Kinetics and Mechanism of the Hydrolysis of 2-Chloroethyl Sulfides

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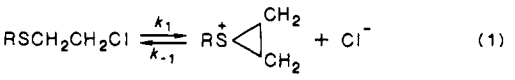
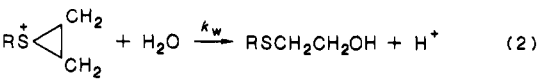
The hydrolysis of 2-chloroethyl sulfides approaches an S_N1 mechanism only under limiting conditions where the substrate is predissolved in an organic solvent prior to addition to water and the concentration is kept below 0.001 M. At greater substrate concentrations the kinetics are complicated by the formation of dimeric sulfonium chloride salts. These salts are formed in pure water, in buffered aqueous solution at pH 10, and in binary acetone–water solutions. The sulfonium chlorides are relatively stable and decompose via an S_N2 mechanism. One pathway includes the reversible formation of the initial sulfide substrate. This reaction presumably accounts for the recurring toxicity of mustard (2,2′-dichlorodiethyl sulfide) in humans and in the natural environment. The presence of a powerful nucleophile such as thiosulfate can effectively capture the transient ethylenesulfonium ion intermediate formed during the initial step of hydrolysis. All dimeric sulfonium chloride salts are eliminated from the solution in the presence of thiosulfate anion, and the observed rate of the displacement reaction at 0.1–0.2 M substrate is equivalent to that measured for the limiting S_N1 mechanism at a substrate concentration below 0.001 M.

Introduction

The kinetics and mechanism of the hydrolysis of mustard ($S(CH_2CH_2Cl)_2$) and its monochloro derivatives ($RSCH_2CH_2Cl$, R = CH_2CH_2OH, CH_3, C_2H_5) have been extensively investigated in a number of fundamental studies.[1-4] These studies have confirmed that the first step is the formation of a transient cyclic sulfonium cation via the intramolecular assistance of the neighboring sulfur (eq 1); the cation then reacts quickly with water to form 2-



(1)



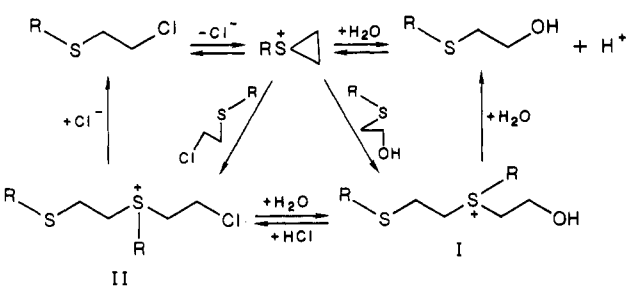
(2)

$$k_{obsd} = k_1\left(\frac{k_w}{k_{-1}[Cl^-] + k_w}\right) \quad (3)$$

hydroxyethyl sulfide ($RSCH_2CH_2OH$) and H^+ (eq 2). By application of a steady-state approximation on the concentration of the short-lived ethylenesulfonium ion intermediate, the observed rate is related to the rate coefficients in eq 1 and 2 according to eq 3. The following limiting controls are necessary to ensure pure first-order kinetics such that k_{obsd} in eq 3 equals k_1: the sulfide is predissolved in a polar, organic solvent, and its concentration is kept low in solution, so that the rate of the reverse reaction ($k_{-1}[Cl^{-1}]$) becomes negligible compared to k_w.

At greater substrate concentrations in the absence of any organic solvent, however, both dissolution and reaction take place simultaneously. As reported in a previous paper,[5] the initial product, $RSCH_2CH_2OH$, from reaction with water accumulated in the aqueous phase and reacted with the ethylenesulfonium cation to form a dimeric sulfonium cation (I, $(RSCH_2CH_2)S^+(R)(CH_2CH_2OH)$), shown in Scheme I), which was identified by NMR for R = C_2H_5 and mustard.

Scheme I



II I

Table I. Reaction Half-lives for the Disappearance of CEES at 20 °C

solvent	substrate concn, M	products	$t_{1/2}$, min
water	4×10^{-4}	HEES and HCl	1.4[a]
water	3×10^{-4} and 0.05 M NaCl	HEES and HCl	2.7[b]
50 vol % acetone	4×10^{-4}	HEES and HCl	14[a]
50 vol % acetone	3×10^{-4} and 0.05 M NaCl	HEES and HCl	132[b]
50 vol % acetone	0.17	I, II, HEES, and HCl	42[c,d]
50 vol % acetone	0.17 and 0.2 M $Na_2S_2O_3$	$C_2H_5SC_2H_4S_2O_3Na$ and NaCl	13[d]

[a] Reference 4. [b] Reference 7. [c] Apparent first-order rate assumed. [d] Rate was followed by NMR.

