

- nitrile solutions which are 0.1 M in sodium perchlorate as supporting electrolyte. Electrochemists traditionally call these  $E^0$ , reserving  $E^0$  for zero supporting electrolyte concentration frequently in water. Although it is possible to extrapolate to zero supporting electrolyte concentration, no additional information would result, and we have not done this.
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## Transition States for the Hydrolysis of 4-Nitroacetanilide and 4-Nitrothioacetanilide in Varying Concentrations of Sulfuric Acid

John T. Edward,\* Gary D. Derdall, and Sin Cheong Wong\*

Contribution from the Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6. Received April 5, 1978

**Abstract:** The rates of hydrolysis of 4-nitroacetanilide (protonation governed by  $h_A$ :  $pK_{SH^+} = -2.08$ ) and 4-nitrothioacetanilide in 22–96% acid, and the activity coefficients of the two compounds in 0–47% acid, have been determined. The change calculated in the activity coefficient (relative to tetraethylammonium ion) of the transition state for the A-2 hydrolysis of 4-nitroacetanilide with changing acid concentration is similar to the change in the activity coefficient of a protonated alcohol, and indicates substantially complete bonding of a water molecule to the protonated amide in the transition state. The same criterion indicates much less complete bonding of a water molecule to the protonated thioamide in the transition state for its hydrolysis.

### Introduction

We have recently reported that *O*-ethyl thiobenzoate hydrolyzes by an  $A_{AC}2$  mechanism in all concentrations of aqueous sulfuric acid, while ethyl benzoate hydrolyzes by an  $A_{AC}2$  mechanism in acid concentrations up to 80%, but by an

$A_{AC}1$  mechanism in more concentrated acid.<sup>1,2</sup> The change in the activity coefficient of the transition state for the A-2 hydrolysis of ethyl benzoate with changing acid concentration indicates that the transition state has a structure similar to that of a protonated alcohol  $ROH_2^+$ , i.e., that the attack of a water

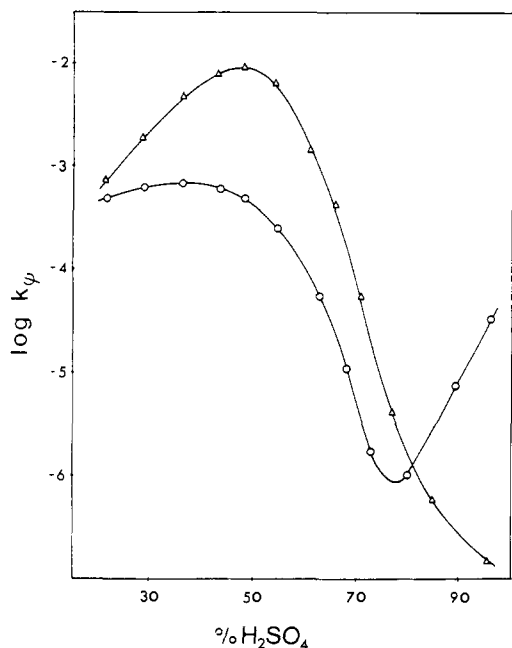
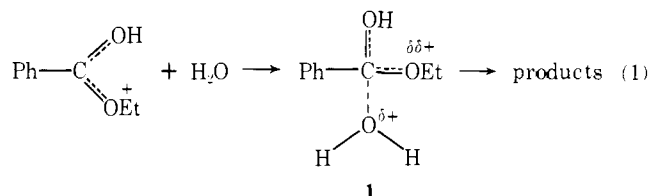


Figure 1. Rate-acidity profiles for the hydrolysis of 4-nitroacetanilide (O) and 4-nitrothioacetanilide (Δ) at 48.6 °C.

molecule is well advanced and most of the positive charge in the transition state **1** resides on the incoming water molecule



( $\delta^+ \gg \delta\delta^+$ ). Similar conclusions had been arrived at earlier by Yates and his colleagues concerning the A-2 hydrolysis of acetate esters<sup>3</sup> and benzamides.<sup>4</sup>

The rapid hydrolysis of *O*-ethyl thiobenzoate prevented the determination of the activity coefficients of its transition state in different acid concentrations. However, thioamides are more stable in acid,<sup>5</sup> and therefore seemed more suitable for such studies.

