# The Mechanism of Alkaline Hydrolysis of Thiazolidines

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**Abstract:** The kinetics of the alkaline hydrolysis of 2-aryl substituted thiazolidines to aldehydes and aminoethanethiols were measured in 0.001–1.0 M NaOH at 25 °C. While the rates for N–$CH_3$ substituted thiazolidines are linearly dependent on $OH^-$ concentration, those for six N–H thiazolidines show rate saturation at high $OH^-$ concentrations. The mechanism of hydrolysis for N–H thiazolidines is interpreted in terms of two equilibrium steps, namely, a prior ring opening to form a zwitterionic intermediate (II), followed by a base-dependent proton loss from nitrogen to give a Schiff base (III) which hydrolyzes in the usual way. The presence of Schiff base intermediates is confirmed from electronic and NMR spectroscopy and rate comparisons with model Schiff bases. A similar equilibrium between thiazolidine and a zwitterionic intermediate is postulated for N–$CH_3$ thiazolidines. However, proton loss from nitrogen is precluded for these intermediates (IV) and hydrolysis proceeds by rate-determining $OH^-$ capture of IV. The effects of substituents in the thiazolidine ring on hydrolysis rates are discussed in terms of shifting the position of equilibrium forming zwitterionic intermediates (II and IV). *N*-Acylthiazolidines are extremely slow to hydrolyze.

## Introduction

The thiazolidine ring system derives special importance from the fact that it is an integral part of medicinally important compounds like the penicillins[1] and some antiradiation drugs.[2] Several photographically useful materials contain thiazolidines as the "active" functional group,[3] and they are also incorporated in flavor-enhancing additives.[4] The synthetic utility of thiazolidines is shown by their use as blocking groups,[5] and as intermediates in the synthesis of aldehydes[6] and aminoethanethiols.[7] In part, some of the synthetic usefulness of thiazolidines stems from the fact that they are rapidly hydrolyzed in the presence of mercuric[5,6] or silver ions.[8]

Examination of the literature reveals that, although the mechanism of thiazolidine formation has been studied in some detail,[9] information concerning the reverse reaction is fragmentary and inconclusive.[10] Recently, a publication by Pesek[11] has appeared regarding the intermediacy of Schiff bases in the decomposition of thiazolidines. We have studied the hydrolysis of various substituted thiazolidines and have thus been prompted to report on our findings.

## Experimental Section

**Thiazolidine Synthesis.** The N–H and N–$CH_3$ thiazolidines were synthesized by reacting equimolar amounts of the appropriate aminoethanethiols[12] with *p*-dimethylaminobenzaldehyde, *p*-(4-hydroxyphenylazo)acetophenone,[14] or *p*-(4-hydroxyphenylazo)benzaldehyde.[15] Compound **13** was prepared by acetylation of **11** in HOAc–$Ac_2O$ at reflux for 1 h, and **14** was obtained by heating **10** with *N*-ethyl isocyanate in pyridine for 15 min. All thiazolidines used for kinetic study met the required analysis for C, H, N, and S, and were analyzed as free bases or their HCl or HOAc salts.

**Synthesis of Schiff Bases.** β-Methylmercaptoethylamine and *S*-methylcysteine were purchased from Sapon Laboratories and Nutritional Biochemicals Corp. Anils derived from β-methylmercaptoethylamine were prepared in ethanol by stirring equimolar quantities of amine and aldehyde for 4 days. *S*-Methylcysteine derived Schiff bases were prepared according to the literature.[16] Schiff base **17** was contaminated with about 15% of aldehyde starting material. Since repeated attempts to purify this compound failed, the kinetics were run on the mixture. All other Schiff bases had correct analysis for C, H, N, and S.

**Kinetic Measurements.** Methoxyethanol (Baker, bp 124–125 °C), ethanol (Gold Shield), NaCl (Mallinckrodt, analytical reagent), and $NaClO_4 \cdot H_2O$ (Gallard-Schlesinger, analytical reagent) were used without purification. Stock 1.0 M NaOH solutions were standardized against potassium acid phthalate, diluted to various concentrations with doubly distilled water, and brought to ionic strength 1.0 M with $NaClO_4$.

Rates of hydrolysis for the various substrates (ca. $5 \times 10^{-5}$) were determined on a Cary 14 or 118 spectrophotometer by monitoring the increase in absorbance at 350 or 500 nm for compounds releasing *p*-dimethylaminobenzaldehyde or *p*-(4-hydroxyphenylazo)benzaldehyde, respectively. Schiff base **18** was monitored by the absorbance decrease at 450 nm. Isosbestic points, which were obtained from repetitive scans of the visual or ultraviolet region, were reasonably tight except in the region near 240 nm. Isosbestic failure in this region occurred because of aerial oxidation of the initially formed aminoethanethiols to disulfides.

Reactions were initiated by injection of 50 μL of methoxyethanol or ethanol substrate solutions into 3 mL of aqueous alkali which was previously thermally equilibrated in a cuvette holder at 24.95 ± 0.1 °C. Optical density measurements were made for at least 3 half-lives and values for the optical density at infinite times were taken after at least 10 half-lives. The values of $k_{obsd}$ were obtained by use of eq 1, and could be determined either graphically or by a weighted least-squares fit of the data points by computer. Typical correlation coefficients obtained for these data were 0.99. Most kinetic runs were performed in triplicate and $k_{obsd}$ values were reproducible to within 3%.

