Tetrahedron. Vol. 31, pp. 907 to 913. Pergamon Press 1975. Printed in Great Britain

DECOMPOSITION OF THIAZOLIDINES IN ACIDIC AND BASIC SOLUTION

SPECTROSCOPIC EVIDENCE FOR SCHIFF BASE INTERMEDIATES

J. J. PESEK and J. H. FROST
Department of Chemistry, Northern Illinois University, DeKalb, IL 60115, U.S.A.

(*Received in USA* 20 *February* 1974; *Received in UK for publication* 24 *October* 1974)

Abstract—Stability of thiazolidine-4-carboxylic acids and chain tautomerism are studied in acidic, basic and neutral solution. In acidic solution aliphatic substituted thiazolidine-4-carboxylic acids are stable, but aromatic substituted thiazolidine-4-carboxylic acids decompose to the mercaptal if there is not steric inhibition. Mercaptal formation establishes the presence of tautomerism because it is the only pathway through which thiol can be provided for in the reaction. It is suggested that this reaction may proceed through a sulfonium ion intermediate. In neutral solution aliphatic substituted thiazolidine-4-carboxylic acids are stable. In strongly basic solution both aromatic and aliphatic substituted thiazolidine-4-carboxylic acids decompose to the aldehyde and the aminothiol. By adjusting the base concentration, the intermediate imine is detected by α-hydrogen exchange for aliphatic systems and by line broadening or direct NMR observation of the ArCH=N proton resonance in aromatic systems.

Extensive study of the thiazolidine ring system has taken place due to its biological and medicinal importance.[1-9] Numerous reports exist in the literature concerning syntheses of substituted thiazolidines. However, it has only been recently that Kallen has made a detailed investigation of the reaction mechanism.[10] His results and previous work strongly indicate that thiazolidine formation proceeds through a Schiff base intermediate. These conclusions have been reached through kinetic evidence because the imine has not been directly observed in solution.

It has also been suggested that thiazolidines exist in equilibrium with the imine intermediate (open chain tautomer) and its carbonyl and aminothiol precursors.[11-13] Again no direct spectral evidence has been obtained for the existence of the open chain tautomer. Even though there is indirect evidence for the existence of these equilibria, no detailed study has been undertaken to elucidate the conditions that might cause the ring structure to be less favored, i.e. what conditions would induce thiazolidines to decompose to either the imine or the carbonyl compound and aminothiol. It has been shown that Ag^+ accelerates the decomposition of certain 2-substituted aromatic thiazolidines.[14]

Synthesis and isolation of imines in nonaqueous media can be easily accomplished and there are several examples of imine formation between aliphatic amines and aliphatic aldehydes in aqueous solution.[15-17] Detection, equilibrium measurements, and kinetic data were obtained by ultraviolet spectroscopy. Similar experiments with thiazolidine systems have failed to conclusively identify the presence of the Schiff base.[13]

NMR spectroscopy has not been used to investigate the formation or stability of the thiazolidine ring in aqueous solution. It has already been shown that imine formation in aqueous solution causes α-hydrogen exchange which can be observed by NMR.[18] A similar H–D exchange might occur in D_2O for 2-substituted aliphatic thiazolidines if it were in equilibrium with the open chain tautomer. In addition, if interconversion occurred at a favorable rate, the imine might be observed by NMR line broadening effects. This should be true for both aliphatic and aromatic substituted thiazolidines. If the imine is present at high enough concentrations, the –CH=N proton resonance should be easily identifiable. For aliphatic systems this would be about 7·5 ppm vs TMS[19] and for aromatic systems about 8·3 ppm vs TMS.[20]

EXPERIMENTAL

The NMR spectra were obtained in D_2O (Merck) on a Varian A 60A spectrometer equipped with a variable temp probe. All chemical shifts are reported in ppm relative to TMS as an external reference. A Perkin–Elmer model RMU–6E high resolution spectrometer was used for mass spectra. The microanalytical data were obtained on a Perkin–Elmer 240 Elemental Analyzer.

Materials. All 2-substituted (Ph, cyclohexyl, Me, Et, i-Pr and Pr) thiazolidine-4-carboxylic acids were synthesized from cysteine and the appropriate aldehyde.[21] The solids were recrystallized from EtOH if the NMR spectrum in DMSO-d_6 (Merck) showed any free cysteine. The 2(2-thienyl)-thiazolidine-4-carboxylic acid and thiazolidine-4-carboxylic acid were purchased from Aldrich.

