

Mechanism of Hydrolysis of C(2)-Methylthiazolium Ions<sup>1</sup>Michael W. Washabaugh,\* Mark A. Gold,<sup>†,‡</sup> and Charles C. Yang<sup>§</sup>

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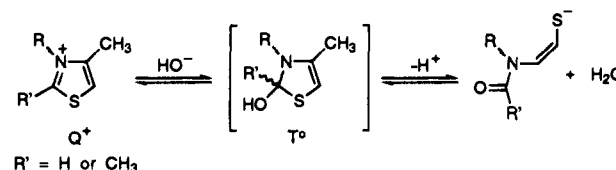
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**Abstract:** Rate constants in the pH range 3–9 for formation of the enethiolate product upon hydrolysis of several 3-R-4-methyl- and 3-R-2,4-dimethylthiazolium ions in oxygen-containing and amine buffers have been determined by irreversible iodination of the enethiolate at 25 °C and ionic strength 1.0 M in aqueous solution. It is concluded that the rate-limiting step for hydrolysis of these thiazolium ions in the pH range 3–11 is breakdown of the neutral tetrahedral addition intermediate (T<sup>o</sup>) to product: general acid catalysis for enethiolate formation is observed and is inconsistent with rate-limiting formation of T<sup>o</sup>. Buffer catalysis results provide no evidence for a change in rate-limiting step. Brønsted values are  $\alpha = 0.45$  for general acid and  $\beta = 0.34$  for general base catalysis of the formation of the hydrolysis product. Catalysis by buffer acids is formulated as concerted general acid catalysis of the departure of the enethiol from T<sup>o</sup>. The buffer base- and water-catalyzed reactions are formulated as concerted general base catalysis of the expulsion of the enethiolate from T<sup>o</sup>. These mechanisms are general for hydrolysis reactions of 3-substituted thiazolium ions where the substituent on the nitrogen atom of the thiazolium ring is not an intramolecular nucleophilic catalyst. The Hammett  $\rho_1$  value for catalysis by water or phosphate dianion is  $12 \pm 2$  for substituents on the nitrogen atom of the thiazolium ring. C(2)-methylation provides an unfavorable steric and electronic effect on the equilibrium constant for breakdown of T<sup>o</sup> to form product rather than formation of T<sup>o</sup> from the thiazolium ion.

Some mechanisms of general acid–base catalysis are determined by the lifetimes of reaction intermediates, and concerted mechanisms may be enforced by the absence of a significant lifetime for an intermediate.<sup>2</sup> Limited studies of general acid and base catalysis of the hydrolysis of iminium ions suggest that the mechanisms of these reactions can also be determined by the lifetime of tetrahedral addition intermediates.<sup>2b–4</sup> The goal of the work reported here was to determine whether ring opening of the thiazolium ion of 3-R-2,4-dimethylthiazolium ions (R' = CH<sub>3</sub>, Scheme 1) in neutral aqueous solution proceeds in a stepwise manner involving rate-limiting formation of a neutral tetrahedral addition intermediate (T<sup>o</sup>; Scheme 1).

Our attention was directed to this hydrolysis reaction, in part, because (i) a ~100-fold rate-reducing effect of a C(2)-methyl substituent was attributed to steric hindrance of hydroxide ion-catalyzed formation of T<sup>o</sup><sup>5</sup> and (ii) reversible ring opening of the thiazolium ring is involved in transport of several thiazolium

Scheme 1



ions, including thiamin (vitamin B<sub>1</sub>) itself, across biological membranes.<sup>4b</sup>

Previous studies have evaluated the rate of hydrolysis of 3-R-4-methylthiazolium ions (R' = H) in neutral and basic aqueous solution and concluded that the formation of T<sup>o</sup> is rate-limiting at pH  $\geq 6.5$ .<sup>5,6</sup> This conclusion is inconsistent with the following observations.

(i) Although the downward deviation (nonlinearity) exhibited in the pH–log(rate) profile for the hydrolysis reaction<sup>3,4</sup> near pH 6.9 would suggest a change in rate-limiting step from rate-limiting formation of T<sup>o</sup> at high pH to rate-limiting breakdown of T<sup>o</sup> at low pH, the linear (rather than curved) plots of the rate constants for enethiolate formation against buffer concentration at or near pH 6.9 are inconsistent with the downward deviation, representing a change in the rate-limiting step for enethiolate formation. The lack of evidence for a change in the rate-limiting step for enethiolate formation in the pH range 3–11 requires either rate-limiting formation or rate-limiting breakdown of T<sup>o</sup>.

(ii) Plots of the second-order rate constants for buffer catalysis against percentage buffer base are not linear, which provides evidence that there is a pH-dependent equilibrium reaction (attributed to formation of T<sup>o</sup>)<sup>3,4</sup> that occurs on the reactant (Q<sup>+</sup>; Scheme 1) prior to the rate-limiting step for ring opening.

(6) See, for example: (a) El Hage Chahine, J. -M.; Dubois, J.-E. *J. Am. Chem. Soc.* **1983**, *105*, 2335–2340; (b) Heiber-Langer, I.; Winter, I.; Knoche, W. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1551–1557. (c) Barrabass, S.; Heiber-Langer, I.; Knoche, W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 131–134.

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(2) (a) See, for example: Fishbein, J. C.; Baum, H.; Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 5790–5800 and references therein. (b) Gravit, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 489–499.

(3) Washabaugh, M. W.; Yang, C. C.; Stivers, J. T.; Lee, K. -S. *Bioorg. Chem.* **1992**, *20*, 296–312.

(4) (a) Washabaugh, M. W.; Yang, C. C.; Hollenbach, A. D.; Chen, P. *Bioorg. Chem.* **1993**, *21*, 170–191. (b) Hollenbach, A. D. *Diss. Abstr. Int., B*, in press. It appears likely that a previously reported pK<sub>a</sub> value of  $12.2 \pm 0.7$  (attributed to T<sup>o</sup> formation)<sup>6b,c,15</sup> is actually pK<sub>a</sub> for ionization of T<sup>o</sup> to form the alcoholate anion T<sup>-</sup> (Scheme 3).<sup>23</sup> It appears likely that a previously reported pK<sub>a</sub> value of  $6.8 \pm 0.4$  for an intermediate in the hydrolysis reaction (attributed to either the mercaptan in the enethiolate or N(3) in T<sup>o</sup> or the enethiolate)<sup>6b,c</sup> is actually pK<sub>R</sub><sup>+</sup> for T<sup>o</sup> formation.<sup>29</sup>

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Reversible, pH-dependent 1–2 ppm shifts with an apparent  $pK_a$  value of 7 of the resonance assigned to the N(3)–CH<sub>2</sub>– group (43–49 ppm) in the <sup>13</sup>C NMR spectrum of several 3-R-4-methylthiazolium ions (R' = H) are consistent with a decrease in the positive charge on N(3) in the thiazolium ring at pH 8 and the presence of an intermediate at equilibrium.<sup>4</sup> Although the UV spectrum of a hydrolysis intermediate derived from thiamin (attributed to T<sup>o</sup>) was reported in the pH range 9.2–9.4,<sup>6a</sup> interpretation of this spectrum is complicated by evidence consistent with a pathway involving an intermediate other than T<sup>o</sup> for hydrolysis of thiamin.<sup>4</sup>

(iii) Observed general acid catalysis of enethiolate formation cannot be reasonably assigned to a step involving formation of T<sup>o</sup>.<sup>3,4</sup>

These results support the conclusion that breakdown, not formation, of T<sup>o</sup> is the rate-limiting step for hydrolysis of 3-R-4-methylthiazolium ions (R' = H) in the pH range 3–11 when the N(3)-substituent is not nucleophilic.

We report here an examination of the mechanism of hydrolysis of 3-R-2,4-dimethylthiazolium ions in the pH range 3–11 (R' = CH<sub>3</sub>). Our results confirm and extend the conclusion that buffer catalysis is detectable for hydrolysis of thiazolium ions.<sup>4,7</sup> The major revisions in the hydrolysis mechanism that follow from this work are (i) the rate-reducing effect of C(2)-methylation on hydrolysis of 3-substituted thiazolium ions represents an unfavorable steric and electronic effect on the equilibrium constant for breakdown of T<sup>o</sup> to form the hydrolysis product and (ii) C(2)-methylation has little or no effect on the equilibrium constant for formation of T<sup>o</sup> from Q<sup>+</sup> (Scheme 1). We conclude that general acid–base catalysis of this reaction occurs by a concerted reaction mechanism even though the species T<sup>-</sup> has a sufficient lifetime to exist as an intermediate.

