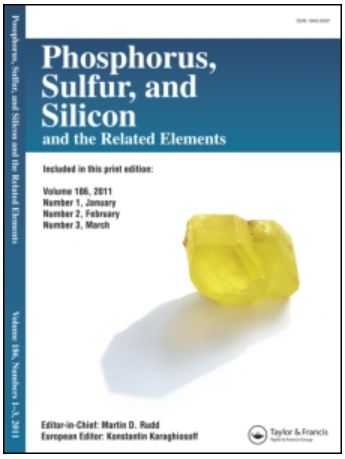


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# CONFORMATIONS OF MUSTARD SULFOXIDE AND MUSTARD SULFONE

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# CONFORMATIONS OF MUSTARD SULFOXIDE AND MUSTARD SULFONE

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Sulfur mustard, bis-(2-chloroethyl)sulfide, has been one of the most commonly used chemicals for chemical warfare since its introduction in World War 1. Decontamination procedures usually involve the oxidation to the corresponding sulfoxide or sulfone. Computational methods were used to identify the most stable conformations and determine their relative energies. The most stable sulfone, determined by Hartree Fock, post Hartree Fock, and density functional methods, was the all trans conformation. For the sulfoxide, the all trans conformer was the most stable by HF and DFT methods; whereas, by MP2 the most stable was the conformation with the chlorides turned away from the lone oxygen.

*Keywords:* mustard sulfoxide; mustard sulfone; Hartree Fock; conformational analysis

## INTRODUCTION

Mustard, *bis*-(2-chloroethyl)sulfide, has been one of the more widely used compounds for chemical warfare purposes. It was used first during World War I[1] and more recently in the Iran/Iraq conflict. Even though its toxicology has been studied for almost a century, the molecular interactions that lead to blisters and erythema are not completely understood.[2] Because of its persistency, active procedures must be employed to remove it from contaminated skin and inanimate surfaces. A frequent method for decontamination is oxidation of the sulfide to the corresponding sulfoxide or sulfone. This can be performed in the laboratory or field with hypochlo-

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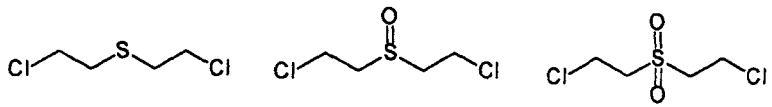
rite. The sulfoxide is generally thought to exhibit little if any toxicity whereas the sulfone may be somewhat toxic but considerably less than mustard itself.[3] Total remediation requires destruction of the diethylsulfide moiety and usually involves more stringent conditions such as combustion at high temperature.

The chemistry of sulfides, sulfoxides and sulfones has received considerable attention recently[4,5] particularly with respect to oxidations.[6] In addition to solution, oxidations have been performed on solid surfaces and in the gas phase. Although gas phase oxidations do not have much synthetic utility, they have important applications in atmospheric chemistry.[7]






Traditionally, oxidation of sulfides have been performed with t-butylperoxide[8] and peracids such as *meta*-chloroperboenzoic acid. With these reagents, temperature was used to control the extent of oxidation. Low temperature gave principally the sulfoxide whereas room temperature oxidations afforded the corresponding sulfone. Frequently, it was difficult to obtain the pure sulfoxide. Oxidation on a surface in which only one side of the molecule is exposed offers the possibility of a stereospecific rather than a stereoselective reaction. For example, the oxidation of glycosyl sulfides by hydrogen peroxide/ acetic anhydride/silica gel in methylene chloride gives exclusively glycosyl sulfoxides.[9] Various inorganic surfaces such as ruthenium,[10] porous carbon,[11,12] silicalite,[13] ferric nitrate and silica gel,[14] cis-dioxomolybdenum VI,[15] and manganese[16] have been utilized in hetergeneous oxidations. Electrochemical methods using a tungstate/pertungstate redox system were very efficient and selective.[17]

Chiral sulfoxides, which may be obtained by a stereospecific oxidation offer many opportunities as reagents for difficult syntheses. Chiral sulfoxides attached to pyrimidines and coordinated to palladium have been used for enantioselective catalysis of allylic substitution[18] and also in the enantioselective synthesis of yohimbine alkaloids.[19]

Chiral sulfoxides have been prepared biochemically by intact *Pseudomonas putida* cells[20] and by a variety of bacterial cyclohexanone monooxygenases.[21]

Pouzet *et al* used x-ray diffraction to determine the structure and deduce the bonding character and aromaticity of 2,5-diphenyl thiophene and its sulfoxide and sulfone analogs.[22] Their data indicated that the substituted thiophenes were planer but the sulphoxide and sulfones were puckered. Their empirical results supported earlier calculations on thiophene sulfoxide using the MNDO Hamiltonian.[23] Both studies suggested that the lack of planarity in the oxides resulted from "pyramidal geometry of the sulfur atom which is more difficult to accommodate in the five member ring because it induces stress in the molecule. Rozas examined a series of thiophenes (containing two, one or no nitrogen atoms) and their sulfoxide and sulfone analogs at the Hartree Fock level with single point 6–31G* energies using STO-3G* geometry.[24] He concluded that the thiophenes themselves were aromatic, but the sulfoxides and sulfones were best described as ylides. Also, there was no evidence of d-orbital participation.