In this study, we will demonstrate that both the sulfide substrate and the sulfide products are strong nucleophiles which react with the ethylenesulfonium ion intermediate to form additional products, resulting in a complex hydrolysis mechanism consisting of the reversible transformations shown in Scheme I. The reaction of 0.17 M sulfide substrate in acetone–water mixtures will be monitored by NMR techniques, so that the kinetics depicted in Scheme I can be compared with rates previously measured conductometrically for low concentrations.[4] We will show by NMR that a strong nucleophile, Y^-, added to the reaction mixture can quickly capture all the ethylenesulfonium ion to form only one stable sulfide product, $RSCH_2CH_2Y$, and simplify the reaction to first-order kinetics. In addition, we will investigate the subsequent and slow decomposition reactions of I and II ($(RSCH_2CH_2)S^+(R)(CH_2CH_2Cl)$), shown in Scheme I) in acidic and basic solutions. Three sulfide substrates (R = CH_3, C_2H_5, and C_2H_4Cl) will be used to further demonstrate their common hydrolysis behavior.

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(2) Yang, Y.-C.; Ward, J. R.; Wilson, R. B.; Burrows, W.; Winterle, J. S. *Thermochim. Acta* **1987**, *114*, 313–317.
(3) McManus, S. P.; Neamati-Mazraeh, N.; Hovanes, B. A.; Paley, M. S.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3393–3395.
(4) Yang, Y.-C.; Ward, J. R.; Luteran, T. *J. Org. Chem.* **1986**, *51*, 2756–2759.
(5) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Ward, J. R. *J. Org. Chem.* **1987**, *52*, 1637–1638.

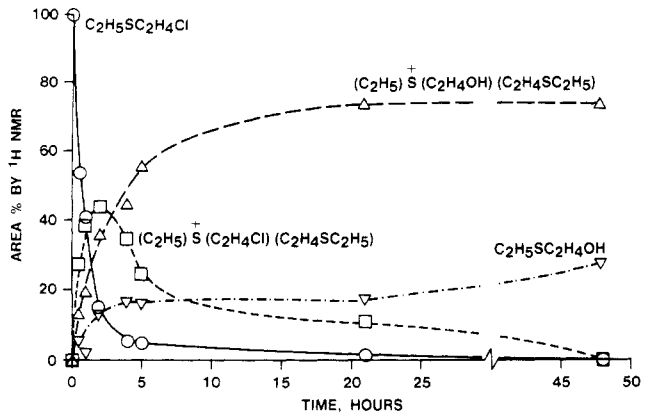

Figure 1. Hydrolysis of CEES in 50 vol % $(CD_3)_2CO$–water at 20 °C.

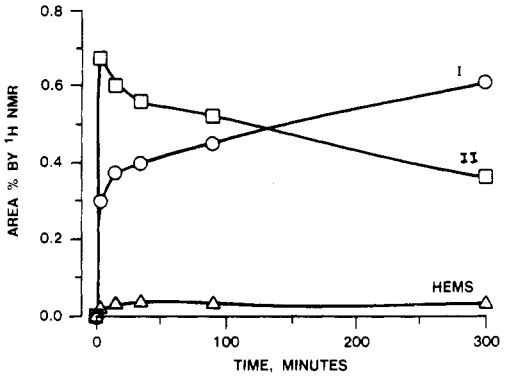

Figure 2. Dissolution and hydrolysis of 0.2 M CEMS in water at 20 °C.