## Experimental Section

**Materials.** Materials and experimental procedures were generally as described previously.<sup>3,4</sup> The synthesis of 3-(carboxymethyl)-4-methylthiazolium bromide (1), 3,4-dimethylthiazolium iodide (2), 3-(cyanomethyl)-4-methylthiazolium chloride (3), and 3-(4-nitrobenzyl)-4-methylthiazolium bromide (4) has been described.<sup>8</sup> The other thiazolium salts were prepared from 4-methylthiazole (Aldrich) or 2,4-dimethylthiazole<sup>9</sup> and an excess of the appropriate alkyl halide. The salts were crystallized from ethanol/diethyl ether unless stated otherwise and dried *in vacuo* over P<sub>2</sub>O<sub>5</sub> at 60 °C.

**3-(2,3,4,5,6-Pentafluorobenzyl)-4-methylthiazolium Bromide (5):** mp 185.4–185.6 °C; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.54 (s, 3H), 6.03 (s, 2H), 8.13 (s, 1H), 10.38 (s, 1H); <sup>13</sup>C NMR (D<sub>2</sub>O, proton-decoupled) δ 15.9 (s), 47.6 (s), 108.7 (t), 123.3 (d), 125.8 (t), 139.2 (t), 142.4 (d), 143.7 (s), 147.0 (m), 150.2 (m), 161.8 (t). Anal. Calcd for C<sub>11</sub>H<sub>7</sub>F<sub>5</sub>NSBr: C, 36.68; H, 1.96; N, 3.89. Found: C, 36.57; H, 1.98, N, 3.89.

**3-(4-Methylbenzyl)-4-methylthiazolium Bromide (6):** mp 172.4–173.2 °C; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.35 (s, 3H), 2.48 (d, 3H), 5.78 (s, 2H), 7.28 (m, 4H), 8.12 (q, 1H), 10.24 (d, 1H). Anal. Calcd for C<sub>12</sub>H<sub>14</sub>NSBr: C, 50.71; H, 4.97; N, 4.93. Found: C, 51.01; H, 5.03, N, 4.93.

**3-(4-Nitrobenzyl)-2,4-dimethylthiazolium Bromide (7):** mp 208.1–209.1 °C dec; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 2.48 (s, 3H), 2.95 (s, 3H), 5.85 (s, 2H), 7.32 (d, 2H), 7.75 (s, 1H), 8.30 (d, 2H). Anal. Calcd for C<sub>12</sub>H<sub>13</sub>O<sub>2</sub>N<sub>2</sub>SBr: C, 43.78; H, 3.98; N, 8.51. Found: C, 44.01; H, 4.02, N, 8.49.

**2,3,4-Trimethylthiazolium Iodide (8):** mp 278.1 °C dec; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.53 (s, 3H), 2.96 (s, 3H), 3.89 (s, 3H), 7.79 (d, 1H, *J* = 0.84 Hz). Anal. Calcd for C<sub>6</sub>H<sub>10</sub>NSI: C, 28.25; H, 3.95; N, 5.49. Found: C, 28.37; H, 3.91, N, 5.48.

**3-(2,3,4,5,6-Pentafluorobenzyl)-2,4-dimethylthiazolium Bromide (9):** mp 246.3–247.2 °C dec; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 2.54 (s, 3H),

3.03 (s, 3H), 5.87 (s, 2H), 7.92 (d, 1H); <sup>13</sup>C NMR (D<sub>2</sub>O, proton-coupled) δ 14.7 (m), 42.0 (t), 105.6 (s), 116.0 (d), 118.7 (d), 135.8 (m), 139.1 (m), 139.9 (m), 143.3 (s), 146.6 (t), 173.0 (s). Anal. Calcd for C<sub>12</sub>H<sub>9</sub>F<sub>5</sub>NSBr: C, 38.52; H, 2.42; N, 3.74. Found: C, 38.60; H, 2.42, N, 3.75.

**3-(Carboxymethyl)-2,4-dimethylthiazolium Bromide (10):** mp 197.2–199.3 °C dec; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ 1.28 (t, 3H), 2.51 (d, 3H), 2.98 (s, 3H), 4.27 (q, 2H), 5.50 (s, 2H), 7.89 (d, 1H). Anal. Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>NSBr: C, 38.58; H, 5.04; N, 5.00. Found: C, 38.71; H, 5.07, N, 5.00.

**Methods.** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AMX-300 NMR spectrometer using sodium 3-(trimethylsilyl)propane-sulfonate as an internal standard for the <sup>1</sup>H spectra and the instrument external standard for the <sup>13</sup>C spectra. Melting point determinations were made using an Electrothermal digital melting point apparatus and are uncorrected. Measurements of pH were made at the reaction temperature on the buffered solution of the thiazolium salts after hydrolysis had occurred.<sup>3</sup> Solution pH was measured with an Orion Model SA 720 pH meter and Radiometer GK2321C combination electrode standardized at pH 7.00 and 4.00, 10.00, or 12.4 (25 °C). Elemental analysis was performed by Galbraith Laboratories.

**Kinetics.** Pseudo-first-order rate constants were determined by following the reversible appearance of the enethiolate hydrolysis product in the pH range 9–12 at 254 nm<sup>10</sup> or in the pH range 3–9 by irreversible iodination of the enethiolate at 351 nm as described and characterized previously.<sup>3</sup> All reactions were performed at 25.0 ± 0.1 °C, and the ionic strength was maintained at 1.0 M with KNO<sub>3</sub> (pH < 9) or KCl (pH > 9). The rate of iodine disappearance was always directly proportional to the concentration of the substrate in these studies and was independent of the concentration of the iodine trap. There was no significant H → D exchange in the C(2)-CH<sub>3</sub> group of the 3-R-2,4-dimethylthiazolium ions used in this study or exchange from the N(3)-methyl group of 2,3,4-trimethylthiazolium ion (8) that provides evidence that iodine trapping of the corresponding carbanions interfered with the rate measurements. When duplicate determinations of  $k_{\text{obsd}}^{\text{int}}$  were made, they agreed within ≤ ±5% of the average value.

Measurements of pH were made at 25 ± 0.2 °C on the buffered solutions after hydrolysis had occurred. From measurements of pH at known concentrations of hydroxide ion at 25 °C and 1.0 M ionic strength, maintained with potassium nitrate, eq 1 was used to calculate the concentration of hydroxide ion at any pH. This equation includes the ion product of water at 25 °C.<sup>11</sup>

$$[\text{HO}^-] = 1.56 \times 10^{(\text{pH} - 13.997)} \quad (1)$$

Second-order rate constants for catalysis by buffer, water, and hydroxide ion were determined graphically<sup>12</sup> from plots of ≥ 4 values of  $k_{\text{obsd}}^{\text{int}}$  against buffer concentration, corrected for the fraction free base of the buffer (20%, 30%, 50%, 70%, 80% free base), and are concentration-based. There was no curvature in the plots of  $k_{\text{obsd}}^{\text{int}}$  against buffer concentration that could be mistaken for a specific salt effect on the rate of hydrolysis.<sup>13</sup> We estimate that the second-order rate constants are accurate to within ≤ ±17% on the basis of the maximum and minimum slopes that could be drawn in these plots.

The  $pK_a$  values of the buffer catalysts in aqueous solution at 1.0 M ionic strength were determined from the pH values of gravimetrically prepared buffer solutions containing the acid and base form at a 1:1 ratio. Errors in the  $pK_a$  values in H<sub>2</sub>O were ≤ ±0.04.

