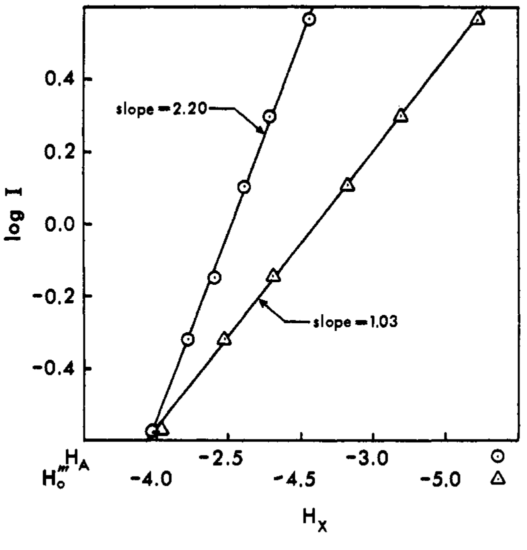

Figure 2. Variation of ionization ratio (*I*) of *N*-benzoylthiourea in 35–60% sulfuric acid with acidity function: (○, $H_A$; △, $H_0'''$).

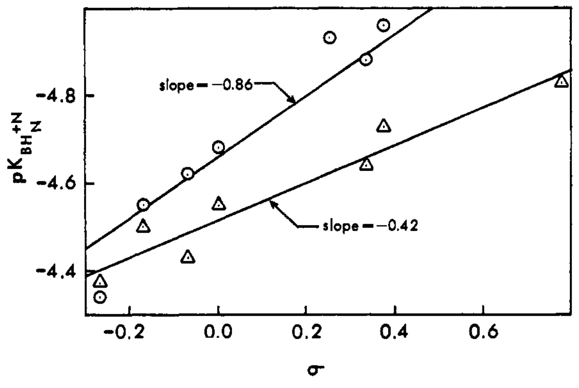

Figure 3. Dependence of p*K*'s of meta- and para-substituted *N*-benzoylthioureas on σ (△, p$K_{BH^+}$; ○, p$K_{BH_2^{2+}}$).

Table II. Mono- and Diprotonation Constants of *N*-Acylthioureas

| Acyl group | −p$K_{BH^+}$ | Slope[a] | −p$K_{BH_2^{2+}}$ | Slope[b] |
|---|---|---|---|---|
| Acetyl | 4.64 ± 0.12[c] | 1.09 | 4.61 ± 0.12[d] | 1.02 |
| Benzoyl | 4.55 ± 0.02 | 1.03 | 4.68 ± 0.06 | 1.07 |
| *m*-Chlorobenzoyl | 4.73 ± 0.06 | 1.09 | 4.96 ± 0.06 | 1.04 |
| *p*-Chlorobenzoyl | | | 4.93 ± 0.05 | 1.00 |
| *m*-Fluorobenzoyl | 4.64 ± 0.04 | 1.10 | 4.88 ± 0.07 | 1.00 |
| *p*-Methoxybenzoyl | 4.37 ± 0.06 | 1.03 | 4.34 ± 0.05[d] | 1.13 |
| *o*-Methylbenzoyl | 4.65 ± 0.05 | 1.12 | 4.67 ± 0.04 | 1.08 |
| *m*-Methylbenzoyl | 4.43 ± 0.20 | 1.05 | 4.62 ± 0.08 | 1.05 |
| *p*-Methylbenzoyl | 4.50 ± 0.18 | 0.97 | 4.55 ± 0.05 | 1.00 |
| *p*-Nitrobenzoyl | 4.83 ± 0.06 | 1.17 | | |

[a] Slope of log ([BH$^+$]/[B]) *vs.* $H_0'''$. [b] Slope of log ([BH$_2^{2+}$]/BH$^+$]) *vs.* $H_A$. [c] Absorbance measurements extrapolated to zero time. [d] Change in absorbance on protonation was small.

the third finding which indicates thiocarbonyl protonation. The Hammett ρ value for protonation of meta- and para-substituted benzamides is −0.92,[4] and the value for protonation on the oxygen of **1** would be expected to lie close to this value. The ρ value for the protonation of the thiocarbonyl would be expected to be considerably less. The protonation of substituted *trans*-cinnamate ions in water at 25° has ρ = −0.466; the protonation of substituted 3-phenylpropionate ions

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(10) M. J. Janssen, *Spectrochim. Acta*, **17**, 495 (1961); J. Sandstrom, *Acta Chem. Scand.*, **16**, 1616 (1962).