Recent advances in computer hardware and software have permitted more rigorous calculations on sulfur. Jenks *et al* examined a series of 13 sulfoxides including thiophene, benzothiophenes, and thiiranes at levels of theory up to MP4. They confirmed the earlier studies that oxidation of thiophenes eliminated aromaticity. Using an isodesmic oxygen transfer reaction, they determined that the S=O bond dissociation energy was not particularly sensitive to structure, strain, or conjugation unless the corresponding sulfide was aromatic or antiaromatic.[25] Jursic used density functional theory with Becke's 88 functional on a series of 12 valance-electron sulfur compounds. The most stable configuration for $F_4SO$ was a trigonal bipyrimid with the sulfur as the central atom in the center and the oxygen in one of the equitorial positions.[26] The mechanism of the oxidation of hydrogen disulfide and methyl disulfides to thiosulfinates by hydrogen peroxide was deduced from calculations performed with the 6–31G** basis set using post Hartree-Fock levels of theory.[27] The reaction occurs in two steps — an initial high energy 1,2 hydride shift in the peroxide followed by a rapid $S_N2$ type of displacement resulting in the transfer of the oxygen to the sulfur and the release of water.

The recent success with chiral sulfoxides on heterogeneous surfaces for catalyzing stereoselective reactions portends an increased effort to develop new compounds and ligands for other reactions. A rational design for catalysts (particularly mustard oxidation) would be facilitated by increasing the understanding of the various conformations of sulfides and the corresponding sulfoxides and sulfones. Donovan *et al* described the conformations of mustard at levels of theory ranging from molecular mechanics to post Hartree-Fock.[28,29] This paper reports similar calculations on the corresponding sulfoxide and sulfone.

## METHODS

Molecular mechanics studies were performed on an Silicon Graphics Iris 4D/210GTX using Macromodel 3.5.[30] Semiempirical calculations were performed with AMPAC 5.0[31] using an IBM RS/6000 Model 260 workstation. Ab initio calculations at the Hartree Fock level were performed on the same workstation using Gaussian 92. Post Hartree Fock calculations were performed with Gaussian 94 using a Convex 3820. Density functional theory calculations were performed on a SGI Power Challenger Array using Gaussian 94.[32]



## RESULTS

The system for numbering the torsional angles for mustard sulfoxide and mustard sulfone is the same as that used in a previous paper with mustard.[29] The Cl-C-C-S dihedral angles are designated $\alpha 1$ and $\alpha 4$. The internal C-C-S-C dihedral angles are designated $\alpha 2$ and $\alpha 3$. For definition purposes, the chloride is connected to the *terminal* carbon, and *terminal* hydrogens are bonded to the terminal carbon. The *internal* carbon atoms are connected to the sulfur, and likewise, the *internal* hydrogens are connected to the internal carbon atoms. An arm refers to one of the chloroethyl groups. The 10 conformations of the sulfoxide and sulfone described in this paper were numbered to coincide with mustard conformations[29] to facilitate comparisons between molecules. The conformations of mustard sulfoxide and sulfone are illustrated in Figures 1 and 2. Unless otherwise indicated, geometries and energies described in the text were determined at the HF/6-31G* and energies at the MP2/6–31G* level with HF/6–31G* geometries.

