solid was recrystallized from absolute ethanol to give yellow-green needles (67%), mp 136–137°.
(7) Houben-Weyl, "Methoden der Organischen Chemie", Band IX, Georg Thieme Verlag, Stuttgart, 1955, p 944.
(8) H. Bauer, *Ber.*, **46**, 92 (1913).
(9) Reference 7, p 1096.
(10) The potassium selenocyanate used in this preparation was made according to G. R. Waitkins and R. Shutt, *Inorg. Synth.*, **2**, 186 (1946).
(11) D. G. Taster, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 771.

Acid-Catalyzed Hydrolysis of Amidosulfites

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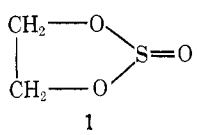
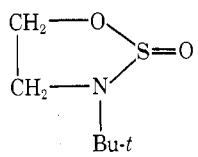
Received September 19, 1974

The mechanisms of the acid-catalyzed hydrolysis of cyclic sulfites, e.g., ethylene sulfite (1), have been studied in some detail.[1] Only recently have successful syntheses been described of the analogous cyclic amidosulfites.[2,3] They hydrolyze in strong acid to the corresponding amino alcohol.[3] We now report the first kinetic study of the acid-catalyzed ring opening of this class of compound on 3-*tert*-butyl-1,2,3-oxathiazolidine 2-oxide (2).



1



2

The rate of hydrolysis of **2** in acid solution at room temperature is much higher than that of **1** and its kinetic behavior had to be studied using stopped-flow spectrophotometry. The first-order rate constants, k_ψ, for the hydrolysis of **2** in aqueous solutions of mineral acids at fairly low acidity (<2 *M*) are shown in Table I. All of the acids studied showed similar catalytic effects at the same molar concentration. This is in marked contrast to the effect of acids on the hydrolyses of **1**. In this latter case the catalytic effect of the acids falls in the order HBr > HCl > $HClO_4$ because ethylene sulfite hydrolyzes by both a bimolecular (A2) and a nucleophilic catalysis mechanism.

Table I
Hydrolysis Rate, k_ψ (sec^{-1}), of 2 in Aqueous Mineral Acids

$HClO_4$ Concn, *M*, at 22°						
0.10	0.20	0.52	0.72	1.04	1.56	2.06
0.59	1.09	2.85	4.36	6.84	11.0	15.4
HCl Concn, *M*, at 22°						
0.10	0.20	0.50	0.70	1.00	1.50	2.00
0.49	1.17	2.92	4.18	6.29	10.7	15.1
HBr Concn, *M*, at 22°						
0.16	0.40	0.56	0.80	0.96	1.20	1.60
0.91	2.37	3.36	5.21	6.40	8.21	12.0
$HClO_4$ (0.52 *M*) at Various Temp, °C						
14.2	21.0	25.0	28.9	33.9	39.7	
1.99	2.85	3.96	4.93	6.39	9.85	

Analysis of the kinetic data for the hydrolysis of **2** shown in Table I in terms of the Bunnett approach[4] leads to a w value of 6.8, suggesting that water is acting both as a nucleophile and a proton transfer agent. The entropy of activation, $\Delta S^\ddagger$ (−19.1 ± 1.4 eu), calculated from the data in Table I also falls in the range associated with a bimolecular rate-determining step.[5]

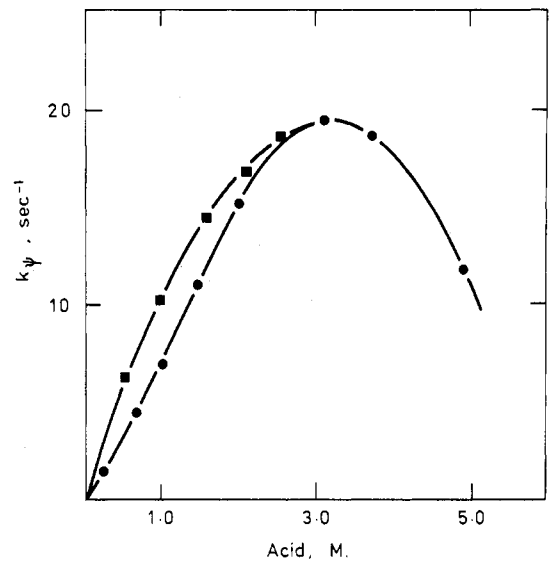
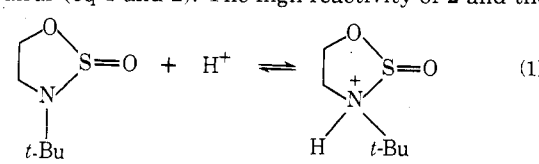


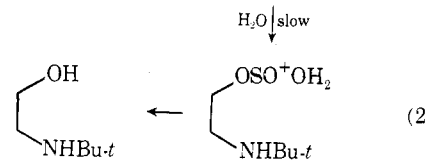
Figure 1. Hydrolysis of **2** in water at 22°: ●, $HClO_4$; ■, $HClO_4$ + $NaClO_4$ (3.0 *M*).