(11) L. Flexser, L. P. Hammett, and A. Dingwall, *J. Amer. Chem. Soc.*, **57**, 2103 (1935).

**Table III.** Melting Points and Analyses of *N*-Acylthioureas and Wavelengths Used for Measurements of Protonation Constants

| Acyl group | Mp, °C | % calcd C | % calcd H | % calcd N | % found C | % found H | % found N | $\lambda(\mathrm{p}K_{BH^+})$, nm | $\lambda(\mathrm{p}K_{BH_2^{2+}})$, nm |
|---|---|---|---|---|---|---|---|---|---|
| Acetyl | 170–171[a] | | | | | | | 265 | 245 |
| Benzoyl | 178–179[b] | | | | | | | 280 | 280 |
| *m*-Chlorobenzoyl | 190–192 | 44.8 | 3.3 | 13.0 | 45.0 | 3.6 | 12.8 | 285 | 275 |
| *p*-Chlorobenzoyl | 218–219 | 44.8 | 3.3 | 13.0 | 44.8 | 3.3 | 12.9 | | 295 |
| *m*-Fluorobenzoyl | 192–193 | 48.5 | 3.5 | 14.1 | 48.6 | 3.7 | 14.3 | 280 | 275 |
| *p*-Methoxybenzoyl | 212–213[c] | | | | | | | 280 | 340 |
| *o*-Methylbenzoyl | 193–194 | 55.7 | 5.1 | 14.4 | 55.9 | 5.3 | 14.6 | 275 | 280 |
| *m*-Methylbenzoyl | 163–164 | 55.7 | 5.1 | 14.4 | 55.7 | 5.4 | 14.6 | 280 | 285 |
| *p*-Methylbenzoyl | 226–228 | 55.7 | 5.1 | 14.4 | 55.8 | 4.9 | 14.6 | 230 | 300 |
| *p*-Nitrobenzoyl | 214–216 | 42.7 | 3.1 | | 43.0 | 3.4 | | 295 | |

[a] M. L. Moore and F. S. Crossley, *J. Amer. Chem. Soc.*, **62**, 3273 (1940), report mp 165°. [b] W. H. Pike, *Ber.*, **6**, 744 (1873), reports mp 169–170°. [c] A. E. Dixon, *J. Chem. Soc.*, **75**, 386 (1899), reports mp 216–217°.

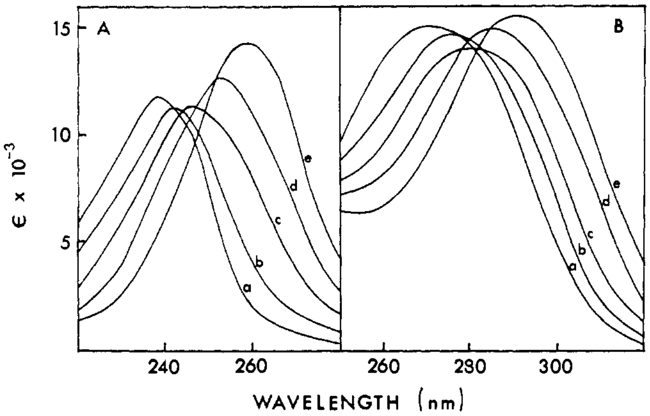


Figure 4. (A) Ultraviolet spectra of *p*-toluamide in a, 0.0%; b, 20.5%; c, 32.8%; d, 42.3%; and e, 57.2% sulfuric acid. (B) Ultraviolet spectra of *N*-*p*-toluoylthiourea in a, 60.0%; b, 73.4%; c, 80.0%; d, 85.7%; and e, 96.1% sulfuric acid.

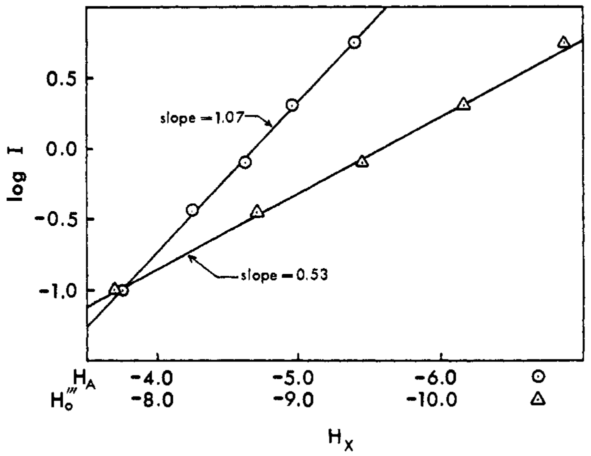
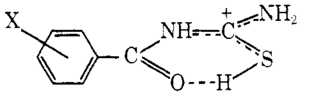