Results and Discussion

(1) Reaction Products and Rates. Observed first-order rate coefficients for the disappearance of 2-chloroethyl ethyl sulfide (CEES, R = C_2H_5) over a large range of concentrations are expressed in half-lives and listed in Table I. The effects of the polarity of the solvent system, chloride ion, and substrate concentration on the observed rate are isolated and compared. At substrate concentrations below 0.001 M,[6] the rate was measured previously by monitoring the generation of H^+ conductometrically,[4] or with a pH-Stat method when chloride was added.[7] The presence of 50 vol % acetone reduced the first-order rate coefficient, k_1, to 10% of its value in pure water.[4] Added chloride ion at 0.05 M retarded the rate about 50% in pure water and as much as 90% in the acetone–water mixture.[7] On the basis of these rates and eq 3, the competition factor[1] of the chloride ion against water, k_{-1}/k_w, for reacting with the cyclic ethylenesulfonium ion intermediate was calculated before; it was 20 M^{-1} in water and 197 M^{-1} in 50% acetone at 0.05 M ionic strength.[7] At 0.17 M substrate, however, not only is the chloride ion effect significant, but the kinetics are also complicated by the formation of I and II. In the homogeneous system of 0.17 M CEES in a 50 vol % $(CD_3)_2CO$–water mixture shown in Figure 1, three products were detected by ^{1}H NMR: I, II, and a small amount of 2-hydroxyethyl ethyl sulfide (HEES). II was a reaction intermediate, which subsequently hydrolyzed to form I. Since CEES primarily reacted with itself, the rate followed that of a second-order rate equation very well (i.e., $-d[CEES]/dt = k_2[CEES]^2$), with a k_2 value of 5.51 × 10^{-3} s^{-1} M^{-1} at 20 °C. For the purpose of comparison, the reported half-life in Table I was based on fitting the same data to a first-order rate equation with a 10% error in the resulting k_{obsd}.

As shown in Table I, in the presence of a far more powerful nucleophile than water or any of the sulfides in the reaction mixture, e.g., $S_2O_3^{2-}$ (with a previously reported competition factor of 27 000 M^{-1} for mustard hydrolysis),[8] the reaction rate clearly became first-order, and only two stable salt products, $C_2H_5SC_2H_4S_2O_3Na$ and NaCl, were formed. For mustard, both chlorines were replaced to form one organic compound $(NaS_2O_3C_2H_4)_2S$. The NMR parameters of these thiosulfate esters can be found in the Experimental Section.

If Y is an added nucleophile that also reacts with the ethylenesulfonium ion intermediate shown in eq 2, a derivation similar to that of eq 3 results in eq 4, which shows that although k_{obsd} remains close to k_1 and is independent of Y at low chloride ion concentrations, it becomes smaller than k_1 as the chloride concentration increases, unless sufficient Y with a large k_y value is present so that $k_y[Y]$ is significantly greater than $k_{-1}[Cl^-]$.

$$k_{obsd} = k_1\left(\frac{k_w + k_y[Y]}{k_{-1}[Cl^-] + k_w + k_y[Y]}\right) \quad (4)$$

The thiosulfate anion not only competes effectively with the sulfide substrate and water, completely eliminating the formation of I, II, and HEES, but also overcomes the rate-inhibiting effect of the chloride ion. Thus, the observed rate approaches that measured for 0.001 M substrate in the absence of any added chloride ion. The agreement shown in Table I is remarkable since the rates measured by pH-Stat were determined for ideally dilute solutions under precise temperature controls. However, it is important to point out that Y does not affect the absolute k_1 value, which is controlled by the solvent polarity only.[4]

Similar product profiles were observed in both pure water and buffer solutions of the sulfide at about 0.2 M total concentration, which were initially two phases, and in which both dissolution and reaction occurred simultaneously. The composition in the top aqueous phase of each mixture was monitored by ^{1}H NMR from time 0 until the sample became one phase,[9] after which time the resulting solution was continually monitored for up to 30 h. No sulfide substrate was ever detected in the aqueous phase in any of the samples, indicating that the concentration of the sulfide dissolved in water had been less than the detection limit of the ^{1}H NMR (about 0.005–0.01 M). We believe this is due to both the small solubility of the sulfide

(6) The limiting substrate concentration under which the sulfide converts stoichiometrically to H^+ was determined: In a pure water solution, 0.001 M $^{13}CH_3SCH_2CH_2Cl$ at 99% ^{13}C enrichment was added and reacted. The ^{13}C NMR data of the final reaction mixture were accumulated for 18 h to determine if compound I were present. The spectrum had three peaks representing 10.6 mol % $(^{13}CH_3SC_2H_4)S^+(^{13}CH_3)(C_2H_4OH)$ and 89.4 mol % $^{13}CH_3SCH_2CH_2OH$. This showed that only 90% of the sulfide produced H^+. These results will be discussed in a separate publication.