At higher concentrations of perchloric acid (>2 *M*) the rate of hydrolysis of **2** goes through a maximum, as shown in Figure 1. Such rate maxima can arise in two common ways, either as a result of extensive protonation of a basic substrate as in the hydrolysis of amides[6] or the superposition of a specific salt effect on an acid-catalyzed reaction such as observed in the hydrolysis of some sulfites,[7] phosphates,[8] and phosphinates.[9] In mixtures of perchloric acid and sodium perchlorate at constant ionic strength (Figure 1) the rate at first increases linearly with increase in acid concentration and then curves over. Similar behavior has been observed in the hydrolysis of amides and related compounds, e.g., hydroxamic acids, and has been attributed to extensive protonation of the substrate.[10] Such a view is supported by the values of the kinetic solvent isotope effect, $k_1^{D_2O}/k_1^{H_2O}$ (KSIE), which are 1.16, 0.67, and 0.58 at 0.516, 4.26, and 4.61 *M* perchloric acid, respectively (compargd at the same molar concentration of acid). A similar fall of the KSIE with increasing acidity observed for the hydrolysis of amides has been discussed by Bell[11] and Wiberg[12] in terms of the increasing extent of protonation of the substrate and the weaker nucleophilic reactivity of D_2O compared to H_2O.

The kinetic behavior of **2**, in particular the absence of nucleophilic catalysis, the occurrence of a rate maximum, and the high reactivity of **2** in acid solution, contrasts markedly with that of ethylene sulfite and suggests a different mechanism. One possible mechanism consistent with such behavior assumes a rapid preequilibrium protonation of **2** in which protonation is assumed to occur on nitrogen followed by slow rate-determining attack of a water molecule at sulfur (eq 1 and 2). The high reactivity of **2** and the



(1)



(2)

nature of the product are consistent with such a mechanism.

Experimental Section

The *tert*-butyl amidosulfite 2 prepared by the method of Deyrup and Moyer[2] had bp 60–62° (0.4 mm) [lit.[2] bp 70–75° (0.3 mm)]. Kinetics were followed at 276 nm using a Durham-Gibson stopped-flow spectrophotometer. Optical densities were measured on the photograph of the oscilloscope trace and rate constants determined graphically. The values of k_ψ in Table I are the average of several runs at each acid concentration. Average deviation from the mean is less than 5%. Initial concentration of amidosulfite in kinetic runs was ca. 10^{-3} *M*.

Registry No.—2, 18366-45-5.

References and Notes

(1) C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958).
(2) H. Takei, H. Shimizu, M. Higo, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **41**, 1925 (1968).
(3) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).
(4) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).
(5) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).
(6) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).
(7) J. G. Tillett, *J. Chem. Soc.*, 5138 (1960).
(8) C. A. Bunton and S. J. Farber, *J. Org. Chem.*, **34**, 767 (1969).
(9) P. Haake and G. Hurst, *J. Am. Chem. Soc.*, **88**, 2544 (1966).
(10) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(11) R. P. Bell, "Acid Base Catalysis," Oxford University Press, London, 1941.
(12) K. R. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

Sulfur-Containing Polypeptides XVII. The S-Carbomethoxysulfenyl Derivative as a Protective Group for Cysteine[1,2]

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Received July 31, 1974

The synthesis of unsymmetrical disulfides via sulfenylthiocarbonates has been reported by Brois et al.[4] In comparison to sulfenyl thiocyanates or sulfenyl iodides, these derivatives of thiols offer the advantage of often being crystalline, stable molecules that yield carbonyl sulfide, methanol, and the disulfide when treated with thiols. Recently,