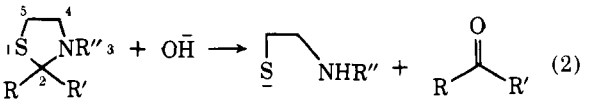
$$\ln (OD_\infty - OD_t) = k_{obsd}t + \text{constant} \qquad (1)$$

**Product Studies.** The thiazolidines and model imines were hydrolyzed at room temperatures in aqueous or 50% aqueous ethanolic NaOH under conditions which were pseudo first order in base. Product aldehydes and aminothiol derivatives were characterized by NMR comparison with known samples. In most cases melting points of the aldehydes were also recorded. Yields of aldehyde product obtained on a weight basis ranged from 73 to 101%.

## Results

The thiazolidines studied are shown in Table I. All have an aryl group in the 2 position, either *p*-dimethylaminophenyl or *p*-(4-hydroxyphenylazo)phenyl. The nitrogen in each series is substituted with a hydrogen, methyl, or an acyl group. Monosubstitution in the 4 or 5 position of the thiazolidine ring allows cis–trans isomerism between this substituent and the aryl group in the 2 position.[17] This isomerism is easily detected by $^1H$ NMR as the proton in the 2 position exhibits a different chemical shift for each isomer. By this criterion compounds **3, 4, 6, 11, 12,** and **13** were shown to be epimeric mixtures, while **8** was one isomer.

Both product studies and superimposition of the products spectrum with that obtained after 10 half-lives for each kinetic



(2)

run confirm that hydrolysis proceeds by way of eq 2.

**N–$CH_3$ Thiazolidines.** For compounds **5, 6, 7, 9,** and **12,** the

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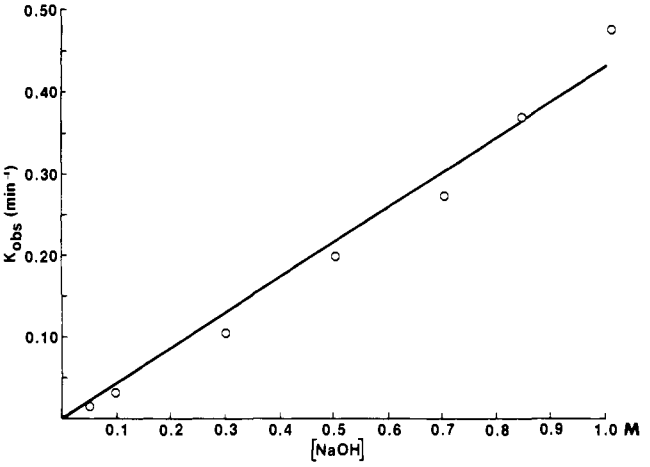



Figure 1. Plot of $k_{obsd}$ vs. NaOH concentration for thiazolidine **5**.

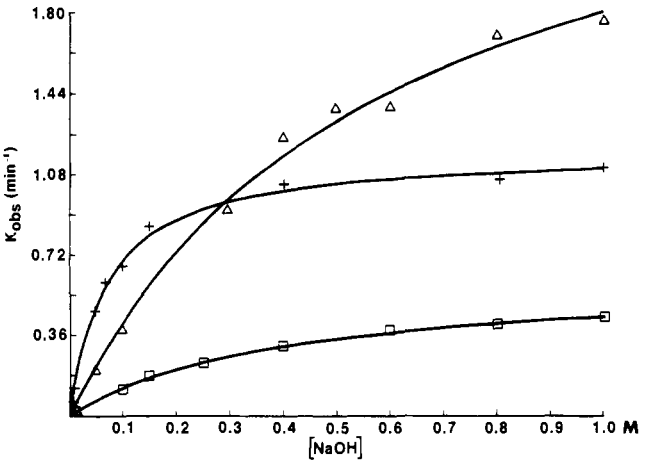
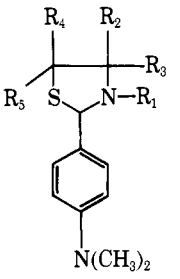
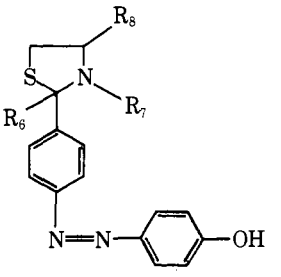



Figure 2. Plot of $k_{obsd}$ vs. NaOH thiazolidines **1** (+), **2** (△), and **3** (□).

**Table I.** Thiazolidine Derivatives




| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | compd | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | H | H | H | H | H | **10** | H | H | H |
| **2** | H | H | H | $CH_3$ | $CH_3$ | **11** | H | H | $CO_2H$ |
| **3** | H | $CO_2H$ | H | H | H | **12** | H | $CH_3$ | $CO_2H$ |
| **4** | H | $CO_2H$ | H | $CH_3$ | $CH_3$ | **13** | H | $COCH_3$ | $CO_2H$ |
| **5** | $CH_3$ | H | H | H | H | **14** | H | CONHEt | H |
| **6** | $CH_3$ | H | H | H | $CH_3$ | **15** | $CH_3$ | H | H |
| **7** | $CH_3$ | H | H | $CH_3$ | $CH_3$ | | | | |
| **8** | $CH_3$ | $CO_2H$ | H | $CH_3$ | $CH_3$ | | | | |
| **9** | $CH_3$ | $CH_3$ | $CH_3$ | H | H | | | | |