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(8) Ogston, A. G.; Holiday, E. R.; Philpot, J. St. L.; Stochen, L. A. *Trans. Faraday Soc.* **1948**, *44*, 45–52.

(9) Determined by making a material balance so that the initial sulfide was accounted for by the sum of the amounts of all the components in the aqueous phase. Separately, the organic phase of a CEES sample in contact with water was monitored by GC/MS for weeks to detect any change in its composition. As the CEES phase dissolved and reacted with water, it remained 100% pure until the CEES completely disappeared into the aqueous phase.

Table II. NMR Parameters of $RSCH_2CH_2Cl$ and Its Hydrolysis Products

	^{13}C NMR parameters[a]				^1H NMR parameters[b]			
R = CH_3	CEMS[c]	II	I	HEMS	CEMS[c,d]	II	I	HEMS
CH_3S	15.8	14.1	14.1	14.2	2.00 (s)	2.19 (s)	2.18 (s)	2.11 (s)
CH_3S^+		22.9	23.1			3.03 (s)	3.00 (s)	
SCH_2CH_2	36.4	27.2	27.2	36.4	2.68 (t)	3.04 (t)	3.04 (t)	2.67 (t)
$^+SCH_2CH_2$		44.7	44.9			3.5–3.9 (t)	3.5–3.9 (t)	
SCH_2CH_2	43.1	42.2	42.1	59.8	3.52 (t)	3.5–3.9 (t)	3.5–3.9 (t)	3.75 (t)
$^+SCH_2CH_2$		37.7	56.2			3.5–3.9 (t)	4.09 (t)	
	^{13}C NMR parameters[a]				^1H NMR parameters[b]			
R = C_2H_5	CEES	II	I	HEES	CEES	II	I	HEES
CH_3CH_2S	17.1	17.1	16.7	17.1	1.21 (t)	1.24 (t)	1.24 (t)	1.21 (t)
$CH_3CH_2S^+$		11.2	11.2			1.56 (t)	1.53 (t)	
CH_3CH_2S	28.1	28.2	28.2	28.2	2.7 (q)	2.7 (q)	2.7 (q)	2.56 (q)
$CH_3CH_2S^+$		37.8	37.5			3.60 (q)	3.53 (q)	
SCH_2CH_2	36.1	28.2	28.2	35.8	2.88 (t)	3.12 (t)	3.09 (t)	2.7 (t)
$^+SCH_2CH_2$		45.2	45.2			3.7–3.8 (t)	3.7–3.8 (t)	
SCH_2CH_2	46.4	41.1	42.9	63.6	3.83[e] (t)	3.7–3.8 (t)	3.7–3.8 (t)	4.1 (t)
$^+SCH_2CH_2$		43.3	59.0			3.97[e] (t)	4.2 (t)	

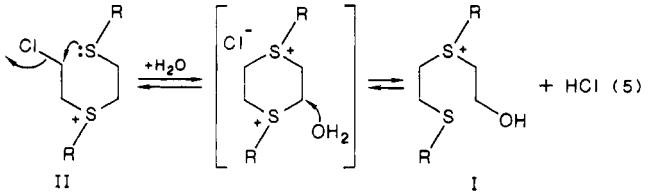
	^{13}C NMR parameters[a]				^1H NMR parameters[b]			
R = C_2H_4Cl	H[f]	CH-TG	H-2TG	TG	H[f]	CH-TG	H-2TG	TG
SCH_2CH_2Cl	35.8				2.92			
SCH_2CH_2Cl	45.0				3.69			
SCH_2CH_2OH		36.3		36.2		2.74		2.66
SCH_2CH_2OH		63.2		63.2		3.6–3.7		3.60
$^+SCH_2CH_2OH$		46.4	46.4			3.6–3.75	3.63	
$^+SCH_2CH_2OH$		59.0	59.0			4.01	4.01	
$SCH_2CH_2S^+$		28.6	28.6			2.96	3.11	
$SCH_2CH_2S^+$		44.2	43.8			3.6–3.7	3.75	

R = C_2H_4OH	^{13}C NMR parameters:[a] CH[g]
SCH_2CH_2Cl	37.7[e]
SCH_2CH_2Cl	47.0
SCH_2CH_2OH	38.1[e]
SCH_2CH_2OH	65.3