The 2-substituted (Ph, thienyl, and Pr) 5,5-dimethylthiazolidine-4-carboxylic acids were synthesized as follows: One gram of D,L-penicillamine (Aldrich) was added to about 30 ml of hot EtOH. Just enough water was added to dissolve all of the solid. Then about 1 ml of the appropriate aldehyde was added to the soln. Precipitation of the product occurred in about 5 min.

The mercaptals were prepared as follows: cysteine (1g) and either benzaldehyde or 2-thiophene carboxaldehyde (approx 0·5 ml) were placed in 4 M HCl (30 ml) and stirred overnight. NaOH was added until precipitation occurred. The initial product was the mercaptal monohydrochloride. This solid was recrystallized from

20 per cent AcOH and dried in a vacuum dessicator at 60° for 4 h. The mass spectrum of 5-(2-thienyl)-4,6-dithia-1,9-diamino-1,9-nonadioic acid exhibits the first major peak at 291 (P-COOH). Found: C, 39·19; H, 5·01; N, 8·20. Calcd. for $C_{11}H_{17}N_2O_4S_3$: C, 39·26; H, 4·76; N, 8·33; Found: C, 47·26; H, 5·80; N, 8·57. Calcd. for $C_{13}H_{18}N_2O_4S_2$: C, 47·27; H, 5·45; N, 8·48.

5-(2-thienyl)-4,6-dithia-1,9-nonadioic acid and 5-phenyl-4,6-dithia-1,9-nonadioic acid were prepared by adding 3-mercaptopropionic acid (1 ml) and benzaldehyde or 2-thiophene carboxaldehyde (0·5 ml) to 4 M HCl (10 ml). An oil formed within 5 min. After evaporation of the solvent, the oil became crystalline. The solid was recrystallized from a 20 per cent AcOH. Found: C, 42·82; H, 4·87. Calcd. for $C_{11}H_{14}O_4S_3$: C, 43·14; H, 4·58. Found: C, 51·80; H, 5·41. Calcd. for $C_{13}H_{16}O_4S_2$: C, 52·00; H, 5·33.

Thiazolidine formation studies. The appropriate amount of cysteine, penicillamine, or 2-aminoethanethiol and aldehyde to make a 0·5 M soln were added to approx. 0·5 ml of D_2O that was 4 M in HCl in an NMR tube. These spectra were compared to the spectra of the synthesized thiazolidine (except those of 2-aminoethanethiol) compounds in 4 M HCl.

Mercaptal formation studies. Cysteine or 2-aminoethanethiol and benzaldehyde or 2-thiophene carboxaldehyde in 1:1 and 2:1 molar ratios respectively were added in an NMR tube to 0·5 ml of D_2O that was 4 M in HCl to make a soln that was 0·5 M in the thiol. These spectra were compared to those of the synthesized mercaptals in 4 M HCl.

Thiazolidine decomposition studies. All solns were made by dissolving the solid thiazolidine-4-carboxylic acids necessary to make it 0·5 M in D_2O under the following conditions: 8 M HCl, 4 M HCl, neutral (if possible), 0·25 M NaoH (if possible), 0·5 M NaOH, 0·75 M NaOH, 1 M NaOH, and 3 M NaOH. The NMR spectra of the solns were obtained for several days. The spectra of these solns were compared to those of the suspected products under similar conditions.

RESULTS

Reactions in acidic solution. If a 2-substituted aliphatic thiazolidine-4-carboxylic acid or thiazolidine-4-carboxylic is placed in a soln containing up to 8 M HCl, no change in the NMR spectrum with time is observed. If the corresponding aliphatic aldehyde and cysteine are placed in acidic soln, the NMR spectrum eventually becomes identical to that of the corresponding thiazolidine ring compound (12–24 h). Similar results are obtained when 2-substituted aliphatic 5,5-dimethylthiazolidine-4-carboxylic acids or the corresponding aldehyde and penicillamine are placed in acidic soln. If 2-aminoethanethiol is placed in acidic soln with an aliphatic aldehyde, the NMR spectrum eventually shows a multiplet at 5·5–5·9 ppm indicative of the thiazolidine ring structure.