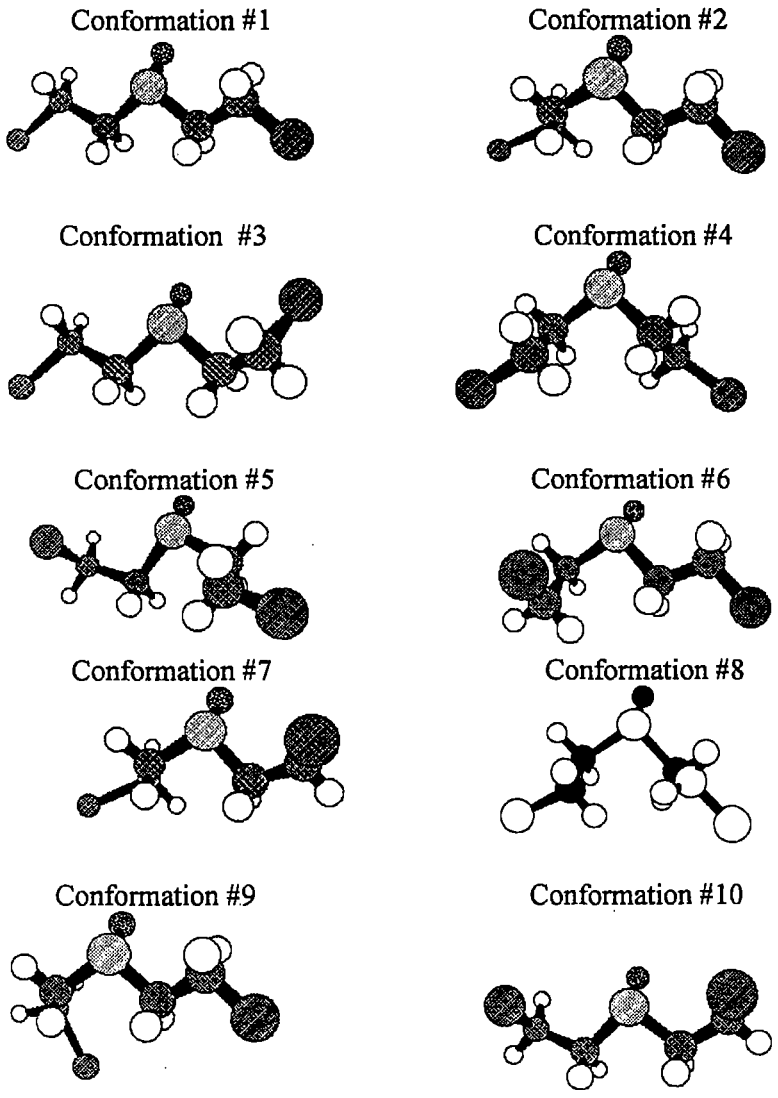



FIGURE 1 Sulfoxide Conformations

Preliminary results were obtained with molecular mechanics and semiempirical methods. The most stable conformations for both sulfoxide and

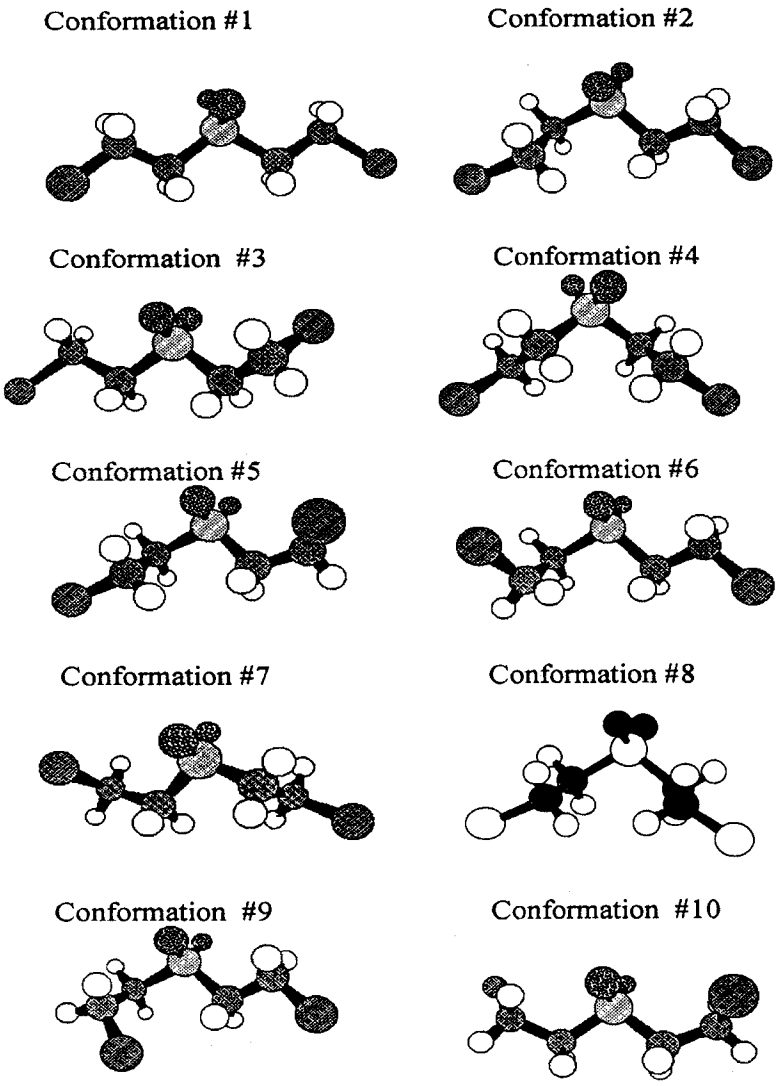



FIGURE 2 Sulfone Conformations

sulfone determined by the MM3 force field were the all *trans* conformation (i.e. conformation #1). With the AM1 Hamiltonian and associated parameters, the most stable sulfoxide conformation had both chlorides in

the gauch positions with α1 through α4 having values of −69°, 110°, 174°, and 66° respectively. For the sulfone, the most stable conformation corresponded to #9 with α1 through α4 equal to 179°, −172°, 91°, −87°. Although this conformation had the lowest energy, four others including the all *trans* (#1) had energies within 0.3 Kcal/mole, an amount too small to be differentiated at the semiempirical level of theory.