rates were found to be linear in hydroxide ion concentration, allowing for calculation of $k_{OH^-}$ by least-squares fitting of the data to the equation

$$k_{obsd} = k_{OH^-}[OH^-] \quad (3)$$

(Table III). Typically, the plots of $k_{obsd}$ vs. $[OH^-]$ showed a slight degree of upward curvature at higher alkali concentrations; an example is shown in Figure 1. This deviation from linearity can be attributed to the nature of the salt used to bring the ionic strength to 1.0 M.[18] Similar pronounced effects of $NaClO_4$ on the hydrolysis of iminium ions have been observed by others.[19] After 70 days at room temperature in 1.0 M NaOH, compound **8** had hydrolyzed about 30%. A crude half-life for its hydrolysis rate is estimated at greater than 90 days ($k \leq 5 \times 10^{-6}$ min$^{-1}$). An analysis of the spectral data for all N-$CH_3$ compounds studied here shows that their spectral curve shapes are alkali independent and that their hydrolysis is accompanied by isosbestic points whose position remains constant in spite of changes in NaOH concentrations.

**N-H Thiazolidines.** In contrast to the above N-$CH_3$ derivatives, the hydrolysis rates for the N-H thiazolidines show a nonlinear alkali dependency. At lower alkali concentrations the rates are linear with hydroxide ion concentration, while rate saturation occurs at higher base levels (Figure 2). Another way in which N-H thiazolidines **1, 2, 3, 10, 11,** and **15** differ from the N-$CH_3$ analogues is that their initial curve shapes vary with alkali concentration. At lower NaOH concentrations the beginning spectra are similar to those of the N-$CH_3$ compounds, as are the isosbestic points observed during hydrolysis. As the alkali concentration is increased, the initial spectra change, as do the isosbestic points (Figure 3). An exception is the penicillamine derivative **4**, whose rates and spectral changes during hydrolysis resembled those of the N-$CH_3$ thiazolidines studied and is included with these derivatives in Table III.

**Schiff Base Intermediates.** These experimental findings, namely, the nonlinear curves of $k_{obsd}$ vs. $[OH^-]$ and the shift in isosbestic point, provide evidence for the existence of an intermediate in the hydrolysis of N-H thiazolidines. Further support comes from $^1$H NMR studies (vide infra). The tendency for rate saturation at high base concentrations is most dramatic for 2-(*p*-dimethylaminophenyl)thiazolidine (**1**), and can be described by a mechanism involving formation of an intermediate in an acid-base type reaction, followed by an alkali-independent destruction of the intermediate (eq 4).[20] Intercepts and slopes from plots of $1/k_{obsd}$ vs. $1/[OH^-]$ gave estimates for $k_2$ and $K_b$ (eq 6). Using these values, the data were fit to eq 6 by an iterative least-squares analysis for nonlinear functions[21] to give optimized values for $k_2$ and $K_b$ shown in Table IV.[22] The curves in Figure 2 were drawn from eq 6 using these constants. Values of $k$ calculated from eq 6 differ from $k_{obsd}$ by a standard deviation of 17, 23, 7, 4, 3, and 7% for

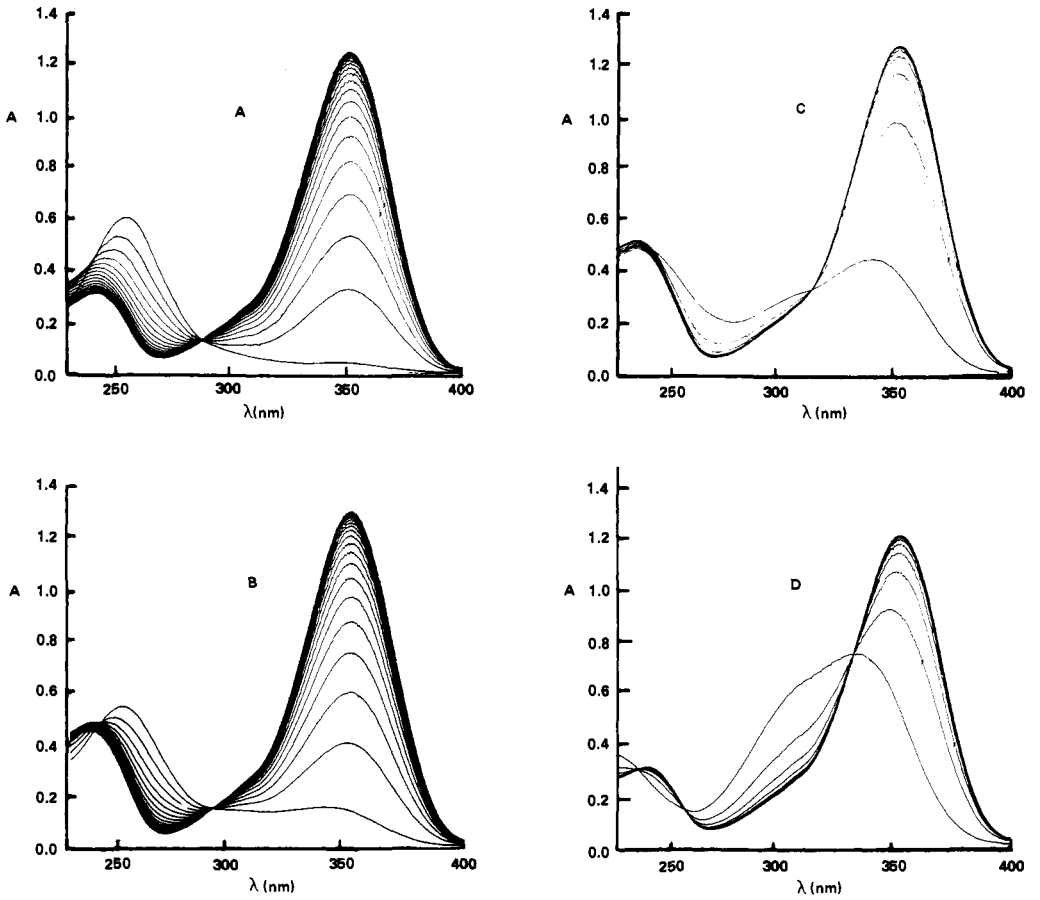
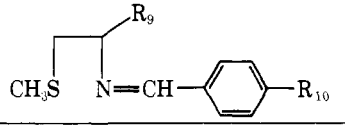



