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Mechanistic Insights into the Hydrolysis of 2-Chloroethyl Ethyl Sulfide: The Expanded Roles of Sulfonium Salts

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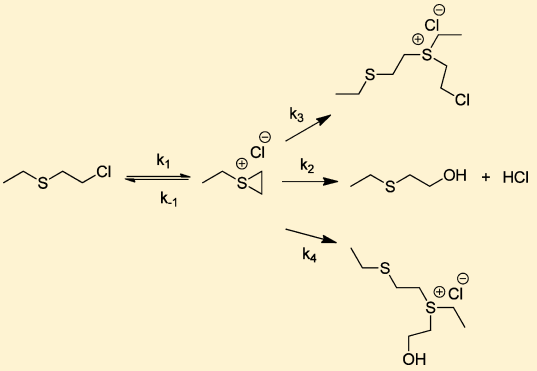
Supporting Information

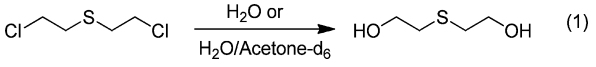
ABSTRACT: The hydrolysis of 2-chloroethyl ethyl sulfide has been examined in an effort to better understand its mechanism under more concentrated conditions. Two salts formed during hydrolysis were synthesized, and an emphasis was placed on determining their effect on the reaction as it proceeded. Unexpected changes in mechanism were seen when excess chloride was added to the reaction. By measuring rates and product distributions as the products were added back into the hydrolysis, a mechanism was developed. The formation of these sulfonium salts represents additional products in the disappearance of 2-chloroethyl ethyl sulfide with k_3 in particular causing a deviation away from expected first-order behavior. Sulfonium salts **3** and **4** do not appear to interconvert, and the system as a whole had fewer pathways available than previously proposed. Initial conditions for studying the hydrolysis were very important and could lead to different conclusions depending on the conditions used. This work will aid in better understanding the hydrolysis of the very toxic chemical warfare agent mustard (bis(2-chloroethyl)sulfide) in the environment and during its decontamination.



INTRODUCTION

The topic of mustard (bis(2-chloroethyl)sulfide) hydrolysis reaches back to the work of Hopkins in 1919.[1] In subsequent years numerous publications exploring this topic have been published.[2−19] In spite of all this work, the mechanism of mustard hydrolysis remains elusive. Last year alone, another 105 publications on facets of mustard chemistry were added to ChemAbstracts, and current world events demonstrate the continued relevance of mustard.

Our interest arose from experiments in our laboratory that continued to suggest the pathway of hydrolysis was more complicated than reported (eq 1).



(1)

Previous reports indicated a stepwise mechanism at concentrations below 0.001 M resulting in a sequential reaction and first-order decay.[7] When we raised concentrations slightly (Figure 1), these decays began to deviate, indicating the likelihood of greater mechanistic complexity, a fact that seems to have been lost over time since it was clearly stated as early as 1923 by Peters and Walker.[20]

Described herein is a more in depth study of the hydrolysis of 2-chloroethyl ethyl sulfide (CEES), a molecule often used as a model compound for mustard.[18,21−27] 2-Chloroethyl ethyl sulfide was chosen because as the concentration of mustard (bis(2-chloroethyl)sulfide) was increased, the number of products identified became intractable as mustard reacted with itself and other hydrolysis products, forming no less than seven identified compounds. 2-Chloroethyl ethyl sulfide yielded only two sulfonium salts and one organic product, greatly simplifying the identification and monitoring of the reaction. Previous work by McManus and co-workers[11−15,17] using 2-chloroethyl ethyl sulfide or 2-chloroethyl methyl sulfide was primarily focused on probes to assess nucleophilic solvent

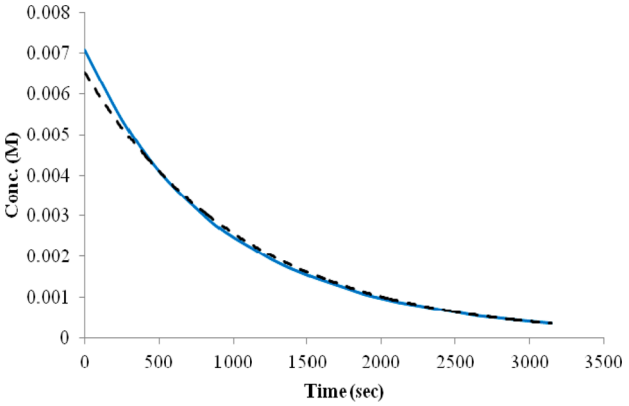


Figure 1. Plot of 0.007 M mustard vs time in 80% D_2O/acetone-d_6. The dashed line indicates the a first-order fit ($f(x) = ae^{bx}$).

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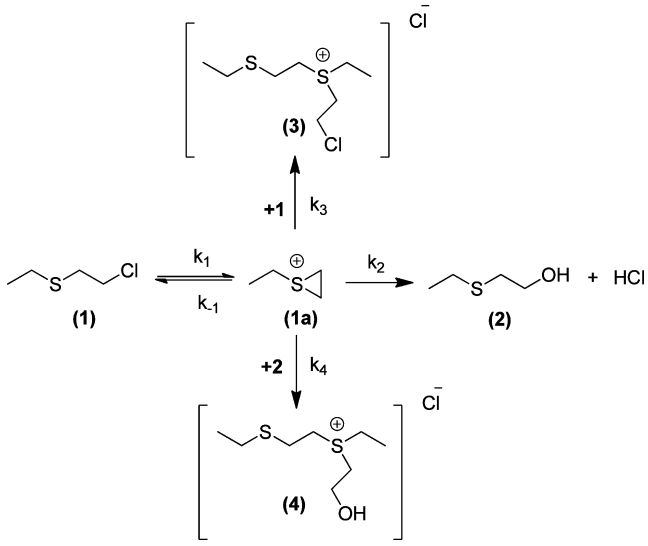
assistance. The mustards used were often more involved structures meant to examine a particular topic regarding solvent assistance and not necessarily the hydrolysis itself. The concentrations used in these studies (0.001 M or less) did not produce enough sulfonium salts, in their conclusions, to be an important factor in their rate measurements.[16] We have now measured the concentrations of these sulfonium salts at 0.001 M and agree that they do not seem to be an influence on the first-order decay observed for 2-chloroethyl ethyl sulfide at these concentrations.[28] Work by Yang and co-workers[8−10] sought to extend this work to higher concentrations, and ultimately an S_N1 mechanism was proposed for the hydrolysis of 2-chloroethyl ethyl sulfide, and an S_N2 mechanism was proposed for the hydrolysis of the sulfonium salts formed as concentrations were increased.[10] This work relied on two basic concentrations of 2-chloroethyl ethyl sulfide. The first was concentrations in the 10^{-4} M range, where agreement was found with the long history on the subject. The second was at 0.17−0.2 M 2-chloroethyl ethyl sulfide, a large increase with no supporting data to support that any of the conclusions from far more dilute work were applicable at these higher concentrations. Solutions of 0.17 M 2-chloroethyl ethyl sulfide in 1:1 water/acetone, the conditions most commonly reported, are not homogeneous, bringing into question how any product concentrations were measured during the course of these reactions. No internal standards were reported being employed in the ^{1}H and ^{13}C NMR work, and periodically shaking samples until homogeneous, as was reported, makes the measurement of rates impossible. From our efforts to confirm the actual products of hydrolysis, we found that the efficiency of stirring, not surprisingly, would change the time needed for homogeneity, thereby changing the rates at which CEES was disappearing. Given this, and the importance of knowing concentrations of species during kinetics, we do not feel that any conclusions in this work are valid, and a reinvestigation was necessary, as this paper has become the most directly referenced work on the subject of mustard hydrolysis.

Knowing the fate of mustard type compounds in the environment and during their decontamination is still valuable, and a better mechanistic understanding of their hydrolysis behavior is crucial and necessary. While we found no disagreement with long-standing work at dilute concentrations (0.001 M or 0.12 mg CEES/ml), this work does not represent realistic real world concentrations of mustard, and that is why we have focused on the more difficult higher concentrations of 2-chloroethyl ethyl sulfide. The Results and Discussion section will describe studies that led to our mechanistic hypothesis for this seemingly simple hydrolysis. The importance of various products, especially the formation of dimeric salts and the addition of excess chloride during the hydrolysis, in the overall path and rate of CEES disappearance is presented. All the reactions were homogeneous unlike previous work, and conclusions differ in a number of important ways that will be highlighted.

RESULTS AND DISCUSSION

1. Hydrolysis Product Identification and Synthesis. Four concentrations (0.02, 0.01, 0.001, and 0.0001 M) of **1** were allowed to hydrolyze in water and 1:1 water/acetone to confirm product formation. Hydrolysis was deemed "complete" in water when the rapidly stirred heterogeneous mixtures became homogeneous. At this point, LC−MS analysis was performed. Molecule **1** is virtually insoluble in water even at levels of 1 mg/mL (0.008 M), making the use of a cosolvent necessary for rate studies to be homogeneous throughout. To verify that the products formed with acetone (cosolvent) were the same as with water, the same concentrations of **1** were allowed to stir for 30 min in 1:1 water/acetone followed by LC−MS analysis. The products formed are shown in Scheme 1. Figure 2 shows a representative LC−MS chromatogram for the water and 1:1 water/acetone reactions.

Scheme 1



Molecules **2**−**4** have been reported previously as products of CEES hydrolysis, but **3** and **4** had not been isolated.[9] Reaction of **1** with **2** at a concentration of at least 0.65 M of each in water resulted in ethyl(2-(ethylthio)ethyl)(2-hydroxyethyl)sulfonium chloride (**4**), the sole byproduct being a small amount of **2**. Purification could be accomplished on silica gel yielding a product virtually devoid of **2**. Reaction of **4** in CH_3CN with thionyl chloride gave (2-chloroethyl)(ethyl)(2-(ethylthio)-ethyl) sulfonium chloride (**3**), the sole byproduct being 5−10% of **1**. Attempts to purify **3** were not successful because of its inherent instability. Compound **3** decomposed further to **1** when placed onto silica gel for purification and was therefore used as originally isolated.