Tables I and II delineate the torsional angles for 10 conformations for the sulfoxide and sulfone determined by ab initio and density functional theory methods. Some of the geometric parameters are listed in Tables III and IV. Table V contains the relative energies for mustard,[29] the sulfoxide and sulfone. For these compounds, the sulfur and adjacent carbon atoms form a plane that is used as a reference when describing position of the distal atoms in the various conformations. The bond lengths of the various sulfur bonds calculated at the HF/6–31G* level are constant in all conformations. Jenks *et al* also observed consistent bond lengths among the sulfoxides they studied.[25] Empirically derived bond lengths for mustard and its sulfoxide and sulfone are not available. The S=O distance is 1.49 Å in the mustard sulfoxide and 1.44 Å in the sulfone. The S=O distance for 2,5-diphenyl thiophene oxide, obtained by x-ray crystallography is 1.484Å. The S=O distance for 2,5 diphenyl thiophene sulfoxide is 1.484Å. For the corresponding sulfone the two S=O distances are 1.418Å and 1.427Å. The average S=O distance in 4 amino 4'-nitrodiphenyl sulfone is 1.434Å.[33] The respective S-C bonds are 1.81 Å and 1.79 Å In the sulfoxide, the dihedral angle of the oxygen ranges from 108 to 111 degrees. In the sulfone, the dihedral angle is larger (i.e. 113° to 116°) thereby increasing the oxygen - oxygen separation. The C-S-C angle was also larger in the sulfone than the sulfoxide. The dihedral angle for a nondistorted gauch conformation is 60°. In mustard sulfoxide and sulfone, the angle for the gauch conformation is usually about 75 degrees thereby increasing the difference between the heavy atoms.

Conformation 1 is the all *trans* conformer. For the sulfone, all methods give a C2v symmetry with the dihedrals of 180 degrees for the heavy atoms. This orientation provides the maximal separation of the heavy atoms and is the lowest energy. In the sulfoxide, the single oxygen bonded to the sulfur induces some asymmetry in the molecule and causes the proximal angles, α2 and α3, to shift about 7 degrees away from the oxygen. This is the most stable sulfone conformation. It is also the most stable sulfoxide conformation at the Hartree-Fock and density functional levels; however, with MP2 calculations, the energy is 0.24 Kcal/mole higher than conformation #10.

TABLE I Dihedral Angles of Mustard Sulfoxide Conformers

| *Angle* | *Method* | *Basis Set* | *# 1* | *#2* | *#3* | *#4* | *#5* | *#6* | *#7* | *#8* | *#9* | *#10* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α1 | HF | 3–21G* | 176 | -176 | 176 | 176 | -175 | -176 | -170 | 174 | 178 | -71 |
| | HF | 6–31G* | 180 | 179 | 180 | 174 | -175 | 180 | -174 | 174 | -179 | -72 |
| | HF | 6–311** | 180 | 179 | 180 | 174 | -176 | 180 | -174 | 175 | -178 | -72 |
| | B3LPY | 6–31G* | 178 | -179 | 178 | 173 | -173 | -178 | -169 | 173 | -179 | -71 |
| α2 | HF | 3–21G* | -167 | 163 | -164 | 81 | -75 | 160 | -80 | 70 | 166 | -165 |
| | HF | 6–31G* | -173 | 174 | -170 | 73 | -77 | 167 | -75 | 69 | -179 | -172 |
| | HF | 6–311G** | -173 | 173 | -169 | 73 | -78 | 167 | -75 | 70 | -178 | -172 |
| | B3LPY | 6–31G* | -173 | 171 | -168 | 75 | -74 | 165 | -76 | 69 | -173 | -170 |
| α3 | HF | 3–21G* | 176 | -80 | -161 | 79 | -165 | 63 | 163 | -107 | 84 | 165 |
| | HF | 6–31G* | 173 | -75 | -157 | 76 | -172 | 62 | 174 | -107 | 75 | 172 |
| | HF | 6–311G** | 173 | -76 | -151 | 76 | -172 | 62 | 173 | -109 | 76 | 172 |
| | B3LYP | 6–31G* | 173 | -76 | -154 | 73 | -169 | 60 | 170 | -108 | 83 | 170 |
| α4 | HF | 3–21G* | -176 | -169 | -67 | 170 | -71 | 59 | 71 | -178 | -94 | 71 |
| | HF | 6–31G* | 180 | -174 | -68 | 175 | -72 | 60 | 71 | 180 | -92 | 72 |
| | HF | 6–311G** | 180 | -174 | -65 | 175 | -72 | 60 | 71 | 180 | -92 | 72 |
| | B3LYP | 6–31G* | -178 | -169 | -65 | 169 | -71 | 58 | 70 | -178 | -92 | 71 |

