



# Investigation of Polysulfide Mustard Analogues and Reactive Intermediates from Levinstein Mustard by Density Functional Theory (DFT)

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## I. INTRODUCTION

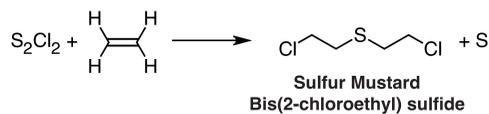
Sampling and analysis of environmental and biomedical samples are key elements of the verification regime of the Chemical Weapons Convention (CWC) as it is the only way to prove the presence (or absence) of chemicals relevant to the Convention. The OPCW Laboratory constantly aims to improve the toolkit available to the Organisation by investigating new analytical methods and new (bio)markers of exposure to chemical warfare agents. Methods to obtain chemical signatures that point to production methods or sources of raw materials of agents (for example by impurity profiling) also fall into this area and have received renewed interest as an important part of Chemical Forensics.

Recently, a OPCW Fact Finding Mission (FFM) was able to confirm "with utmost confidence" that at least two people were exposed to sulfur mustard in the town of Marea in Syria during an attack on 21 August 2015 allegedly carried out by a non-state actor. The OPCW has also recently worked with Iraqi authorities leading to the confirmation of the use of sulfur mustard in the Kurdistan Region of Iraq.

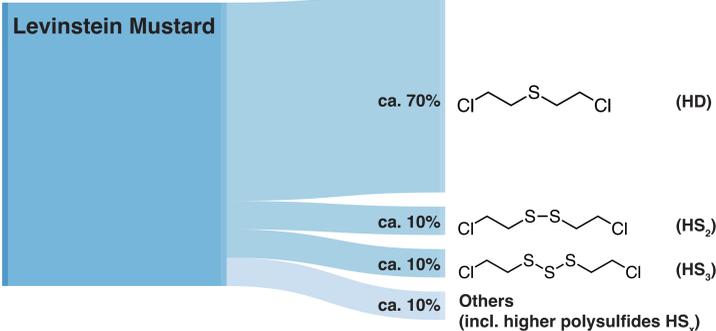
As thiodiglycol (TDG), the main precursor for the production of highly pure sulfur mustard, is a highly regulated chemical (Schedule 2.B.13 of the CWC) and is on the export control list of the Australia Group, non-state actors might turn to alternative production methods that result in an impure but still highly toxic form of "crude" sulfur mustard. One of these alternative methods is the Levinstein Process.

## 2. LEVINSTEIN MUSTARD

Sulfur Mustard was first used in combat by German troops near Ypres in July 1917. Germany employed the Meyer-Clarke Process in which TDG is the key precursor component and that resulted in a product of high purity. As key intermediates in this process were not available from the Allied chemical industries at short notice, the UK and the USA employed an alternative route known as the Levinstein Process in which sulfur monochloride is reacted with dry ethylene under controlled conditions to directly yield sulfur mustard<sup>[1]</sup>:



The final product is an impure mixture containing about 70% sulfur mustard (HD). The two main impurities (ca. 10% ± 5% of each depending on the reaction conditions and age of the sample) are the di- and trisulfide analogues of sulfur mustard: Bis(2-chloroethyl) disulfide (HS<sub>2</sub>) and Bis(2-chloroethyl) trisulfide (HS<sub>3</sub>)<sup>[2]</sup>. These compounds and the higher polysulfides are also known as the "Levinstein Mustards". Because of their large relative amounts HS<sub>2</sub> and HS<sub>3</sub> might lead to significant amounts of degradation/reaction products in the environment resulting in a unique chemical signature. Therefore, the reactivity and potential reaction pathways of HS<sub>2</sub> and HS<sub>3</sub> are of significant interest but were not subject of intense study since the 1940s<sup>[3]</sup>.



## 3. DENSITY FUNCTIONAL THEORY

Density Functional Theory (DFT) is a method to determine the quantum mechanical ground state of a many-electron system (such as atoms and molecules) based on the location-dependent electron density. DFT is founded on the Hohenberg-Kohn Theorem that states that the ground-state of a system of  $N$  electrons is fully described by the location-dependent electron density  $n(\vec{r})$ . All other properties of the system, for example the total energy, can be derived from the density. These other properties are therefore functionals (functions of functions) of the density. DFT is among the most popular methods in computational chemistry and one of its theoretical pioneers, Walter Kohn, was awarded the Nobel Prize in Chemistry in 1998.