[a] Chemical shifts relative to external TSP; solvent = H_2O. [b] Chemical shifts relative to internal TSP; solvent = H_2O for R = CH_3 and C_2H_4Cl; solvent = 50% $(CD_3)_2CO$ in water for R = C_2H_5. Also, s = singlet, t = triplet, q = quartet. [c] Solvent = none. [d] Chemical shift relative to external TSP–D_2O. [e] Assignments may be reversed. [f] H is mustard; solvent = none; ^{13}C chemical shifts relative to external TMS; ^1H chemical shifts relative to internal TMS; all ^1H resonances are triplets. [g] CH is mustard chlorohydrin; solvent = acetone; chemical shifts relative to external TSP.

in water and the fact that the reaction rate was faster than the rate of solution. As shown in Figure 2, three products, I, II (R = CH_3), and a small amount of 2-hydroxyethyl methyl sulfide (HEMS), were formed in the 0.2 M 2-chloroethyl methyl sulfide (CEMS)–water mixture, which became one phase after about 40 min.

Both Figures 1 and 2 show that II was initially the primary product which then converted to I directly. We propose that this may be accomplished by an intramolecular attack of the bivalent sulfur in II to form a transient dithiane disulfonium ion intermediate with a six-membered ring structure, followed by attack of water at any of the four cyclic CH_2 groups (see eq 5).



II I

In the 0.17 M CEES–water and CEES–buffer mixtures, only compound I and HEES were found in the aqueous phase. Although II could not be identified, this may have resulted from overlapping ^1H signals of the methyl groups in I and II. Furthermore, CEES presumably has a lower solubility than CEMS; and the concentration of II in the above solutions is smaller than in the CEMS solution. In the presence of OH^- in the buffer solution, although HEES at 0.03 M was the only product in the aqueous phase for the first 30 min, compound I subsequently started to form from reaction of CEES with HEES. A maximum concentration of I of 0.06 M (36% of the total CEES) was reached in the solution at 24 h. This shows that even in the 0.5 M carbonate buffer of 1×10^{-4} M hydroxide ion, which has a reported competition factor of 8000 M^{-1} for mustard hydrolysis,[8] formation of the dimeric sulfonium salts cannot be completely prevented.

In summary, as hydrolysis occurs, both the sulfide substrate and the sulfide product are strong nucleophiles that react with the same cyclic ethylenesulfonium ion intermediate to form additional products. Table II summarizes both the ^1H and ^{13}C NMR shifts of the compounds identified.

(2) Hydrolysis of I. Compound I was stable in both the above acidic and basic solutions for at least 1 day. It slowly hydrolyzed via an S_N2 mechanism to form 2 mol of $RSCH_2CH_2OH$ and 1 mol of HCl at a rate dependent on the hydroxide ion concentration.[10,11] In the pH 10 buffer, the observed first-order rate coefficient for hydrolysis of I (R = C_2H_5) was 2.01×10^{-6} s^{-1} at 20 °C, corresponding to a second-order rate constant of 2.01×10^{-2} s^{-1} M^{-1}. In pure water, however, the hydrolysis of I did not fit a first-order rate equation because H^+ was being produced with time. After about 4 months, there was still 10 mol % of I left in solution, and an equilibrium among I, HEES,

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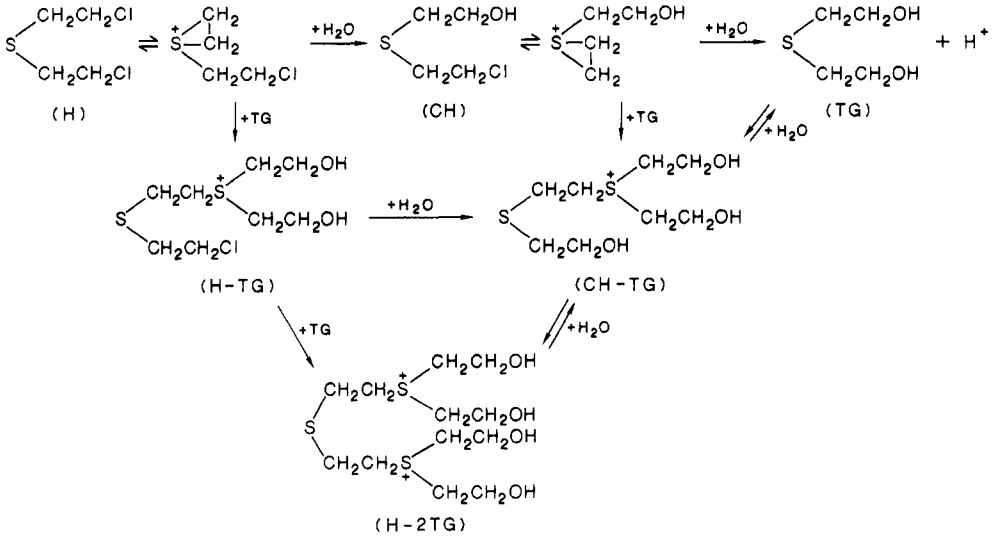
Scheme II