TABLE II Dihedral Angles of Mustard Sulfone Conformers

| *Angle* | *Method* | *Basis Set* | *#1* | *#2* | *#3* | *#4* | *#5* | *#6* | *#7* | *#8* | *#9* | *#10* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α1 | HF | 3–21G* | 180 | 180 | 180 | -177 | 176 | 180 | -177 | 173 | 179 | 76 |
| | HF | 6–31G* | 180 | 180 | 180 | -179 | 178 | 180 | -179 | 175 | 180 | 78 |
| | HF | 6–311G** | 180 | 180 | 179 | -179 | 179 | 180 | -179 | 176 | 180 | 77 |
| | B3LYP | 6–31G* | 180 | 180 | 180 | -177 | 177 | 180 | -178 | 174 | -179 | 77 |
| α2 | HF | 3–21G* | 180 | -178 | 177 | -78 | 76 | -178 | -80 | 85 | 178 | 161 |
| | HF | 6–31G* | 180 | 179 | 178 | -75 | 73 | 180 | -79 | 73 | 175 | 164 |
| | HF | 6–311G** | 180 | 179 | 177 | -74 | 74 | -179 | -79 | 83 | 174 | 163 |
| | B3LYP | 6–311G* | 180 | -179 | 175 | -76 | 74 | -178 | -79 | 78 | 178 | 162 |
| α3 | HF | 3–21G* | 180 | 78 | 159 | -78 | 161 | 79 | 159 | -85 | 84 | 161 |
| | HF | 6–31G* | 180 | 75 | 164 | -75 | 164 | 77 | 164 | -93 | 80 | 164 |
| | HF | 6–311G** | 180 | 75 | 161 | -74 | 162 | 76 | 161 | -83 | 80 | 162 |
| | B3LYP | 6–31G* | 180 | 76 | 159 | -76 | 161 | 76 | 159 | -87 | 82 | 161 |
| α4 | HF | 3–21G* | 180 | 176 | 76 | -177 | 76 | 83 | 75 | -177 | -81 | 76 |
| | HF | 6–31G* | 180 | 178 | 78 | -178 | 79 | 86 | 78 | -179 | -81 | 78 |
| | HF | 6–311G** | 180 | 179 | 77 | -179 | 77 | 86 | 76 | -176 | -81 | 77 |
| | B3LYP | 6–31G* | 180 | 177 | 76 | -178 | 77 | 83 | 76 | -175 | -80 | 77 |

TABLE III Selected Geometric Parameters of Mustard Sulfoxide Conformers

| *Parameter* | *#1* | *#2* | *#3* | *#4* | *#5* | *#6* | *#7* | *#8* | *#9* | *#10* |
|---|---|---|---|---|---|---|---|---|---|---|
| S=O | 1.49 | 1.49 | 1.48 | 1.49 | 1.49 | 1.49 | 1.49 | 1.48 | 1.49 | 1.49 |
| C3-S | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 |
| C5-S | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.81 | 1.82 | 1.81 | 1.81 |
| C-S-C | 97.3 | 99.3 | 96.4 | 101.0 | 98.4 | 98.8 | 99.0 | 100.0 | 101.4 | 96.6 |
| C3-S=O | 106.7 | 107.0 | 105.6 | 105.6 | 104.8 | 104.2 | 106.9 | 104.7 | 106.3 | 105.4 |
| C5-S=O | 106.7 | 106.3 | 108.5 | 106.2 | 105.8 | 105.9 | 105.3 | 106.0 | 106.4 | 105.4 |
| O-S-C-C | 110. | 110. | 111. | 110. | 108. | 109. | 109. | 110. | 111. | 108. |

TABLE IV Selected Geometric Parameters of Mustard Sulfone Conformers

| *Parameter* | *#1* | *#2* | *#3* | *#4* | *#5* | *#6* | *#7* | *#8* | *#9* | *#10* |
|---|---|---|---|---|---|---|---|---|---|---|
| S=08 | 1.44 | 1.44 | 1.43 | 1.44 | 1.43 | 1.43 | 1.44 | 1.43 | 1.44 | 1.44 |
| S=09 | 1.44 | 1.44 | 1.43 | 1.44 | 1.44 | 1.44 | 1.43 | 1.44 | 1.44 | 1.44 |
| C3-S | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 |
| C5-S | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 | 1.79 |
| C3-S-C5 | 103.8 | 105.3 | 102.9 | 106.7 | 104.4 | 104.3 | 104.1 | 107.1 | 107.3 | 101.7 |
| C3-S=O8 | 108. 1 | 107.7 | 107.5 | 107.6 | 106.9 | 107.4 | 106.7 | 106.0 | 108.1 | 109.9 |
| C3-S=O2 | 108.1 | 107.5 | 107.8 | 106.8 | 107.5 | 107.4 | 107.9 | 107.8 | 107.2 | 106.7 |
| O8-S-C3-C5 | 115. | 115. | 116. | 114. | 113. | 116. | 116. | 114. | 116. | 113. |
| O9-S-C3-C5 | -115 | -114 | -113 | -115 | -116 | -113 | -113 | | -113 | -115 |



In conformation 2, one arm of the molecule is in the trans orientation and the other in the gauch. For the sulfoxide, $\alpha 3$ has rotated to a value of 77 degrees bringing one of the chloromethyl moieties out of the plane and away from the oxygen. In the sulfone, $\alpha 3$ has a similar value of 75 degrees. The C-S-C bond has increased about 2 degrees; however, there is little change in the oxygen bond angles. Because the chloride dihedral ($\alpha 4$) remains at 180°, the chloride is oriented away from the oxygens. Conformation #2 is one of the more stable.