In this paper, we report on the kinetic and activity coefficient behavior of 4-nitrothioacetanilide and 4-nitroacetanilide, in 22–96% sulfuric acid at 48.6 °C.

## Results and Discussion

The variation in pseudo-first-order hydrolysis rate constant  $k_\psi$  with sulfuric acid concentration for the amide and thioamide is shown in Figure 1. The curve for 4-nitroacetanilide is similar in shape to that obtained by O'Connor et al. at 100.1 °C:<sup>6</sup>  $k_\psi$  increases with sulfuric acid concentration to a maximum in 35–40% acid, decreases to a minimum in ~80% acid, and then increases again above 80% acid. Such a rate profile is consistent with an A-2 mechanism<sup>7</sup> for hydrolysis of the amide in acid concentrations below 80% (Scheme I, X = O), and with an A-1 mechanism<sup>8</sup> in acid concentrations above 80% (Scheme II, X = O).

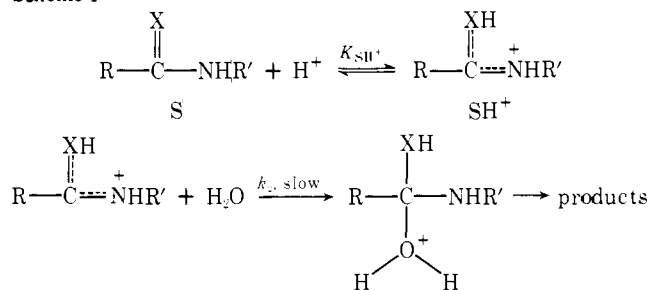
The curve for 4-nitrothioacetanilide shows  $k_\psi$  reaching a maximum at ~48% acid but no upturn at even the highest acidities, indicating an A-2 mechanism in all acid concentrations. The absence of an A-1 mechanism, also absent with thione esters,<sup>1</sup> is most probably due to the high energy nature of the thioacylium ion (**2**, X = S).

**Rate-Acidity Correlations.** The Yates-McClelland hydration treatment<sup>9</sup> (eq 2) and Bunnett-Olsen LFER treat-

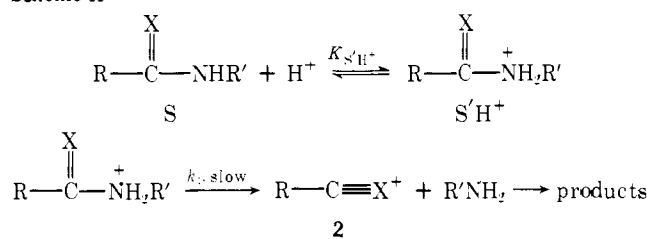
Table I.  $r$  and  $\phi$  Parameters for the Hydrolysis of 4-Nitroacetanilide and 4-Nitrothioacetanilide at 48.6 °C

substrate	% H <sub>2</sub> SO <sub>4</sub>	$r$	$\phi$
4-nitroacetanilide	22–73	2.82	0.91
4-nitrothioacetanilide	80–96	-0.56	-0.64
4-nitrothioacetanilide	22–78	2.78	0.91

### Scheme I



### Scheme II



ment<sup>10</sup> (eq 3) of the kinetic data supported these mechanistic interpretations.

$$\log k_\psi - \log \frac{h_S}{h_S + K_{\text{SH}^+}} = r \log a_{\text{H}_2\text{O}} + \text{constant} \quad (2)$$

$$\log k_\psi - \log \frac{h_S}{h_S + K_{\text{SH}^+}} = \phi(H_0 + \log [\text{H}^+]) + \text{constant} \quad (3)$$