Figure 3. Time-dependent spectral changes accompanying the hydrolysis of (A) **1** in 0.001 M NaOH; (B) **1** in 0.01 M NaOH; (C) **1** in 0.05 M NaOH; (D) **16** in 0.05 M NaOH.

Table II. Schiff Base Derivatives and Their Observed Rate Constants for Hydrolysis at 24.95 °C, Ionic Strength 1.0 M



| compd | $R_9$ | $R_{10}$ | $[OH^-]$ studied, M | $k_{obsd}$, $min^{-1}$ | $\delta$[a] |
|---|---|---|---|---|---|
| **16** | H | $-N(CH_3)_2$ | 0.005, 0.05, 1.0 | 0.316 | 0.028 |
| **17** | $CO_2K$ | $-N(CH_3)_2$ | 0.001, 0.01, 0.10, 1.0 | 0.103 | 0.006 |
| **18** | H | $-N{=}NC_6H_4OH$-*p* | 0.01, 0.10, 0.50, 1.0 | 0.160 | 0.007 |
| **19** | $CO_2K$ | $-N{=}NC_6H_4OH$-*p* | 0.01, 0.10, 0.50 | 0.0367 | 0.001 |

[a] Standard deviation.

**1, 2, 3, 10, 11,** and **15,** respectively.[23]

$$SH \underset{+H^+}{\overset{-H^+,\,K_a}{\rightleftharpoons}} S^- \xrightarrow{k_2} \text{products} \quad (4)$$

$$k_{obsd} = \frac{k_2 K_a}{K_a + [H^+]} \quad (5)$$

Substituting $K_a = K_b K_w$ into eq 5 gives

$$k_{obsd} = \frac{k_2 K_b [OH^-]}{1 + K_b [OH^-]} \quad (6)$$

$$\text{where } K_b = \frac{[S^-][H_2O]}{[SH][OH^-]}$$

A natural choice for the intermediate in accord with eq 4 is a Schiff base having one proton less than the starting material. Previous workers have also cited Schiff bases as intermediates in the reactions of thiazolidines.[11,24] Models for these intermediates derived from thiazolidines **1, 3, 10,** and **11** were prepared from *S*-methyl-2-aminoethanethiols and the appropriate aldehydes (Table II) and their hydrolysis rates were measured. Not surprisingly, they hydrolyze to the expected aldehydes, which were isolated in no less than 73% yields. Additionally, as required by eq 4, their hydrolysis rates are independent of hydroxide ion in the region of 0.001-1.0 M NaOH (Table II).

By comparing A, B, and C with D in Figure 3, it can be seen that the spectral changes accompanying hydrolysis of N-H thiazolidine **1** tend toward those observed for model **16** as the base concentration increases. In agreement with eq 4, it is possible to extract $pK_a$ values for the equilibrium between thiazolidine and Schiff base from the spectral data. The first spectrum recorded after immediate dissolution of **1** in an aqueous medium at a pH equal to its $pK_a$ should correspond to a 50:50 mixture of **1** and its appropriate Schiff base. This spectrum was simulated by adding the absorbance of **1** (recorded at low alkali concentration where insignificant amounts of Schiff base or aldehyde are present) to the absorbance of an equivalent amount of **16,** (recorded before hydrolysis). This was done for every 10 nm of the spectrum and a smooth line was drawn between points.

Other curves corresponding to different percentages of conversion to aldehyde were constructed by adding fractional amounts of the above curve to the appropriate absorbance due to *p*-dimethylaminobenzaldehyde. Superposition of these curves results in a display similar to that in Figure 3, and simulates the spectral output expected if **1** were to hydrolyze in alkali at a pH where it is half in the thiazolidine form and