## Results

Second-order rate constants for catalysis of enethiolate formation from several 3-R-4-methylthiazolium ions (1–6) and 3-R-2,4-dimethylthiazolium ions (7–10) (see Table 1) by added buffers in aqueous solution at 25 °C and ionic strength 1.0 M

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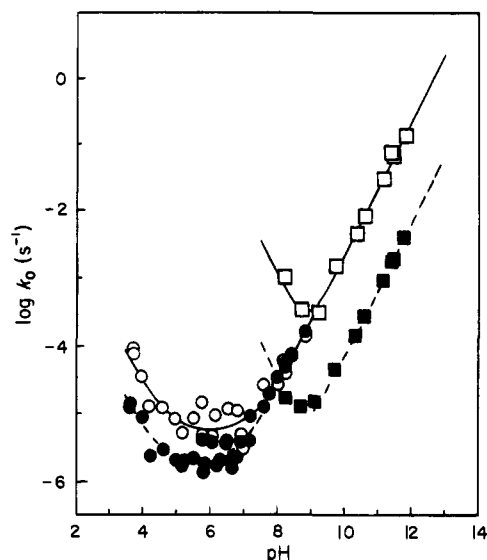
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**Table 1.** Rate Constants for General Base and General Acid Catalysis of the Ring Opening of 3-(4-Nitrobenzyl)-4-methylthiazolium Ion (4) and 3-(4-Nitrobenzyl)-2,4-dimethylthiazolium Ion (7)<sup>a</sup>

catalyst (base form)	pK <sub>a</sub> <sup>b</sup>	C(2)-H (4) <sup>c</sup>		C(2)-CH <sub>3</sub> (7) <sup>c</sup>	
		10 <sup>6</sup> k <sub>B</sub> (M <sup>-1</sup> s <sup>-1</sup> )	10 <sup>3</sup> k <sub>BH<sup>+</sup></sub> (M <sup>-1</sup> s <sup>-1</sup> )	10 <sup>6</sup> k <sub>B</sub> (M <sup>-1</sup> s <sup>-1</sup> )	10 <sup>3</sup> k <sub>BH<sup>+</sup></sub> (M <sup>-1</sup> s <sup>-1</sup> )
H <sub>2</sub> O <sup>d</sup>	-1.74	0.097	270	0.094	55
CH <sub>3</sub> COO <sup>-</sup>	4.61	23	0.052	≤5.1	0.012
CF <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>	5.83	140	0.23		
(CH <sub>3</sub> ) <sub>2</sub> AsO <sub>2</sub> <sup>-</sup>	6.18	25	0.044	5.3	0.0044
HPO <sub>4</sub> <sup>2-</sup>	6.50	48	0.029	18	0.010
CH <sub>3</sub> CH <sub>2</sub> PO <sub>3</sub> <sup>2-</sup>	7.60	210		280	≤0.0064
(HOCH <sub>2</sub> ) <sub>3</sub> CNH <sub>2</sub>	8.43	600		180	

<sup>a</sup> At 25 °C and ionic strength 1.0 M (KNO<sub>3</sub>) in H<sub>2</sub>O. <sup>b</sup> Apparent pK<sub>a</sub> of the conjugate acid at 25 °C and ionic strength 1.0 M (KNO<sub>3</sub>) in H<sub>2</sub>O (see text). <sup>c</sup> The rate constants k<sub>B</sub> and k<sub>BH<sup>+</sup></sub> are defined in eq 8. <sup>d</sup> The second-order rate constant for catalysis by water was calculated from the observed first-order rate constant on the basis of a standard state of 55.4 M for pure H<sub>2</sub>O at 25 °C.



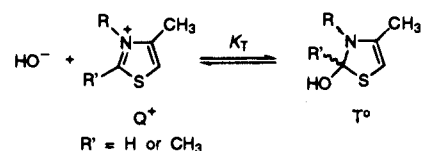
**Figure 1.** Dependence on pH of the observed first-order rate constants for reversible formation in the absence of iodine (squares) and irreversible formation in the presence of iodine (circles) of the enethiolate hydrolysis product from 3-(4-nitrobenzyl)-4-methylthiazolium ion (4) (open symbols) and 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (7) (solid symbols) in H<sub>2</sub>O at 25 °C and *I* = 1.0 M maintained with KCl (squares) or KNO<sub>3</sub> (circles). Reactions with buffers do not significantly affect the pH–log(rate) profile above pH 9; the observed first-order rate constants were extrapolated to zero buffer concentration below pH 9. The rate constants for enethiolate formation follow eqs 4 and 6 as shown by the lines drawn through the data (see text).

(KNO<sub>3</sub>) were determined in the pH range 3–9 by irreversibly trapping the enethiolate hydrolysis product (Scheme 1) with iodine under initial rate conditions. Formation of the enethiolate obeys the rate law described by eq 2. The observed first-order

$$k_{\text{obsd}}^{\text{irr}} (\text{s}^{-1}) = k_0 + k'_{\text{cat}}[\text{buffer}]_{\text{total}} \quad (2)$$

rate constants for buffer-independent formation of the enethiolate (*k*<sub>0</sub>) that were determined as described in the Experimental Section are depicted in the pH–log(rate) profiles shown in Figure 1 (circles) for 3-(4-nitrobenzyl)-4-methylthiazolium ion (4) (open circles) and 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (7) (solid circles). Experiments demonstrating that the iodine trapping assay is following the rate of hydrolysis of a thiazolium ion were described in detail previously.<sup>3,4</sup> No changes in the UV/vis or <sup>1</sup>H NMR spectrum of 4 or 7 that might suggest reactions other than reversible hydrolysis of the thiazolium ring or C(2)-proton transfer were detected in the pH range 3–12. The pH–log(rate) profiles for irreversible ring opening of Q<sup>+</sup> (Figure 1) are not directly comparable<sup>3,4</sup> to previously reported pH–log(rate) profiles for reversible recl-

## Scheme 2



sure of the enethiolate derived from Q<sup>+</sup> in the pH range 0–14.5.<sup>6b,c,7a</sup>

The observed first-order rate constants shown in the pH–log(rate) profile in Figure 1 for irreversible formation of the enethiolate determined in the pH range 3–9 (circles) obey the rate law outlined in eq 3. The equilibrium constant *K*<sub>T</sub> is defined

$$k_0 (\text{s}^{-1}) = \frac{k_{\text{H}_2\text{O}} + k_{\text{H}^+}[\text{H}^+] + k_{\text{HO}^-}[\text{HO}^-]}{1 + [\text{H}^+]/K_w K_T} \quad (3)$$

in Scheme 2 and eq 4. The lines in Figure 1 (circles) represent the curves determined from the rate constants for proton-, water-,

$$K_{R^+} (\text{M}) = K_w K_T = [\text{H}^+][\text{T}^0]/[\text{Q}^+] \quad (4)$$

and hydroxide ion-catalyzed formation of the enethiolate, corrected for a hydroxide ion-dependent equilibrium represented by *K*<sub>T</sub>.<sup>3,4</sup> The pH-dependent equilibrium representing *K*<sub>T</sub> is attributed to addition of hydroxide ion at equilibrium to free thiazolium ion prior to ring opening.<sup>3,4</sup>

Apparent pK<sub>a</sub> values of 6.9 ± 0.1 for 4 (open circles) and 7.0 ± 0.2 for 7 (solid circles) that we attribute to pseudobase formation were obtained from the negative abscissa intercept of plots of 1/*k*<sub>0</sub> against hydronium ion activity according to eq 5 (Figure 2).<sup>12</sup> These apparent pK<sub>a</sub> values are similar to the

$$\frac{1}{k_0} = \frac{1}{k_{\text{H}_2\text{O}}} + \frac{a_{\text{H}^+}}{k_{\text{H}_2\text{O}} K_{R^+}} \quad (5)$$

pK<sub>R<sup>+</sup></sub> value for another nitrogen heterocycle, 1,3-dimethyl-2-oxopyrimidinium ion,<sup>14</sup> and are not significantly different from apparent pK<sub>a</sub> values of 6.9 ± 0.1 reported previously for several 3-R-4-methylthiazolium ions.<sup>3,4</sup> Apparent pK<sub>a</sub> values of 6.9 ± 0.2 were calculated for 1-3, 5, 6, and 8-10. This shows that the observed apparent pK<sub>a</sub> value of 6.9 ± 0.2 is independent of steric or electronic effects of C(2)-substituents on the thiazolium ring in the range R' = H to CH<sub>3</sub> (Scheme 2) and confirms the previous conclusion that the observed apparent pK<sub>a</sub> value is independent of an electron-withdrawing inductive effect by N(3)-substituents on the thiazolium ring.<sup>4</sup> The equilibrium

(14) Frick, L.; Yang, C.; Marquez, V. E.; Wolfenden, R. *Biochemistry* 1989, 28, 9423–9430.