When 2-substituted aromatic thiazolidine-4-carboxylic acids are subjected to strongly acidic conditions, the following changes in the spectrum are observed: all proton resonances of the ring compound begin to disappear and are replaced by new resonances; resonances for the protons at the 4 and 5 position undergo a downfield shift and that at the 2 position and aromatic protons undergo an upfield shift. A peak characteristic of the free aldehyde is observed near 10 ppm. No peaks appear in the new spectrum which are characteristic of free cysteine. If equimolar amounts of aldehyde and cysteine are allowed to react in acidic soln, there is no evidence of cysteine, but some aldehyde remains. If a 2:1 molar ratio of cysteine to aldehyde is used, there is no evidence of either reactant after the reaction is complete. However, dissolving cysteine and an aromatic aldehyde in a 20 per cent acetic acid soln results in the ring compound precipitating from soln. Similar results are obtained when 2-aminoethanethiol and an aromatic aldehyde are placed in a strongly acidic soln.

When a 2-substituted aromatic 5,5-dimethylthiazolidine-4-carboxylic acid is dissolved in acidic soln. no change in the NMR spectrum is observed. If penicillamine and an aromatic aldehyde are subjected to similar conditions, the NMR spectrum eventually becomes identical to that of the ring compound.

Reactions in neutral solution. The aromatic substituted thiazolidine compounds are not soluble enough in neutral solution to observe the NMR spectrum. The aliphatic substituted compounds show no change in the NMR spectrum in neutral soln even after several days.

Reactions in basic solution. In strongly basic solution (>3 M NaOH) the 2-substituted aliphatic thiazolidine-4-carboxylic acids readily decompose into cysteine or penicillamine and the aldehyde. These results are obtained by comparison to the NMR spectra of penicillamine or cysteine and the aldehyde in basic soln. Thiazolidine-4-carboxylic acid does not decompose under these conditions. The NMR spectrum of cystine is sufficiently different from that of cysteine to preclude rapid disulfide formation. In fact, the spectrum of cysteine in 3 M NaOH remains unchanged after two weeks. However if a strong oxidizing agent such as H_2O_2 is added to the soln, the spectrum rapidly changes to that of cystine. Addition of cysteine and isobutyraldehyde to 1–3 M NaOH soln produces decreasing amounts of ring compound with increasing base concentration. In moderately basic soln (0·50–0·75 M NaOH) all spectra of these compounds undergo the following changes: the multiplet representing the proton at the 2-position on the ring collapses into a singlet, the resonance for the α-hydrogens on the aliphatic side chain disappears, the multiplicity of the β-hydrogen resonance is reduced, and general line broadening of all peaks occurs. No loss of protons at the 4-position is observed. This result is illustrated in Fig. 1 for 2-ethylthiazolidine-4-carboxylic acid.

The spectra of 2-substituted aromatic thiazolidine-4-carboxylic acids undergo a series of changes with increasing base concentration. At low base concentrations (0·5–1·0 M NaOH), all peaks undergo line broadening. At somewhat higher base concentrations (1·0–1·5 M NaOH), decomposition begins. At this stage a peak near 8·3 ppm appears in the spectrum. Its initial intensity increases with increasing base concentration. The peak decreases in intensity as the decomposition reaction goes to completion. This peak (b) is shown in Fig 2 for 2-thienylthiazolidine-4-carboxylic acid. The peak representing 2-thiophenecarboxaldehyde (c) increases during the course of thiazolidine decomposition, reaches a maximum, remains constant, and then begins to decrease as the aldehyde is converted to the alcohol and acid by the

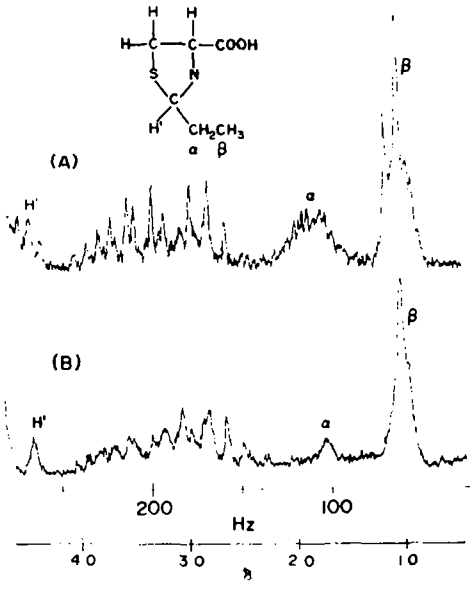

Fig. 1. NMR spectra of 0·5 M 2-ethylthiazolidine-4-carboxylic acid in D_2O and 0·75 M NaOH. (A) Initial spectrum; (B) Spectrum after 24 hr.

