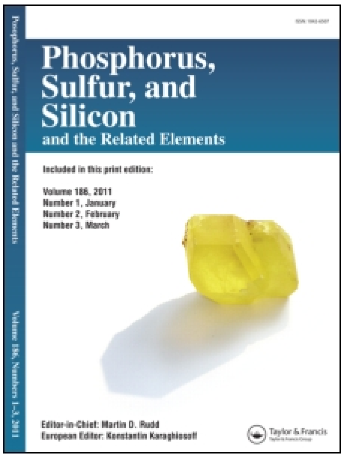

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# Oxidation of Organic Sulfides by *N*-Halamine Compounds

Akin Akdag[a]; Jie Liang[a]; S. D. Worley[a]
[a] Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama, USA

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# Oxidation of Organic Sulfides by *N*-Halamine Compounds

**Akin Akdag**
**Jie Liang**
**S. D. Worley**
Auburn University, Department of Chemistry and Biochemistry,
Auburn, Alabama, USA

*N-halamine chemistry has been an important research topic in these laboratories for over two decades, offering many exciting opportunities both from practical and pedagogical points of view. One of these opportunities is in the use of polymer- and silica gel-bound N-halamines as selective oxidizing agents for organosulfur compounds. In this study, they have been employed to selectively oxidize organic sulfides including dimethyl sulfide and chloroethyl ethyl sulfide, the chemical mustard stimulant. The latter oxidation produced the less toxic sulfoxide derivative with about 70% conversion, with no sulfone produced, and only about 30% accompanying conversion to sulfoxide hydrolysis products. In this article, we report a combination of experimental and computational results.*

**Keywords** N-halamines; organic sulfides; oxidation; polymer bound reagents

## INTRODUCTION

Oxidation of sulfide compounds has been explored extensively.[1] Reasons for these studies relate to possible biological, chemical, and environmental implications.[2] Although these compounds are used as medicinal agents, they can be toxic and used as chemical warfare agents.[3] As warfare agents, probably the most infamous organosulfur compound is sulfur mustard which is bis(2-chloroethyl)sulfide (Figure 1).[4] The mustard agent is an extremely dangerous material that induces blisters on the skin and in lungs and has caused numerous deaths and disfigurements under battlefield conditions.

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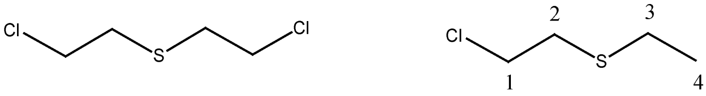
Address correspondence to S. Worley, Auburn University, Department of Chemistry and Biochemistry, Auburn, AL 36849, USA. E-mail: worlesd@auburn.edu



Bis(chloroethyl)sulfide, the sulfur mustard agent

Chloroethylethylsulfide(CEES), the mustard simulant

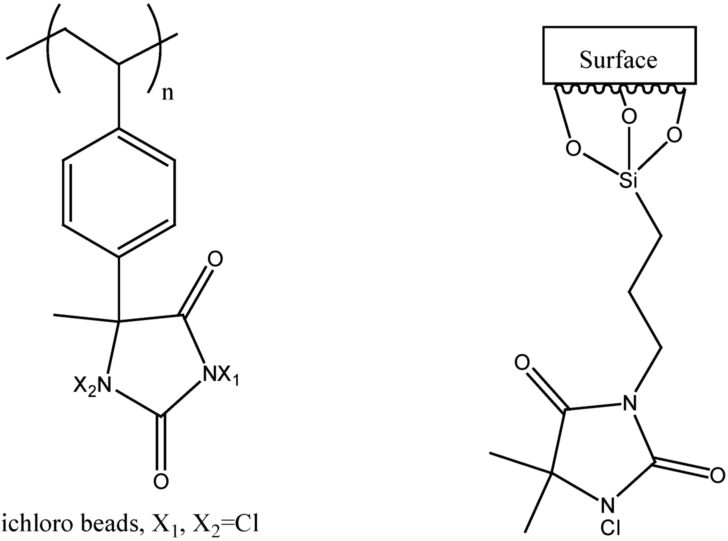
**FIGURE 1** Structure of mustard and CEES.

Even though sulfides can be easily oxidized by a variety of oxidizing agents,[5] most of the oxidizing agents are inefficient for the mustard analogue in terms of terminating the reaction at the sulfoxide stage; there is usually further oxidation on to sulfones or fragmented products, which are known to be more toxic than the sulfoxide.[6] Therefore, there is a need for an efficient and selective oxidizing agent for chemical mustard, and in general, an oxidizing agent that is specific for converting sulfides into sulfoxides, rather than to the more highly oxidized sulfones.