constant  $K_{R^+}$  is analogous to the  $pK_a$  of a Brønsted acid and is the hydrogen ion concentration at which  $T^\circ$  and the thiazolium ion ( $Q^+$ ) are present in equal amounts: this interpretation is supported by spectroscopic studies.<sup>3,4</sup>

Values of  $k_{H_2O}/[H_2O] = 5.4 \times 10^{-6} \text{ s}^{-1}/55.4 \text{ M} = 9.7 \times 10^{-8} \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{H^+} = 0.27 \text{ M}^{-1} \text{ s}^{-1}$ , and  $k_{HO^-} = 25 \text{ M}^{-1} \text{ s}^{-1}$  for formation of the enethiolate derived from **4** (Figure 1, open circles) were calculated using eq 3 with  $K_w = 10^{-13.997}$  and  $K_T = 10^{7.1} \text{ M}^{-1}$ . Values of  $k_{H_2O}/[H_2O] = 1.8 \times 10^{-6} \text{ s}^{-1}/55.4 \text{ M} = 3.3 \times 10^{-8} \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{H^+} = 0.055 \text{ M}^{-1} \text{ s}^{-1}$ , and  $k_{HO^-} = 26 \text{ M}^{-1} \text{ s}^{-1}$  for formation of the enethiolate derived from **7** (Figure 1, solid circles) were calculated similarly with  $K_T = 10^{7.1} \text{ M}^{-1}$ . The ratio  $k_{HO^-}/k_{H_2O} = 5 \times 10^6$  and  $1 \times 10^7 \text{ M}^{-1}$  for **4** and **7**, respectively, is similar to the ratio of  $10^6$ – $10^7 \text{ M}^{-1}$  observed for several other heterocyclic iminium ions.<sup>4,15</sup>

Figure 1 also shows the dependence on pH of the observed first-order rate constants for reversible formation of the enethiolate derived from **4** (open squares) and **7** (solid squares) in the absence of iodine in the pH range 9–12. The pH–log(rate) profile for reversible hydrolysis of **4** and **7** is consistent with the approach to an equilibrium concentration of the enethiolate via  $T^\circ$  in the pH range 9–12 and obeys the rate law described by eq 6; the observed rate constant is the sum of the

$$k_{\text{obsd}}^{\text{rev}} (\text{s}^{-1}) = k_{HO^-}[HO^-] + k_{H^+}[H^+] \quad (6)$$

individual first-order rate constants for formation ( $k_{HO^-} = 25 \text{ M}^{-1} \text{ s}^{-1}$  for **4** and  $0.54 \text{ M}^{-1} \text{ s}^{-1}$  for **7**) of the enethiolate from, and decomposition ( $k_{H^+} = 1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  for **4** and  $3 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$  for **7**) of the enethiolate to, the thiazolium ion. Consistent with previous observations,<sup>3,4,10</sup> there are no significant pH-independent terms for the formation or decomposition of the enethiolate derived from **4** and **7** in this pH range.

The observed buffer catalysis for enethiolate formation obeys the rate law outlined in eqs 7 and 8. Figure 3 shows a plot of

$$(k_{\text{obsd}}^{\text{irr}} - k_0)(1 + [H^+]/K_w K_T) = k'_{\text{cat}}[\text{buffer}]_{\text{total}} \quad (7)$$

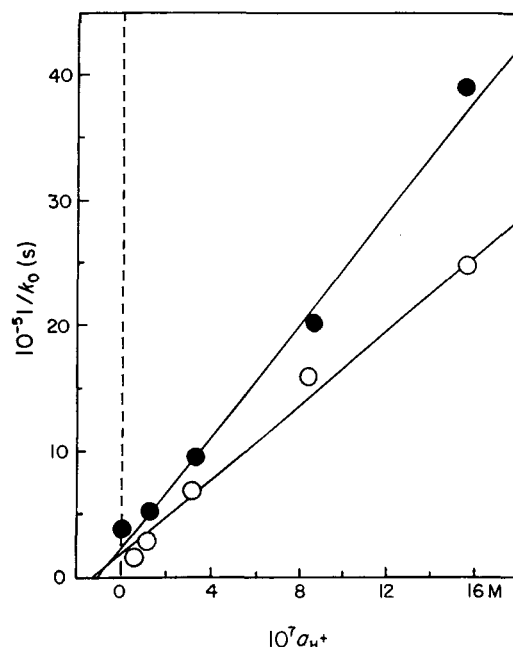
$$k'_{\text{cat}}[\text{buffer}]_{\text{total}} = k_{BH^+}[BH^+] + k_B[B] \quad (8)$$

$k_{\text{obsd}}^{\text{irr}}$ , corrected for the hydroxide ion-dependent equilibrium representing  $K_T$ , against total phosphate buffer concentration for ring opening of **7** in the presence of iodine. Values of the second-order rate constants for general base and general acid catalysis of enethiolate formation were obtained from plots of the second-order rate constants for buffer catalysis,  $k'_{\text{cat}}$ , against the percentage buffer base and extrapolating to 100% and 0% free base, respectively. Values of the second-order rate constants for general base and general acid catalysis of the reaction of **4** and **7** are summarized in Table 1. Experiments with other buffer catalysts and thiazolium ions were carried out in the same manner as those shown in Figure 3 with the same number of observed rate constants.

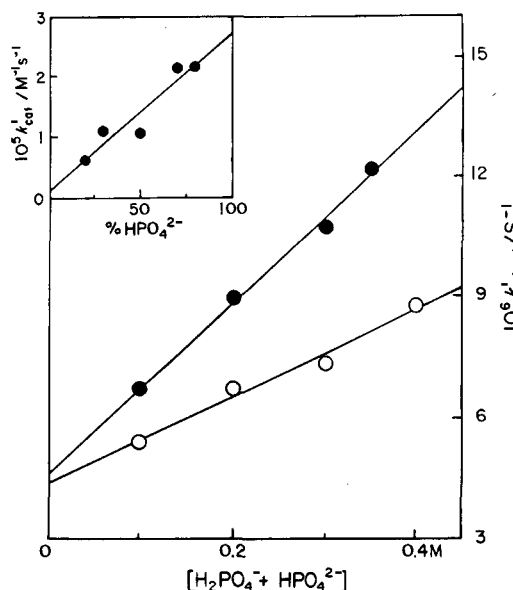
Values of the second-order rate constants for catalysis of enethiolate formation from **1**–**10** by water and phosphate dianion are listed in Table 2. Table 2 also contains  $\sigma_I$  values for the  $N(3)$ -substituents.<sup>8,16,17</sup>

## Discussion

**Nature of the Rate-Limiting Step.** Previous workers observed a  $\sim 100$ -fold decrease in the rate of hydrolysis of 3-substituted thiazolium ions after substitution of methyl for H



**Figure 2.** Determination of  $pK_{R^+}$  and the rate constant for water-catalyzed hydrolysis of 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) and 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid circles) in  $H_2O$  at  $25^\circ C$  and  $I = 1.0 \text{ M}$  maintained with  $KNO_3$  according to eq 5 (see text).



**Figure 3.** Dependence of the observed rate constant for formation of the enethiolate hydrolysis product derived from 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) in the presence of iodine on the concentration of phosphate buffer containing 50% (open circles) or 70% (solid circles)  $HPO_4^{2-}$  at  $25^\circ C$  and  $I = 1.0 \text{ M}$  ( $KNO_3$ ) in  $H_2O$ . Values of  $k_{\text{obsd}}^{\text{irr}}$  are corrected for the hydroxide ion-dependent equilibrium formation of  $T^\circ$  as determined by  $K_T$  (see text). The slope of the plot against buffer concentration gives the apparent rate constant of the phosphate buffer-catalyzed reaction,  $k'_{\text{cat}}$ . The inset shows the dependence of the apparent catalytic constant for buffer catalysis,  $k'_{\text{cat}}$ , on the composition of the phosphate buffer.

at the C(2) position.<sup>5</sup> This was attributed to an unfavorable steric and electronic effect on the equilibrium constant ( $pK_{R^+}$ ) for rate-limiting formation of the pseudobase ( $T^\circ$ ) from the thiazolium ion. The 50-fold negative deviation in Figure 1 of the observed rate constants for 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid squares) from the observed rate constants for 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open squares) for hydroxide ion catalysis of the reversible formation

(15) See, for example, Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.

