An NMR Study of the Decomposition of a 2,2-Disubstituted Thiazolidine. Kinetic Evidence for a Schiff Base Intermediate

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The *p*H-rate profile for the decomposition of 2,2,5,5-tetramethyl-4-thiazolidinecarboxylic acid is used to identify the presence of a Schiff base intermediate. Activation parameters for the reaction are reported at various *p*H's and in particular the negative values of entropy support the presence of a carbinolamine in the rate-determining step.

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The importance of the thiazolidine ring system in medicinal and biological chemistry has been documented in numerous previous investigations [1-8]. Penicillin is an example of a medicinally active thiazolidine [9]. Previous studies have shown that the formation and decomposition of the thiazolidine ring proceeds through a Schiff base intermediate [10,11]. Schiff bases occur as intermediates in many enzymatic reactions so their formation and decomposition is of great interest [12-18]. The mechanisms of these processes are now fairly well-understood [19,20].

In a previous report [11] we demonstrated how nmr could be used to detect the presence of a Schiff base intermediate in the decomposition of 2-substituted thiazolidines formed from the condensation of an amino thiol and an aldehyde. The techniques used in the identification of the Schiff base include hydrogen-deuterium exchange, line broadening, and direct observation of the imine hydrogen resonance. Attempts to identify a Schiff base intermediate in the decomposition of 2,2-disubstituted thiazolidines (formed from an amino thiol and a ketone) by these same techniques have failed. However, the decomposition of some of these compounds in aqueous solution proceeds slowly enough so that the rate can be measured by directly integrating the appropriate nmr signal of either the ring compound or one of the reaction products as a function of time.

If the rate-determining step in thiazolidine decomposition involves a Schiff base intermediate, then the rate characteristics of the reaction should be identical to or very similar to the rate characteristics of Schiff base decomposition. One such possible distinguishing feature is the *p*H-rate profile which has already been described for Schiff base decomposition [20]. Its shape is complex and reflects the changes in the mechanism that occur as a function of hydrogen ion concentration. Therefore, it should be possible to use this pattern to identify the presence of a Schiff base intermediate in a particular reaction.

Results and Discussion.

Figure 1 is a plot of the log of the first-order rate constant for the decomposition of 2,2,5,5-tetramethyl-4-thiazolidine-carboxylic acid as determined from the integrated area of the acetone peak as a function of time *vs.* *p*H. The shape of the curve is very similar to several of the curves determined by Kayser and Pollack [20] for the decomposition of a series of Schiff bases derived from cyclohexene-1-carboxaldehyde. In fact, the greatest similarities occur when the Schiff bases used in the previous study contain internal carboxylate ions.

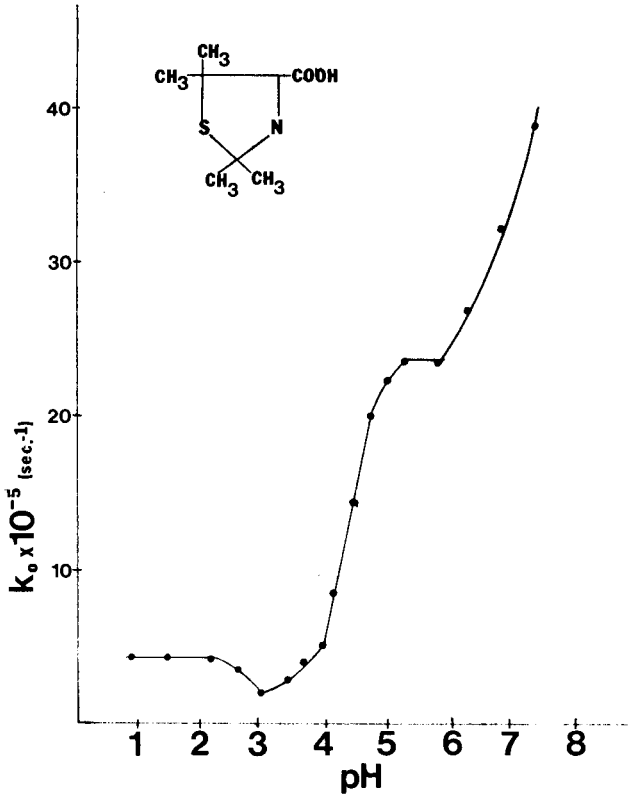

Figure 1. The variation in the observed rate constant (k_o) for the decomposition of 2,2,5,5-tetramethyl-4-thiazolidinecarboxylic acid *vs.* *p*H.