In order to apply these equations, it is necessary to know the protonation constant  $K_{\text{SH}^+}$  of the substrate and the acidity function  $h_S$  governing its ionization. We have already shown that the protonation of 4-nitrothioacetanilide, like that of other thiocarbonyl compounds, follows the  $h_T$  acidity function, and that it has a  $pK_{\text{SH}^+}$  of -4.02 at 25 °C.<sup>11</sup> We have now found that the protonation of 4-nitroacetanilide follows  $h_A$ , with a  $pK_{\text{SH}^+}$  of -2.08 (see Experimental Section). These data were used to calculate the fraction protonated ( $\equiv h_S/(h_S + K_{\text{SH}^+})$ ) at 25 °C; it was assumed that the fraction protonated at 50 °C would not be greatly different.  $a_{\text{H}_2\text{O}}$ <sup>12</sup> and  $h_0$ <sup>13</sup> values for sulfuric acid at 50 °C are available in the literature, and  $[\text{H}^+]$  was equated with stoichiometric acid concentration.<sup>10</sup>

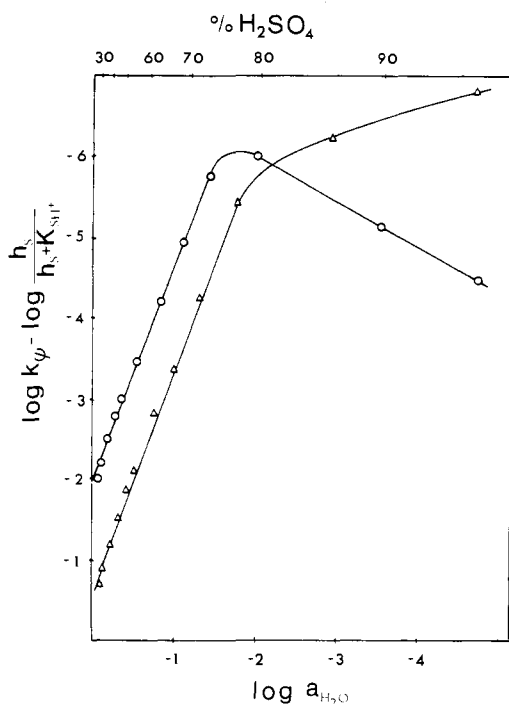
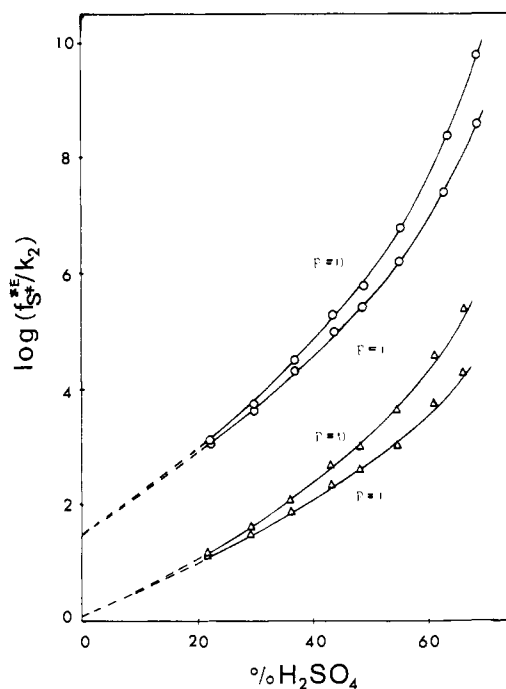
The plots of eq 2 for the two compounds are shown in Figure 2. In acid concentrations below 73% plots for 4-nitroacetanilide had a slope  $r$  close to 3, characteristic of the A-2 hydrolysis of amides;<sup>14</sup> above 80% acid,  $r$  was negative, indicating an A-1 mechanism. Plots for 4-nitrothioacetanilide also had a slope  $r$  of ~3 in acid concentrations up to 78% but the curve deviated from a straight line in the most concentrated acids. It is difficult to estimate the significance of this deviation because hydrolysis rates in these acid concentrations were extremely slow and subject to large experimental errors.