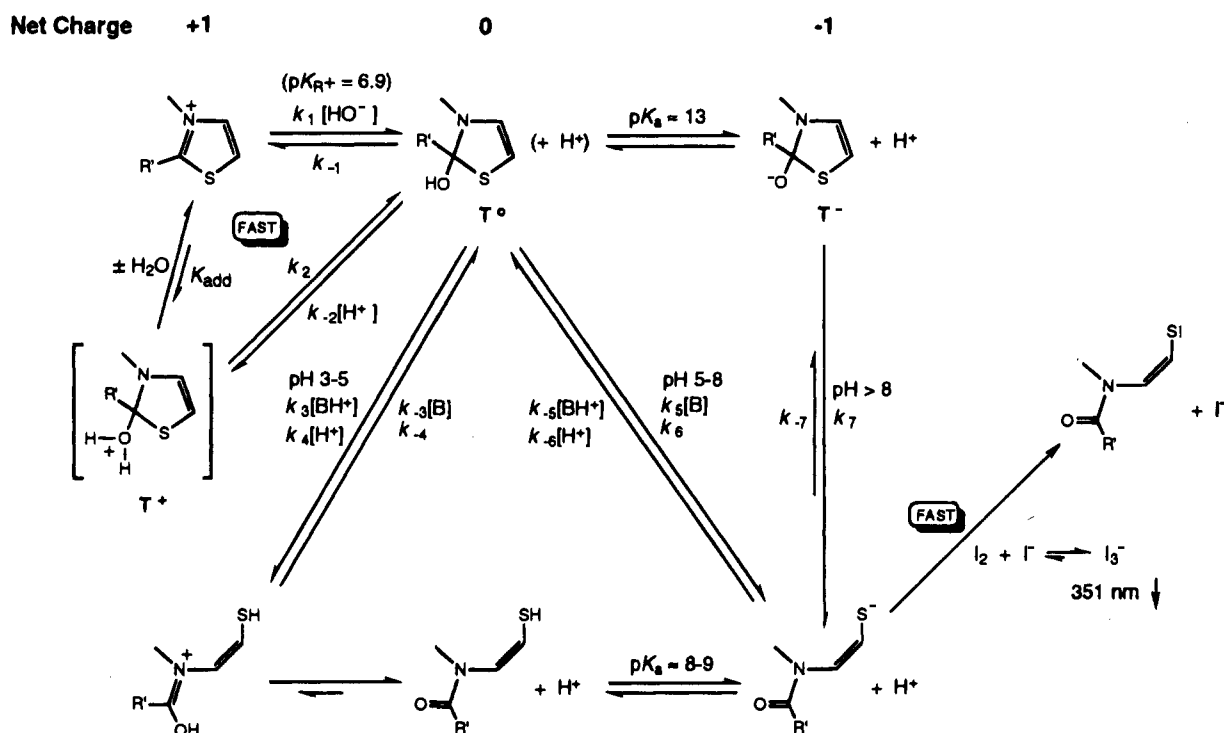
(16) (a) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222–1227. (b) Charton, M. *J. Org. Chem.* **1972**, *37*, 3684–3687.

(17) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.

**Table 2.** Rate Constants for Water- and Phosphate Dianion-Catalyzed Ring Opening of 3-R-4-Methylthiazolium (1–6) and 3-R-2,4-Dimethylthiazolium Ions (7–10)<sup>a</sup>

3-R	$\sigma_1^b$	C(2)-H		C(2)-CH <sub>3</sub>	
		$10^8 k_{H_2O}^c$ (M <sup>-1</sup> s <sup>-1</sup> )	$10^5 k_B^d$ (M <sup>-1</sup> s <sup>-1</sup> )	$10^8 k_{H_2O}^c$ (M <sup>-1</sup> s <sup>-1</sup> )	$10^5 k_B^d$ (M <sup>-1</sup> s <sup>-1</sup> )
Me	-0.01	1.2	≤0.17	0.45	≤0.45
4-MeBz	0.04 <sup>e</sup>	3.3	≤0.63		
4-NO <sub>2</sub> Bz	0.092 <sup>f</sup>	9.7	4.9	3.2	1.9
2,3,4,5,6-F <sub>5</sub> Bz	0.11 <sup>g</sup>	39	15	15	5.1
CH <sub>2</sub> CO <sub>2</sub> Et	0.15	130	27	40	17
CH <sub>2</sub> CN	0.20	360	120		

<sup>a</sup> At 25 °C and ionic strength 1.0 M (KNO<sub>3</sub>) in H<sub>2</sub>O. <sup>b</sup>References 16 and 17 unless otherwise noted. <sup>c</sup>The second-order rate constant for catalysis by water was calculated from the observed first-order rate constant on the basis of a standard state of 55.4 M for pure H<sub>2</sub>O at 25 °C. <sup>d</sup>The rate constant  $k_B$  is defined in eq 8. <sup>e</sup> $\sigma_1$  is the product of  $\sigma_1 = 0.10$  for R = 4-MePh<sup>17</sup> and an attenuation factor of 0.40 for a methylene group.<sup>18</sup> <sup>f</sup>Reference 8. <sup>g</sup>Reference 19.

**Scheme 3**

of the enethiolate at pH > 9 suggests that formation of the enethiolate involves rate-limiting formation of T<sup>0</sup> at pH > 7 and that C(2)-methylation sterically hinders T<sup>0</sup> formation. This conclusion can be ruled out, however, on the basis of the results described in this work.

A mechanism of the hydrolysis of simple 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions that is consistent with the results is outlined in Scheme 3.<sup>3</sup> The mechanism for hydrolysis of other iminium ions<sup>14,15</sup> also proceeds in a stepwise manner through tetrahedral addition intermediates involving general acid–base catalysis of the formation and breakdown of these tetrahedral intermediates.<sup>2b,20</sup>

In neutral and mildly basic aqueous solution (pH < 12), simple 3-R-4-methylthiazolium ions exist in three forms: the iminium ion Q<sup>+</sup>, T<sup>0</sup>, and the ring-opened enethiolate<sup>3,4</sup> (Scheme 1). The pH–log(rate) profile for irreversible formation of the enethiolate hydrolysis product derived from a 3-R-2,4-dimeth-

ylthiazolium ions (Figure 1, solid circles) and the sensitivity of the ring-opening reaction to general acid catalysis in the pH range 3–9 (Figure 3 and Table 1) provide evidence that breakdown of T<sup>0</sup>, not formation of T<sup>0</sup>, is the rate-limiting step for enethiolate formation from a 3-R-2,4-dimethylthiazolium ion in the pH range 3–12.

Since there is no evidence for a change in the rate-limiting step for enethiolate formation in the pH range 3–9 (Figure 1, circles),<sup>3,4</sup> the pathways for hydrolysis shown in Figure 1 must represent either rate-limiting formation or rate-limiting breakdown of T<sup>0</sup>. Because observed general acid catalysis of enethiolate formation cannot be reasonably assigned to a step involving formation of T<sup>0</sup>, the hydrolysis of both 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions must involve rate-limiting breakdown of the tetrahedral intermediate in the pH range 3–9. The pH–log(rate) profiles for irreversible enethiolate formation from 4 and 7 are nearly identical to the profiles obtained for other 3-substituted thiazolium ions.<sup>3,4</sup>

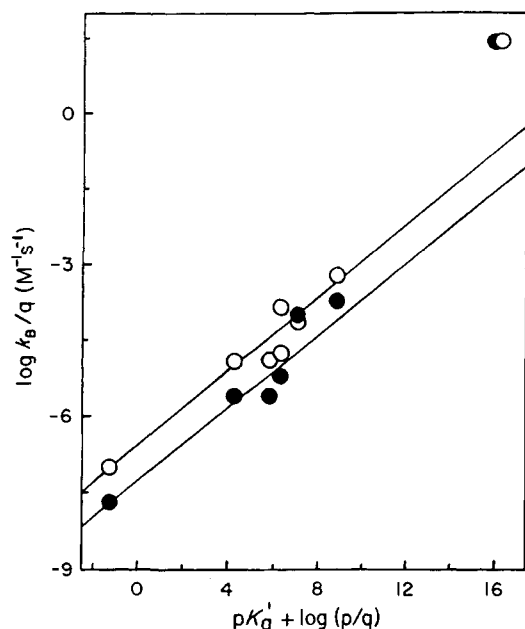
The hydroxide ion-catalyzed reaction at pH > 8 must proceed by a mechanism involving specific base catalysis, in which the intermediate anion T<sup>-</sup> is formed from T<sup>0</sup> at equilibrium followed by rate-limiting breakdown of T<sup>-</sup> to product. Formation of T<sup>-</sup> through rate-limiting proton transfer can be excluded as a

(18) Wells, P. R. *Linear Free Energy Relationships*; Academic Press: New York, 1968; p 38.