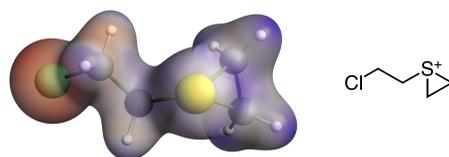
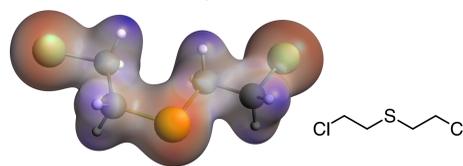
This work was carried out using the software Amsterdam Density Functional (ADF) 2016 employing the OLYP functional and the TZ2P basis set.

## REFERENCES

- [1] R. Macy, G.N. Jarman, A. Morrison, E. Emmet Reid, *Science*, 1947, **106** (2755), 355-359
- [2] D.H. Rosenblatt, M.J. Small, T.A. Kimmell, A.W. Anderson; Background Chemistry for Chemical Warfare Agents and Decontamination Processes in Support of Delisting Waste Streams at the U.S. Army Dugway Proving Ground, Utah; ANL/EAD/TM-56, Argonne National Laboratory, 1996
- [3] A.M. Kinnear, J. Harley-Mason, *J. Soc. Chem. Ind.*, 1948, **67** (3), 107-110
- [4] S. Franke, Lehrbuch der Militärchemie, Bd.1, Deutscher Militärverlag, Berlin(Ost), 1969
- [5] National Research Council of the National Academies, Interim Design Assessment for the Blue Grass Chemical Agent Destruction Pilot Plant, 2005, Appendix C

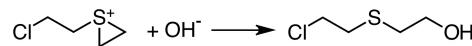
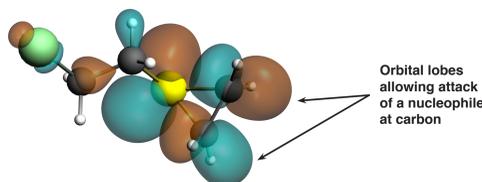
## 4. REACTIVITY OF SULFUR MUSTARD

The chemistry of HD is dominated by the polar carbon-chlorine bonds and the ability of the sulfur atom to stabilize a reactive episulfonium ion which is an effective electrophile and reacts with numerous nucleophiles (including the mildly nucleophilic sulfur atoms of other HD molecules).



According to Molecular Orbital (MO) Theory the Highest Occupied Molecular Orbital (HOMO) of the nucleophile will interact with the Lowest Unoccupied Molecular Orbital (LUMO) of the episulfonium ion (the electrophile). Visual inspection of the LUMO clearly shows orbital lobes at the two cyclic carbon atoms, allowing attack of the nucleophile at these sites.

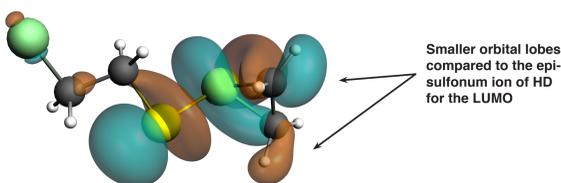
Example of the reaction of a nucleophilic hydroxide ion with the episulfonium ion resulting in ring opening and the effective substitution of chlorine by a hydroxyl group. If both chlorine atoms are replaced this leads to thiodiglycol lacking the specific toxicity of HD.



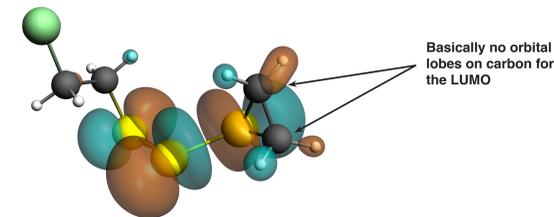
Starting from the optimized structure of HS<sub>2</sub> the abstraction of chloride from the molecule and subsequent geometry optimization also leads to formation of the episulfonium ion as the most stable structure. However, visual inspection of the LUMO clearly shows that most of the molecular orbital is centered around the sulfur atoms with only small lobes at the ring carbons. This is indicative of a reduced reactivity of HS<sub>2</sub> compared to HD as nucleophilic attack on the sulfur does not result in any good leaving group to complete the reaction.