In conformation 3, one of the terminal chlorides is in the gauch conformation. The values of $\alpha 4$ in the sulfoxide and sulfone are −65° and −77° respectively. This rotation brings the chloride into close proximately to the oxygen. Even with a shift of about 20° in $\alpha 3$, the O-Cl distance is the shortest (i.e. 3.55 Å) among the 10 conformers. This conformation has one of the highest energies.

TABLE V Relative Energies of Conformers (in Kcal/Mole)

| | *Method* | *#1* | *#2* | *#3* | *#4* | *#5* | *#6* | *#7* | *#8* | *#9* | *#10* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MUSTARD SULFOXIDE | HF/3–21G* | 1.37 | 0.33 | 5.52 | 2.74 | 3.09 | 2.20 | 0.0 | 7.24 | 0.75 | 0.72 |
| | HF/6–31G* | 0.00 | 2.36 | 4.47 | 2.96 | 2.58 | 2.67 | 0.97 | 5.83 | 0.88 | 0.77 |
| | HF/6–311G** | 0.00 | 0.06 | 4.41 | 2.23 | 2.12 | 2.25 | 0.41 | 5.17 | 1.00 | 0.43 |
| | B3LYP/6–31G* | 0.00 | 0.26 | 3.37 | 2.21 | 1.78 | 2.05 | 0.34 | 4.57 | 0.56 | 0.13 |
| | MP2/6–31G*// HF/6–31G* | 0.24 | 0.50 | 3.65 | 2.78 | 2.21 | 2.28 | 0.44 | 5.69 | 0.91 | 0.00 |
| MUSTARD SULFONE | HF/3–21G* | 0.00 | 0.45 | 2.68 | 0.82 | 3.32 | 4.70 | 6.33 | 2.20 | 2.71 | 5.43 |
| | HF/6–31G* | 0.00 | 1.00 | 2.03 | 1.96 | 4.61 | 5.20 | 4.78 | 3.16 | 0.90 | 7.09 |
| | HF/6–311G** | 0.00 | 0.60 | 3.49 | 1.16 | 4.11 | 4.87 | 4.30 | 2.45 | 0.46 | 6.99 |
| | B3LYP/6–31G* | 0.02 | 0.50 | 2.62 | 0.92 | 3.19 | 4.14 | 3.20 | 1.83 | 0.00 | 5.15 |
| | MP2/6–31G*// HF/6–31G* | 0.00 | 0.55 | 2.61 | 1.01 | 3.24 | 4.16 | 3.29 | 2.16 | 0.91 | 5.13 |
| MUSTARD | MP2/6–31G*// HF/6–31G* | 1.97 | 0.93 | 3.03 | 0.00 | 1.93 | 2.65 | 2.23 | 0.74 | 2.19 | 4.19 |

In conformation 4, both internal angles are in the gauch position but oriented such that one of the chloromethyl groups is in front of the plane and the other behind. The sulfone is symmetrical with α2 and α3 having values of 75° and α1 and α4 having values of 179°. For the sulfoxide, one arm is on the same side as the oxygen and the other is opposite. The sulfoxide is slightly distorted with α2 and α3 having values of 73° and 75°. Also α1 and α4 have shifted about 5° depending on the basis set. This was the most stable mustard conformer; however, the oxygen atoms create moderate steric hindrance making this an intermediate energy conformation for the sulfoxide and sulfone.

In conformation 5, one of the internal angles (α2) and the opposite external (α4) are in the gauch orientation. In the sulfone conformation #5, rotation of α4 into the gauch position (77°) orients one side of the molecule similar to conformation #3 and brings the chloride into proximity to the oxygen. On the other arm, rotation of α2 into the gauch position (74°) creates a local structure resembling part of conformation #2. Addition of the relative energies for conformations #2 and #3 (i.e., 0.55 + 2.61 = 3.16) approximates the energy of conformation #5 (i.e. 3.24 Kcal/mole). Similar comparisons cannot be made for the sulfoxide because the lone oxygen imposes additional dissymmetry. In the sulfoxide, rotation of the chloride (α4 = −71°) away from the heavy atoms creates a favorable orientation. Orienting the opposite chloromethyl group (α2 = −74°) toward the oxygen induces some steric interactions and results in a sulfoxide conformation that is 2.21 Kcal/mole (3.24 Kcal/mole for the sulfone) above the most stable.