(19) Stivers, J. T.; Washabaugh, M. W. *Bioorg. Chem.* **1992**, *20*, 155–172.

(20) Bell, R. P.; Evans, P. G. *Proc. R. Soc. London A* **1966**, *291*, 297–323.

(21) See, for example, Novak, M.; Bonham, G. A.; Mulero, J. J.; Pelecanou, M.; Zemis, J. N.; Buccigross, J. M.; Wilson, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 4447–4456 and references therein.



**Figure 4.** Brønsted plot for general base catalysis of irreversible formation of the enethiolate hydrolysis product during hydrolysis of 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) and 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid circles) in the presence of iodine in the pH range 3–9 at 25 °C and  $I = 1.0$  M ( $\text{KNO}_3$ ) in  $\text{H}_2\text{O}$ . Statistical corrections were made according to Bell and Evans.<sup>20</sup> The lines of slope  $0.34 \pm 0.05$  are the best fits through the rate constants for buffer bases and water.

mechanism because the Brønsted plot for general base catalysis (Figure 4) is inconsistent with an “Eigen curve” typical for general acid–base-catalyzed reactions involving rate-limiting proton transfers:<sup>22</sup> thermodynamically unfavorable rate-limiting proton transfer from  $\text{T}^\circ$  to water and buffer bases would give a Brønsted slope of  $\beta = 1.0$  rather than the observed slope of  $\beta = 0.34 \pm 0.05$  for general base catalysis of enethiolate formation from **4** and **7**.

General base-catalyzed breakdown of  $\text{T}^\circ$  by hydroxide ion is unlikely because proton removal from  $\text{T}^\circ$  by hydroxide ion is thermodynamically favorable<sup>3,23</sup> and, consequently, provides no driving force for concerted catalysis.<sup>26</sup> The absence of significant buffer catalysis at  $\text{pH} \geq 8$  and the fact that the rate constant for hydroxide ion-catalyzed enethiolate formation is  $10^2$ – $10^3$ -fold faster than predicted from the Brønsted plot for general base catalysis (Figure 4) are in accord with this formulation. This breakdown reaction does not involve general acid catalysis by water because there is little or no thermodynamic advantage to proton transfer from water to the leaving enethiolate ion.<sup>26,27</sup>

The observed Brønsted slope of  $\beta = 0.34$  (Figure 4) for the observed general base-catalyzed enethiolate formation in the pH range 5–8 is consistent with catalysis involving a concerted mechanism.<sup>2b</sup> The proposed mechanism represents a nonen-

forced class  $e$  mechanism for the breakdown of  $\text{T}^\circ$ , in which a proton is removed from the oxygen atom by the general base, because  $\text{T}^-$  exists; in the reverse direction it involves general acid catalysis of  $\text{RS}^-$  attack ( $\text{p}K_a \approx 9$ ).<sup>29</sup> This is consistent with the previous suggestion that addition of a relatively weak nucleophile, such as  $\text{RSH}$ , to a carbonyl group would involve a fully concerted class  $e$  mechanism of general acid catalysis, in which the catalyst interacts with the electrophilic carbonyl group.<sup>7,32</sup> Accordingly, the pH-independent water reaction represents general base catalysis by water of the breakdown of  $\text{T}^\circ$ . The rate constant for catalysis by water falls on the extrapolated Brønsted line for general base catalysis, in accord with this formulation.

There is a change to a third pathway for breakdown of  $\text{T}^\circ$  to product below pH 5. Evidence for a third pathway for breakdown of  $\text{T}^\circ$  includes (i) the upward deviation in the pH–log(rate) profile (Figure 1, circles) at pH 5 from pH-independent water to  $\text{H}^+$ -catalyzed hydrolysis and (ii) the increasing contribution of observed general acid catalysis of enethiolate formation with decreasing pH, which gives a Brønsted plot of slope  $\alpha = 0.45 \pm 0.05$  (Figure 5).

The mechanism of the observed general acid-catalyzed reaction could be assigned to either general acid catalysis of the breakdown of the neutral intermediate  $\text{T}^\circ$  or the kinetically equivalent specific acid–general base catalysis of the breakdown of a cationic intermediate involving an unstable S-protonated hydrate. We suggest that specific acid–general base catalysis is kinetically impossible because it requires microscopic rate constants that are faster than those for diffusion-controlled processes. Assuming the thermodynamically favorable proton transfer from the S-protonated hydrate to water is diffusion controlled and depending on the assumption one makes regarding the acidity of the S-protonated hydrate, the diffusion-limited rate constant for the thermodynamically unfavorable protonation of  $\text{T}^\circ$  by the hydronium ion (the microscopic reverse of proton transfer from the S-protonated hydrate to water) is comparable to the observed second-order rate constant for the hydronium ion-catalyzed hydrolysis reaction.<sup>33</sup> If the observed general acid catalysis involves the kinetically equivalent specific acid–general base catalysis, it cannot proceed faster than the thermodynamically unfavorable diffusion-controlled protonation of the sulfur in  $\text{T}^\circ$ . The observed second-order rate constants for general acid catalysis (Table 1) fall well above a theoretical

(27) Nucleophilic catalysis can be ruled out for two reasons. First, the reaction shows little sensitivity to steric requirements as is shown, for example, by the reactivity of 2,2,2-trifluoroethylamine and tris(hydroxymethyl)aminomethane. Nucleophilic reactions of carbonyl compounds show marked sensitivity to steric hindrance in the nucleophile but general acid–base catalysis is much less sensitive to steric effects. Second, the catalytic constants of the bases for the 3-R-2,4-dimethylthiazolium ion (**7**) do not deviate more than a factor of 3 from the line in Figures 4 and 5 (with the exception of  $\text{HO}^-$ ). In contrast, the rate constants for the reactions of nucleophilic reagents of similar basicity but different structure with carbonyl compounds vary over a range of several orders of magnitude.<sup>28</sup>

(28) Robinson, D. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1967**, *89*, 7089–7098, 7098–7103.

(29) A value of  $\text{p}K_a = 9$  for the mercaptan in the enethiolate was estimated from a Hammett correlation for the ionization of thiols that follows  $\text{p}K_a = 10.22 - 3.50\sigma^*$ :<sup>30a</sup>  $\sigma^* = 0.36$  for  $\text{R} = \text{CH}=\text{CHCH}_3$ .<sup>31</sup> A  $\text{p}K_a$  value of 7.9 was determined from the pH–log(rate) profile for reclosure of the enethiolate derived from 5-(2-hydroxyethyl)-3,4-dimethylthiazolium ion.<sup>7a</sup> A value of  $\text{p}K_a \geq 8$  for  $\text{N}(3)$  in  $\text{T}^\circ$  and the enethiolate was estimated from a Hammett correlation for the ionization of tertiary aminium ions that follows  $\text{p}K_a = 9.61 - 3.30\sigma^* + 0.2$ :<sup>30b</sup>  $\sigma^* = 0.36$  for  $\text{R} = \text{CH}=\text{CHCH}_3$ ,  $\sigma^* = 0$  for  $\text{R} = \text{CH}_3$ , and  $\sigma^* = 0.36$  for  $\text{R} = \text{CH}(\text{OH})\text{CH}_3$ .<sup>31</sup> A factor of  $0.2\text{p}K_a$  unit has to be added because ring formation takes place through the nitrogen in  $\text{T}^\circ$ .<sup>31</sup>

(30) (a) Kreevoy, M. M.; Eichinger, B. E.; Stary, F. E.; Katz, E. A.; Sellstedt, J. H. *J. Org. Chem.* **1964**, *29*, 1641–1642. (b) Hall, H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444.

(31) Reference 25, pp 25, 111, 114, 116.

(32) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931–7947.