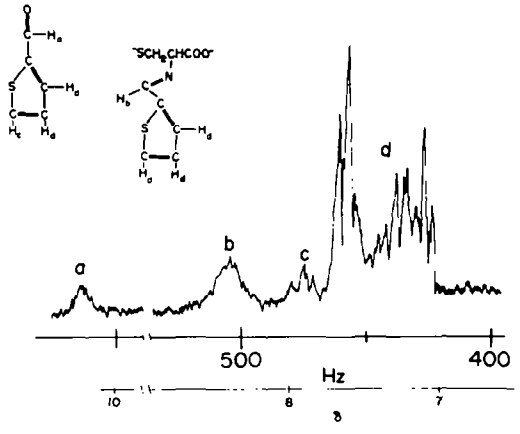

Fig. 2. Partial NMR spectrum of 0·5 M 2-(2-thienyl)thiazolidine-4-carboxylic acid in D_2O and 1·0 M NaOH showing: (a) CH resonance of 2-thiophene carboxaldehyde; (b) imine CH resonance; (c) part of aromatic resonance of 2-thiophene carboxaldehyde; and (d) the remainder of the aromatic resonances.

Cannizarro reaction. At very high base concentrations (>4 M NaOH), the aldehyde peak is never detected. Only resonances for the alcohol and acid appear. Addition of cysteine and an aromatic aldehyde to 1–3 M NaOH produces no evidence of the ring compound, although it appears a small amount of Schiff base is present at 1 M NaOH.

DISCUSSION

The product produced by decomposition of 2-substituted aromatic thiazolidine-4-carboxylic acids and the reaction of cysteine or 2-aminoethanethiol with an aromatic aldehyde in acidic soln can be identified as the mercaptal. Elemental analysis and mass spectral data for the isolated products support this conclusion. Part of the NMR spectra for the product produced by the reaction of benzaldehyde with cysteine and with 3-mercaptopropionic acid (only mercaptal formation is possible) are shown in Fig 3. These spectra show that the

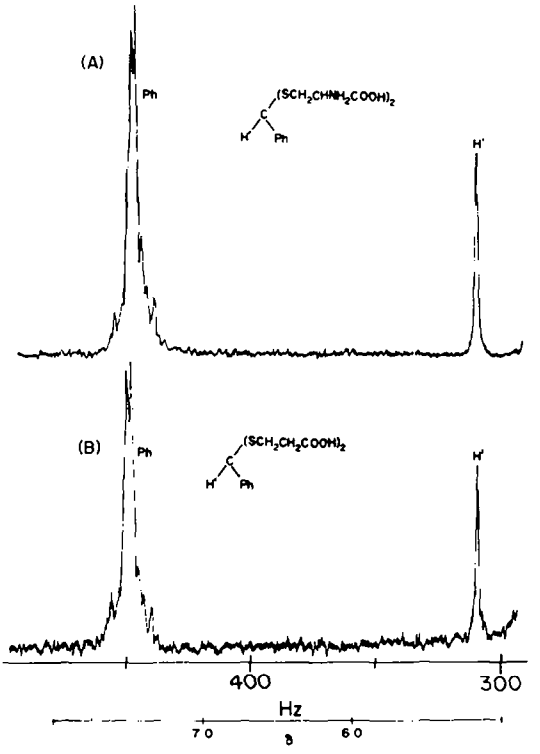

Fig. 3. Partial NMR spectra of the products produced by the reaction of 0·25 M benzaldehyde and 0·5 M cysteine (A) and 0·25 M benzaldehyde and 0·5 M 3-mercaptopropionic acid (B) in 4 M HCl.

resonances for both the aromatic protons and the proton at the S–C–S linkage are almost identical in these two compounds. The other possible product involving a S–C–N linkage should give an NMR spectrum which would be more similar to the thiazolidine compound. The proton resonance at the 2-position in the ring system is shifted upfield by 0·33 ppm from the resonance (H') in Fig 3 and the aromatic resonance is shifted upfield by 0·08 ppm from the aromatic resonance in the ring compound and has a different peak multiplicity.