Having all three products of the reaction available, a careful review of the ^{1}H NMR spectra from hydrolysis reactions was carried out to confirm the results of LC−MS analysis. Molecules **2**−**4** were spiked into 0.02 M hydrolysis reactions to confirm assignments and look for extraneous unassigned peaks, and a J-resolved spectrum on a reaction of 0.02 M CEES in 1:1 D_2O/acetone-d_6 showed only the reactant and the three identified products from Scheme 1. The synthesis and isolation of sulfonium salts **3** and **4** allowed for the first detailed examination of their role during the hydrolysis of **1**.

1.1. Kinetics: General Practice. The disappearance of **1** (t, 2.78 ppm) during the hydrolysis was monitored using ^{1}H NMR spectroscopy. Formation of **2** (q, 2.44), **3** (m, 3.79), and **4** (t, 1.39) was correlated with the disappearance of **1**. The shifts remained constant as the D_2O to acetone-d_6 ratios were changed throughout the study. All NMR experiments were run using D_2O and acetone-d_6, while the $Na^{35}Cl$ experiments and initial rates studies used H_2O and acetone. No rate differences were observed between D_2O and H_2O. An internal standard of

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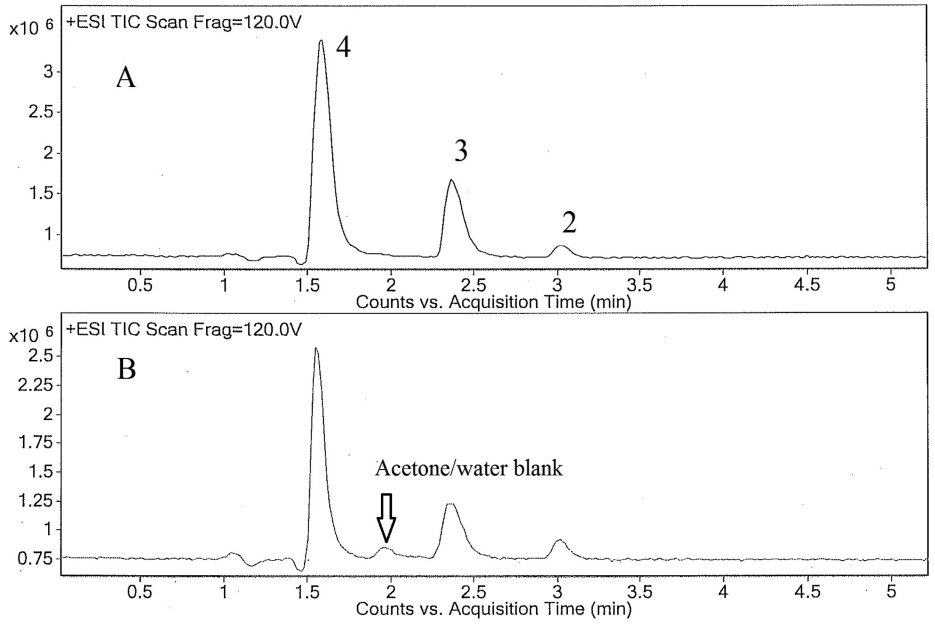

Figure 2. LC−MS total ion chromatograms of (A) 0.02 M CEES in H_2O, (B) 0.02 M CEES in 1:1 H_2O/acetone.

either methylene chloride or *p*-xylene was used depending on the length and composition of the run for ^{1}H NMR. All data are the result of a minimum of 3 independent experimental runs.

2. Kinetics: Effects of Varying Water Concentrations and the Concentration of 1. The questions we set out to investigate were as follows. (1) The lack of first-order behavior observed in our experiments as concentrations of **1** were increased; why were the kinetics becoming more complex? On the basis of the widely proposed S_N1 mechanism for mustard hydrolysis,[11−13,15,16,29−33] the formation of **1a** (Scheme 1) should have been rate-controlling and independent of nucleophile concentration giving a first-order decay. (2) Could a better understanding of water's influence on the reaction be obtained?[34−41] Two different concentrations of water had been used in the two most cited references. The first[7] was investigated at mustard derivative concentrations of 0.001 M in 95% water/acetone. Our investigation mostly agreed with these results. The second suggested more complicated kinetics above 0.001 M **1** but relied on heterogeneous reactions, and only one concentration of water, to extrapolate these results to represent the hydrolysis of **1** as a whole. A large body of work exists on solvolysis and the role of solvents and nucleophiles in S_N1 reactions.[42−53] It is not our intent to review this work. The focus will be on the reaction of **1** in water and acetone, the factors that are influencing the decays observed, and how they differ or contradict the most cited source on this topic; this relates most closely to the hydrolysis of mustard in the environment and during its decontamination.

The most cited reference[10] on the hydrolysis of CEES used primarily one concentration of water throughout. Water in a hydrolysis reaction is both solvent and nucleophile (albeit in large excess), and the proposed S_N1 mechanism for CEES hydrolysis should be first-order regardless of the water concentration, as its addition is not rate-controlling. To see what effect changing the concentration of water (in this case for ^{1}H NMR D_2O) would have on the rate and product distribution of CEES hydrolysis, three concentrations of D_2O were used, 40, 60, and 80% v/v with acetone-d_6 as the cosolvent for solubility (22.3, 33.5, and 44.7 M D_2O, respectively).

Observing the disappearance of 0.02 M **1** under pseudo-first-order conditions (Figure 3) in 80% D_2O showed an exponential decay consistent with the proposed first-order reaction.

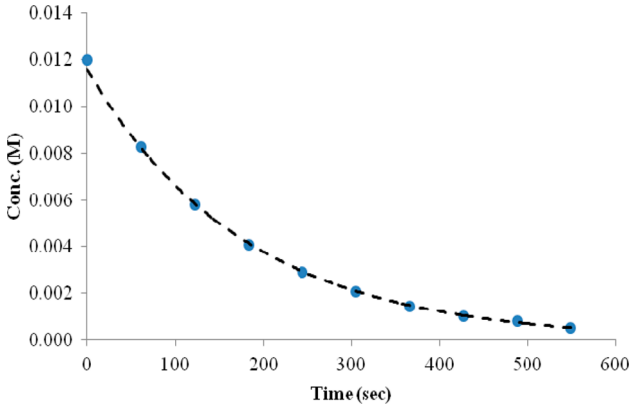

Figure 3. Plot showing 0.02 M **1** vs time in 80% D_2O/acetone-d_6 fit to $f(x) = ae^{bx}$ with $k_{obs} = 5.62 \times 10^{-3}$ s^{-1}.

When the reaction was repeated in 60% D_2O, the disappearance of **1** began to deviate slightly away from a first-order fit (Figure 4).

Finally, running the same concentration of **1** in 40% D_2O shows the disappearance of **1** not only has now slowed further, but also is clearly exhibiting unconventional behaviors (Figure 5).

Decreasing the concentration of **1** to 0.01 M did not change the time needed to observe four half-lives as compared to 0.02 M. Concentrations higher than 0.02 M **1** were investigated, but solubility limitations at higher D_2O concentrations became problematic, as did mass balance issues. Evidence was seen for higher oligomers of salts **3** and **4** when analyzed by LC−MS. These were very difficult to distinguish from **3** and **4** and are

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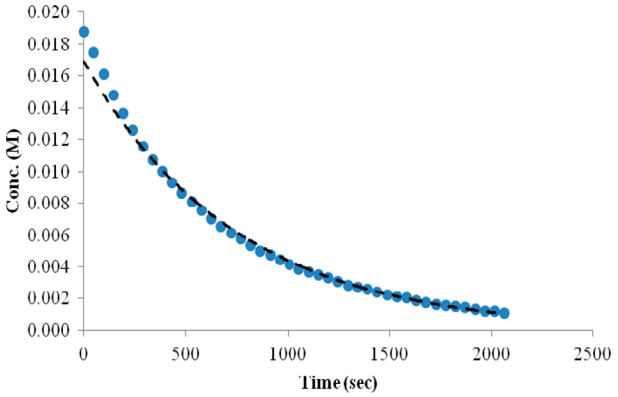

Figure 4. Plot showing 0.02 M **1** vs time in 60% D_2O/acetone-d_6. The dashed line shows the first-order fit ($f(x) = ae^{bx}$).

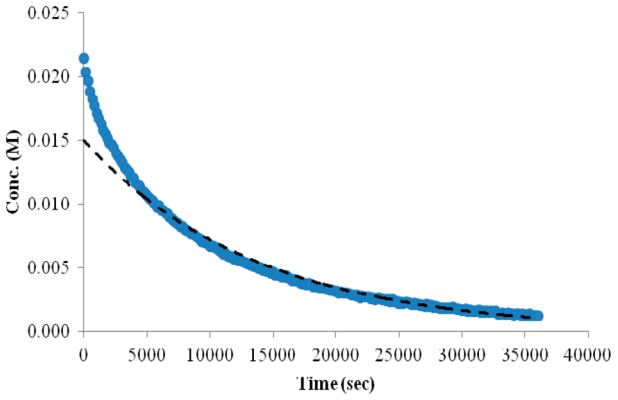

Figure 5. Plot showing 0.02 M **1** vs time in 40% D_2O/acetone-d_6. The dashed line shows the first-order fit ($f(x) = ae^{bx}$).

outside the context of the present report. As the concentration of D_2O was reduced, successive half-lives during the hydrolysis became increasingly longer, but the product distribution of **2**–**4** at the end of the hydrolysis remained relatively constant across all D_2O concentrations examined (Table 1).

Table 1. Product Distribution (by %) for 1–4 after Four Half-Lives of 0.02 M 1 in 40–80% D_2O/Acetone-d_6

% D_2O	1	2	3	4	time (s) 4 half-lives
40	6	65	4	25	35 000
60	5	63	11	22	2 000
80	2	61	15	23	500

The fact that product distributions remained constant while the disappearance of **1** varied over a 70-fold time range showed that k_2, k_3, and k_4 (Scheme 1) stayed constant relative to each other regardless of reaction conditions. This suggested that formation of **2**–**4** was post rate-controlling and that the concentration of D_2O was having a general medium effect on the formation of **1a**, as all concentrations of water give pseudo-first-order conditions with the D_2O concentration essentially constant. A first-order decay of **1** would be expected, but what is actually observed is a system that fits neither a first-order nor a second-order reaction. The deviation away from this first-order behavior must then be the result of one or more of the products or their formation influencing the reaction.