**Table III.** Specific Rate Constants for the Hydrolysis of Thiazolidines at 24.95 °C, Ionic Strength 1.0 M

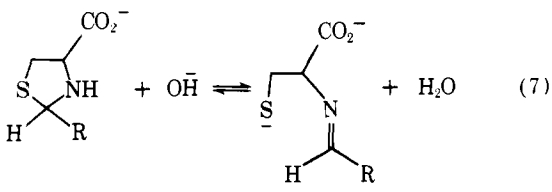
| compd | [OH⁻] studied, M | $k_{OH^-}$, $min^{-1}$ $M^{-1}$ | correlation coefficient | % δ[a] |
|---|---|---|---|---|
| **4** | 0.10, 0.30, 0.50, 0.65, 0.76, 1.01 | $3.46 \times 10^{-2}$ | 0.996 | 14 |
| **5** | 0.05, 0.10, 0.30, 0.50, 0.70, 0.84, 1.01 | $4.33 \times 10^{-1}$ | 0.993 | 24 |
| **6** | 0.10, 0.30, 0.50, 0.70, 0.84, 1.00 | $1.58 \times 10^{-1}$ | 0.992 | 20 |
| **7** | 0.10, 0.30, 0.50, 0.65, 0.80, 1.01 | $1.75 \times 10^{-2}$ | 0.993 | 16 |
| **8**[b] | 1.0 | $<5 \times 10^{-6}$[c] | | |
| **9**[b] | 0.70, 0.80, 1.00 | $1.26 \times 10^{-3}$ | 0.985 | 9 |
| **12** | 0.05, 0.10, 0.25, 0.40, 0.50, 0.70, 1.00 | $8.78 \times 10^{-3}$ | 0.997 | 16 |

[a] See footnote 23. [b] Kinetics run at room temperature. [c] Units are $min^{-1}$.

half in the form of ring-opened Schiff base. In the same way, a family of curves was constructed for compounds **2** and **3** using **16** and **17**, respectively, as models for the Schiff base intermediate. Isosbestic points were obtained from these simulated spectra. From plots of the observed isosbestic point vs. [OH⁻], the alkalinity and hence the p$K_a$ (p$K_a$ = pH = 14 − log [OH⁻]) at which these calculated isosbestic points occur could be obtained. Values of 12.7, 13.5, and 13.3 were obtained for the p$K_a$ of **1**, **2**, and **3**, which is in agreement with the values determined from the kinetic data (Table IV).

One of the assumptions inherent in the above treatment is that the spectra of the closed thiazolidine, the open Schiff base, and the aldehyde product are not affected by the base concentration. While being valid in the above cases, this premise does not hold for *p*-(4-hydroxyphenylazo)benzaldehyde or Schiff bases **18** and **19** derived from this aldehyde. That is, the spectra of these compounds change with OH⁻ concentration. Hence, the treatment based on simulated spectral changes cannot be readily applied to thiazolidine derivatives **10** or **11**. Nevertheless, hydrolysis of these compounds, as well as **15**, is accompanied by OH⁻ dependent spectral shifts which, at higher alkalinity, tend to resemble the features of Schiff base models **18** and **19**.

**NMR Confirmation of Schiff Base Intermediate.** The NMR spectra of **3** in $Me_2SO$-$d_6$ shows a doublet at δ 5.5 and two broad multiplets at δ 3.7-4.4 for the C-2 and C-4 protons, respectively, indicating the presence of cis-trans isomers.[17] In excess KOD, the initial NMR spectrum of **3** shows a new one-proton absorption at δ 8.1, which is attributed to the Schiff base proton. Complementary loss of the signal near δ 5.5, as well as agreement with the chemical shift of the Schiff base proton of **17** and other reported imines,[11,25] supports this assignment. Subsequent scans of the spectrum indicate that the initially formed Schiff base hydrolyzes to aldehyde. The peak at δ 8.1 is significantly broader than that of model **17**. This broadening and that of the δ 5.5 signal at lower hydroxide concentration are in agreement with previous observations by Pesek and Frost,[11] who interpreted their results in terms of an equilibrium between thiazolidine and Schiff base. In relatively dilute alkali equilibrium 7 is largely in favor of closed thiazolidine and is responsible for averaging the two signals near δ 5.5, representative of two epimers. In more concentrated base, the equilibrium is shifted to the right and presumably results in averaging the syn-anti Schiff base isomers.



(7)

***N*-Acylthiazolidines.** Compared to the N-H or N-$CH_3$ thiazolidines, the N-acylated compounds are considerably more stable to hydrolysis. The estimated half-life of *N*-acetylthiazolidine **13** in 0.05 M NaOH at room temperature is greater than 1000 days ($k \leq 5 \times 10^{-7}$ $min^{-1}$).[8a] Rather than undergoing hydrolysis, *N*-ethylcarbamyl derivative **14** suffers general chromophore collapse (350-550 nm) with a half-life of about 39 days ($k \leq 1 \times 10^{-5}$ $min^{-1}$) in 0.10 M NaOH at room temperature. Since the aldehyde control spectrum is stable under these conditions, the normal hydrolysis of **14** must be preempted by another pathway.

**Table IV.** Reaction Coordinate Parameters for the Hydrolysis of N-H Thiazolidines

$$SH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} S^- \xrightarrow{k_2} \text{products}$$

| compd | $k_2$, $min^{-1}$[a] | p$K_a$[b] |
|---|---|---|
| **1** | 1.19 | 12.86 |
| **2** | 2.86 | 13.77 |
| **3** | 0.62 | 13.61 |
| **10** | 0.89 | 13.71 |
| **11** | 0.35 | 14.35 |
| **15** | 0.69 | 13.14 |

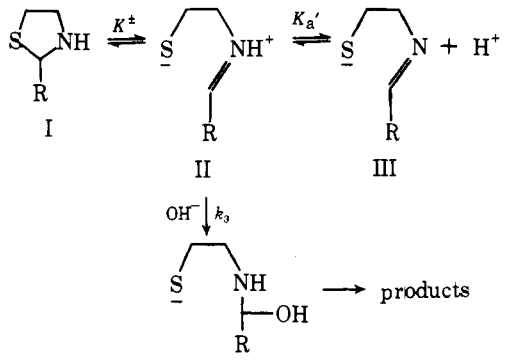
[a] Obtained from hydrolysis rates measured at 24.95 °C at ionic strength of 1.0 M. [b] p$K_a$ = p$K_b$ + 14.