and HCl appeared to have been reached, which is discussed below.

(3) Formation of I from Protonated $RSCH_2CH_2OH$. In solutions containing $RSCH_2CH_2OH$ and excess HCl at 4 M concentration, all of the 2-hydroxyethyl sulfide was slowly converted to compound I for R = CH_3 and C_2H_5 at 20 °C. The dimerization mechanism of $RSCH_2CH_2OH$ including protonation followed by dehydration is also proposed in Scheme I. The rate data on the disappearance of HEMS during the first 100 h (80% completion of the reaction) fit a second-order rate equation very well, with a k_2 value of 3.38×10^{-6} s^{-1} M^{-1} at 20 °C. Similarly the k_2 obtained for HEES was 3.97×10^{-6} s^{-1} M^{-1} from the rate data up to 60% reaction. The rate-determining step may also be the formation of the cyclic ethylenesulfonium cation as dehydration took place.

Beyond 80% reaction for HEMS and 60% for HEES, additional reactions of I and HEES were suspected, because the observed rate of the disappearance of $RSCH_2CH_2OH$ increased and that line broadening of the groups adjacent to the bivalent sulfur was observed in both the ^{13}C and ^1H NMR spectra of I in the final solution. One possibility might be the formation of a trimer, $RS(CH_2CH_2S^+R)_2CH_2CH_2OH$, from reaction of I with the cyclic ethylenesulfonium ion as I becomes the primary nucleophile in the mixture.

In protonated thiodiglycol (TG, R = CH_2CH_2OH) solutions, the two sulfonium salts, $HOCH_2CH_2SCH_2CH_2S^+(CH_2CH_2OH)_2$ (CH-TG) and $S(CH_2CH_2S^+(CH_2CH_2OH)_2)_2$ (H-2TG), which are shown in Scheme II for mustard–water mixtures and were identified previously,[5] were produced. CH-TG started to form first, and subsequently a small amount of H-2TG was detected. Therefore, we have also provided direct evidence for the reverse reactions shown in Scheme II, in which the forward reactions of mustard with water were proposed by Bergmann and co-workers[12] 40 years ago.

(4) Thermal Decomposition of I. As water was being evaporated from the final acidic (HCl) solution at room temperature under vacuum, I (R = C_2H_5) decomposed slowly (in days) to form CEES and HEES, perhaps partially via the formation of II, which was then attacked by Cl^- to form 2 mol of CEES (see the reverse reaction of eq 5 and Scheme I). Similarly, when a sample of the final acidic solution containing I was analyzed by gas chromatography (GC), compound I decomposed in the GC injection port and on the column: two major products, CEES and HEES, were observed for R = C_2H_5; and three major products, H, CH, and TG, were observed from a mixture of CH-TG and H-2TG salts (see Scheme II).

At atmospheric pressure with heating to about 90 °C, I (R = C_2H_5) decomposes quickly to form an organic layer containing three major compounds: $RSCH_2CH_2Cl$, $(RSCH_2CH_2)_2O$, and $RSCH_2CH_2SR$ at molar ratios of 2:1:1 (GC/MS was used to confirm the NMR identification of the above compounds). This shows that I decomposes via a number of different paths. In fact, any of the three carbons adjacent to S^+ can be attacked by any of the nucleophiles in the solution. It also shows that, at elevated temperatures, mustard is not likely to be produced from the direct substitution of the two hydroxyl groups in TG by two chlorines, as was reported in the literature in the past,[13,14] but rather from the decomposition of the intermediate sulfonium salts, CH-TG and H-2TG, which form readily from TG in concentrated HCl solutions. Indeed, a number of recent publications[15-17] on the synthesis of these (alkylthio)ethyl halides from their corresponding hydroxide derivatives have all overlooked the presence of the dimers as reaction intermediates.