We have previously demonstrated that thiols can be oxidized selectively to disulfides with use of monochloro poly(styrenehydantoin) beads.[7] Many other reports had appeared in the literature regarding oxidizing organosulfur compounds with N-halamines, such as N-chlorosuccinimide and N-bromosuccinimide;[8] however, use of the polymer-bound N-halamines for the purposes mentioned above was unique.

Surface bound N-halamine chemistry has been developed in these laboratories since the late 1980s (see Figure 2 for some examples).[9] The main purpose of these compounds has been for microbiological inactivation, and in this regard, they have been subjected to numerous biocidal studies. They have been shown to be excellent biocides and proposed to be antibiological warfare agents (for biocidal activities, see Ref. 9 and for the activity of chlorine grafted medical textiles against anthrax see Ref. 10). However, these compounds have not been tested as anti chemical warfare agents, e.g. for the sulfur mustard agent.

In this article, our aim was to examine the oxidation of thioethers by use of monomer and polymer-bound N-halamine-containing compounds. The mechanism of the oxidation reaction for dimethyl sulfide was investigated with *ab initio* DFT calculations at the B3LYP/6-311+G(2d,p) level. This computational method was chosen because it has been demonstrated to give excellent mechanistic predictions for other reactions involving N-halamines.[11] Experimentally, dimethyl sulfide and a mustard derivative, chloroethyl ethyl sulfide (CEES), were also subjected to oxidation with several N-halamine containing



dichloro beads, $X_1$, $X_2$=Cl
monochloro beads, $X_1$=H, $X_2$=Cl
monobromo beads $X_1$=H, $X_2$=Br

A surface functionilized with a hydantoinyl siloxane

**FIGURE 2** Examples of the N-halamine-based materials.

materials. Characterization of the products was accomplished by analyses of their $^{13}$C-NMR spectra, which were also calculated using the GIAO method.

## RESULTS AND DISCUSSION

In initial studies, dimethyl sulfide (DMS) was used as a model compound. It was reacted with 1-chloro-5,5-dimethylhydantoin (**mcH**) in water to yield a single sulfur-containing product, dimethylsulfoxide (DMSO), along with 5,5-dimethylhydantoin (**H**). The reaction was monitored by observance of the disappearance of the white solid **mcH**, which was water insoluble; whereas **H** is water soluble. Encouraged by this result, we then reacted DMS with 1,3-dichloro-5,5-dimethylhydantoin (**dcH**) in water. The $^{13}$C-NMR spectrum showed that the sulfoxide was produced along with the sulfone. This result was due to the fact that the imide N-halamine function (on the **dcH**), which is less stable than the amide N-halamine function in water toward hydrolysis, was readily dissociated into hypochlorous acid.[11] The HOCl was more reactive and less selective than was the **mcH**. After these reactions were completed, the solutions were acidic.