2.1. Initial Rates during the Hydrolysis of 1. The medium effect of D_2O seemed responsible for setting the rate of formation of **1a** by k_1 and should have meant that the rate of hydrolysis should be independent of the initial concentration of **1**. This was not true as the initial concentration of **1** at a given water concentration was the determining factor in how long the hydrolysis needed to reach four half-lives. As the concentration of **1** was increased (Table 2), the time needed to reach 4 half-lives increased.

Table 2. Time Needed to Reach Four Half-Lives of Conversion for Differing Starting Concentrations of 1 in 40 and 60% D_2O/Acetone-d_6

initial conc. **1**	40% (22.3 M)	60% (33.5 M)
0.01	30 000	2 000
0.02	35 000	2 000
0.04	55 000	3 500
0.06	72 000	5 500

Yang and co-workers stated that to ensure pure first-order kinetics, the sulfide concentration **1** needed to be kept low in solution so that the rate of the reverse reaction k_{-1} would become negligible compared to k_2. This implies that at higher concentrations of **1**, the rate of formation of **1a** would be different, and therefore the formation of **1a** is no longer an intramolecular process. Even if at higher concentrations other products start forming other than **2** (and in this case sulfonium salts **3** and **4**), the formation of **1a** should be unaffected unless these products start to alter k_1 and/or k_{-1}. To demonstrate that the value of k_1 is at least initially determined by the concentration of water and is constant across varying concentrations of **1**, a series of initial rate studies were carried out (Figures 6–8).

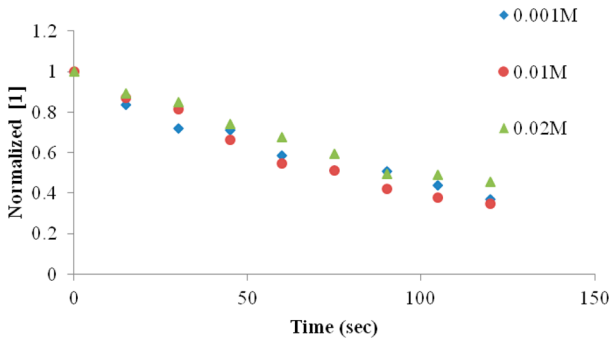

Figure 6. Plot of normalized [**1**] vs time for 0.001, 0.01, and 0.02 M **1** in 80% H_2O/acetone.

The initial rate of disappearance of **1** is equal for a given water concentration regardless of the starting concentration of **1**. Keeping the concentration of **1** low does not, as Yang and co-workers suggest, have any influence on the formation of **1a** by k_1. The slowing in the rate of disappearance of **1** as the reaction proceeds is a result of one or more of the products of the reaction altering k_1 or k_{-1}, as at the end of four half-lives, the ratio of products **2**–**4** is equal in differing water concentrations as long as the starting concentration of **1** is constant (Table 1).

3. Role of Chloride in the Overall Mechanism of Hydrolysis. *3.1. Buffered Hydrolysis: Role of HCl during Hydrolysis.* Yang and co-workers had run the hydrolysis reaction buffered to observe what effect the removal of HCl had on the course of hydrolysis. We examined this hydrolysis

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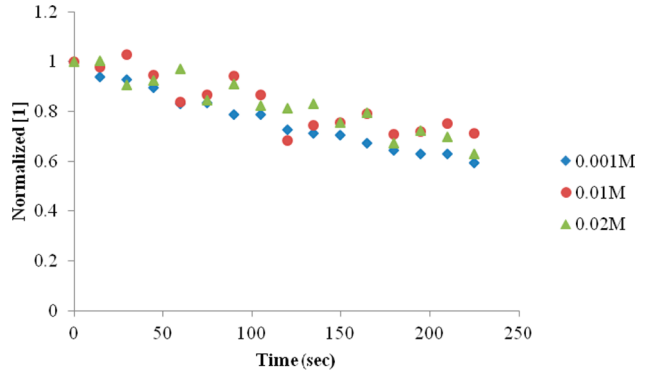


Figure 7. Plot of normalized [**1**] vs time for 0.001, 0.01, and 0.02 M **1** in 60% H_2O/acetone.

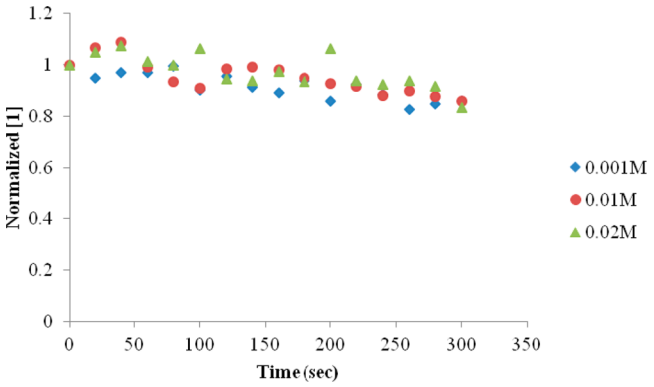


Figure 8. Plot of normalized [**1**] vs time for 0.001, 0.01, and 0.02 M **1** in 40% H_2O/acetone.

more carefully. When the reaction was buffered with sodium bicarbonate/sodium carbonate at a pH of 9.8, a first-order decay was observed (Figure 9). Under these conditions the

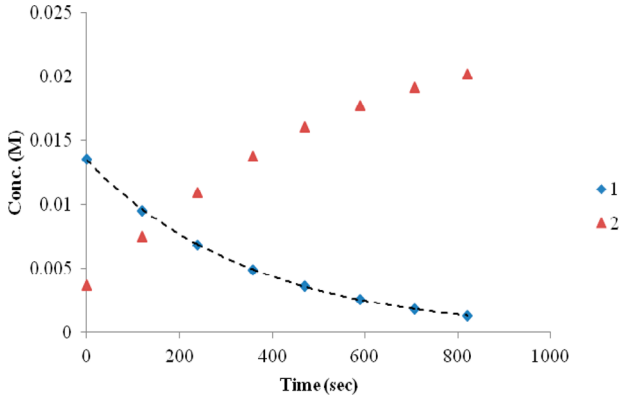
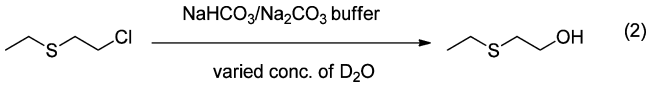


Figure 9. Plot showing 0.02 M **1** vs time in 60% buffered D_2O/acetone-d_6 fit to $f(x) = ae^{bx}$ with k_{obs}= 2.82 × 10^{-3} s^{-1}.

major product observable by ^{1}H NMR was alcohol **2** (eq 2). Small amounts of sulfonium salts **3** and **4** could be observed in the baseline but were difficult to integrate and had no detectable bearing on the course or rate of the reaction.



(2)

The amount of time necessary to observe four half-lives did decrease from 2000 to 800 s when buffered, which seemed to indicate that the elimination of free HCl from solution decreased k_{-1}, resulting in an increased disappearance of **1** as the back reaction was either slowed or eliminated. To confirm if it was the elimination of free HCl or the increased nucleophilicity of the OH^- responsible for the rate increase, the hydrolysis was repeated using 2,6-lutidine as a proton scavenger. When run with the proton scavenger, the hydrolysis showed no difference in rate when compared to the control hydrolysis in 60% D_2O.[54] The presence of a more nucleophilic OH^- seemed the more plausible explanation for the increase in rate, though in the classic S_N1 mechanism proposed for this hydrolysis, this should not have been possible. In an S_N1 reaction the formation of **1a** should have been rate-controlling and been independent of nucleophile character or concentration.

3.2. Effect of Added Chloride on the Course of Hydrolysis. A great deal of effort in earlier published work on mustard hydrolysis was focused on the role chloride played during the course of the reaction.[4,7,10,20] It has been proposed that as the reaction proceeds, the build-up of HCl as a product causes an increase in k_{-1} and that it is this increase in k_{-1} that causes the system to deviate away from expected first-order behavior. However, as previously shown, when a proton scavenger such as 2,6-lutidine was added to the reaction no change was seen in the two decay curves, meaning either HCl had no effect on k_{-1} or that the chlorinated amine salt produced by the protonation of 2,6-lutidine could also slow the reaction by increasing k_{-1}. Adding sodium chloride has been used historically and has been shown to slow the reaction. The addition of any chloride salt ($CaCl_2$, NH_4Cl, LiCl, etc.) at an equal concentration gave similar decays for **1**. Other salts (bromides, iodides, etc.) did not affect the rate of decay of **1**, and the reaction proceeded as if they were not present, demonstrating a common ion effect specific to chloride. The slowing of the reaction by added chloride and the lack of rate increase by other salts added further support that the increased rate of reaction when buffered was not due to an increase in ionic strength but an increase in the strength of the nucleophile. The effects of increasing amounts of excess HCl are shown in Figure 10.

The reaction slowed measurably as the HCl concentration increased, but the product distribution was again unaffected (Table 3). Sodium chloride gave very similar decay curves and

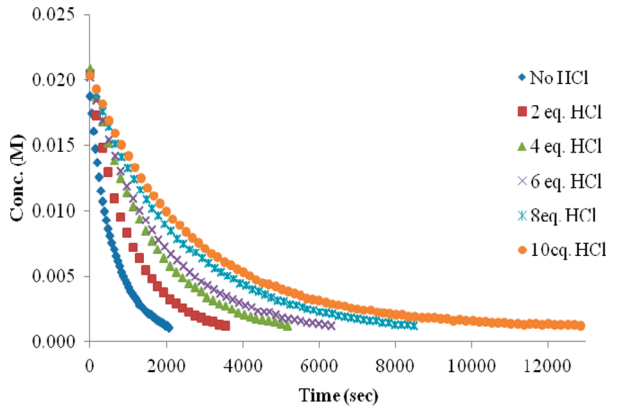


Figure 10. Plot showing 0.02 M CEES vs time in 60% D_2O/acetone-d_6 with increasing amounts of HCl.