(5) Formation of Sulfonium Aggregates in Pure and Concentrated $RSCH_2CH_2Cl$. For accurate rate measurements, it is important to point out that I also forms slowly in the pure sulfide substrate as it ages, and in solutions of the sulfide in organic solvents. After acquiring ^{13}C NMR scans for over 18 h, a trace amount of I was detected in pure CEMS that had been stored for about a year at ambient conditions. We believe that the dimerization and subsequent hydrolysis reactions shown in eq 5 also occur in the pure sulfides, although at much slower rates than in aqueous solutions. Consistently, 1,4-dithiane was identified as a common thermal degradation product in a number of aged 2-chloroethyl sulfide samples in a separate study.[18] Significant dimerization also occurred

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(17) Trujillo, D. A.; McMahon, W. A.; Lyle, R. E. *J. Org. Chem.* **1987**, *52*, 2932–2933.

in a 2% stock solution of CEMS in acetone, which had been stored at 5 °C in a refrigerator for about 3 months. Similarly, McManus and co-workers[19] recently noted that their previous rate data for (methylthio)ethyl tosylate were inaccurate because dimerization had occurred in their stock solution using $CDCl_3$ as the solvent.

Recently, Sunko and co-workers[20] measured only 50% of the theoretical $[H^+]$ in the hydrolysis of (methylthio)-ethyl halides in binary solvent mixtures of very low water content. We repeated their synthesis of the (methylthio)ethyl iodide and found that the compound contained 50% dimers, which may account for the loss of 50% $[H^+]$ in their data. Within a few days the compound degraded further to a tar-like material. It is conceivable that, in these pure or very concentrated solutions (including both aqueous and organic solvents), I and II may continue to react as nucleophiles with the substrate to form trimers, which in turn form the next higher aggregates of the general formula of an *n*-mer, $RS(CH_2CH_2S^+R)_{n-1}CH_2CH_2X$ (X = OH or Cl), thus resulting in a chain reaction until all of the substrate is reacted.

On the basis of the above, the reaction mechanism proposed in Scheme I has been proven. We believe I and II (and perhaps their higher aggregates in more concentrated solutions) are the key compounds in the reversible and complex transformations of the 2-chloroethyl sulfides in aqueous solutions and are likely to be responsible for the recurring toxicity of mustard in humans and in the natural environment.[21] The physiological effects and toxicities of a series of the above sulfonium salts need to be investigated,[12] particularly since the proposed cell-poisoning mechanism of mustard in humans is based on the simplified S_N1 hydrolysis mechanism and is not fully understood.[13] The recent use of mustard in the Iran–Iraq War[22] makes it clear that there is an urgent need in seeking effective cures for mustard burns and in improving our knowledge of the toxic effects of mustard.

Experimental Section

Materials. Vacuum-distilled mustard was used. **WARNING:** Mustard (H) is a potent vesicant and must be handled in a closed system or in a hood with a minimum velocity of 100 ft/min. The mustard derivatives $CH_3SC_2H_4Cl$ (CEMS) and $C_2H_5SC_2H_4Cl$ (CEES) and their hydroxy analogues, $CH_3SC_2H_4OH$ (HEMS) and $C_2H_5SC_2H_4OH$ (HEES), as well as $S(C_2H_4OH)_2$ (thiodiglycol or TG) were doubly vacuum distilled products from Fairfield Chemical Co. Acetone-d_6 (99.5% D) was used as received from Norell Chemical Co. The pH 10 buffer solution was composed of 0.25 M HCO_3^{2-} and 0.25 M CO_3^{2-}. HPLC grade acetone and doubly distilled, deionized water were used for the preparation of all solutions.

