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Harmony of computational quantum chemistry and experimental chemistry: Comprehensive DFT studies, microsynthesis, and characterization of mustard gas polysulfide analogues

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ABSTRACT

After microsynthesis, structures of mustard gas polysulfide analogues were characterized using electron impact (EI) mass spectrometry. General EI fragmentation pathways for such compounds are proposed. The structure of sulfur mustard (HD) and its two other polysulfide analogues have been examined through B3LYP/6-311++G(2d, 2p) calculations. Geometrical analysis of HD shows that the calculated bond distances are satisfactorily comparable with experimental results. Calculated NMR chemical shifts for HD also were compared with experimental data, indicating good agreement both for ^{1}H and ^{13}C atoms. The vibrational frequencies of HD and polysulfide analogues have been precisely assigned. At the end, based on visual inspection of lowest unoccupied molecular orbitals and the relative difference in the total energies of their episulfonium ions, relative reactivity of HD and its polysulfide analogues were investigated.

1. Introduction

The Chemical Weapons Convention (CWC) prohibits the production, development, storage, and use of chemical warfare agents (CWAs) [1]. Organization for the Prohibition of Chemical Weapons (OPCW) is a responsible body to implement CWC [2]. Vesicant or blister agents due to their toxicity, and relative ease of preparation, are of great concern. Sulfur mustard, namely bis(2-chloroethyl) sulfide, (HD) is a vesicant chemical agent which can bond to hydroxyl (OH) and thiol (SH) groups of enzymes [3,4]. HD as a chemical warfare agent, for the first time was used by German troops near Ypres in July 1917. During Iran-Iraq war (1980–1988), Iraqi forces used HD against Iranians and the Kurd defenseless people [5]; and OPCW confirmed that HD was used in Syria conflict [6]. Such tragic events show that despite international community activities, chemical warfare agents especially HD are still a threat. To implement CWC verification, detection of banned chemicals at trace levels and identification of CWC-related compounds in suspected samples are required. Due to the internationally sensitive nature of verification process, unambiguous identification should be considered, in which the final structure of the suspected analyte is confirmed through the use of reference chemical. In most cases, reference chemicals are selected based on collected NMR, FT-IR, and mass spectroscopic data; and after synthesis/preparation, their physical and chemical properties such as chromatographic retention data are compared with that of the analyte [7]. Therefore, availability of such analytical data and interpretation knowledge provide immense help through the way of unambiguous identification [8–10]. Today, analytical data of many CWC-related compounds are available through OPCW Central Analytical Database (OCAD), which is used during inspections by OPCW inspectors and by laboratories in OPCW proficiency tests [11].

The synthesis of HD by reaction of sulfur monochloride with dry ethylene gas in carbon tetrachloride at 35 °C is generally known as the Levinstein process [12]. The final product in this reaction is an impure mixture containing about 70% HD, and 10% two main impurities: bis(2-chloroethyl)disulfide (HS_2) and bis(2-chloroethyl) trisulfide (HS_3) (Scheme 1) [13].

Finding a mustard gas polysulfide analogue in a sample, is considered as a useful hint on looking after blistering agent in the inspection site. On the other hand, study on the chemical reactivity of HD, HS_2 and HS_3 is of significant interest. To the best of our

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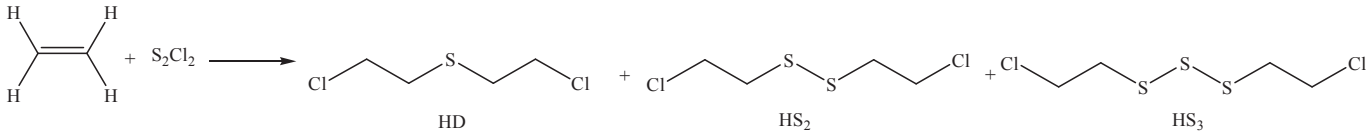


Scheme 1. Levinstein process for the production of HD and its two polysulfide analogues.

knowledge, detailed investigation report on electron impact mass spectrometry fragmentation, NMR and IR spectra of HS_2 and HS_3, as well as their relative reactivity data are not available in unclassified scientific literature. In this work, HS_2 and HS_3 were synthesized by the reaction of sodium polysulfide with 2-chloroethanol (Scheme 2) [14] and the products were characterized using electron-impact mass spectrometry (EI-MS). General EI fragmentation pathways of them were proposed in this paper. DFT calculations were performed in order to investigate physico-chemical properties of HD, HS_2 and HS_3. There is an obvious advantage to the application of computational methods in the study of such highly toxic chemicals. This paper will also make a contribution to support OPCW activities by providing analytical data for insertion into OCAD.