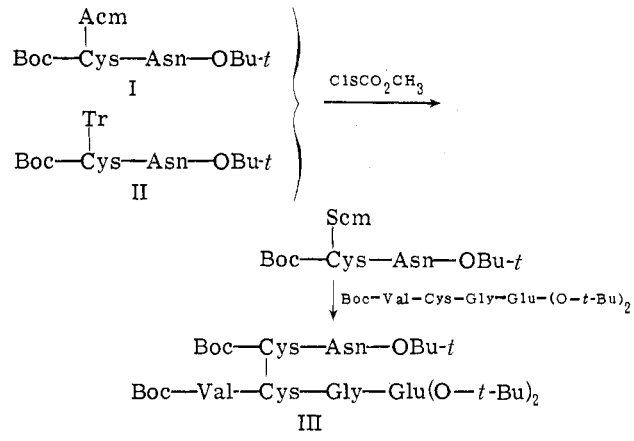
$$R'\text{—}S\text{—}X \xrightarrow{ClSCO_2CH_3} R'\text{—}S\text{—}S\text{—}CO_2CH_3 \xrightarrow{RSH} R'\text{—}S\text{—}S\text{—}R + COS + CH_3OH$$

X = H, Tr, Bzh, Bzl, Acm

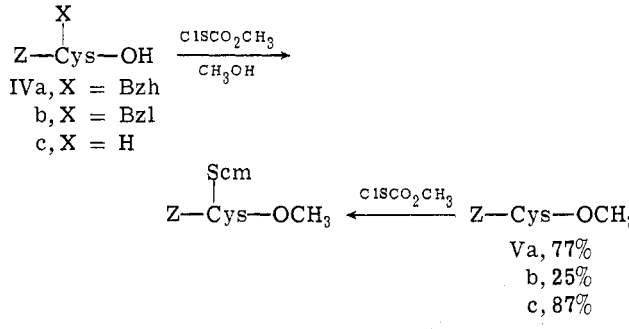
Kamber[5] has shown not only that carbomethoxysulfenyl chloride can be utilized to convert cysteine to the intermediate *S*-carbomethoxysulfenyl derivative[6] but also that the *S*-trityl and *S*-acetamidomethyl derivatives are cleaved by the sulfenyl chloride. Kamber also utilized the method to prepare fully protected open-chain cystine derivatives as illustrated by the conversion of I or II to III.

The present report concerns our studies with the *S*-carbomethoxysulfenyl (Scm) group; these experiments establish that the group is stable to many of the conditions employed for deblocking and coupling operations used in peptide synthesis. Thus, the Scm group can serve as an S-protective group as well as a labile intermediate useful for the selective conversion of a cysteine residue to cystine in the late stage of a synthesis.

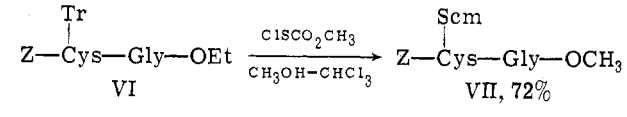
Our preliminary experiments established that the *S*-benzhydryl, *S*-trityl, and (in low yield) the *S*-benzyl



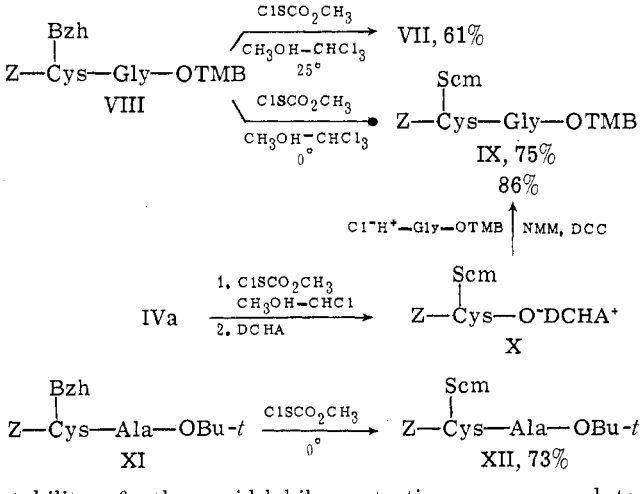
thioethers of cysteine could be converted to the corresponding Scm derivative. However, these experiments also



indicated that esterification of free carboxyl groups or transesterification were potential problems. A study of conditions designed to circumvent this problem indicated that esterification or ester interchange could be avoided by conducting the reaction at 0° or by the addition of calcium carbonate to the reaction mixture.[7] The preparation of the di-



peptides IX and XII (both containing acid-labile ester groups) as well as the salt of the carboxylic acid, X, indicated that the undesirable reactions could be suppressed. The



stability of other acid-labile protective groups, used to block certain side-chain functionalities in peptides, toward carbomethoxysulfenyl chloride was indicated by the conversion of the octapeptide derivative (XVIII) to the corresponding Scm peptide (XIX).

The fact that coupling reactions could be successfully conducted in the presence of the Scm group without cleav-