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product distributions up to 5 equiv, at which point solubility issues became problematic.

Table 3. Product Distribution (by %) for 1−4 after Four Half-Lives of 0.02 M 1 in 60% D_2O/Acetone-d_6 with Varying Amounts of HCl

HCl (equiv)	1	2	3	4
none	5	62	11	22
2	6	58	13	23
4	6	60	12	22
6	6	55	14	25
8	6	58	12	24
10	6	55	13	26

However, if a 3 molar equiv excess of NaCl was added to a 60% D_2O/acetone-d_6 buffered solution, the NaCl had no effect either on the rate of disappearance of **1** or the products formed, in both cases forming **2** (Figure 11).

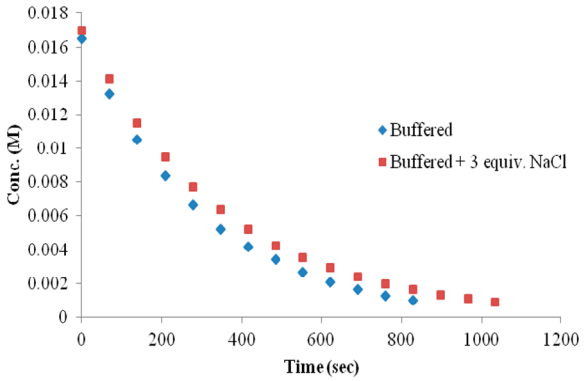
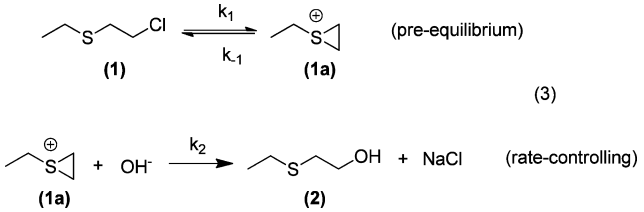


Figure 11. Plot comparing two 0.02 M **1** vs time in 60% D_2O/acetone-d_6. Buffered vs buffered + 3 equiv NaCl.

Compounds **3** and **4** exist as chloride salts, HCl is a product of the hydrolysis, and **1a** is proposed to be a cyclic sulfonium chloride salt intermediate, and it is not surprising that the reaction is very sensitive to chloride concentration. Given the proposed mechanism, any added concentration of chloride should have slowed the reaction by increasing k_{-1}, but this was not true when the solution was buffered, creating a more nucleophilic OH^-. Under these conditions a different mechanism now seemed to be controlling the reaction. The only chemical transformations that HCl has been proposed in are the conversions of **2** and **4** back to their chlorinated counterparts. While possible in 37% concentrated HCl, these transformations could not be observed at the concentrations in this paper. A solution of 0.02 M **1** and 0.02 M HCl showed no signs of any product formation when monitored by ^{1}H NMR and LC−MS over several months. A 3 equiv addition of either HCl or NaCl while slowing the hydrolysis did give the reaction a more first-order character,[55] seeming to indicate that added chloride might be establishing a first-order pre-equilibrium between **1** and **1a** where k_{-1} becomes much greater than the rates (k_2, k_3, and k_4). The addition of excess chloride changed the mechanism, as the character and concentration of the nucleophile were now involved in the rate-controlling step, not the formation of **1a**, and would explain the increased rate seen in the buffered hydrolysis. Given the data presented, it now seems possible that adding chloride to the hydrolysis of mustards could have been changing the reaction mechanism. This is explored later in the paper.[56−58]

3.3. Use of $^{35}Cl/^{37}Cl$ Ratio to Investigate the 1 to 1a Equilibrium. All of the most referenced mechanistic discussions on this hydrolysis have all been presented with the view that this reaction is an S_N1 reaction and that the formation of **1a** is rate-controlling. We have not been able to find any mention of viewing this hydrolysis as reacting under the conditions of a first-order pre-equilibrium and a second-order reaction. The equilibrium between **1** and **1a** has been very difficult to observe directly, with all information about the nature of this equilibrium being gleaned from initial rates, analyzing decay curves of **1**, etc. Attempts to synthesize a labeled **5** or **6** that remained unscrambled, where the conversion between **1** and **1a** could be monitored versus the disappearance of **1**, by observing the change in the remaining unlabeled proton in **5** or **6** by ^{1}H NMR were unsuccessful. All synthetic attempts resulted in an equilibrated 1:1 mix of **5** and **6**. Other than a report by McManus et al.[17] of a deuterated 2-(phenylthio)ethyl chloride exchanging, there has been no work on trying to observe the nature of the equilibrium between **1** and **1a**.

We wanted to find a way to observe this equilibrium to confirm that added excess chloride was being incorporated back into the remaining **1** during hydrolysis. If it was, we could then observe if this exchange was still taking place in the case of experiments run in buffered solutions where only one product was seen, the rate increased, and the reaction was now exhibiting a first-order decay in 60% water where previously it had not been. Because the addition of NaCl has been used historically in the study of mustard hydrolysis, it was hoped that the use of excess $Na^{35}Cl$ might provide a view into the equilibrium between **1** and **1a**. By monitoring the ratio of $^{35}Cl/^{37}Cl$ in the remaining concentration of **1** versus time, we hoped to observe an increase in the $^{35}Cl/^{37}Cl$ ratio as the hydrolysis proceeded. If the $^{35}Cl/^{37}Cl$ ratio increased in a first-order fashion faster than **1** was being converted to products, the buffered hydrolysis might be shown to have a first-order pre-equilibrium with rate-controlling nucleophilic addition under these specific conditions, and the hydrolysis was not reacting in a classical S_N1 fashion (eq 3).



The rate-controlling step would then no longer be the formation of **1a** but would be k_2. The hydrolysis reactions were run as before, but isotopically pure $Na^{35}Cl$ was used. The hydrolysis was quenched at specific time intervals by addition to an excess of methylene chloride to allow for analysis by GC−MS to measure the $^{35}Cl/^{37}Cl$ ratio in the remaining concentration of **1**.[59−63] No reaction is observable by ^{1}H NMR when **1** is placed into a solution containing 10% or less water even after weeks of observation. For all runs a 3 molar

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equiv excess of $Na^{35}Cl$ was used, giving a maximum ratio of 92:8 for the two isotopes of chlorine in solution, taking all chlorine sources into account. The hydrolysis was repeated at 0.01 M **1**, both buffered and unbuffered. The ratio of $^{35}Cl/^{37}Cl$ in the remaining **1** increased versus time, and the rate of increase between the buffered and unbuffered reactions is shown in Figure 12. The increase in the $^{35}Cl/^{37}Cl$ ratio versus time was nearly equal even though the disappearance of **1** in buffered solution is approximately 3 times faster than when unbuffered.

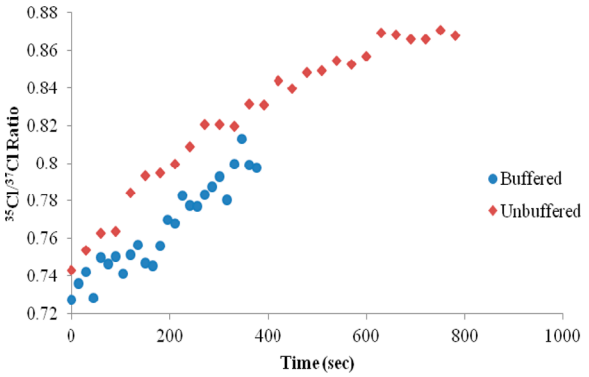
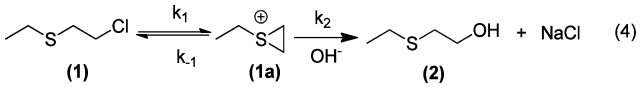


Figure 12. Plot showing the $^{35}Cl/^{37}Cl$ ratio vs time for 0.01 M **1** in 60% water buffered and unbuffered, both with a 3 mol equiv excess of $Na^{35}Cl$ added.

Under these conditions, the formation of **1a** (k_1) is a function of the concentration of water, and the excess chloride establishes the equilibrium between **1** and **1a**. The increase in the disappearance of **1** in the buffered solution is now due to the more nucleophilic OH^- created by the basic conditions, and k_2 becomes rate-controlling. For the unbuffered case, the added NaCl again establishes the **1** and **1a** equilibrium, but a strong enough nucleophile is not present to push the reaction to one product. The decay observed for **1** should still be first-order, and the fact that it is not, and only moves toward becoming more first-order, was further proof that other products besides HCl had to be responsible for the decays observed during the disappearance of **1** (eq 4).



(4)

It has now been demonstrated that **1** and **1a** are in equilibrium under conditions where excess chloride is added and that k_{-1}, even with a more nucleophilic OH^-, is greater than k_2 as the $^{35}Cl/^{37}Cl$ ratio increased at a rate greater than the rate of disappearance of **1**. A large body of work has been published with excesses of chloride added that had to be reacting in this fashion and not by the traditional S_N1 mechanism. We believe that under these conditions the hydrolysis should be viewed as having a first-order pre-equilibrium with a second-order reaction.[64] The equilibrium constant is determined by the water concentration in the system and the excess NaCl, causing k_2-k_4 to become rate-controlling.

3.4. Sodium Thiosulfate As a Nucleophile. Sodium thiosulfate has also been used historically as a very strong nucleophile to study the course of reaction during mustard hydrolysis.[7,10,12] Bartlett and Swain reported no rate increase for mustards, while Yang and co-workers report an increase in rate and a simplification to first-order kinetics. The concentrations reported in the paper by Yang et al. were found in our hands to again be heterogeneous, calling into question their results, as actual concentrations in solution at any point in time could not be determined.