Table I

Activation Parameters for the Decomposition of 2,2,5,5-Tetramethyl-4-thiazolidinecarboxylic Acid at Various *p*H's

*p*H	E_a (Kcal/mole)	$\Delta H^{\ddagger}$ (Kcal/mole)	$\Delta S^{\ddagger}$ (cal/mole °K)
1	15.3	14.7	−30.4
3	17.1	16.5	−32.0
4	14.3	13.6	−33.4
5	13.3	12.7	−33.8
6	13.2	12.6	−34.2
7	12.4	11.8	−36.4

The shape of the curve in Figure 1 is consistent with the general mechanism of Schiff base decomposition and the variations observed in this study confirm those observed previously for carboxylate containing species. The shape of the curve in Figure 1 can be explained to support the presence of a Schiff base in the following way. The increase above *p*H 5.5 is due to the base catalyzed attack of water on the Schiff base to form a carbinolamine. The break in the curve at *p*H 5 is the result of the transition in the rate-determining step from the attack of water on the Schiff base to the breakdown of the carbinolamine. The increase in the rate between *p*H 3 and 5 is controlled by a proton switching process that converts the carbinolamine to a zwitterion [$\rangle C(NHR)(OH) \rightleftharpoons \rangle(H_2^{+}NR)(O^{-})$]. Another important similarity between this study and the work of Kayser and Pollack [20] is the increase of the rate below *p*H 3 for carboxylate containing species. Therefore, our results further support the theory that such a rate increase is probably caused by protonation of the carboxylate anion which decreases the basicity of the nitrogen and accelerates carbinolamine breakdown. The plateau in the *p*H-rate profile between *p*H 1-2 has also been observed for other Schiff bases and can be attributed to a change in the carbinolamine species present [20]. Therefore, all the features of the *p*H-rate profile in Figure 1 can be adequately explained by the presence of a carboxylate containing Schiff base.

Table I is a list of the activation parameters for the decomposition reaction determined at several *p*H's. While there are no direct comparisons which can be made to the previous mechanistic studies, it is interesting to note the values which have been obtained for this system. As expected the activation energy is inversely proportional to the observed change in rate, *i.e.* a lower activation energy results in a faster rate of decomposition. This same trend is also noted in the enthalpy of activation. Finally, the entropy changes are negative at all *p*H's which would be expected if the rate-determining step involved a carbinolamine intermediate. This is due to the fact that solvent addition to the Schiff base should result in a lower entropy for the system.

In summary, it appears that a kinetic characteristic such as a *p*H-rate profile is an effective means of identifying an intermediate in a reaction. In this study the *p*H-rate profile of the decomposition of a 2,2-disubstituted thiazolidine supports the assumption that the reaction proceeds through a Schiff base intermediate. The shape of the curve indicates the presence of a carbinolamine in the rate-determining step and also reflects the presence of the carboxylate moiety as part of the molecule studied. Finally, the activation parameters reported, while they cannot be compared to similar systems, are reasonable and, in particular, the entropy values are consistent with the formation of a species (carbinolamine) in the rate-determining step which is the result of solvent addition.

EXPERIMENTAL

2,2,5,5-Tetramethyl-4-thiazolidinecarboxylic acid was purchased from Aldrich (Milwaukee, WI) and used without further purification. No extraneous signals were observed in the nmr spectrum. All samples were 0.05-0.10 *M* in water or deuterium oxide and the ionic strength was maintained at 1.0 with sodium chloride. Buffers were used to maintain constant *p*H from 3-8 while hydrochloric acid was used in the *p*H range 1-3.

The nmr spectra were recorded on either a Varian A60A spectrometer or an IBM Instruments NR80 spectrometer. Both were equipped with variable temperature units. The *p*H measurements were made with a Corning Model 12 *p*H meter.

First-order rate constants for the decomposition reaction were determined from plots of the log of the integrated area of the acetone peak *vs.* time using linear least squares analysis. The activation parameters, E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$, were determined from plots of log k *vs.* 1/T also using linear least squares analysis and then employing standard calculations.

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