The data involving reactions in acidic soln suggest the existence of chain tautomerism which includes the presence of the cationic imine. Previous work in thiazolidine formation[10] has shown this to be the most likely intermediate. Mercaptal formation cannot be accounted for by the presence of the cationic imine. The most likely species to produce the mercaptal is the

sulfonium ion (-$^{+}$S=CH-). The fact that these reactions and others previously reported[22] proceed in aromatic systems support the above type of intermediate which would be stabilized by conjugation. Although Kallen[16] has ruled out the presence of sulfonium ion intermediates in thiazolidine formation, it appears that under the proper conditions (highly acidic solns and aromatic adducts) such species can exist. Another possible mechanism is decomposition of the thiazolidine to the aminothiol and aldehyde followed by mercaptal formation (pathway (2), Fig 4). It has already been suggested that this reaction proceeds through a carbonium ion intermediate similar to 4.[23] It might be pointed out that another possibility is the attack of the cationic imine (2) by thiol followed by decomposition to 4 and further attack by thiol to produce the mercaptal. This pathway is also consistent with the reported data. The reaction of penicillamine and aromatic aldehydes in acidic soln to produce a stable thiazolidine indicates that the two Me groups on the C atom adjacent to the thiol sterically prevent mercaptal formation or lead to greater stability of the ring.

The absence of α-hydrogen exchange in aliphatic substituted thiazolidine-4-carboxylic acids does not discount the presence of the imine in acidic soln. In neutral soln α-hydrogen exchange is also not observed. However, addition of a phenylhydrazine precipitates out the aldehyde indicating the presence of chain tautomerism. Kallen has also suggested that the imine intermediate can be found under these conditions. The lack of α-hydrogen exchange may be explained by a smaller fraction of imine present, a reduced exchange rate, or a combination of both such that no loss of the α-proton signal occurs during the time period (3–5 days) that the spectrum is observed. Our results might suggest that the protonated imine (C-=$\overset{+}{N}$H-) does not undergo α-hydrogen exchange, but this conclusion is not supported by the results of a previous study.[17]

The proposed equilibria in acidic soln are summarized in Fig 4. It includes two species which have not previously been suggested in thazolidine formation or the chain tautomerism of thiazolidine in soln. These are the sulfonium ion (4) and the mercaptal (5). 5 is the predominant species when carbonium ion formation is favored (aromatic systems). 3 is the predominant species when carbonium ion formation is not favored or possibly when steric considerations prevent mercaptal formation.

The scheme of Fig 4 is only valid for reasonably acidic solns. When a weakly acidic soln is used (acetic acid-water), the ring structure is favored even for aromatic systems. Therefore, it is probably the fully protonated ring structure 3 rather than the zwitterion that induces sulfonium ion (4) formation which leads to the mercaptal (5).

The aromatic substituted thiazolidine-4-carboxylic acids are formed in weakly basic solution (pH ~ 8). The aliphatic compounds, which are soluble in D_2O, exhibit no change in the NMR spectrum even after several days. This indicates that the ring structure, as predicted by Kallen,[10] is the most favored form. Previous studies that have indicated the aliphatic substituted thiazolidines are

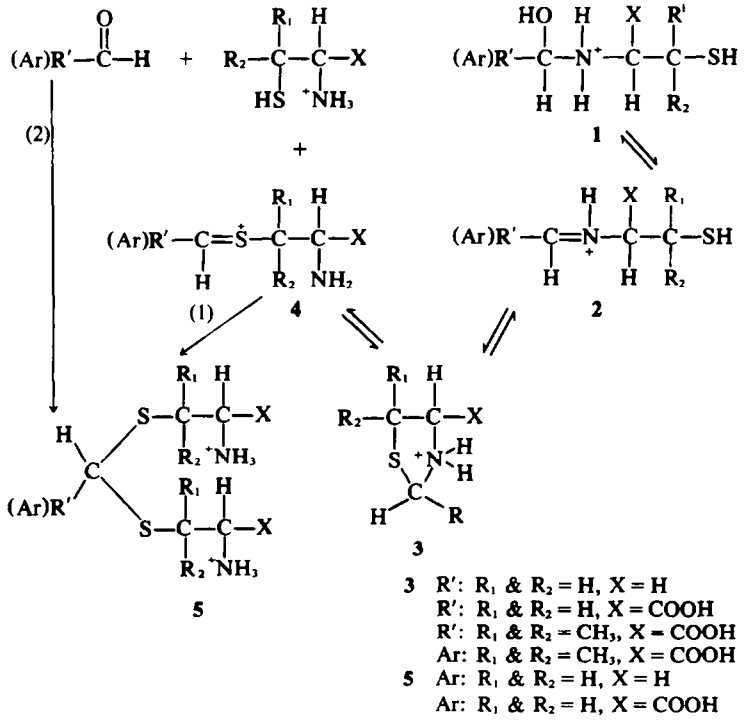

Fig. 4. Equilibria present in acidic solution for thiazolidines.