Figure 13 shows the results of adding 2 equiv of sodium thiosulfate to a reaction of 0.02 M **1** in 60% D_2O. On seeing the

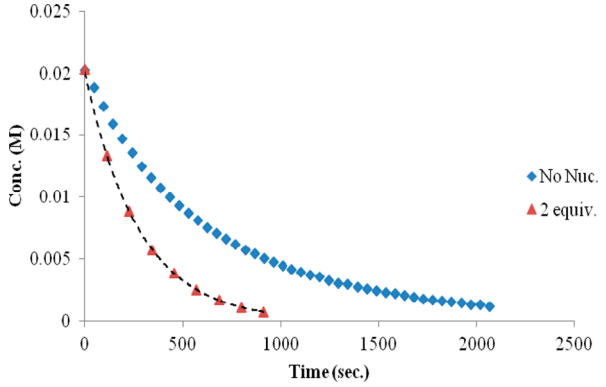
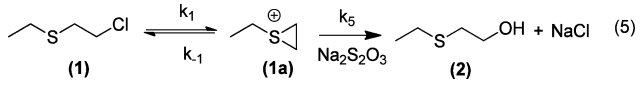


Figure 13. Plot showing 0.02 M **1** vs time in 60% D_2O/acetone-d_6 with 2 equiv of sodium thiosulfate. The dashed line shows the first-order fit ($f(x) = ae^{bx}$).

increased rate, the amount of thiosulfate was increased to 10 equiv to see if the reaction was now overall second-order, but no increase in the rate was observed.

The lack of an increase in rate, when 10 equiv of thiosulfate was added, could be viewed as evidence that the system is more of a conventional S_N1 reaction, but when compared to the control hydrolysis, it should have exhibited no increase in rate at all if the formation of **1a** was rate-controlling (eq 5).



(5)

It seems that viewing the hydrolysis of **1** as purely S_N1 under all conditions is difficult to support, and a more involved borderline S_N1 reaction is taking place, as addition of thiosulfate did increase the rate, but further increases in thiosulfate did not continue to increase the rate.

The reaction was repeated, this time with 3 equiv of $Na^{35}Cl$ added to the reaction along with thiosulfate. The $Na^{35}Cl$ addition had no effect on the rate of disappearance of **1**, and the $^{35}Cl/^{37}Cl$ ratio in remaining **1** did not increase versus time, demonstrating that k_{-1} was no longer occurring under these reaction conditions. The addition of sodium thiosulfate, a very strong nucleophile, has apparently again changed the mechanism of the system to something different than what was observed for the hydrolysis when buffered, where the $^{35}Cl/^{37}Cl$ ratio still increased with time. The use of sodium thiosulfate has been used historically to justify the S_N1 character of the reaction, but it does not seem to be applicable to the hydrolysis mechanism, which under conditions of excess chloride has an equilibrium present reforming **1**. Bartlett and Swain possibly did not see an increase in rate when using sodium thiosulfate at a 95% water concentration, because k_1 is so large at this water concentration that a rate difference could have been difficult to distinguish.

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3.5. Effect of Water Concentration on the Time Required for the $^{35}Cl/^{37}Cl$ ratio to Equilibrate in ***1****.* When 0.01 M solutions of **1** were monitored at three different water concentrations (Figure 14), the rate at which the $^{35}Cl/^{37}Cl$ ratio increased in the remaining **1** was clearly seen to change with water concentration, in the case of going from 60 to 40% water quite substantially.

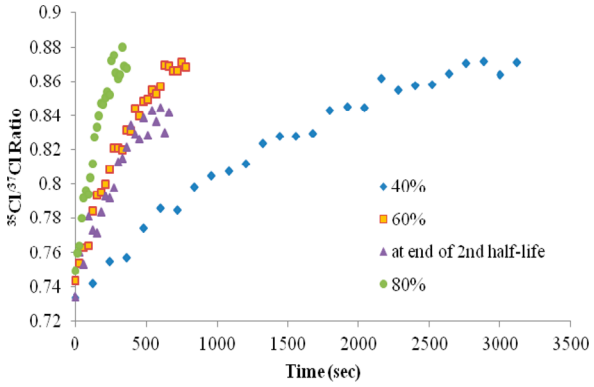


Figure 14. Plot of the $^{35}Cl/^{37}Cl$ ratio vs time for 0.01 M **1** in varying amounts of water/acetone with a 3 molar equiv excess of $Na^{35}Cl$.

All growth curves fit a first-order growth as would be expected from this process. What is interesting to note is how quickly the $^{35}Cl/^{37}Cl$ ratio increased versus the disappearance of **1** (Table 4). The overall isotopic ratio of 92:8 is approached much faster in **1** than **1** reacts to products **2**–**4**.

Table 4. Comparison Showing the Time Needed to Reach Four Half-Lives in Three Different Water Concentrations, Each with 3 equiv of $Na^{35}Cl$ Added, and the Time Needed for the $^{35}Cl/^{37}Cl$ Ratio to Reach a Maximum in the Remaining Unreacted 1 under Identical Conditions

	80% water or D_2O	60% water or D_2O	40% water or D_2O
time to 4 half-lives (s)	1 000	4 000	90 000+
time for max $^{35}Cl/1^{37}Cl$ ratio (s)	240	600	3 000

Previous work on this subject had proposed that k_{-1} became negligible at lower concentrations compared to the corresponding forward rates (in this case k_2–k_4). Our studies have shown that this is not likely the case. Initial rates are the same for any concentration of **1**, with the water concentration establishing the equilibrium between **1** and **1a**. All other rates remain constant as evidenced by constant product distributions. By adding 3 equiv of NaCl, k_{-1} is increased compared to a normal hydrolysis run, and even without this added excess NaCl, the equilibrium demonstrated surely exists to some degree. When the $Na^{35}Cl$ was added at the beginning of the third half-life of a hydrolysis run, the rate at which the $^{35}Cl/^{37}Cl$ ratio increased in **1** remained unchanged, demonstrating that an excess of $Na^{35}Cl$ establishes the k_1–k_{-1} equilibrium. Without added chloride, the **1** to **1a** equilibrium would be changing throughout the reaction as HCl, **3**, and **4** are formed. The establishment of this equilibrium leads to the near first-order decay observed when excess chloride was added at the beginning of hydrolysis runs.

It also seems that viewing the hydrolysis of **1** as purely S_N1 under all conditions is difficult to support. Several more complex views of S_N1 chemistry invoking more nuanced types of ion-pairs seem more applicable,[53,65] as do studies showing that ion pair formation and recombination is competitive with ion pair formation and substitution.[66−69]

3.6. Effect of Initial Concentration of ***1*** *on the Time Required for the $^{35}Cl/^{37}Cl$ Ratio to Equilibrate in* ***1****.* The initial concentration of **1** had no impact on the rate at which the $^{35}Cl/^{37}Cl$ ratio increased in remaining **1**, in agreement with the initial rate studies previously mentioned above.[70] This is in contrast to the substantial time differences seen to four half-lives when comparing the decay curves of 0.02 M **1** in 40% water to that of 0.06 M in 40% water (36 000 vs 72 000 s; see the Supporting Information). The main difference in changing the initial concentration of **1** is the amount of salts **3** and **4** (especially **3**) that are formed throughout the course of the reaction. Other plots in the Supporting Information show the effects of cosolvents on the $^{35}Cl/^{37}Cl$ ratio in **1**.

4. Role of Products 2, 3, and 4 on the Course of Hydrolysis. *4.1. Effect of 2-(Ethylthio)ethanol,* ***2****, on the Course of Hydrolysis.* The complexity of the hydrolysis was surprising when compared against the published literature, and its sensitivity to added chloride made the focus on just the products of the reaction more important to examine, as addition of other probes might give interesting data that was not applicable to the hydrolysis to be studied. The rate of disappearance of **1** in 60% D_2O/acetone-d_6 was unaffected by increasing the concentration of **2** (Figure 15). This result supported a more traditional S_N1 view of the mechanism or what we now believe is a mechanism involving an equilibrium where k_{-1} is less than the forward rates to products (eq 6).

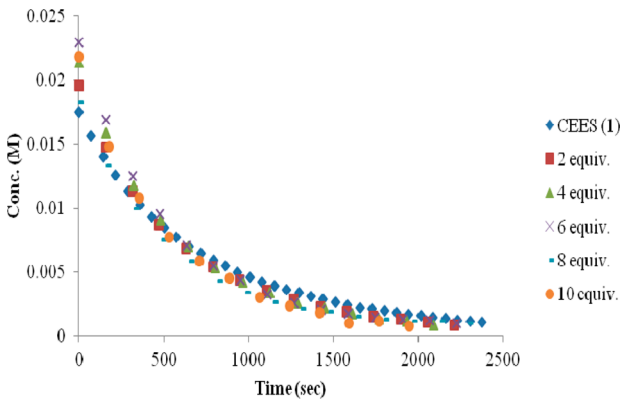
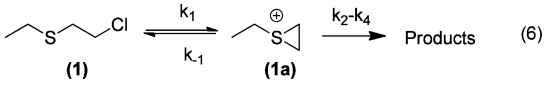


Figure 15. Plot showing 0.02 M **1** vs time in 60% D_2O/acetone-d_6 with increasing amounts of **2**.



From the $^{35}Cl/^{37}Cl$ exchange experiments above, it appears that k_{-1} is substantially larger than rates k_2–k_4 when added chloride is present. Because of this rapid pre-equilibrium, the reaction of **1a** with **2** would become rate-controlling, instead of the formation of **1a**. If this was still the case, the addition of excess **2**, with no excess chloride, should show an increase in the rate of disappearance of **1** as k_4 would be rate-controlling (eq 7). This was not the case as Figure 15 demonstrates.