**Transition State Activity Coefficients.** For the A-2 mechanism of Scheme I, the Brønsted-Bjerrum rate equation leads to<sup>1,15</sup>

$$\log (f_{\text{S}^*}^{\text{E}}/k_2) = -\log k_\psi (1 + I) - \log K_{\text{SH}^+} + \log f_{\text{S}} + \log a_{\text{H}^*} + p \log a_{\text{H}_2\text{O}} \quad (4)$$

Table II. Comparison of Cationic Activity Coefficients

% H <sub>2</sub> SO <sub>4</sub>	log $f_{S^{\ddagger}E}$		log $f^*_{ROH_2^+}$	log $f^*_{RCOH\cdots NH_2^+}$
	4-nitroacetanilide	4-nitrothioacetanilide		
10	0.7	0.4		0.5
20	1.4	0.9		1.1
30	2.2	1.4		1.6
35	2.6	1.7	2.8	
40	3.1	2.0	3.4	2.4
45	3.6	2.3	4.0	2.8
50	4.2	2.7	4.7	3.2
55	4.7	3.1	5.4	3.5
60	5.5	3.5	6.2	3.9
65	6.4	4.0		4.3

Figure 2.  $r$  plots for the hydrolysis of 4-nitroacetanilide (O) and 4-nitrothioacetanilide ( $\Delta$ ).Figure 3. Plots of  $\log (f_{S^{\ddagger}E}/k_2)$  and  $\log (f_{S^{\ddagger}}/k_2)$  against acid concentration for the hydrolysis of 4-nitroacetanilide (O) and 4-nitrothioacetanilide ( $\Delta$ ).

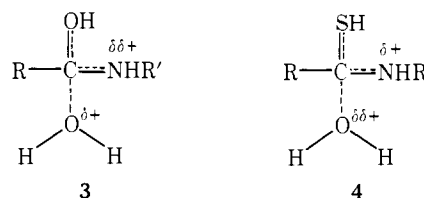
where  $S^{\ddagger}$  is the transition state for the slow step,  $I$  is the ionization ratio  $[SH^+]/[S]$ , and the single ion activities have asterisks to show that they are relative to tetraethylammonium ion.<sup>17</sup>  $a_{H^+}$  values for sulfuric acid solutions at 25 °C are available,<sup>16</sup> and we have determined the activity coefficients  $f_S$  of the amide and thioamide in various acid concentrations at 25 °C from their partition coefficients between the acid solution and methylene chloride.<sup>18</sup> If we assume that  $p = 1$ , all quantities on the right-hand side of eq 4 are known, and  $\log (f_{S^{\ddagger}E}/k_2)$  may be calculated. Values of  $\log (f_{S^{\ddagger}E}/k_2)$  for the two compounds are shown in Figure 3, along with  $\log (f_{S^{\ddagger}}/k_2)$  values calculated from the equation of Yates et al.<sup>16</sup> (eq 4 having  $p = 0$  and  $f_{S^{\ddagger}}$  replacing  $f_{S^{\ddagger}E}$ ).

Log  $k_2$  values ( $\sim -1.5$  for the amide;  $\sim -0.1$  for the thioamide) were obtained by extrapolating the curves of Figure 3 to zero acid concentration, in which all activity coefficients are unity by definition. These values subtracted from  $\log (f_{S^{\ddagger}E}/k_2)$  give  $\log f_{S^{\ddagger}E}$  values, which are shown plotted in Figure 4 against acid concentration. Also plotted in Figure 4 are  $\log f^*_{ROH_2^+}$  and  $\log f^*_{RCOH\cdots NH_2^+}$ . The relative activity coefficients  $f^*_{ROH_2^+}$  of a typical protonated alcohol<sup>19</sup> were calculated from the  $H_{ROH}$  function<sup>20</sup> and from activity coefficients of alcohols in various concentrations of acid,<sup>18</sup> according to

$$H_{ROH} = -\log a_{H^+} - \log f_{ROH} + \log f^*_{ROH_2^+} \quad (5)$$

The activity coefficients of a typical protonated amide<sup>21</sup>  $f^*_{RCOH\cdots NH_2^+}$  were calculated using the readjusted  $H_A$  scale.<sup>22</sup>

