Tetrahedron Letters No. 15, pp 1285 - 1288, 1973. Pergamon Press. Printed in Great Britain.

THE EFFECT OF SILVER ION ON THE ALKALINE HYDROLYSIS OF THIAZOLIDINES

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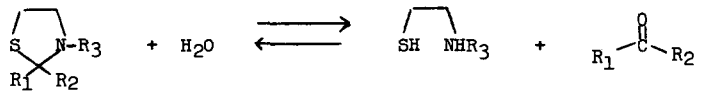
(Received in USA 6 December 1972; received in UK for publication 2 March 1973)

For many years it has been known that thiazolidines are in hydrolytic equilibrium with mercaptoethylamines and the corresponding aldehydes or ketones (1). Although some studies have been carried out on the kinetics of formation of this five-membered heterocycle (1b, 2), we are

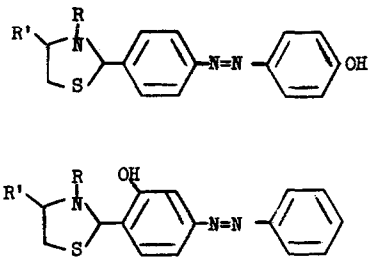


not aware of any detailed reports concerning the rate of the hydrolysis reaction (3).

Some metal ions are known to promote hydrolysis (4), or ring opening of thiazolidines to Schiff bases (5). The analogous benzothiazolines undergo metal ion induced rearrangements and in this heterocyclic series silver ion is one such reagent (6). However, to the best of our knowledge there are no reported cases of silver ion mediated hydrolysis of thiazolidines. Indeed, accounts in the literature involving silver ion and thiazolidines range from a case in which the product is claimed to be a simple silver-complex with thiazolidine-4-carboxylic acid (7), to others in which the products are allegedly thiazolidine sulfoxide and sulfone (8), or unidentified (2a, 9).

We have found that silver ion generally plays a role in effecting the hydrolysis of thiazolidines and that in suitably substituted derivatives the rate is dramatically accelerated by the presence of this metal ion even when it is complexed with a strong ligand like thiosulfate.

Table I shows the results obtained for the pseudo first order reactions. Rates were followed by observing the spectral appearance of aldehyde product with time on a Cary 14 or Durrum-Gibson stopped-flow spectrophotometer. Unless noted otherwise, the initial concentration of thiazolidine in each run was 5×10^{-5} M (10). Ionic strength of the aqueous 0.05 M NaOH solutions was maintained at 1.0 with added $NaClO_4$ and the temperature was constant at $24.95 \pm .05^{o}C$.



Compound	R	R'
I	-H	$-CO_2H$
II	$-CH_3$	$-CO_2H$
III	$-\overset{O}{\overset{\|}{C}}-CH_3$	$-CO_2H$
IV	-H	$-CO_2H$
V	-H	-H
VI	$-(CH_2)_3\ N(C_2H_5)_2$	-H

TABLE I

	Observed k (min^{-1})				
NaOH $Na_2S_2O_3$ AgCl	0.05M ----- -----	0.05M 0.003M ------	0.05M 0.003M 0.001M		Rate Factor (a) -------
Compound					
I	0.00750	0.00660	0.0185		2.8
II	0.000346	0.000322	9.72	(b)	30,000
III	< 0.00000048 (c)	--------	< 0.0000024	(c)	1-6
IV	0.187	0.185	0.436	(d)	2.3
V	1.22	1.23	0.0094	(e)	0.0076
VI	0.0140	0.0140	331	(f)	23,600

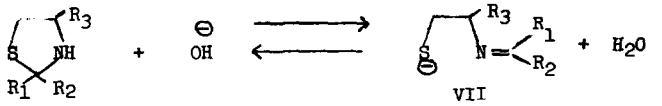
(a) Rate in column three divided by that in column two.
(b) Initial concentration of substrate was 7.5 X 10^{-5} M.
(c) Rate constant was estimated from % reaction after 1.5 months.
(d) Initial concentration of substrate was 2.4 X 10^{-6} M. At higher levels first order plots showed curvature toward faster rates which was shown to be due to formation of cysteine as one of the hydrolysis products.
(e) Heterogeneous. See below.
(f) Initial concentration of substrate was 1 X 10^{-5} M.

As seen from TABLE I the effect of complexed silver ion on the rates varied and in some cases was pronounced, ranging from a 30,000 fold acceleration to substantial retardation; the presence of thiosulfate had little or no effect on rates.

Several interesting structure-rate relationships are available from the unassisted alkaline hydrolysis rates. The most reactive thiazolidines are those with hydrogen on nitrogen (I, IV and V). N-Alkyl substitution led to a 20 - 80 fold decrease in reactivity toward alkali (compare I and II, V and VI), while N-acyl substitution resulted in a compound which was very

resistant toward base, being less than 3% hydrolyzed in a month.

The mechanism for hydrolysis of the N-H thiazolidines is postulated to proceed through a Schiff base intermediate VII which is in a rapid base-dependent equilibrium with thiazolidine. Partial supportive evidence for formation of the intermediate follows (11). Compound I has an initial spectrum in 0.05 M NaOH with λmax 434 nm (ε25,300). Increasing alkali concentration shifts this initial curve until in 1.0 M NaOH the λmax is 443 nm (ε27,300). The model for VII, namely the Schiff base of S-methylcysteine and 4-(4'-hydroxyphenylazo) benzaldehyde



VII

has a λmax at 450 nm (ε29,100) and shows no base dependent spectral shift.

The N-alkyl and N-acyl derivatives, which show no base-dependent spectral shifts, are thought to be more stable because of the less favorable equilibrium to their open-chain cationic Schiff base forms.

With respect to silver ion reactivity the N-alkyl thiazolidines (II and VI) show the largest rate factors (20-30,000). For these compounds the rates with silver ($t_{1/2}$ of 4.3 and 0.125 sec respectively) were very rapid and required stopped-flow techniques. The hydrolysis of N-acyl thiazolidine III is little affected in rate, while the N-H derivatives display only marginal rate enhancement (see I and IV), or marked deceleration as with compound V. As in the unassisted alkaline hydrolyses these latter N-H derivatives gave evidence for intermediate formation. Thus the initial spectrum for I in 0.05 M NaOH has an absorption maximum at 434 nm (ε25,300) but with silver present it appeared at 450 nm (ε28,200). Comparisons of absorption maxima and curve shapes lead us to conclude that the silver-thiosulfate solution led to an intermediate more closely resembling the Schiff base than that obtained in alkali alone.

Presumably the role played by metal ion is to trap intermediate VII present in solution by forming a silver mercaptide salt. The retardation in rate obtained with compound V in alkaline silver-thiosulfate solution is explained on the basis that the intermediate silver salt, lacking the carboxylate group of I and IV, is partly insoluble and subsequent hydrolysis of the Schiff base is slow due to heterogeneity. Indeed, this run was accompanied by a Tyndall effect which cleared with time.

In summary, the alkaline hydrolysis rates of several thiazolidines were found to be affected by the presence of complexed silver chloride. Rate acceleration for suitable substituted

derivatives as high as 30,000 are reported and seem all the more remarkable considering the presence of a strong silver-ion ligand like thiosulfate. Both the unassisted and silver-ion assisted hydrolysis of N-H thiazolidines proceed through an intermediate and evidence in support for a Schiff base structure was cited.

Further work on these and other related compounds is in progress and will be reported on later.

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10. All thiazolidines satisfied C, H, N and S analysis.

11. Current pH-rate profile curves and nmr studies on these and other N-H thiazolidines support this view.