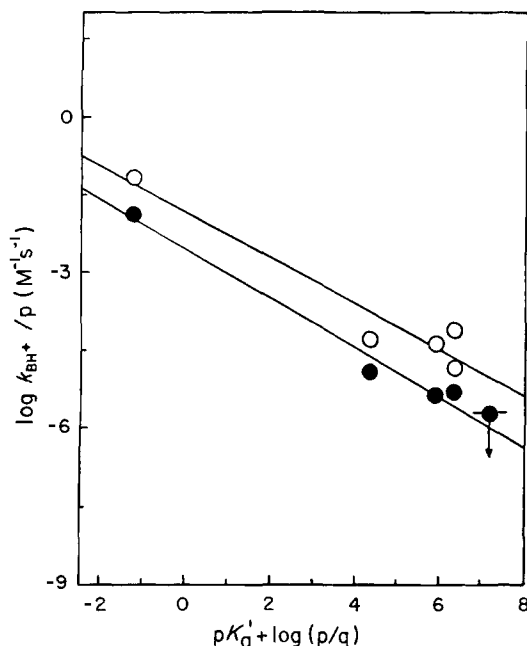
(22) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.

(23) A value of  $\text{p}K_a = 13 \pm 1$  for  $\text{T}^\circ$  derived from either a 3-R-4-methylthiazolium ion or a 3-R-2,4-dimethylthiazolium ion was estimated from a Hammett correlation for the ionization of alcohols that follows  $\text{p}K_a = 15.9 - 1.42\sum\sigma^*$ :<sup>24</sup>  $\sigma^* = 0.32$  for  $\text{R} = \text{N}(\text{CH}_3)_2$ ,  $\sigma^* = 1.31$  for  $\text{R} = \text{SCH}=\text{CH}_2$ ,  $\sigma^* = 0$  for  $\text{CH}_3$ , and  $\sigma^* = 0.49$  for  $\text{R} = \text{H}$ .<sup>25</sup>

(24) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798.

(25) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK<sub>a</sub> Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981; p 114.

(26) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718. This minimal explanation of the data is consistent with the pH–log(rate) profile (Figure 1) and a single Brønsted line defined by this heterogeneous set of buffers (Figures 4 and 5). The  $\leq 4$ -fold deviations of the second-order rate constants for general base and general acid catalysis by the buffers are not unusual, are randomly scattered about the Brønsted line, and provide no evidence that a unique Brønsted correlation is required for each buffer class.



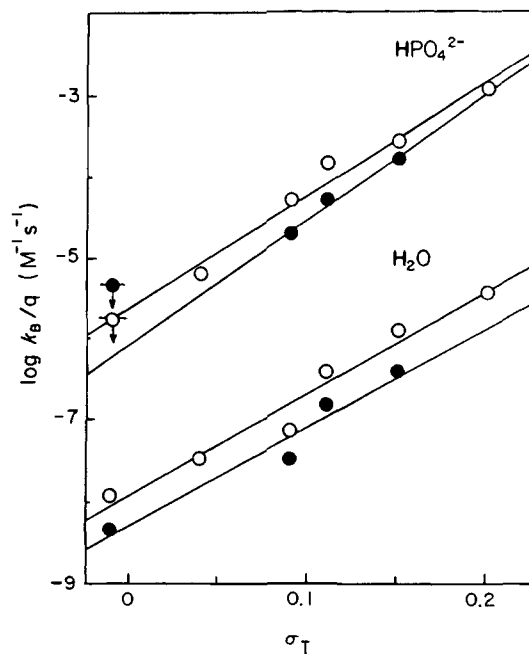
**Figure 5.** Brønsted plot for general acid catalysis of irreversible formation of the enethiolate hydrolysis product during hydrolysis of 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) and 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid circles) in the presence of iodine in the pH range 3–9 at 25 °C and  $I = 1.0$  M ( $\text{KNO}_3$ ) in  $\text{H}_2\text{O}$ . Statistical corrections were made according to Bell and Evans.<sup>20</sup> The upper limit for catalysis by protonated tris(hydroxymethyl)aminomethane is indicated. The lines of slope  $0.45 \pm 0.05$  are the best fits through the rate constants for buffer acids and  $\text{H}_3\text{O}^+$ .

diffusion-limited Eigen curve<sup>22</sup> with a Brønsted slope of  $\alpha = 1.0$  for the thermodynamically unfavorable diffusion-limited protonation of  $\text{T}^\circ$  drawn through the rate constant for hydronium ion-catalyzed hydrolysis. The observed general acid catalysis is consistent with a concerted mechanism of catalysis of the expulsion of the leaving enethiolate from  $\text{T}^\circ$  by proton donation. There is precedence for general acid-catalyzed breakdown of  $\text{T}^\circ$  derived from a phthalimidium ion, which serves to avoid the formation of an O-protonated hydrate as a discrete entity, that may be relevant.<sup>2b</sup> Similar values of  $\alpha$  were obtained for general acid catalysis by protonated amines and oxygen-containing acids of the ring opening of several 3-R-4-methylthiazolium ions.<sup>3,4</sup>

The second-order rate constants for catalysis by water and phosphate dianion of the ring-opening reactions of simple 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions follow Hammett correlations with the inductive substituent constant  $\sigma_I$  for R with a slope of  $\rho_I = 12 \pm 2$  for both catalysts, as shown in Figure 6. The value of  $\rho_I = 12$  for both catalysts implies similar transition states, and therefore similar mechanisms, for these reactions. This supports the conclusion that both the buffer base- and water-catalyzed reactions can be

(33) The electron-withdrawing influence of the thiazolium ring will lower the  $pK_a$  of the S-protonated hydrate approximately 3 units<sup>23</sup> below that of a protonated simple thioether ( $pK_a \approx -8$ ).<sup>34</sup> The  $pK_a$  of the S-protonated hydrate is approximately  $-11$ , and assuming a rate constant of  $10^{10} \text{ M}^{-1} \text{ s}^{-1}$  for protonation of water (55.4 M) by this species, the rate constant for protonation of the hydrate is  $6 \text{ M}^{-1} \text{ s}^{-1}$ , comparable to the observed rate constants in the range  $0.06\text{--}0.3 \text{ M}^{-1} \text{ s}^{-1}$  for catalysis by  $\text{H}_3\text{O}^+$  (Table 1). Alternatively, the observed rate constant would require a rate constant for deprotonation of the S-protonated hydrate of  $> 10^{10} \text{ s}^{-1}$  if this species is at equilibrium and its breakdown is rate determining.

(34) (a) March, *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 219–220. See footnotes 7 and 8. (b) Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 3rd ed.; McGraw-Hill: New York, 1970; pp 306–307. (c) Lee, D. G.; Cameron, R. *Can. J. Chem.* **1972**, *50*, 445. Simple S-protonated thioethers have  $pK_a$  values ( $-8$ ) that are approximately 1.4 units less than the  $pK_a$  values of simple O-protonated ethers ( $-6.2$ ).



**Figure 6.** Hammett correlation with  $\sigma_I$  for ring opening of the thiazolium ion of 3-R-4-methylthiazolium ions **1–6** (open circles) and 3-R-2,4-dimethylthiazolium ions **7–10** (solid circles) in the presence of iodine catalyzed by water or phosphate dianion at 25 °C and  $I = 1.0$  M ( $\text{KNO}_3$ ) in  $\text{H}_2\text{O}$ . The second-order rate constant for water-catalyzed hydrolysis was calculated by dividing the observed first-order rate constant by 55.4 M, the concentration of water at 25 °C. The lines of slope  $12 \pm 2$  are the best fits through the rate constants, ignoring the upper limits for catalysis of the ring-opening reaction by phosphate dianion.

formulated as concerted general base catalysis of the expulsion of the enethiolate from  $\text{T}^\circ$  (see above). A dependence of the rate of enethiolate formation on an electron withdrawing effect by substituents on the nitrogen atom of the thiazolium ring has been noted previously with  $\rho_I = 12 \pm 1$ .<sup>4</sup>

The similar  $\rho_I$  values for simple 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions are also consistent with little or no effect of C(2)-methylation on the structure of the rate-limiting transition state involving general base catalysis. Similar values of  $\alpha$  and  $\beta$  for general acid and general base catalysis of the ring opening of simple 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions (Figures 4 and 5) support this conclusion and the conclusion that there is little or no effect of C(2)-methylation on the structure of the rate-limiting transition state involving general acid catalysis.