2. Experimental

2.1. Reagents and chemicals

All required chemicals were obtained from Sigma-Aldrich (St. Louis, MO. USA), Fluka (Neu-Ulm, Germany), and Merck (Darmstadt, Germany), and were used as received.

2.2. GC/MS analyses

GC/MS analyses were performed by the use of an Agilent 6890-N gas chromatograph equipped with a 5973 Mass-Selective Detector, an HP-5MS capillary column of length 30 m, 320 μm i.d., and 0.25 μm film thickness, and helium carrier gas at a constant flow of 1.8 mL min^{-1}. Oven temperature was maintained at 40 °C for 3 min, then increased to 280 °C at 10 °C/min^{-1}, and held at 280 °C for 6 min. Samples were injected in splitless GC inlet, at 250 °C. The temperatures of the EI ion source and mass analyzer were at 230 and 150 °C, respectively. The scan range was *m/z* 35–500.

2.3. Computational details

Geometry optimizations and frequency calculations for all species were performed by the use of Gaussian 09 program [15]. DFT calculations with the Becke three-parameter hybrid functional (DFT-B3LYP) were performed, using 6–311++G (2d, 2p) basis set. Vibrational frequencies were calculated at the same level to ensure that each stationary point was a true minimum. The harmonic-oscillator approximation was also employed to prepare the thermodynamic partition functions. After geometry optimization and frequency calculations, zero-point energies (ZPEs) and thermal corrections were performed at 298 K.

2.4. General procedure for microsynthesis of mustard gas polysulfide analogues HS_2 and HS_3

To a solution of freshly prepared sodium trisulfide (0.8 mmol) in CH_2Cl_2 (3 mL), 2-chloroethanol (0.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then 1 mL HCl (37%) was added dropwise to the solution. The mixture was stirred for an additional 2 h at 70 °C. The solid material was filtered off. Subsequently, extraction with CH_2Cl_2 (3 × 1 mL), drying the organic phase with Na_2SO_4 and concentration under vacuum, afforded a solution containing HS_2 and HS_3 which was analyzed using GC/MS.

3. Results and discussion

3.1. Interpretation of HD, HS_2 and HS_3 EI-MS spectra

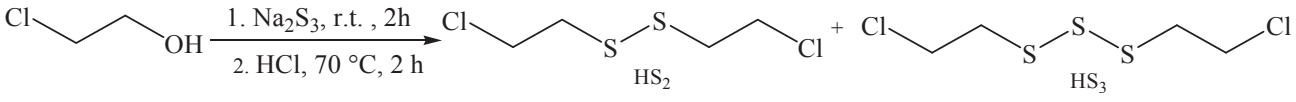
EI-MS spectra of sulfur mustard and its polysulfide analogues, HS_2 and HS_3, are shown in Fig. 1. Major EI fragment ions of these compounds as well as their retention indices (RI) are given in Table 1.

The plausible fragmentation pathways for HD, HS_2 and HS_3 are illustrated in Scheme 3. Plausible mechanism for the elimination of ethylene from $M^{+\bullet}$ of HS_2. The molecular ions ($M^{+\bullet}$) of HS_2 and HS_3 are observed in their EI–MS spectra as base peak. Expected isotopic ratios of chlorine and sulfur containing fragments were observed (Table 1). The most important fragmentations in mass spectra of HD, HS_2 and HS_3 were cleavage of C–C bond initiated from sulfur atom and cleavage of C–S bond with charge retention at the chloroethyl fragment which led to ions [B] and [F], respectively. Elimination of vinyl chloride from $M^{+\bullet}$ led to fragment ion [C] in all EI-MS spectra. Fragment ion [E] can be formed with expulsion of chloroethyl radical from $M^{+\bullet}$. This fragmentation pathway is favor for HS_2 and HS_3 due to the formation of five and six membered rings, respectively.

Generally, the fragmentation pathways of HS_2 and HS_3 are as of HD, except direct ethylene elimination from $M^{+\bullet}$ of HS_2 and HS_3. This gives rise to the peak at *m/z* 162 and 194 with relative moderate abundance in HS_2 and HS_3 mass spectra, respectively. Plausible mechanism for formation of this fragment ion, is depicted in Scheme 4 and involves elimination of a neutral ethylene molecule from $M^{+\bullet}$ in a concerted manner with a 5- and 6-membered transition state. This may explain why ethylene elimination is not favorable for HD, in which formation of a 5- and 6-membered transition states is impossible.

3.2. HD, HS_2 and HS_3 calculated physico-chemical properties

Since toxic nature of sulfur mustard and its analogues impose restrictions on experimental studies, a high-level computational



Scheme 2. General method for synthesis of HS_2 and HS_3.