In conformation 6, one arm of the molecule is unchanged. Rotation of α3 brings the methyl group out of the plane; subsequent rotation of α4 shifts the chloride into a gauch conformation. In the sulfoxide, because the rotation is away from the oxygen, this is a relatively stable conformer. In the sulfone with oxygens on both sides of the molecule, the combination of gauch orientations for α3 and α4 reduces the O-Cl distance to 3.4Å, the shortest among the 10 conformers and leads to the highest energy.

Conformation 7 is similar to conformation 5 (opposite orientations in Figures 1 and 2) except the chlorine is rotated (α4) in the opposite direction. Because the sulfone has 2 oxygens, the interactions among the atoms are equivalent leading to essentially equal energies for conformers #5 and #7. In the sulfoxide, the rotation of the chloride (α4 =70°) in the opposite direction away from the oxygen creates a very stable conformation, which is only 0.44 Kcal/mole above the reference.

Conformation #8, would not have been included due to the high sulfoxide energy except this conformation for mustard is the second most stable conformer with a relative energy of 0.71 Kcal/mole. This conformation is similar to conformation #4 except that both chloromethyl groups are in front of the plane. Both chlorides retain their *trans* orientation. To minimize the steric interactions, $\alpha 2$ and $\alpha 3$ are 77° and −102° in mustard and 70° and −109° in the sulfoxide. The sulfone differed significantly with $\alpha 2$ and $\alpha 3$ equal to 83° and −83° respectively. The sulfone conformation was almost symmetrical with one oxygen and one hydrogen on each of the chloromethyl groups forming a triangle at the top of the molecule with O-H distances of 2.69 and 2.66 Angstroms. To minimize the possibility of missing the corresponding conformation, the sulfoxide dihedrals were reset at 175, 75, −75, −175 and the sulfone at 175, 67, −107, −175. Upon reoptimization, the molecules returned to conformation #8 geometries. As mentioned above, this is one of the most stable conformations for mustard, which has no oxygens. It has the highest energies for the sulfoxide, which has the oxygen away from the chloromethyl groups. It is intermediate energy for the sulfone, in which one of the oxygens is in the center of the alkyl groups. The high energy in the sulfoxide conformation probably results from steric repulsion ($H_9$-$H_{15}$ = 2.54Å) between two of terminal hydrogens located on different arms. This problem is abated somewhat in the sulfone (even though the H-H distance is reduced to 2.35Å) by interactions of the other terminal hydrogens with the oxygen. This type of interaction also occurs in conformation #9. Hydrogen bonding is not possible in the sulfoxide because the lone oxygen is on the other side of the molecule.

In conformation #9, both heavy atoms on one arm of the molecule are in the *trans* orientation and both on the other the arm in the gauch. Both chlorides are pointing down and away from the oxygens. For the sulfones, the only difference between conformations 6 and 9 is the direction of the chloride. In the sulfoxide, the chloromethyl group is oriented into the plane of the paper toward the single oxygen. In the illustration, for the sulfone (Figure 2), the left arm is depicted out of the plane for clarity. For the sulfone, $\alpha 3$ and $\alpha 4$ have values of 80° and −81° respectively. In the sulfoxide, the corresponding values are 75° and −92°. The most interesting aspect of this conformation is the proximity of one of the terminal hydrogens to the oxygen. This distance (2.45Å in the sulfoxide and 2.57Å in the sulfone) is considerably shorter than 2.8Å for the hydrogens on the other arm of the molecule. The C-H bond distance for the two hydrogens is constant at

1.078Å. Mulliken partial charges on the hydrogens reflect the O-H distance as indicated in Table VI.

TABLE VI Partial Charges on Terminal Hydrogens and O-H Bond Distance (MP2/6–31G*//HF/6–31G*)

| | *Sulfoxide* | | *Sulfone* | | |
|---|---|---|---|---|---|
| | *Charge* | *O-H* | *Charge* | *O6-H* | *O7-H* |
| H9 | .227 | 3.53 | .244 | 4.66 | 3.95 |
| H10 | .258 | 2.80 | .272 | 4.14 | 2.57 |
| H15 | .235 | 3.85 | .260 | 2.74 | 3.52 |
| H16 | .277 | 2.45 | .256 | 3.42 | 2.87 |



The Mulliken charges for the two hydrogens having O-H distances of 2.45Å and 3.85Å are .277 and .235 in the sulfoxide. In the sulfone, the distance between $O_7$ and $H_{10}$ is 2.57Å leading to a partial charge of .272 on the hydrogen. For reference purposes, partial charges and O-H bond distances in conformation #1 of mustard sulfone are 0.260 and 2.82Å.

In conformation 9A of the sulfoxide, the chloromethyl group is oriented away from the oxygen - thereby eliminating any hydrogen bonding between the terminal hydrogens and the oxygens. Table VII delineates the torsional angles and relative energies.