## Discussion

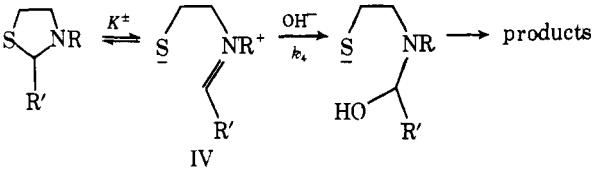
The kinetics and spectral data (electronic and NMR) obtained during the alkaline hydrolysis of N-H thiazolidines support a mechanism involving equilibrium formation of a Schiff base via acid dissociation from its precursor, followed by an alkali-independent hydrolysis of this intermediate. Both forms of data indicate that the Schiff base is formed by proton loss from a species which has a p$K_a$ in the region of 13-15 for the compounds shown in Table IV. Such a low p$K_a$ cannot be attributed to amine ionization of the thiazolidine, for dissociation of this type occurs with a p$K_a$ near 30.[26] A more likely candidate for the Schiff base precursor is a ring-opened zwitterionic species II, as depected in Scheme I. Although present at too low concentration to be detected, intermediate II is postulated to be in rapid equilibrium with both I and III. Being base dependent, the latter equilibrium determines the relative amounts of thiazolidine (I) and Schiff base (III) present at any pH. Thus, at low alkali concentrations, the rate-determining step for hydrolysis of N-H thiazolidines is the hydroxide ion dependent formation of Schiff base III, as shown by the linear portion of the plots in Figure 2. At high alkali concentrations where the rates tend to level off, the position of equilibrium in Scheme I is shifted in favor of Schiff base III, and the rate-limiting step then becomes the base-independent hydrolysis of this species.

Table IV cites the hydrolysis rates ($k_2$) for intermediate Schiff bases (III) as determined by fitting the rate data to eq 6. These $k_2$ values fall within a range close to that reported for the intermediate derived from 2-(2-thienyl)thiazolidine-4-carboxylic acid (0.13 $min^{-1}$) in alkaline $D_2O$.[11] More impor-

Scheme I



Scheme II



tantly, these $k_2$'s are all within an order of magnitude of the hydrolysis rates found for the *S*-methyl Schiff base models (Table II), and thus tend to support the kinetic treatment used in evaluating $k_2$'s. Yet, in all four cases where comparisons with models are possible, the rates for the intermediates in the thiazolidine hydrolysis are somewhat faster (four to ten times). Since the mechanism for Schiff base hydrolysis in this pH range involves the attack of hydroxide ion on protonated Schiff bases,[27] these rate differences may arise from a retardation in rate in the models due to the presence of the sterically retarding *S*-methyl group. Alternatively, rate enhancements in the hydrolysis of thiazolidine intermediate III may exist as a result of the influence of the negative mercaptide anion on the basicity or intramolecular hydrogen-bonding properties of the Schiff base.

The mechanism proposed for hydrolysis of N-substituted thiazolidines is an extension of that for N-H thiazolidines. Heterolytic fragmentation of starting substrate leads to zwitterionic intermediate IV. Although analogous to II, intermediate IV does not have a proton on nitrogen available for removal by base, and it must therefore either recyclize to thiazolidine or suffer attack by hydroxide ion or water. In the alkaline regions studied, hydroxide ion capture becomes the rate-limiting step in the hydrolysis as evidenced by the linear relationship between rates and base concentrations (Table III).

In light of Scheme II the rate retardations observed for *N*-acyl substituted thiazolidines becomes clear. The degree of retardation is substantial being a factor of at least 11 000 for *N*-acetyl or *N*-ethylcarbamyl (comparing **11** vs. **13** in 0.05 M NaOH and **10** vs. **14** in 0.10 M NaOH). Stabilization of the thiazolidine ring by *N*-acyl groups has been reported by others[7d,28] and is presumably due to the relatively low stability of a positive charge $\alpha$ to an amide vs. an amine nitrogen.[29] In other words, delocalization of the nitrogen lone electron pair into the amide carbonyl group results in relatively low concentrations of intermediate IV and consequently reduced hydrolysis rates. The importance of nitrogen's nucleophilicity is also reflected in the dissociative tendency of $\alpha$-amino sulfides, which are the open-chain analogs of thiazolidines. With these compounds, dissociation is inhibited by N-acetylization[30] or N-quaternization by protons[31] or alkyl groups.[32]