A contradiction between the outcomes predicted with and without added chloride would be significant, as much of the published literature on mustard hydrolysis is based on previous

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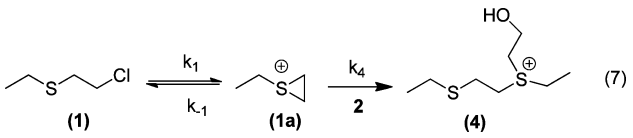


(7)

work that utilized high chloride concentrations.[7] Figure 16 shows that when an excess of **2** is added to the beginning of a

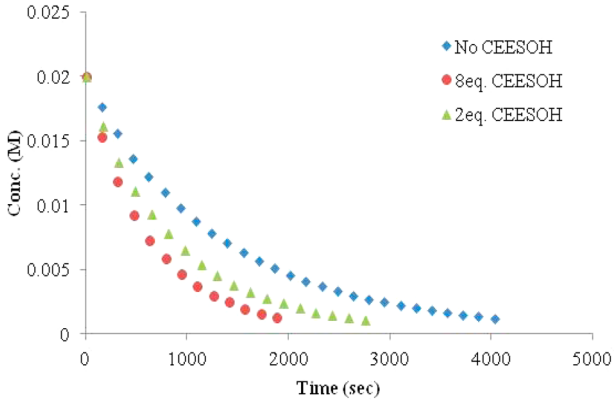


Figure 16. Plot comparing the time to four half-lives for 0.02 M **1** with 4 equiv of HCl and either 2 or 8 equiv of **2** added vs time in 60% D_2O/acetone-d_6.

0.02 M solution of **1** with 4 equiv of HCl added, an increase is seen in the rate of disappearance of **1**, and demonstrates the mechanistic difference added chloride has on the hydrolysis.

The addition of excess amounts of **2** changed the product distribution of the reaction to near complete formation of **4** and showed that **2** is a stronger nucleophile than water, and even a relatively low molar excess of 2 equiv changed the product distribution (Figure 17). The zero-order dependence on **2**

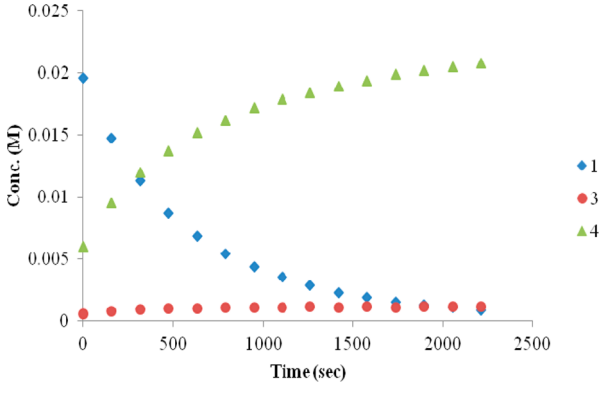
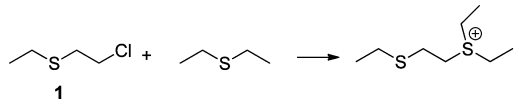


Figure 17. Plot showing 0.025 M **1** vs time in 60% D_2O/acetone-d_6 with 2 equiv of **2**. Compound **2** is not shown for clarity, as it is the final hydrolysis product and reacts no further once **1** has been consumed.

supports the rate-controlling step to be the formation of **1a** in a system with an equilibrium where k_{-1} is much less than k_4. In the case of a normal hydrolysis run of **1**, in 60% D_2O/acetone-d_6, with an equilibrium between **1** and **1a**, k_{-1} would be much less than k_2–k_4 and k_{obs} would be equal to k_1, making the formation of **1a** rate-controlling, and could be easily interpreted as an S_N1 reaction. Whatever the exact mechanism for the formation of **1a** is, a large deviation is still observed away from a first-order decay as the concentration of water is reduced.

Amounts of **2** above 10 equiv were very difficult to interpret by ^1H NMR as the starting material was pushed too far into the baseline. LC–MS analysis could not observe the starting material **1**, and GC–MS analysis could not observe the sulfonium salts **3** and **4**. The product distribution being set at 2 equiv of **2** negated the need to further flood the system, as no rate increase was seen between 2 and 10 equiv of **2**. Any moderately unhindered sulfide reacted in a similar fashion at the same rate. For example, diethyl sulfide formed the salt shown below completely with a **2** equiv excess (eq 8). A



(8)

mixture of excess diethyl sulfide and **2** yielded the same proportional mix of salts. Even in runs with a 10 equiv excess of **2**, small amounts of sulfonium salt **3** could still be measured.

4.2. Effect of Ethyl(2-(ethylthio)ethyl)(2-hydroxyethyl) Sulfonium Chloride, 4, On the Course of Hydrolysis. Because of the system's sensitivity to added chloride, the effects of sulfonium salts **3** and **4** were examined closely to see how they were affecting the hydrolysis. The amount of time necessary for the disappearance of four half-lives of 0.02 M **1** in 60% D_2O/acetone-d_6 increased as the concentration of **4** was increased. (Figure 18)

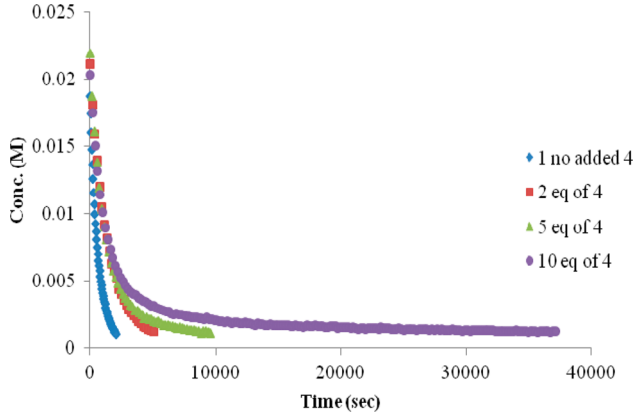


Figure 18. Plot showing 0.02 M **1** vs time in 60% D_2O/acetone-d_6 with increasing amounts of **4**.

The concentrations of **2** and **3** at the end of four half-lives when 2 equiv of **4** was added remained unchanged (Figure 19) and did not differ from the control experiment, indicating that **4** was behaving similarly to added HCl from previous studies effecting k_{-1} and the equilibrium between **1** and **1a**.

At higher concentrations of added **4**, the disappearance of **1** was lengthened as k_{-1} increased because of the increased chloride salts and HCl, and the reversion of **4** back to **1** and **2** by k_{-4} began to distort curves and influence final product concentrations (eq 9).

When 5 or 10 equiv of **4** was added, final concentrations of **2** and **3** were increased at the end of four half-lives as **4** now had time to revert to its constituent molecules, which could then enter back into the hydrolysis. The rate at which **4** reverted back to its constituents was unaffected by either water concentration and/or HCl concentration. This was in line with the intramolecular nature of the decomposition. A plot of 0.005 M **4**, the maximum concentration observed for a 0.02 M

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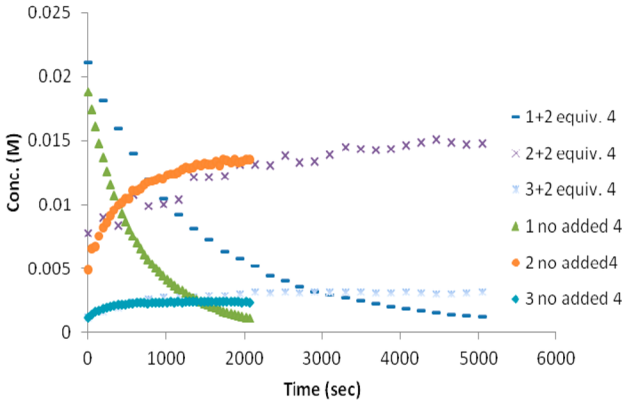
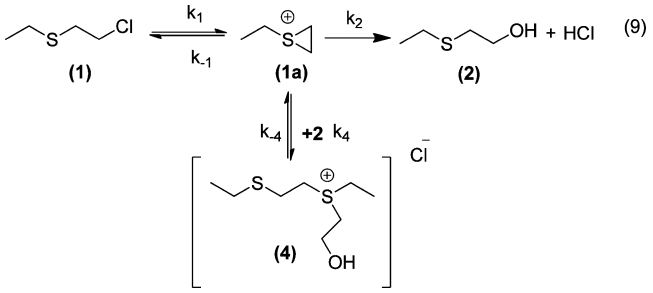


Figure 19. Plot comparing two 0.02 M **1** vs time in 60% D_2O/acetone-d_6 runs. First set with 2 equiv of **4** added, and the second control set with no additional **4**. Compound **4** is not shown for clarity purposes.



hydrolysis of **1**, under various conditions is in the Supporting Information and shows no dependence in the rate of decay of **4** toward the concentration of water or the amount of excess HCl added. For a normal hydrolysis of **1** in water/acetone, as the water concentration is decreased, the reversion of **4**, back to **1a** and **2**, would have a greater effect on how **1** appears to be consumed in the reaction.

*4.3. Effect of (2-Chloroethyl)(ethyl)(2-(ethylthio)ethyl) Sulfonium Chloride, **3**, On the Course of Hydrolysis.* When a 2.3 equiv excess of **3** was added to **1** in 60% D_2O/acetone-d_6, an unusual decay curve was observed (Figure 20).

A change in slope at approximately 5000 s indicated the possibility of two separate mechanistic realms. The curve after the change in slope fit a first-order decay; the initial decay to the change in slope did not. Compound **3** is not soluble to a

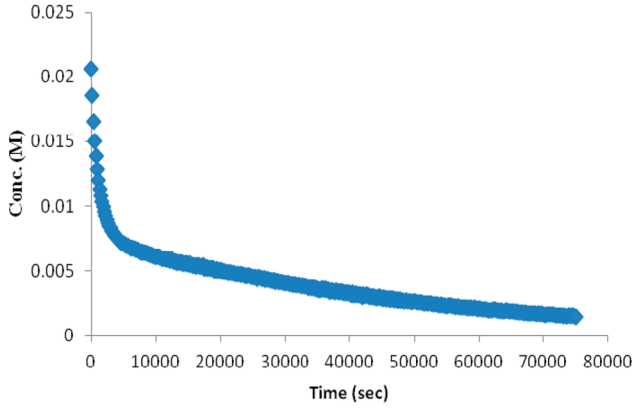
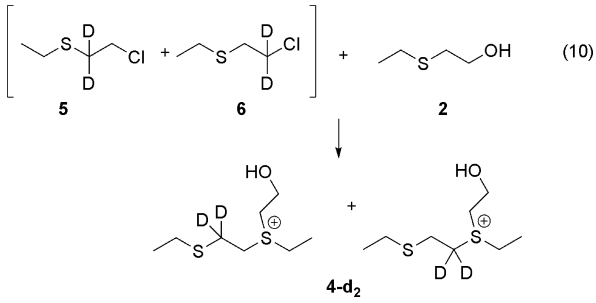


Figure 20. Plot showing 0.02 M CEES vs time in 60% D_2O/acetone-d_6 with 2.3 equiv of **3**.

usable degree in acetone-d_6, but when **3** was placed in CD_3CN and observed over time, it reverted back to **1**. Compound **4** reverted back to **1** and **2** when observed in CD_3CN. The rate of reversion for both salts was independent of initial concentration or solvent, as long as concentrations were kept under 0.1 M. Compound **3** decomposed 10 times faster than **4** in CD_3CN.