In the sulfone, conformation 9 and 9A are the same because oxygens are on both sides of the molecule.

In conformation 10, the sulfoxide and sulfone are oriented differently. For both compounds, $\alpha 4$ is rotated 77°, which brings the chloride out of the plane. In the sulfone, $\alpha 1$ is also rotated 77°; whereas the sulfoxide is rotated –71°. The result is the positioning of the 2nd chloride in front of the plane for the sulfoxide and behind the plane for the sulfone. Thus, both chlorides are away from the oxygen in the sulfoxide. In the sulfone, which has oxygens on both sides of the molecule, the chlorides are positioned so they are maximally separated from each other. Based on MP2/6–3 1G*//HF/6–3 1G* energy calculations, this was the most stable conformation for the sulfoxide but one of the highest for mustard and the sulfone.

TABLE VII Torsional Angles and Relative Energies for Conformation 9A

| *Method* | *α1 (degrees)* | *α2 (degrees)* | *α3 (degrees)* | *α5 (degrees)* | *Redlative Energy (Kcal/mole)* |
|---|---|---|---|---|---|
| HF/3–21G* | 173 | -168 | -103 | 68 | 3.33 |
| HF/6–31G* | 179 | -175 | -103 | 70 | 1.61 |
| HF/6–311G** | 179 | -174 | -104 | 70 | 2.01 |
| B3LYP/6-31G* | 177 | -175 | -104 | 70 | 1.63 |
| MP2/6–31G* | | | | | 2.1 1 |

## DISCUSSION



Monte Carlo conformational searches generated numerous conformations that served as initial geometries for the higher level calculations. Frequently, semiempirical methods produce reasonably accurate geometries; however, the truncated Hamiltonian is insufficient for precise energy calculations - particularly the small differences between conformations. Although semiempirical methods provided some insight into the nature of the conformations, they were of limited value in this study. The geometries differed so much from the ab initio results that it was not possible to match some semiempirical geometries to specific conformations determined at higher levels of theory. Similar discrepancies between semiempirical and ab initio geometries were observed with aryl sulfides and sulfones.[33] It is important to note that sulfur is a second row element, and our calculations were performed with the AM1 and to a lesser extent with PM3. More sophisticated semiempirical methods incorporating d orbitals such as SAM1 and MNDO-d may give different results.

The calculations on mustard, mustard sulfoxide, and mustard sulfone indicate a number of conformations with similar energies. Approximately half of the 10 reported here are within 1 Kcal/mole of the most stable conformation. The oxygen atoms play a major role in determining the relative stability; however, stability is not a direct function of oxygen chlorine repulsion because a plot of the oxygen chlorine distance did not correlate with energy. In some conformations (i.e., #8 and #9) the proximity of one terminal hydrogen to an oxygen resulted in a shift in electron density from

the hydrogen to the oxygen - thereby making the hydrogen more positive than the other hydrogen attached to the same carbon. This C-H-O hydrogen bonding, appears to lower the energy of some conformations that would appear to be considerably less stable based solely on steric considerations. The acidity of the C-H group, making the long range interaction possible, is increased by the electronegative chloride attached to the carbon atom.

The C-S-C angle varied from 96.6° to 101.4° for the sulfoxide and 101.7° to 107.3° for the sulfone. The smaller bond angles occurred when α2 and α3 were 180°. When the chloromethyl group was in one of the gauch conformations, the C-S-C angle increased. This feature was somewhat additive because the largest C-S-C bond angles occurred when both chloromethyl groups were gauch.



In the absence of hydrogen bonding, conformations with adverse steric interactions are usually higher energy than those in which the larger atoms are separated. A molecule like n-heptane can minimize steric interactions by adapting the all *trans* conformation in which the dihedral angles of the heavy atoms are 180°. Mustard has a bivalent sulfur atom containing 2 pairs of nonbonded electrons. The most stable conformations for mustard are #2 and #4, in which the chloromethyl groups are twisted to maximize their separation. The most stable conformation for mustard sulfoxide with a single point MP2 calculation is #9 in which both chloromethyl groups are on the same side away from the oxygen. With Hartree-Fock and DFT calculations, the all trans (conformation #1) was most stable. In the sulfone, oxygens are on both sides of the molecule so the maximal separation can be achieved with all heavy atoms in the *trans* orientation.

The orientation and strength of binding of a substrate to a surface depends on the molecular nature of the surface and how the substrate adapts. Based on the gas phase calculations, the number of conformations with similar energies suggests that the binding of each of three compounds to surfaces should not be limited by the inability of the molecule to conform to the surface. Except for conformation 2, the stable conformations were different for mustard, the sulfoxide, and sulfone. Therefore, during oxidation of mustard to the sulfoxide or the sulfoxide to the sulfone, there are several possibilities for mustard or mustard sulfoxide in a high energy conformation to be oxidized to a product in a low energy conformation without changing conformations.

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