The differing slopes of the curves in Figure 4 may be rationalized by a consideration of the differing extents to which the various cations are hydrated, and hence stabilized. This in turn depends on the extent to which the charge is localized or delocalized: hydration is very pronounced for  $ROH_2^+$ , less pronounced for  $RCOH\cdots NH_2^+$ . Consequently, the lessened hydration accompanying increasing acid concentration, and concomitant decreasing water activity, causes a sharp increase in  $f^*_{ROH_2^+}$  and a smaller increase in  $f^*_{RCOH\cdots NH_2^+}$  (Figure 4). It is apparent from the change in  $f_{S^{\ddagger}E}$  with acid concentration that the transition state for amide hydrolysis<sup>4,23</sup> resembles  $ROH_2^+$ , which accords with the idea of a transition state 3 close to the tetrahedral intermediate, with almost



complete bonding of the incoming water molecule to the protonated amide, and the charge  $\delta^+$  close to  $1+$ —an idea already

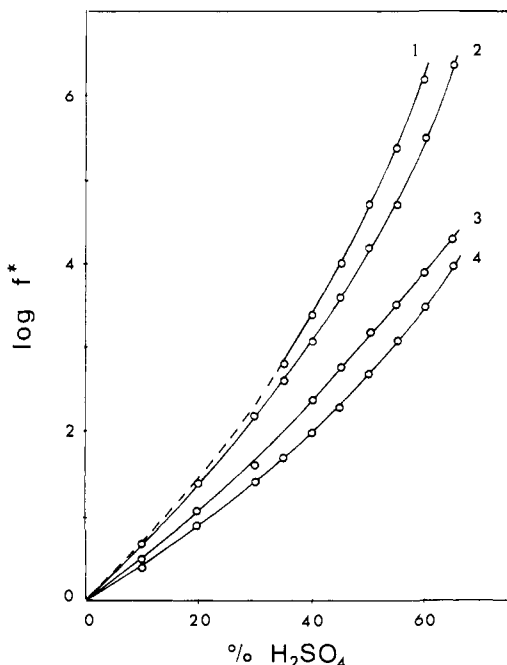
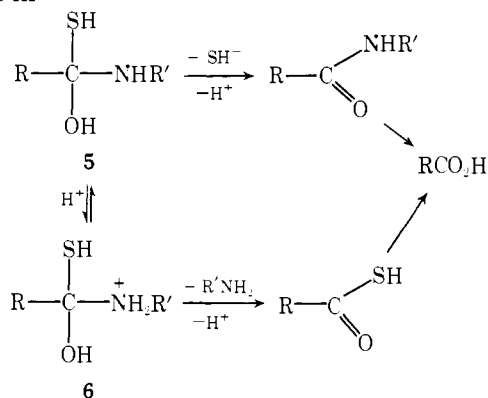


Figure 4. Change in activity coefficients with acid concentration of following cationic species: (1)  $\text{ROH}_2^+$ ; (2)  $\text{S}^\ddagger$  of amide A-2 hydrolysis; (3)  $\text{R-C(OH)}\cdots\text{NH}_2^+$ ; (4)  $\text{S}^\ddagger$  of thioamide A-2 hydrolysis.