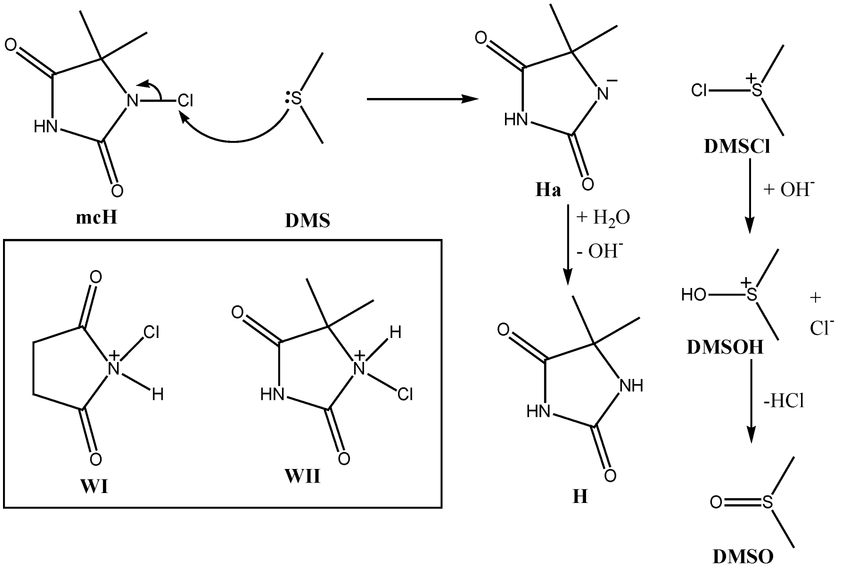


**FIGURE 3** Proposed mechanism of oxidation of DMS to DMSO.

Based upon the previous observation, we have proposed a reaction mechanism (Figure 3) in which the first step involves the lone pairs on the sulfur abstracting the oxidative chlorine from **mcH**, which then abstracts a proton from water to form hydroxide and **H**. The resulting sulfenyl chloride then is attacked by hydroxide to form sulfenyl hydroxide, and then the chloride abstracts the proton to yield hydrogen chloride and dimethyl sulfoxide (DMSO). This reaction mechanism was supported by *ab initio* calculations at the level of B3LYP/6-311+G(2d,p). These calculations are summarized in Figure 3 and Table I. The intermediate **WI** was proposed in the literature for oxidation of aromatic sulfides with N-chlorosuccinimide.[12] Although we have not employed any acid to initiate the reaction, such an intermediate is not likely due to the electronic nature of the nitrogen in structures **WI** and **WII**. Moreover, calculations at the level of B3LYP/6-311+G(2d,p) level of theory showed that **WII** undergoes bond breakage between the nitrogen and the neighboring carbons. The computations for **mcH** reacting with DMS to form **H** and DMSO predict that the overall reaction is exothermic and spontaneous (Table I). When solvation effects were included in the calculations, all steps in the proposed mechanism became reasonable energetically.

With these results in hand, we employed dichloro (polystyrenehydantoin) beads to oxidize DMS in water. Although we had observed that we

**TABLE I The Energies, Enthalpies, and Gibbs Free Energies of the Individual Steps in the Reaction Mechanism**

| Reaction | ΔE (kcal/mol) | ΔH (kcal/mol) | ΔG (kcal/mol)[a] | ΔG (kcal/mol)[b] |
|---|---|---|---|---|
| mcH + DMS → Ha + DMSCl | 123.75 | 122.78 | 123.06 | 24.94 |
| Ha + H2O → H + $OH^-$ | 42.12 | 42.14 | 43.87 | −8.01 |
| DMSCl + OH— → DMSOH + $Cl^-$ | −60.14 | −58.01 | −56.10 | −28.07 |
| DMSOH + $Cl^-$ → DMSO + HCl | −117.12 | −120.09 | −121.99 | −3.28 |
| Overall reaction | −11.39 | −13.17 | −11.15 | −14.41 |

[a] Without solvation effects included; [b] With solvation effects included (see text).

obtained the sulfoxide and the sulfone when **dcH** was employed, the sole product was DMSO with the dichloro beads. This can be attributed to steric hinderance for the polymer beads, which allowed little hydrolysis of the imide N-Cl for the beads.

The experiments were then extended to inactivation of the mustard stimulant. The chemical warfare agent bis(chloroethyl)sulfide is extremely dangerous to handle; thus chloroethyl ethyl sulfide was employed in this work as the mustard derivative, as has been used in previous studies.[5,6] A similar procedure to that employed in the DMS oxidation was applied to that of CEES. CEES was first reacted with **mcH** to yield only the sulfoxide derivative in water. Despite the fact that we obtained two products, sulfoxide and sulfone, for the oxidation of DMS with **dcH**, the CEES reaction with **dcH** yielded only the sulfoxide. From the analysis of the NMR spectra, it was also observed that a small amount of elimination (ethyl vinyl sulfoxide) and substitution (ethyl hydroxyethyl sulfoxide) products were obtained. The reactions were complete within *ca.* 3 min.

The products were characterized with $^{13}$C-NMR; comparisons were made with the literature[13] and calculated data at the level of B3LYP/6-311+g(2d,p) using the GIAO method.[14] The structure was first optimized at the same level; then single point calculations were performed on the optimized structure to obtain isotropic shielding values, which were subtracted from those for calculated tetramethylsilane to give the calculated $^{13}$C-NMR spectrum. As seen in Table II, the calculated and experimental data are in agreement qualitatively, but not quantitatively. Because the calculations were performed for the compounds in the gas phase, media effects and conformational averaging were ignored.[15]

The N-halamine polymer-bound materials developed in these laboratories, such as monochloro poly(styrenehydantoin) beads, the

**TABLE II Theoretical (Experimental) $^{13}$C-NMR values**[a]

| Carbon # | CEES (ppm) | CEESO (ppm) |
|---|---|---|
| C1 | 51.6<br>(43.6) | 50.2<br>(37.4) |
| C2 | 44.9<br>(33.0) | 65.3<br>(53.0) |
| C3 | 38.0<br>(25.1) | 58.1<br>(43.6) |
| C4 | 14.1<br>(14.7) | 9.6<br>(7.0) |

[a] Experimental values were obtained for the compounds dissolved in DMSO-$d_6$.

monobromo- and dichloro-bead derivatives, and the halogenated hydantoinylsiloxane-coated silica gel (monomer or polymer),[16] which have so far mainly been utilized for water disinfection and eliminating noxious odors from cutting oil fluids, should be useful in detoxifying chemical agents. Unlike monochloro and dichloro hydantoin, these polymeric materials are very stable to hydrolysis in water and selective toward most chemical oxidation reactions.