Compound **3**, when added to the hydrolysis, caused a slowing in the disappearance of **1**. The change in slope around 5000 s seen in Figure 20 corresponds very closely to when 2 equiv of **4** was added to the reaction. In the addition of 2 equiv of **4**, approximately 5000 s was required for the reaction to reach 4 half-lives. We interpreted this 5000 s correlation in Figure 20 as the point where all the initial **1** had been consumed. The changing slope is a result of **3** reverting back to 2 equiv of **1**, a conversion independent of concentration explaining the first-order disappearance of **1** after the change in slope. At the 5000 s mark, the majority of compounds in solution are salts or HCl, and at these elevated chloride salt amounts, as the previous work with excess HCl and NaCl showed, the equilibrium between **1** and **1a** is established as the chloride concentration changes little in an almost pseudo-first-order effect, allowing the reaction to exhibit a first-order decay. Sulfonium salts **3** and **4** serve dual roles in the deviation away from expected first-order behavior. As their concentrations increase, and water concentrations are high giving shorter reaction times, they appear to function like added HCl, building up chloride concentrations and changing the equilibrium between **1** and **1a**. When water concentrations are lower, k_{-1} is still increased, but their reversion back to constituent components is significant enough to alter the decay curve of **1**. Because of its higher rate of decay and second-order nature of formation, sulfonium salt **3** has a large effect on the decay of **1**. As the concentration of **1** is increased, **3** forms in higher concentrations and causes the disappearance of **1** to greatly slow. The roles of sulfonium salts **3** and **4** had not been previously examined as they had not been isolated, even though they have been implicated in mustard's toxicity.[71−73]

5. Deuterium-Labeled 4-d_2. Compound **4**-d_2 was synthesized as described previously using deuterium scrambled **5** and **6** (eq 10).



In order to show that **4**-d_2 was reverting back to its starting components **1** and **2**, a 0.02 M solution of **1** in 40% D_2O/acetone-d_6 was treated with 1.2 equiv of labeled **4**-d_2 and monitored by ^1H NMR. A partially deuterated **1** could be seen incorporated into the remaining **1** after 17 h (Figure 21), demonstrating that **4** reverts back to **1** and **2** through **1a**. We had hoped to also see incorporation of the label in **3**, but the only nonoverlapped proton was not in a correct position in the molecule to show this. Compound **3** could never be isolated cleanly enough to repeat the above experiment, as it always had 5−10% of **1** in it, but we are confident that the above result and

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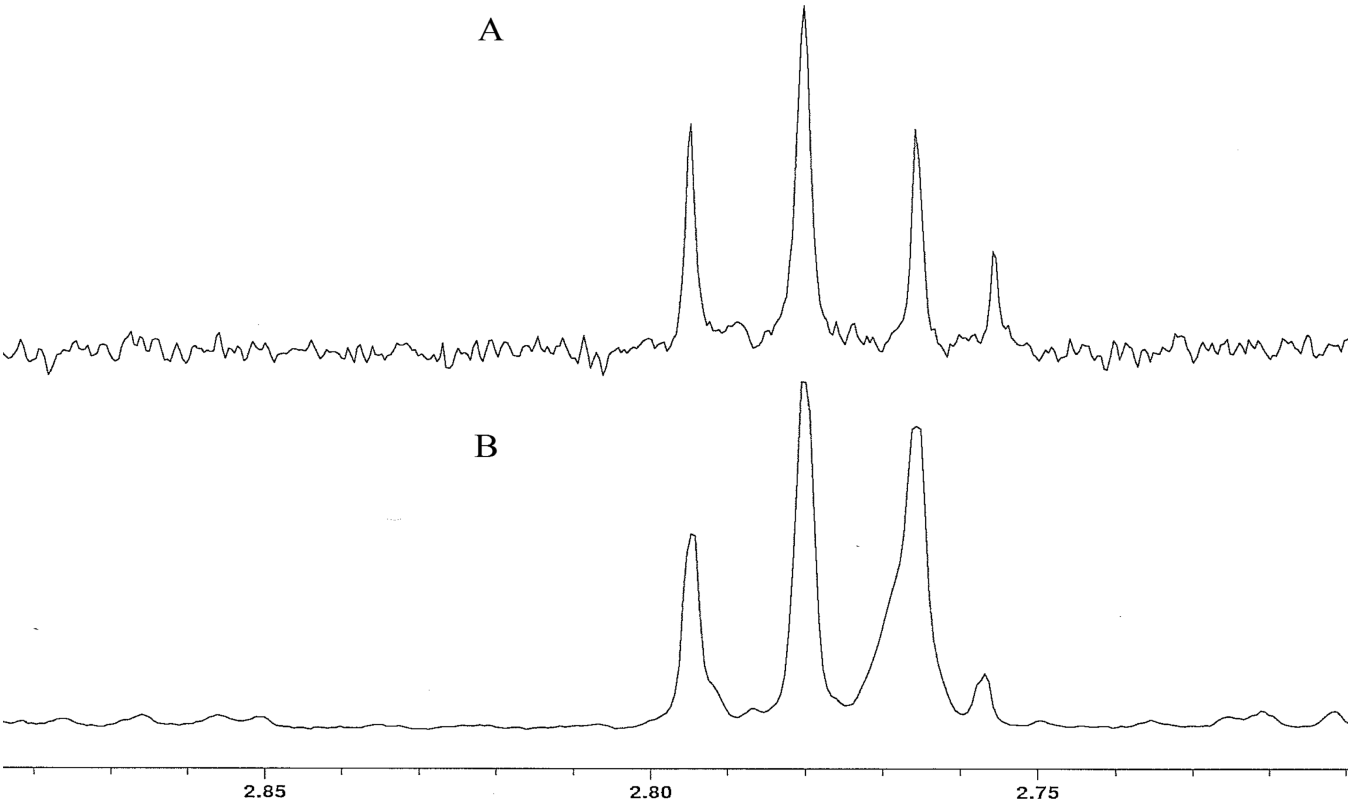


Figure 21. (A) ^{1}H NMR after three half-lives of a 0.02 M solution of **1** with 1.2 equiv of **4**. (B) ^{1}H NMR after three half-lives of a 0.02 M solution of **1** with 1.2 equiv of labeled **4**-d_2. A control spectrum of labeled and unlabeled **2** is available in the Supporting Information to support the splitting observed.

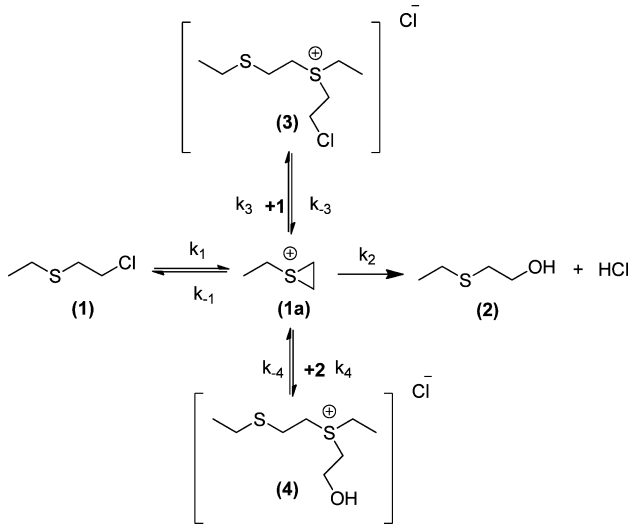
the curve observed when **3** is added back to the hydrolysis (Figure 20) proves that **3** is reverting back to **1** through **1a**, contributing to the unconventional curvatures seen in the hydrolysis of **1** as reaction times increase.

Yang and co-workers reported that **4** underwent an S_N2 hydrolysis with water to form 2 equiv of **2**. Experiments with varying amounts of water show that this is not occurring, as **4** decays at a rate independent of water concentration, and its decay in D_2O was nearly identical to the control sample in CD_3CN. Compound **3** could never be isolated purely enough away from **1** to clearly observe this first-order decay in D_2O, but in CD_3CN where the 5−10% of **1** could not hydrolyze, **3** showed a first-order decay independent of initial concentration. We disagree that sulfonium salts **3** and **4** are in equilibrium as has also been depicted.

6. Proposed Mechanistic Model. The rate and $^{35}Cl/^{37}Cl$ studies were used to develop the mechanism proposed in Scheme 2.[74] The mechanism in Scheme 2 represents the simplest that could be proposed to fit the experimental data observed. The most cited mechanism from the literature[10] was used as a starting point and allowed all compounds to be in equilibrium with their logical counterpart. This view of the hydrolysis quickly proved inadequate at explaining the experimental data.

The hydrolysis of **1** at concentrations up to 0.02 M has been reinvestigated and is more nuanced and involved, as was so eloquently stated by Peters and Walker[20] when they wrote in 1923, "the reaction from the broad standpoint resembles a monomolecular reaction. It is apparent however that we may be dealing with a balance of factors, masking a more complicated reaction..."