Figure 5. Variation of ionization ratio (*I*) of *N*-benzoylthiourea in 65–96% sulfuric acid with acidity function (○, $H_A$; △, $H_0'''$).

has $\rho = -0.212$.[12] The efficiency of an amide group in transmitting electrical effects is somewhere between that of a vinyl and that of a dimethylene group.[13] The $\rho$ of $-0.42$ for the S-protonation of *N*-benzoylthioureas is accordingly rather high, and may indicate that electrical effects are being transmitted through the hydrogen-bonded form **2a**.[14]



**2a**

Only minor changes are observed in the ultraviolet spectra of *N*-benzoylthioureas as the sulfuric acid concentration is increased from 60 to 68%, but at higher acid concentrations a second protonation is indicated by systematic changes in the spectra. This is shown in Figure 4, in which the spectral changes of *N*-*p*-toluamide and *N*-*p*-toluoylthiourea are compared. The similarity in the character of the spectral changes gives the first reason for believing that protonation is now taking place on the amide oxygen. For the other *N*-benzoylthioureas also the spectral changes in 70–100% sulfuric acid, reported in Table I, are similar to those occurring when the corresponding benzamides are protonated.

A second reason for believing that protonation is now taking place on the amide oxygen comes from the fact that the change in log ($[BH_2^{2+}]/[BH^+]$), obtained by analysis of spectral changes in the usual way,[4,11] follows $H_A$[15] and not $H_0'''$. An example is given in Figure 5. A third reason comes from the fact that the $\mathrm{p}K_{BH_2^{2+}}$ values of meta- and para-substituted *N*-benzoylthioureas, obtained by application of eq 1 to the spectral data, and recorded in Table II, indicate $\rho = -0.86$ (see Figure 3; correlation coefficient: 0.964), in reasonable agreement with $\rho$ of $-0.92$ for the protonation of benzamides.[4]

The basicities listed in Table II indicate that diprotonation of these *N*-benzoylthioureas should be almost complete in 100% sulfuric acid. This was confirmed for *N*-*p*-chlorobenzoylthiourea by cryoscopic and conductivity measurements.[18] A comparison of the mono- and diprotonation constants listed in Table II shows

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(12) L. P. Hammett, "Physical Organic Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1940, p 190.

(13) R. G. Pews, *Chem. Commun.*, 458 (1971), and references therein.

(14) We are indebted to Professor R. Stewart for this suggestion.

(15) Because of its positive charge, the protonation of **2** would be expected to follow an as yet undetermined acidity function $H_A{}^+$, and not $H_A$. However, the parallelism of $H_0$ and $H_+$ in strongly acid solutions[16] makes it probable that $H_A$ and $H_A{}^+$ will also be parallel in strongly acid solutions. This parallelism will not extend all the way down through increasingly dilute acids to the standard state, dilute aqueous solution, so that the absolute value of $H_A{}^+$ is likely to be about 0.3 unit higher than that of $H_A$ in 100% sulfuric acid,[17] and the $\mathrm{p}K_{BH_2^{2+}}$ values in Table III consequently are likely to be systematically in error by this amount.

(16) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 364 (1957).

(17) J. C. D. Brand, W. C. Horning, and M. B. Thornley, *ibid.*, 1374 (1952).

(18) R. J. Gillespie, in unpublished experiments, found a mean $\nu$ value (from cryoscopic measurements) of 2.9, and a mean $\gamma$ value (from conductivity measurements) of 1.7, both indicating fairly complete diprotonation.

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 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 ± 0.1° 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 ± 1.0°. The spectral data in Table I were all recorded at 25.0 ± 0.1°. The wavelengths of absorbance readings from which p*K* values were determined are listed in Table III. The p*K* 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 described[4] to obtain the results recorded in Table II.

**Acknowledgment.** We thank the National Research Council of Canada for financial support.

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

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

**Wayne I. Congdon**[1] **and John T. Edward***

*Contribution from the Department of Chemistry, McGill University, Montreal 101, Canada.* *Received December 3, 1971*

**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 $\rho$ 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 spectros-

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(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. Egamie, *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.