## 5. EPISULFONIUM IONS OF HS<sub>2</sub> AND HS<sub>3</sub>

A similar procedure for HS<sub>3</sub> leads to an episulfonium ion with orbital lobes for the LUMO almost exclusively located at the sulfur atoms but not at the ring carbons.



Basically no orbital lobes on carbon for the LUMO



This trend is mirrored by the vesicant properties<sup>[4]</sup> of HS<sub>2</sub> (1-2% of the vesicant power of HD) and HS<sub>3</sub> (no vesicant properties) although other factors (e.g. toxicokinetics) will play an important role as well. It is important to note the differences in the relative Gibbs Free Energies of the episulfonium ions. Relative to the episulfonium ions of HD the one for HS<sub>2</sub> is 7.64 kJ/mol less stable and the one for HS<sub>3</sub> is 33 kJ/mol less stable in the gas phase. There is a more pronounced effect when including solvation effects using the COSMO solvation model and water as the solvent. Here the episulfonium ion for HS<sub>2</sub> is 15.58 kJ/mol less stable and the one for HS<sub>3</sub> 57.44 kJ/mol less stable.

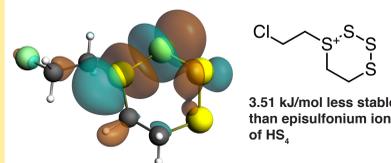
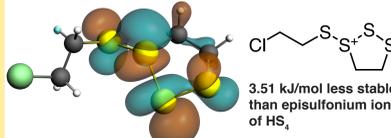
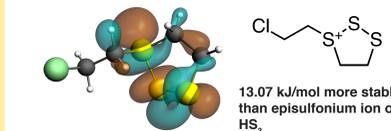
## 6. ORBITAL ENERGY LEVELS

Analysis of the MO energy levels of the episulfonium ions of HD vs. HS<sub>2</sub> and HS<sub>3</sub> reveals that the sulfur centered LUMOs for HS<sub>2</sub> and HS<sub>3</sub> are the LUMO+1 for the HD ion. Addition of a second or more sulfur atoms therefore leads to a stabilization of the MOs with a strong sulfur component due to possibility to delocalize the positive charge on the polarizable sulfur atoms.



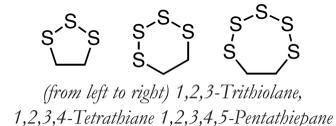
## 7. OTHER SULFONIUM IONS

Starting with HS<sub>2</sub> it is theoretically possible to generate sulfonium ions where more than one sulfur atom is part of the ring structure. Investigating such structures for HS<sub>2</sub>, HS<sub>3</sub> and HS<sub>4</sub> showed that no four-membered ring structures are formed. Therefore the episulfonium ion is the only reactive intermediate for HS<sub>2</sub>. However, for HS<sub>3</sub> and HS<sub>4</sub> such alternative structures are possible with similar energies compared to the episulfonium ions or even more stable. LUMO MOs are all predominantly located at the sulfur atoms.



## 8. CONCLUSIONS

The presence of significant quantities of HS<sub>2</sub>, HS<sub>3</sub> and higher polysulfides in Levinstein Mustard and the differences in the electronic structure of reactive intermediates give rise to a number of distinct degradation products. For example, the cyclic sulfonium ions with five-, six- or even seven-membered rings can undergo elimination reactions leading to the sulfur-rich heterocycles 1,2,3-Trithiolane, 1,2,3,4-Tetrathiane and 1,2,3,4,5-Pentathiepane respectively. These three compounds were found during analysis of old Levinstein Mustard from artillery shells in the USA prior to destruction<sup>[5]</sup>.



While knowledge of degradation and reaction products from old munitions after decades of storage is important to understand possible reactions of Levinstein Mustard, very little is available in the open literature regarding agent fate of the Levinstein polysulfides from fresh Levinstein Mustard in common matrices such as soil, building materials, vegetation and water. Finding specific markers of the polysulfide mustards would enhance the verification mechanism in an investigation of Alleged Use in general but might also yield markers with long half-lives that would allow post-incident analysis for prolonged periods of time.