Nuclear Magnetic Resonance (NMR) Experiments. The NMR spectra were recorded by using a Varian XL-200 superconducting FTNMR system operating at 50 MHz for ^{13}C spectra and at 200 MHz for ^1H spectra. In all cases, the spectra were recorded at probe temperature (ca. 20 °C) and were referenced either internally or externally to TSP, sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4. The accuracies of the reported chemical shift values (δ) are ±0.1 ppm for ^{13}C and ±0.05 ppm for ^1H. Quantitative data were obtained from the digital integration of the peak areas of interest. The ^{13}C NMR spectra were accumulated with the following parameters: pulse width = 3–5 μs (31–45°); sweep width = 12 kHz; acquisition time = 1.25–2.7 s; and pulse delay = 2.0–3.5 s. The number of transients varied for each experiment depending on the signal-to-noise ratios required or desired; and, in all cases, WALTZ decoupling was used. The ^1H NMR spectra were accumulated with the following parameters: pulse width = 3 μs (30°); sweep width = 4 kHz; acquisition time = 3.75 s; and pulse delay = 10.0 s.

(1) Dissolution and Hydrolysis Studies. One milliliter of doubly distilled water or buffer solution at pH 10 was placed in a 5 mm o.d. Pyrex NMR tube to which 20 μL of CEMS or CEES was added. The sample was capped, wrapped with Parafilm, and periodically shaken vigorously to dissolve the sulfide. Between shakings, ^1H NMR spectra of the solution were recorded with the automatic intensity mode of the spectrometer. Quantitative data were obtained by digital integration of the methyl region of the spectrum as a function of time. The spectrometer had previously been tuned to a D_2O–TSP sample, and the spectra were run unlocked since there was no deuterium in the sample and only four transients were required. Due to the heterogeneous nature of the samples during dissolution, the data obtained have ±(10–15)% accuracy. After the 2-chloroethyl sulfide had completely dissolved and the sample was one phase,[9] the precision of the quantitation increased to ±(3–5)%.

The slow hydrolysis of I was monitored by ^{13}C and/or ^1H NMR until almost all of I was hydrolyzed to form HEES and HCl. Concentrations in area % for both I and HEES were determined by the average of the separate digital integrations of the OCH_2 and SCH_2 resonances in the ^{13}C spectrum and are of ±(5–7)% accuracy. Alternately, the CH_3 region in the ^1H spectrum was used to determine the amounts of I and HEES present.

For a typical rate measurement, 20 μL of CEES was added to 1.0 mL of a solution of 50% acetone-d_6 and 50% distilled water (by volume), which was contained in a 5 mm o.d. Pyrex NMR tube. The tube was shaken so that the sample became homogeneous before analysis started. The disappearance of CEES and the formation of products were monitored by ^1H NMR. The deuteriated acetone was the lock solvent, and the quantitative data from integration of the CH_3 peaks have an accuracy of ±(2–3)%.

Sodium thiosulfate solutions of 0.7 M in water were used to repeat the above dissolution and hydrolysis studies for both CEES and mustard. In the acetone–water mixture, however, the concentration of $Na_2S_2O_3$ was reduced to 0.2 M to keep the solvent system one phase. Only one organic product was detected by NMR during reaction; it did not react further when it was subsequently monitored for 3 months in the same solution. $CH_3CH_2SCH_2CH_2S_2O_3^-$: ^{13}C NMR (H_2O, external TSP–D_2O) 16.8 (CH_3), 27.7 (CH_3CH_2S), 32.9 ($SCH_2CH_2S_2O_3^-$), and 37.3 ppm ($SCH_2CH_2S_2O_3^-$); ^1H NMR (4.8 ppm std HDO) (in the same order) 1.35 (t, 3 H, J = 7.4 Hz), 2.75 (q, 2 H, J = 7.4 Hz), 3.09 (t, 2 H, $J \approx$ 7.4 Hz), and 3.43 ppm (t, 2 H, $J \approx$ 7.4 Hz). The ^{13}C shifts (H_2O, external TSP–D_2O) for the product from mustard ($^-O_3S_2CH_2CH_2SCH_2CH_2S_2O_3^-$) are 37.5 ($^-O_3S_2CH_2$) and 33.4 ppm ($CH_2S$).

(2) NMR Kinetic Runs of Protonated $RSCH_2CH_2OH$ Reactions. Equal volumes (0.2 mL) of $RSCH_2CH_2OH$ (R = CH_3, C_2H_5, or C_2H_4OH), distilled water, and concentrated hydrochloric acid (38%) were placed in a 5 mm o.d. Pyrex NMR tube, and the tube was shaken to mix the three components. The composition of the sample was monitored by ^1H NMR with time until all of the initial $RSCH_2CH_2OH$ was reacted. ^{13}C NMR spectroscopy was used to confirm the structures of the sulfonium chloride salts formed.

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