More direct evidence for the role of nitrogen's nucleophilicity stems from the hydrolysis results of *N*-methyl-, *N*-benzyl, and *N*-furfuryl-2-dimethylaminophenylthiazolidines in 0.5 M NaOH.[33] A plot of log $k_{obsd}$ vs. the p$K_a$ of methyl-, benzyl-, and furfurylamine gives a slope of 0.57, showing that hydrolysis dependency on the ring nitrogen's basicity is substantial and that there is positive charge buildup on nitrogen in the transition state. Complementary substantiation of this cationic character is provided by the $\rho$ of $-1.4$ obtained from the $\sigma$-$\rho$ plots of 2-aryl-3,5,5-trimethylthiazolidines studied in 1.0 M NaOH.[33] Other reactions postulated to proceed via equilibrium formation of a cationic Schiff base followed by rate-determining attack by hydroxide ion are the alkaline hydrolysis of Schiff bases ($\rho^+ = -0.21$),[34] and possibly that of 2-substituted *N*,*N*-dimethyl-1,3-imidazolidines ($\rho = -0.35$)[35] and 2-substituted 3-methyl oxazolidines ($\rho = -1.1$).[36] In two-step reactions like these the overall $\rho$ is the result of $\rho$'s for each step. For the above examples, the effects of polar substituents on the prior equilibrium reaction are opposite to those of the second step, which has a $\rho^+$ of 1.26.[34] The $\rho$ of $-1.4$ obtained for 2-substituted 3,3,5-trimethylthiazolidines indicates that the net influence of substituents on the ring-opening reactions is therefore greater than that of the second step.

In keeping with Scheme I, the p$K_a$s (Table IV) derived from fitting the rate data to eq 6 are only apparent acidity constants since they reflect the product of two equilibrium constants:

$$K_a = K_a'K^{\pm} \tag{8}$$

Whereas $K^{\pm}$ expresses the propensity for a thiazolidine to exist in a zwitterionic form II, $K_a'$ is the dissociation constant of a protonated Schiff base. The p$K_a'$ values for intermediates (II) derived from thiazolidines **1, 2,** and **3** were calculated as follows. Jencks and Cordes reported a correlation between the dissociation constants of the conjugate acids of substituted benzaldehyde Schiff bases and $\sigma^+$.[34] Using $\sigma^+$ of $-1.7$ for the *p*-$N(CH_3)_2$ group,[37] a p$K_a$ of 9.42 was calculated for the conjugate acid of *p*-dimethylaminobenzylidene-1,1-dimethylethylamine. Thus, the acidity of $t$-$C_4H_9NH_3^+$ is increased by more than one order of magnitude (from p$K_a$ of 10.68[38] to 9.42) upon conversion to its Schiff base derivative with *p*-dimethylaminobenzaldehyde. If the calculation is performed using $\sigma$ rather than $\sigma^+$, as suggested by Charette et al.[39] the p$K_a$ of the amine is lowered by 2.20 units. Assuming a similar 1.26–2.20-unit drop in the conversion of protonated aminoethanethiolates[40] to the zwitterionic species (II), the p$K_a'$ values for these intermediates derived from **1** and **2** are estimated to be 8.61–9.55, while that derived from **3** is 8.00–8.94. Using these $K_a'$ values, those of $K_a$ in Table IV and eq 8, $K^{\pm}$ estimates (Table V) were obtained.

Although resembling N-$CH_3$ derivatives in kinetic and spectral output, the behavior of **4** is easily understood in terms of a substrate with a high p$K_a$ or reduced $K_b$ in eq 6. Subsequent discussion will ascribe this to the increased substitution of this derivative. Under these circumstances, the rate-limiting step becomes the base-dependent formation of III and eq 6 reduces to

$$k_{obsd} = k_2K_b[OH^-] \tag{9}$$

If $k_2$ falls within the range observed for N-H derivatives **1, 2,** and **3,** a p$K_a$ of 15.2–15.9 can be calculated from eq 9. Using this p$K_a$ and assuming the appropriate microscopic constant for penicillamine to be the same as cysteine, the $K^{\pm}$ for **4** is calculated to be within the range shown in Table V.[41]

It is also possible to find the corresponding $K^{\pm}$ values for *N*-methylthiazolidines. According to Scheme II, the observed rate constant for hydrolysis ($k_{OH^-}$) is related to $k_4$ and $K^{\pm}$:

$$k_{OH^-} = K^{\pm}k_4 \tag{10}$$

An estimated second-order rate constant of $2.2 \times 10^5$ $M^{-1}$ $min^{-1}$ can be calculated for the attack of hydroxide ion on

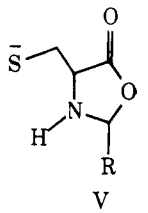
Table V. Estimated $K^{\pm}$ Values for Thiazolidines

| compd | $K^{\pm}$ |
|---|---|
| **1** | $5 \times 10^{-4}$ to $6 \times 10^{-5}$ |
| **2** | $6 \times 10^{-5}$ to $7 \times 10^{-6}$ |
| **3** | $2 \times 10^{-5}$ to $3 \times 10^{-6}$ |
| **4** | $5 \times 10^{-7}$ to $1 \times 10^{-8}$ |
| **5** | $2 \times 10^{-6}$ |
| **6** | $7 \times 10^{-7}$ |
| **7** | $8 \times 10^{-8}$ |
| **8** | $3 \times 10^{-11}$ [a] |
| **9** | $6 \times 10^{-9}$ |

[a] See text for calculation.

protonated *p*-dimethylaminobenzylidene-1,1-dimethylethylamine.[34] On the basis that this rate is on the same order of magnitude as $k_4$ in Scheme II,[43] estimates for $K^{\pm}$ can be calculated from eq 10, where $k_{OH^-}$'s are given in Table III. Thiazolidine **8** was too stable toward hydrolysis to measure in less than 1.0 M NaOH. The $K^{\pm}$ for **8** was calculated assuming that it behaved like other *N*-methyl derivatives in showing a linear relationship between rate and hydroxide ion concentration. These results are tabulated in Table V.