Scheme III



advanced by Modro, Yates, and Beaufays<sup>4</sup> from their studies of amide hydrolysis. On the other hand, the change in  $f_{\text{S}^\ddagger}^{\text{E}}$  for the hydrolysis of the thioamide in changing acid concentration indicates a transition state with a delocalized charge, like  $\text{RC(OH)}\cdots\text{NH}_2^+$ . This can be accommodated by the transition state **4** with only partial bonding of the water molecule to the protonated substrate, so that the charge  $\delta\delta^+$  is very small. From the Hammond principle, such a difference in transition states might be expected from the 25-fold greater reactivity of the protonated thioamide as compared with the protonated amide (see the  $k_2$  values above), and from the superior reactivity of thiocarbonyl compounds generally.<sup>24</sup>

**Breakdown Path of the Tetrahedral Intermediate.** In 8.5 M hydrochloric acid at 60 °C the hydrolysis of thiobenzamide is reported to lead initially to 25% benzamide, possibly arising from the breakdown of **5** ( $\text{R} = \text{Ph}$ ;  $\text{R}' = \text{H}$ ) in Scheme III, and to 75% thiobenzoic acid, possibly arising from the breakdown of **6**.<sup>25</sup> However, analysis of the spectral changes accompanying the hydrolysis of 4-nitrothioacetanilide in 20–96% sulfuric acid shows that only *p*-nitroaniline and acetic acid (from the rapid hydrolysis of thioacetic acid<sup>26</sup>), and no 4-nitroacetanilide, are formed. It seems likely that the hydrolysis pathway via the amide will usually be found in more dilute acid solutions, in

which conversion of **5** to **6** ( $\text{R} = \text{CH}_3$ ;  $\text{R}' = \text{Ph}$ ) is not complete.<sup>27</sup>

## Experimental Section

**Materials.** 4-Nitrothioacetanilide was prepared by reaction of 4-nitroacetanilide (a commercial product) with phosphorus pentasulfide in refluxing pyridine.<sup>11</sup> Sulfuric acid solutions were prepared by diluting reagent grade sulfuric acid (96% minimum) with distilled water and were standardized by titration.

**Ionization Measurements.** The ultraviolet spectra of 4-nitroacetanilide in 0–80% sulfuric acid were taken by a Unicam SP 800 spectrophotometer thermostated at  $25.0 \pm 0.1$  °C. Isosbestic points were not obtained, indicating strong medium effects, and these were corrected for by characteristic vector analysis.<sup>28</sup> Ionization ratios  $I$ , given in Table IV of supplementary material, were calculated by the usual procedure,<sup>29</sup> and followed the  $h_A$  acidity function<sup>22</sup> very closely ( $-\log I/dh_A = 0.98$ ), giving a  $\text{p}K_{\text{SH}^+}$  value of  $-2.08 \pm 0.03$ .

**Kinetic Measurements.** Rates of hydrolysis were followed spectrophotometrically at  $48.6 \pm 0.2$  °C. Change in optical density was recorded for at least 1–2 half-lives, and a least-squares computer program was used to calculate pseudo-first-order rate constants  $k_{\text{p}}$ . Results are shown in Figure 1 and given in Table III of supplementary material. The reproducibility was within 1–3%, except for very slow reactions when data were analyzed graphically.

**Activity Coefficient Measurements.** Activity coefficients  $f_{\text{S}}$  of 4-nitroacetanilide and 4-nitrothioacetanilide in sulfuric acid were determined at  $25.0 \pm 0.1$  °C by the distribution method using methylene chloride as the inert solvent.<sup>18</sup> Optical densities were extrapolated to the time of mixing solutions to compensate for changes due to hydrolysis. Results are given in Table V of supplementary material.

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**Supplementary Material Available:** Tables III (pseudo-first-order rate constants in different sulfuric acid concentrations), IV (ionization ratios), V (activity coefficients  $f_{\text{S}}$ ), and VI (transition state activity coefficient ratios  $f_{\text{S}^\ddagger}^{\text{E}}/k_2$  and  $f_{\text{S}^\ddagger}/k_2$ ) (4 pages). Ordering information is given on any current masthead page.

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