Scheme 2



We have proposed a mechanism in Scheme 2 on the basis of the following observations:

(1) Water is a weak enough nucleophile to allow an equilibrium to exist between **1a** and **1**. The equilibrium (the formation and recombination of some type of ion pair in this case) is always present, as all attempts to synthesize an unscrambled deuterated form of **1** were unsuccessful even when performed in less polar solvents hoping to decrease the formation of the cyclic sulfonium **1a**. Therefore, k_{-1} is never negligible compared to k_2−k_4, and the hydrolysis is a balance of rates between the parties. The equilibrium between **1a** and **1** is

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determined by the concentration of water as initial rates showed, and as the reaction proceeds and HCl and salts **3** and **4** are formed, k_{-1} increases, slowing the reaction as it begins to compete with the forward rates. Under conditions where the disappearance of **1** is relatively rapid, this along with the formation of **3** are the factors in the reaction deviating away from first-order behavior. Added sulfides can change the product distribution of the reaction as they are stronger nucleophiles, but they are not strong enough to alter the mechanism. As the concentration of **2** increases during hydrolysis, the formation of **4** begins to be favored. The formation of **3** impacts the concentration of **1** altering its first-order decay, becoming more pronounced as initial concentrations of **1** are increased. When the concentration of water is lowered, the slower formation of **1a** allows decomposition of sulfonium salts **3** and **4** to regenerate **1** and **2**, altering the decay curve of **1** further. The role of the sulfonium salts **3** and **4** in the mechanism has been underestimated for concentrations of **1** above 0.001 M, especially as water is removed from the system and the reaction slows.

(2) A very strong nucleophile (sodium thiosulfate) eliminated k_{-1}. This was demonstrated in the $^{35}Cl/^{37}Cl$ experiments where even added NaCl could not increase k_{-1} enough to observe an increase in the $^{35}Cl/^{37}Cl$ ratio in **1** as the reaction proceeded. All other sulfides added still exhibited the existence of k_{-1} during these exchange experiments. Because sodium thiosulfate was able to increase the rate of disappearance of **1**, the formation of **1a** cannot be viewed in a rigid S_N1 framework, as this mandates a rate independent of nucleophile nature or concentration. The exact type of ion pair and the stage at which there is nucleophilic involvement is still a topic for further investigation.

(3) Compounds **3** and **4** are not in equilibrium, and **3** is not hydrolyzed to **4**, nor are they hydrolyzed in an S_N2 manner to constituent components as their disappearance is independent of the concentration of water. The rate of decomposition in any concentration is equal to that seen in CD_3CN.

(4) Once formed, **2** does not lose water to reform **1a**. Compound **2** can react with **1a** to form **4** but is not in equilibrium with **1a**. This is the reaction's sink; if observed long enough, the final product regardless of initial concentration of **1** will be solely **2**, a process that can take months depending on initial conditions of **1**.

(5) Finally, the entire system is easily manipulated. Our focus was on the hydrolysis of **1** in water/acetone mixtures at concentrations up to 0.02 M. All the experiments used to propose the mechanism were performed using conditions as similar as possible to the hydrolysis, especially once it was observed that added chloride could shift the rate-controlling step to be dependent on the sulfide concentration. By using NaCl or sodium thiosulfate, the danger of altering the reaction mechanism to be studied by the introduction of components not involved in the original reaction was revealed.

CONCLUSIONS

The hydrolysis of 2-chloroethyl ethyl sulfide (**1**) in concentrations up to 0.02 M have been studied in varying water concentrations between 40 and 80%. A mechanism involving an equilibrium between 2-chloroethyl ethyl sulfide (**1**) and its cyclic sulfonium intermediate (**1a**) has been put forth where k_{-1} is always present and is only eliminated by the use of an extremely strong nucleophile altering the mechanism away from that proposed for hydrolysis. The isolation and role of salts formed at higher concentrations revealed the large influence they have on the course of the hydrolysis. A better understanding of how mustards behave at more elevated concentrations is critical in their decontamination and how they are dealt with once present in the environment.

EXPERIMENTAL SECTION

Reagents and Solvents. 2-Chloroethyl ethyl sulfide (**1**) and 2-(ethylthio)ethanol (**2**) were purchased commercially and distilled prior to use. Hydrochloric acid and sodium chloride were used as purchased. Acetone-d_6 was distilled prior to use and was used as the cosolvent unless noted otherwise.

NMR Spectroscopic Analysis. The ^1H and ^{13}C NMR spectra for **1**–**4** in the Supporting Information were recorded on a 400 MHz instrument and referenced to the residual solvent peaks. All ^1H NMR spectra for kinetic runs were performed on a 500 MHz instrument. A macro was used so that gradient shimming would be performed before the collection of each ^1H spectrum after a specified time interval. At the conclusion of a run, another macro was used to process and integrate all the ^1H NMR spectra back against the internal standard. This allowed for a greater number of points to be collected and eliminated bias. All spectra were referenced back to the residual acetone-d_6 signal.

Separation and Characterization of Hydrolysis Products by LC–MS. All compounds were characterized using a liquid chromatography system with a time-of-flight mass spectrometer equipped with an electrospray ionization (ESI) interface. The capillary voltage was operated at 3.5 kV, and the drying gas temperature was 350 °C for all compounds. A sampling fragmentor voltage of 120 V was used. Nitrogen nebulizer gas was operated at a flow rate of 30 psig. The LC-ESI-TOF MS data were acquired in positive ion scan mode over a mass range of 70 to 300 Da. The liquid chromatography separation for compounds **2**–**4** was performed on a Phenomenex C18 Aqua column, 150 × 2.1 mm, 3.0 μm with a mobile phase consisting of solvent A (acetonitrile) and solvent B (0.1% formic acid in H_2O) and a sample volume of 2 μL. Separations were achieved using a gradient of 20–95% A for 5 min, 95% A for 5–8 min, 95–20% A for 8–8.5 min, and 20% A for 8.5–12 min, with a flow rate of 0.3 mL/min. The column temperature was maintained at 30 °C using a thermostatted column compartment.

Synthesis of Ethyl(2-(ethylthio)ethyl)(2-hydroxyethyl) Sulfonium Chloride 4. Compounds **1** (222 mg, 1.78 mmol) and **2** (202 mg, 1.90 mmol) were weighed into a 10 mL round-bottom flask, and 2.7 mL of H_2O was added. The heterogeneous mixture was stirred rapidly with a magnetic stirrer until homogeneous, at which point the flask was placed under a vacuum in a room temperature water bath and stirred rapidly until a thick clear viscous oil was observed. Six milliliters of 1:1 MeOH/CH_3CN was added, the stir bar was removed, and the solution was placed on the rotary evaporator. The oil was then taken up in 2 mL of 10% acetone/chloroform and loaded onto 2 g of silica gel. The column was eluted with 25 mL of 10% acetone/chloroform followed by 5% MeOH/chloroform. The 5% MeOH/chloroform was collected, and removal of solvent yielded 311 mg of **4** (85% yield). Compound **4** was stored in a −40 °C freezer: ^1H NMR (400 MHz, D_2O) δ 3.94 (m, 2H), 3.55 (m, 2H), 3.45 (M, 2H), 3.34 (q, J = 7.8 Hz, 2H), 2.94 (t, J = 7.6 Hz, 2H), 2.53 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.3 Hz, 3H), 1.13 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 56.2, 42.1, 39.8, 34.7, 25.2, 25.0, 13.8, 8.2; HRMS (ESI-TOF) m/z $[M]^+$ Calc for $C_8H_{19}OS_2$ 195.0918, found 195.0911.

Synthesis of (2-Chloroethyl)(ethyl)(2-(ethylthio)ethyl) Sulfonium Chloride 3. Compound **4** (400 mg, 1.73 mmol) was dissolved in 2 mL of CH_3CN, and thionyl chloride (343 mg, 2.88 mmol) was added. The solution was allowed to stand for 4 h, at which point the solvent was removed to yield a waxy solid. This solid was washed 3 times with pentane and then placed under a vacuum until a constant mass was achieved. Compound **3** always contained, even after pentane washings, 5–10% of **1** and was stored in a −40 °C freezer: ^1H NMR (400 MHz, D_2O) δ 3.96 (m, 2H), 3.74 (m, 2H), 3.59 (m, 2H), 3.39 (q, J = 7.4 Hz, 2H), 2.95 (m, 2H), 2.54 (t, J = 7.4 Hz, 2H), 1.38 (t, J =

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7.4 Hz, 2H) 1.13 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 42.0, 39.9, 37.9, 34.7, 25.3, 25.0, 13.8, 8.1; HRMS (ESI-TOF) m/z $[M]^+$ Calc for $C_8H_{18}ClS_2$ 213.0535, found 213.0528.

NMR Kinetic Runs. All kinetic runs were performed in the following manner. Compound **1** was weighed into a 4 mL vial. Into a separate 4 mL vial was placed the D_2O and acetone-d_6. This solvent vial was tared, the internal standard (methylene chloride or p-xylene) was added, and the mass was recorded. Final solvent volumes were 600 μL (v/v). To start the run, the solvent was pipetted all at once into the vial containing **1**, agitated 5−6 times, and then placed into an NMR tube, which was then immediately placed into the magnet. The kinetics macro was run after locking the instrument. Approximately 2−3 min were consumed on average before the t = 0 point was collected.

GC−MS Kinetic Runs. All GC−MS kinetic runs to follow the $_{35}Cl/_{37}Cl$ ratios in **1** were performed in the following manner. Compound **1** was placed into a 4 mL vial. Into a separate 4 mL vial was weighed the $Na^{35}Cl$, which was then dissolved in the appropriate amount of H_2O and acetone. Final solvent volumes were 3 mL (v/v). The run was started by adding all of the solvent at once to the vial containing **1**, stirring rapidly, and then withdrawing a 100 μL aliquot, which was added to 900 μL of CH_2Cl_2 in a GC vial following by immediate vortexing. This was recorded as t = 0. All subsequent time points were 100 μL aliquots handled in the same manner. GC−MS analysis was then performed to measure the $^{35}Cl/^{37}Cl$ ratio in the remaining **1**.

For all initial rate studies, **1** was placed into an appropriate vial (either 4 or 40 mL), depending on the concentration to be studied, and the amount of **1** and internal standard (sulfolane) was added. The water/acetone mixture was added all at once with rapid stirring, and then an aliquot for the desired analysis concentration was withdrawn and added to 1.5 mL of CH_2Cl_2 in a GC vial, followed by immediate vortexing. This was recorded as t = 0. All subsequent time points were prepared in the same fashion. The resulting decays were normalized, and the rates of decay were compared.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for **1**−**4**, and additional rate data and plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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