unstable in soln have merely shifted the equilibrium by addition of phenylhydrazines to precipitate out the carbonyl.[24]

Our results indicate that both 2-substituted aromatic and aliphatic thiazolidine-4-carboxylic acids are unstable in strongly basic soln. Rapid disulfide formation is ruled out because of the long term stability of cysteine under the experimental conditions (Results). Experiments involving the addition of aldehyde and cysteine to basic soln (1–3 M NaOH) also confirm the instability of the thiazolidine ring. Aromatic aldehydes and cysteine show no evidence of ring formation under these conditions. It does appear that a small amount of Schiff base may be formed in the 1 M NaOH soln. The solns were monitored until detectable amounts of alcohol and acid were formed by the Cannizarro reaction. Isobutyraldehyde was chosen for formation studies with cysteine in basic soln because of its resistance to aldol condensation.[25] Under the concentrations employed in the formation experiments isobutyraldehyde is about 30 per cent in the aldol form. The results show that as the concentration of base is increased the extent of ring formation decreases. These results cannot be directly compared with other aliphatic aldehydes that more readily undergo aldol condensation, but can be used to indicate the general instability of 2-substituted alphatic thiazolidine-4-carboxylic acids in the absence of extensive aldol condensation. These results and the fact that thiazolidine-4-carboxylic acid is stable in strongly basic soln are consistent with the formation of adducts to carbonyl compounds. The order of stability is formaldehyde $\gg$ aliphatic aldehydes > aromatic aldehydes.[26,27] Therefore, the equations of Kallen[10] which imply alkaline stability do not apply to 2-substituted thiazolidine-4-carboxylic acids.

Although decomposition of both aromatic and aliphatic substituted thiazolidine-4-carboxylic acids proceeds readily in strongly basic soln, it is in moderately basic soln that direct spectroscopic detection of the imine is possible. Figure 1 illustrates the result of placing an aliphatic substituted thiazolidine-4-carboxylic acid in moderately basic soln. Only an equilibrium between the ring structure and the imine could account for these NMR spectra. The ring structure is the predominant form, but α-hydrogen exchange can only occur in the imine form. Therefore, the chemical shifts represent the ring structure and replacement of the α-hydrogens by deuterium and loss of coupling represent the effect of the imine being present for some small fraction of the time. Figure 5 is the plot of the log of the integral of the α-hydrogen peak vs time for 2-methyl and 2-ethylthiazolidine-4-carboxylic acid. From the slopes the calculated first order rate constants are $7{\cdot}3 \times 10^{-5}$ sec^{-1} and $6{\cdot}0 \times 10^{-5}$ sec^{-1} for the ethyl and methyl substituted thiazolidines respectively. These results are comparable to those reported for α-hydrogen exchange-rates range between $0{\cdot}2 \times 10^{-5}$ and $8{\cdot}9 \times 10^{-5}$ sec^{-1} in imines formed between isobutyraldehyde and various amino acids.[17] Our rates would be expected to be lower because the fraction of imine present (7/7 + 6) is quite small whereas in the previous study there is 100 per cent imine. However, our results were obtained at a

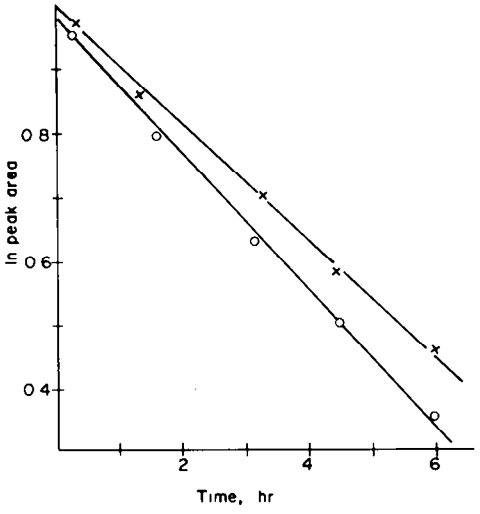

Fig. 5. Log of the peak area for the α-hydrogens vs time for 2-methylthiazolidine-4-carboxylic acid (×), pD = 11·8, and 2-ethylthiazolidine-4-carboxylic acid (0), pD = 12·2.

pH ~ 12 and the other work was done at pH ~ 5. These results are consistent with the previous results that show the rate of H–D exchange is faster at high pH.