In a typical reaction with these polymeric materials, the oxidizing agents (monochloro poly(styrenehydantoin) or dichloro poly(styrenehydantoin) beads, or chlorinated hydantoinylsiloxane-coated silica gel) were suspended in water, and then CEES was added and allowed to react for 6 h (complete disappearance of the CEES was observed after 2 h reaction time). Extended reaction times for 6 additional h were employed to ensure that the sulfoxide was not oxidized further to the sulfone. In addition to the sulfoxide of CEES, we have observed only small amounts (about 30 %) of hydroxyl and vinyl compounds (See Figure 4) which can arise from direct hydrolyses of CEES. No sulfone, a mustard derivative which is also toxic,[17] was observed in

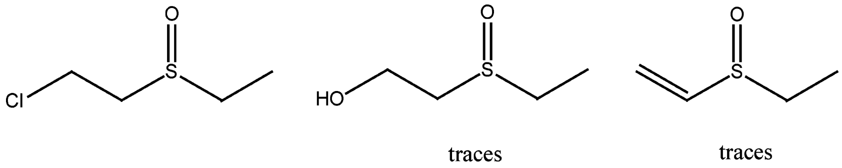


**FIGURE 4** The products from oxidation of CEES with N-halamine-coated materials.

any of the reactions of these polymer materials with extended amounts of reaction time.

## CONCLUSIONS

In this study we have concentrated on the oxidation of organic sulfides, including the sulfur mustard simulant CEES with N-halamine materials. A reaction mechanism was proposed for the oxidation process which was supported by DFT calculations. The product characterization was accomplished by $^{13}$C-NMR, utilizing literature and calculated values. The N-halamine-containing materials, i.e., N-halamine-bound polystyrene and silica gel, can deactivate the sulfur mustard simulant to its sulfoxide, which is less toxic. This work thus demonstrates the utility of employing polymer-bound oxidizing agents to selectively perform an important detoxification reaction.

## EXPERIMENTAL

### General

The N-halamine-containing polystyrene beads were supplied by the HaloSource Company (Seattle, WA), and N-halamine-coated silica gel was prepared according to our published procedure.[16] The calculations were performed with Gaussian 03.[18] Solvation effects were included to the stationary geometries obtained at B3LYP/6-311+G(2d,p) level with the conductor-like polarizable continuum(CPCM) using UAKS cavities.[19] A 1.9 kcal/mol correction factor was added to all solvation free energies, and another 2.4 kcal/mol correction factor was added to the water molecule.[20] $^{1}$H and $^{13}$C NMR spectra were recorded on either a Bruker AC 250 spectrometer or a Bruker AV 400 spectrometer, referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Relative product yields were determined by integration of the areas of the $^{1}$H NMR signals for the products in the crude product mixtures.

### 1-Chloro-5,5-dimethylhydantoin

To a suspension of 1,3-dichloro-5,5-dimethylhydantoin (4.0 g, 0.020 mmol) in 100 ml of water was added 5,5-dimethylhydantoin (2.6 g, 0.020 mol). The mixture was stirred for 2 h at room temperature and then filtered. The white solid was dried at ambient temperature. Spectral data were: $^{1}$H-NMR (250 MHz, $CDCl_3$): $\delta$ 1.5 (s, 6 H), 9.4(s, 1H); $^{13}$C-NMR(62.5 MHz, $CDCl_3$) $\delta$ 174.9, 154.0, 67.3, 22.0.

## Reaction of Sulfides with 1-Chloro-5,5-dimethylhydantoin or 1,3-Dichloro-5,5-dimethyl Hydantoin

To a suspension of 1-chloro-5,5-dimethylhydantoin (1 mole equivalent) in 100 ml of water was added dimethyl sulfide or chloroethyl ethyl sulfide (1 mole equivalent). The mixture was stirred until all white solid disappeared. The reaction is complete within *ca.* 3 min. Then the solvent was removed, and the products in DMSO-$d_6$ were analyzed by NMR (see text). The reaction with 1,3-dichloro-5,5-dimethylhydantoin was repeated with 1:2 mole ratio of **dcH** and the sulfides.

## Reaction of the Sulfides with the N-Halamine-containing Bead Materials

To a suspension of the solid bead materials or N-halamine-coated silica gel (3 g) in 50 ml of water was added the dimethyl sulfide or chloroethyl ethyl sulfide (0.5 g), and the mixture was stirred for 12 h. The reaction was complete within *ca.* 120 min. Then the mixture was filtered from the beads or the silica gel, and excess solvent was removed by evaporation. The residue in DMSO-$d_6$ was analyzed by $^{13}$C-NMR (see text).

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