Another important conclusion that follows from this work is that a major form of 3-R-4-methyl- and 3-R-2,4-dimethylthiazolium ions is a neutral species designated  $\text{T}^\circ$  at  $\text{pH} \approx 7$ , which is formed in a pH-dependent equilibrium with an apparent  $pK_a$  of  $6.9 \pm 0.1$ , and that hydrolysis is quite slow (Scheme 3). The pH dependence of the resonance assigned to the bridge methylene  $[\text{N}(3)\text{--CH}_2\text{--}]$  group in the  $^{13}\text{C}$  NMR spectrum of **2**<sup>3</sup> and oxythiamin<sup>4</sup> provides spectral evidence to confirm this conclusion and the conclusion that ring opening of  $\text{T}^\circ$  is the slow forward step. Minimally these results demonstrate that the species  $\text{T}^\circ$  has a sufficient lifetime to exist as an intermediate in aqueous solution in the pH range 3–11. There were no detectable changes in the ultraviolet/visible spectrum of **1–10** that suggest the presence of  $\text{T}^\circ$  in the pH range 6–8.

It is likely that these mechanisms are general for hydrolysis reactions of simple 3-R-4-methylthiazolium ions and 3-R-2,4-dimethylthiazolium ions where the substituent on the nitrogen atom of the thiazolium ring is not a potential intramolecular nucleophilic catalyst because a similar pH–log(rate) profile and pattern of general acid–base catalysis was obtained for irrevers-

ible hydrolysis of 3-benzyl-4-methylthiazolium ion, *N*(1')-methylthiamin, and oxythiamin.<sup>4</sup> *N*(1')-unsubstituted ("free") thiamin is not a simple thiazolium ion in this respect because the exocyclic 4'-amino group is an intramolecular nucleophilic catalyst of the ring-opening reaction in neutral aqueous solution.<sup>4</sup> The exocyclic 4'-amino group also participates in an intramolecular cyclization with the thiazolium ring in basic solution to form a neutral tricyclic species<sup>35</sup> and adds to the acetyl group of 2-acetyl-TDP (TDP = thiamin diphosphate) in neutral aqueous solution.<sup>36</sup>

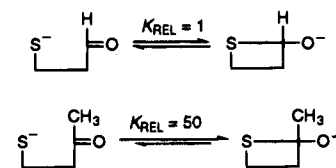
**Effect of C(2)-Methylation.** Figure 2 shows that C(2)-methylation has little or no effect on the equilibrium constant ( $pK_{R^+}$ ) for formation of  $T^0$  from  $Q^+$  (Scheme 1). The pH-log(rate) profile for irreversible formation of the enethiolate hydrolysis product derived from a 3-R-2,4-dimethylthiazolium ion (Figure 1, solid circles) and the sensitivity of the ring-opening reaction to general acid catalysis in the pH range 3–9 (Figures 3 and 5) provide evidence that breakdown of  $T^0$ , not formation of  $T^0$ , is the rate-limiting step for enethiolate formation from a 3-R-2,4-dimethylthiazolium ion in the pH range 3–12. This shows that C(2)-methylation does not provide an unfavorable steric or electronic effect on  $T^0$  formation from  $Q^+$  and the rate-reducing effect of C(2)-methylation must involve steps subsequent to  $T^0$  formation.

There is a ~4-fold negative deviation in Figure 1 of the rate constants for  $H^+$ - and water-catalyzed enethiolate formation from 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid circles) compared to the rate constants for 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) (Figure 1) at pH 3–8. This is consistent with an unfavorable steric or electronic effect of C(2)-methylation on the microscopic rate constants  $k_3$  for general acid (Scheme 3, pH 3–5 pathway) and  $k_5$  for general base (pH 5–8 pathway) catalysis of  $T^0$  breakdown to form the enethiolate product. The ~4-fold negative deviation in Figures 4 and 5 of the rate constants for general base and general acid catalysis, respectively, of  $T^0$  breakdown from **4** (open circles) compared to **7** (solid circles) supports this conclusion. There is precedence for steric hindrance of general acid–base catalysis that may be relevant.<sup>37,38</sup> Remote C(2)-methylation is not expected to change the  $pK_a$  of the mercaptan in the enethiolate significantly.

There is no negative deviation in Figure 1 of the rate constants for  $HO^-$ -catalyzed irreversible enethiolate formation from 3-(4-nitrobenzyl)-2,4-dimethylthiazolium ion (**7**) (solid circles) compared to the rate constants for 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) (Figure 1) at pH > 8. This is consistent with no effect of C(2)-methylation on the rate constant for unassisted collapse of the alcoholate anion derived from  $T^0$  ( $T^-$ ) to form the enethiolate at pH > 8 (Scheme 3,  $k_7$ ). The absence of a significant effect of C(2)-methylation at pH > 8 supports the conclusion that there is little or no effect of C(2)-methylation on the ionization of  $T^0$  to form  $T^-$ . The intermediate anion  $T^-$  is formed from  $T^0$  at equilibrium, and because a change in the  $pK_a$  of  $T^0$  would shift this rate-determining preequilibrium step, different observed rate constants for **7** compared to **4** would have been obtained for irreversible enethiolate formation at pH > 8.

There is, however, a ~50-fold negative deviation in Figure 1 of the rate constants for  $H^+$ - and  $HO^-$ -catalyzed reversible enethiolate formation from 3-(4-nitrobenzyl)-2,4-dimethylthi-

#### Scheme 4



azolium ion (**7**) (solid circles) compared to the rate constants for 3-(4-nitrobenzyl)-4-methylthiazolium ion (**4**) (open circles) (Figure 1) at pH > 8. This is consistent with an unfavorable steric or electronic effect of C(2)-methylation on the equilibrium constant for unassisted breakdown of  $T^-$  to form the enethiolate product (Scheme 3, pH > 8 pathway). Because  $k_7$  (Scheme 3) does not change with C(2)-methylation (see above), we attribute this ~50-fold decrease in the equilibrium constant for  $T^-$  collapse to a ~50-fold increase in the rate constant for formation of  $T^-$  from the enethiolate ( $k_{-7} = k_7/K_{eq}$ ) as illustrated in Scheme 4. The identical values of  $k_{HO^-} = 25 \text{ M}^{-1} \text{ s}^{-1}$  for reaction of **4** in the presence of iodine (ionic strength maintained with  $KNO_3$ ) or the absence of iodine (ionic strength maintained with  $KCl$ ) (Figure 1) provides evidence against a specific salt effect on the reversible reaction at pH > 8.

We conclude that the ~50-fold rate-reducing effect of C(2)-methylation on ring opening of 3-substituted thiazolium ions represents an unfavorable steric and electronic effect on each of the three pathways (Scheme 3) for  $T^0$  breakdown to form the enethiolate hydrolysis product. The results at pH 3–8 are consistent with an unfavorable steric and electronic effect of C(2)-methylation on the ability of buffers to catalyze  $T^0$  breakdown: this is not simple steric hindrance of buffer approach because the buffer-catalyzed reactions show little sensitivity to steric requirements as is shown, for example, by the reactivity of 2,2,2-trifluoroethylamine and tris(hydroxymethyl)aminomethane (Figure 4). The results at pH > 8 are consistent with a steric and electronic effect from C(2)-methylation that increases the rate constant for the unassisted reverse, ring-closure reaction ( $k_{-7}$ ).

The unfavorable effect of C(2)-methylation on the unimolecular ring-opening reaction of 3-substituted thiazolium ions is in the opposite direction expected from studies on the bimolecular addition of a thiolate to a series of carbonyl compounds. These reactions show a decrease in the stability of the addition adduct with increasingly alkylated carbonyl compounds in the order formaldehyde, acetaldehyde, and acetone.<sup>39,40</sup>

There is precedence that suggests the apparent discrepancy in the effect of methylation on the stability of the bimolecular and unimolecular addition adducts simply represents a balance between the disadvantage from alkylation and the advantage from the intramolecular cyclization reaction. The ratio of equilibrium constants for five-membered cyclic compounds in equilibrium with their ring-opened form are in the range  $Me/H = 5-10^4$ ; methylation drives the reaction toward cyclization.<sup>41</sup> This effect has been attributed to enthalpic and entropic effects on ring closure with increasing alkylation.<sup>42</sup> The results reported here support the conclusion that the ratio of equilibrium constants for 3-R-thiazolium ions is  $C(2)-Me/C(2)-H \geq 50$ .

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