For aromatic substituted thiazolidine-4-carboxylic acids in moderately basic soln (0·5–1·0 M NaOH), interconversion between the ring (6) and open form (7) takes place at a rate which can be observed on the NMR time scale. The equilibrium involved is shown in Fig 6. There are no α-hydrogens available for exchange. However, line broadening of the resonance (slow exchange approximation) can be used to determine the average lifetime of the species in soln.[28] A plot of the average lifetime from line broadening of the proton at the 2-position for 2-thienyl and 2-phenylthiazolidine-4-carboxylic acid vs concentration of base is shown in Fig 7. From the slope the interconversion rate (k_1) for both aromatic thiazolidines is 25 M^{-1} sec^{-1}. A lowering of the temperature produces sharper lines as would be expected when the rate of interconversion between 6 and 7 is diminished.

Direct observation of the imine is possible when an aromatic substituted thiazolidine-4-carboxylic acid is placed in somewhat more basic soln. The broad peak for the ArCH=N– proton resonance occurs at a chemical shift that is consistent with those reported for other aromatic imines as neat solns or in nonaqueous solvents[20] and with those which we have observed for more stable aromatic imines in D_2O.[29] Similar peaks at the appropriate chemical shift are not observed for aliphatic substituted thiazolidines. It would be reasonable to expect that the aromatic imine is more stable due to conjugation effects and, therefore, is more readily observable.

The variations in intensity of the imine resonance with increase in base concentration indicates that there is a rapidly established equilibrium between the thiazolidine (6) and the Schiff base (7). The rate expression for change

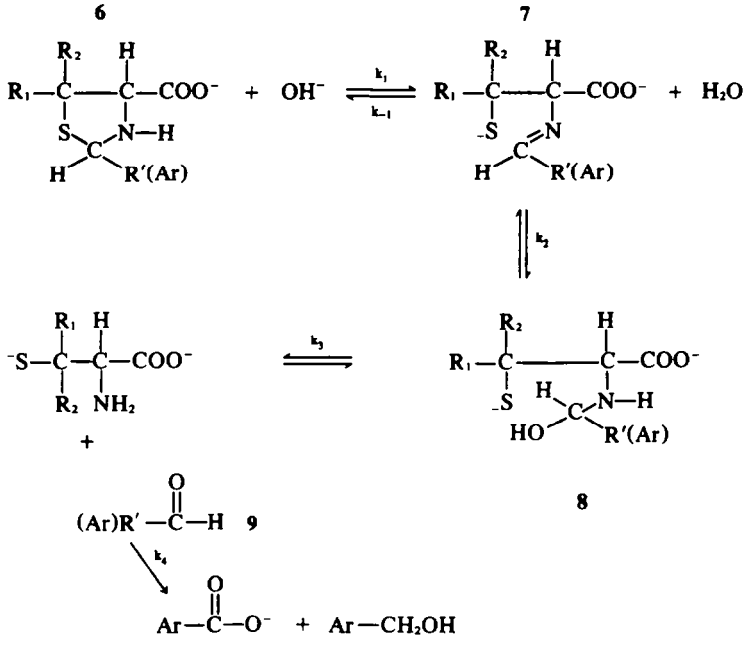

Fig. 6. Equilibria present in basic solution for thiazolidines.

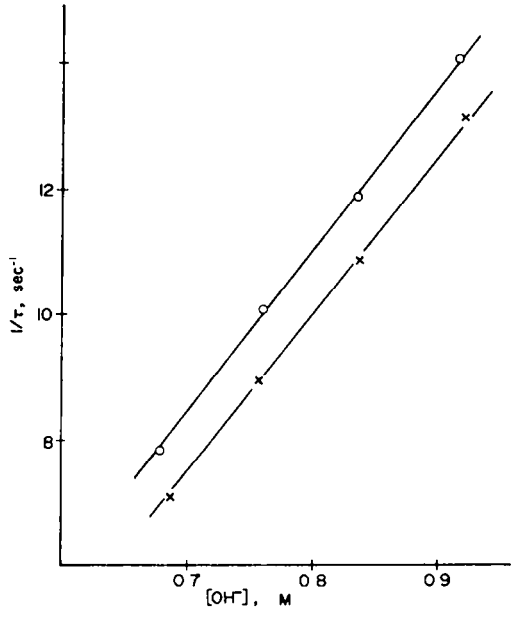

Fig. 7. Average lifetime ($1/\tau$) of proton at 2-position vs base concentration for 2-thienylthiazolidine-4-carboxylic acid (0) and 2-phenylthiazolidine-4-carboxylic acid (×).