Inspection of Table V shows that increased substitution in the 3, 4, or 5 position of the thiazolidine ring leads to smaller $K^{\pm}$'s, which are generally associated with slower hydrolysis rates. The shift toward stabilizing the ring-closed forms by methyl substitution is effected most by N-methylation, and by 4-*gem*-dimethyl more than 5-*gem*-dimethyl substitution. As seen from the $K_a$ values in Table IV, the ring-closing propensities brought about by 4-carboxylate substitution are unaffected by the change in the nature of the 2-substituent. The possibility for nucleophilic carboxylate participation on ring-opened forms to give oxazolidinones (V) is discounted on the



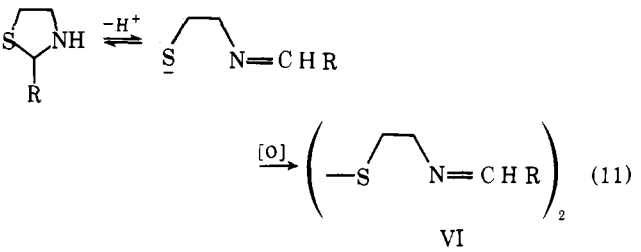
V

basis of literature precedence[44] and the fact that similar intermediates are not observed in the hydrolysis of model *S*-methyl Schiff bases **17** or **19.**

Similar ring stabilizing effects due to increased substitution are well documented in other cyclic-acyclic equilibrium reactions.[45] In agreement with common interpretations, the influence of substituents on $K^{\pm}$ may be related to one or more of the following: (1) increased rates of ring closure due to an increase in the population of open-chain conformers which are favorable for reclosure;[45b,46] (2) inhibition to ring opening due to greater steric compression in the open-chain forms;[47] (3) stereoelectronic control;[48] and (4) the effect of changing basicity of the nitrogen atom.

With compound **15,** the general trend of decreasing hydrolysis rates (0.01-1.0 M NaOH) with increasing methyl substitution is reversed; i.e., thiazolidine **15** hydrolyzes faster than **10.** Others have also noted the relative lability of thiazolidines derived from ketones as opposed to aldehydes.[10b,f,h] Examination of Table IV shows that 2-methyl substitution leads to a fourfold increase in $K_a$ (**15** vs. **10**), and indicates that the increased hydrolysis rates are due to a shift in equilibrium favoring Schiff base III in Scheme I. Similar conclusions can be obtained from oxazolidine derivatives.[36] Presumably, this shift reflects the greater stability of aldiminium ions compared to ketiminium ions.[49] Similarly, the relative stability of Schiff bases derived from *p*-dimethylaminobenzaldehyde, as opposed to *p*-hydroxyphenylazobenzaldehyde, is the reason for the observed $K_a$ ratios of 7 and 6 for **1**/**10** and **3**/**11,** respectively.

Trapping of proposed intermediates provides strong evidence for their existence in a reaction pathway. Many literature examples provide such evidence for Schiff base intervention in the reaction of thiazolidines. Thus, when treated with aerated dimethyl sulfoxide solutions, or alkaline iodine or hydrogen peroxide, 2-substituted thiazolidines lead to disulfide Schiff bases (VI) via oxidative capture of the presumed imine intermediates.[24a,b] Other mercaptide "capping" reagents, such as benzyl chloride and 2,4-dinitrochlorobenzene, have resulted in formation of the *S*-benzyl and *S*-aryl Schiff bases under basic conditions,[24c] while trapping by metal ion has led to a nickel(II) Schiff base complex.[50] Interception of the C=N



VI

moiety of intermediate Schiff base by hydride transfer is the probable mechanism for the sodium borohydride or lithium aluminum hydride reduction of thiazolidines to N-substituted aminoethanethiols.[7b] While these examples all pertain to N-H thiazolidines, a recent study of dipolar additions lends support for the existence of zwitterionic 1,5 dipolar intermediates in equilibrium with *N*-alkylthiazolidines.[51]

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**Supplementary Material Available:** Table listing physical properties of **1-19;** rate and isosbestic point vs. NaOH concentration plots for **10, 11,** and **15,** and **1, 2,** and **3,** respectively; $^1$H NMR data for **3** (4 pages). Ordering information is given on any current masthead page.

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$$K_a = a_{H^+} \frac{[\bar{S}]}{[HS]} \frac{\gamma_{[O\bar{H}]}}{\gamma_{[H_2O]}}$$

(23) $$\% \sigma = \left[ \sum \frac{\left( \frac{k_{obsd} - k_{calcd}}{k_{obsd}} \right)^2}{n-1} \right]^{1/2} \times 100$$

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(41) If **4** hydrolyzes by the mechanism proposed for N–$CH_3$ thiazolidines, the $K^{\pm}$ calculated from eq 10 is within the range found assuming the pathway for N–H thiazolidines. In this case, the difference in mechanism reduces to whether the initially formed protonated Schiff base suffers proton abstraction faster than nucleophilic attack by hydroxide. Although the present data do not allow a clear choice to be made, the former process appears more likely on the basis that similar proton transfer rates are known to be diffusion controlled,[42] while hydroxide ion capture rates of iminium ions are significantly slower.[34]
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