in concentration of the imine with time is

$$\frac{d[7]}{dt} = k_1[6] - k_h[7] - k_{-1}[7]. \quad (1)$$

where k_h = rate of hydrolysis of Schiff's base. The term k_h is really composed of three rates. The rates of hydrolysis of the fully protonated Schiff base, the monoanion and the dianion. At the high base concentrations used in the decomposition experiments we can presume that the Schiff base exists in the dianion form. Because the carbinolamine is known to be a short-lived species, i.e. k_3 is very fast, then the rate of hydrolysis is controlled by k_2. However, there is no way to estimate from the available data the values of k_1 and k_{-1}. The rate expression for the change in concentration of the aldehyde with time is

$$\frac{d[9]}{dt} = k_h[7] - k_4[9]^2[OH]^2. \quad (2)$$

The results indicate that during the initial measurement of the aldehyde resonance (c in Fig 2), the hydrolysis term in Eqn (2) controls the increase in the peak. When the intensity becomes constant, the two terms are equal. Finally, as the aldehyde resonance decreases, the second term controls the intensity of the peak. Therefore, a plot of $(d[9]/dt)\cdot(1/[7])$ vs time for the initial points on the curve should yield a constant value equal to k_h. This result is shown in Fig 8. As the second term in Eqn (2) becomes important, the value of $(d[9]/dt)\cdot(1/[7])$ begins to decrease. For the Schiff base formed from the decomposition of 2-thienyl-thiazolidine-4-carboxylic acid the value of k_h is $2{\cdot}2\times10^{-3}$ sec^{-1}. This is comparable to the rates of hydrolysis of Schiff bases formed from benzaldehyde and aliphatic amines which range from $1{\cdot}7\times10^{-2} - 1{\cdot}7\times10^{-1}$ sec^{-1} in basic soln,[30] and a recent study on hydrolysis rates for Schiff bases formed from substituted benzaldehydes

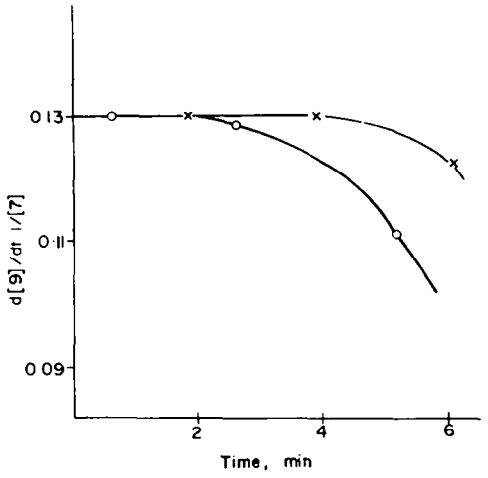

Fig. 8. Plot of d[9]/dt . 1/[7] vs time for 2-thienylthiazolidine-4-carboxylic acid in 2 M (×) and 3 M (0) NaOH.

and substituted benzylamines which reports rates from 5×10^{-5} to 5×10^{-1} sec^{-1}.[31] For very high base concentration, the rate of the Cannizarro reaction is so fast that a resonance for the aldehyde is not observed.

In summary, this work presents the following new results concerning the thiazolidine ring system: (1) In acidic soln, some aromatic thiazolidines decompose to the mercaptal; (2) decomposition in acidic soln probably proceeds through a sulfonium ion intermediate; (3) thiazolidine ring opening to the Schiff base is base catalyzed; (4) indirect spectral evidence for the Schiff base intermediate in basic soln is obtained for aliphatic thiazolidines by α-hydrogen exchange; (5) finally, direct spectral evidence for the Schiff base intermediate in basic soln is obtained for aromatic thiazolidines.

Acknowledgements—The authors would like to thank Drs. David Piatak, Charles Sprangler and John Bendler for their helpful discussions and the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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