Determining the absolute chirality of soman stereoisomers through molecular modeling

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Introduction
When nerve agents enter the body, they inhibit the acetylcholine enzymes in the synapse resulting in overstimulation of post synaptic neurons and eventual death. With no post-exposure treatments for these nerve agents, exposed victims would die from these chemical warfare agents. This project focuses on restoring the functionality of acetylcholinesterase (AChE) by determining the absolute chirality of the nerve agent soman (GD). Nerve agents can exist in one of two stereoisomeric forms. These forms differ only in the orientation, also known as the chirality or absolute configuration, of the groups attached to the phosphorous atom. When visualized, they appear as mirror images of the molecule reflected about a chiral center atom. The two mirror images are called stereoisomers, denoted as the “R” and “S” configurations.

Soman has two chiral centers (phosphorous and carbon) with each center having two stereoisomers for a total of four stereoisomers [denoted in this project as PRCR, PRCS, PSCR, and PSCS]. The Infrared (IR) and Vibrational Circular Dichroism (VCD) spectra can be measured with a circular dichroism spectrometer for each of the separated stereoisomers. Then computational computing can be used to determine a theoretical IR and VCD spectra for isomers with a known “R” or “S” absolute chirality. Comparison of the calculated VCD spectrum with the measured VCD spectra for one of the stereoisomer allows for the identification of the absolute chirality of the measured isomer. One stereoisomer is more lethal than the other so identifying the chirality of the lethal stereoisomer can lead to developing an effective AChE reactivator (Maxwell, 1992).

Each isomer of a nerve agent can exist in multiple conformations known as conformers. A conformer is a specific arrangement of atoms at a local energy minimum. A single computed VCD spectrum is calculated as a linear combination of the VCD spectra at the lowest energy conformations of the modeled isomer (He, Wang, Dukor, & Nafie, 2011). Therefore each conformer will have the VCD spectrum calculated and will be energy-minimized, thus re-orienting the atoms to a state where energy between bonds is at a local minimum.

Materials and Methods
The process of determining the chirality of soman was completed in three phases. The first phase was the orientation of 100 soman conformers. The conformers were created with the MMFF94 minimization tool in ChemBio3D Ultra. A program was written in Visual Basic for Applications (VBA) to orient the conformers to the same location constraints. This was accomplished by first subtracting the phosphorous coordinates of each conformer from all the other atoms’ coordinates then multiplying the coordinates by three rotational matrices to align the conformers with the fluoride on the positive y-axis and ethoxy oxygen on the negative y-z plane. The oriented conformers were then modeled in Visual Molecular Dynamics (VMD) producing the models in Figure 1.

The second phase was the energy minimization of the conformers. In order to have a wide representation of minimization wells in the conformer sample, the conformers were manually aligned to 32 distinct orientations. Using ChemBio3D Ultra, the oxygen-carbon bond was rotated to each of four ordinal directions as visualized by looking down the phosphorous-ethoxy oxygen bond. Then for each ordinal direction the methyl group was rotated either up or down on the y-axis essentially creating eight distinct orientations for each of the four stereoisomers totaling 32 unique conformer orientations. The 32 conformers were then MMFF94 energy-minimized and sent to the ARL supercomputers where a computational software, Gaussian, was used to perform calculations on the conformers.

The third phase consisted of analyzing the results from Gaussian. Gaussian outputted frequencies, IR intensities, and VCD densities in the form of eigenvectors (modes of vibration) for each conformer. The same VBA program was used to reorient the resulting conformers. Then another program was developed in VBA to extract the final energies from the output files and calculate the probability of the stereoisomer to exist in each conformation. The conformation probabilities were multiplied by the IR and VCD eigenvalues to produce combined spectra that account for the average values of each stereoisomer (Graph 1).

Results

Since the measured IR and VCD spectra have not yet been produced by the circular dichroism spectrometer, the absolute chirality of soman cannot be determined. The measured GD spectra will be finished later and at that time the calculated and measured spectra will be compared. If the peaks of the two VCD spectrums for the same stereoisomer are identical and have the same sign, then the absolute chirality of the calculated isomer is the same as the chirality of the measured GD spectrum. Otherwise, if the two VCD spectra have contrasting signs (Graph 2), then the absolute chirality of the calculated isomer is opposite of the GD spectrum.

Conclusion
The purpose of this study was to determine the chirality of a soman isomer to identify which stereoisomer of the molecule is lethal. The chirality of the soman stereoisomer has yet to be confirmed but the resulting IR and VCD spectra of the stereoisomers appear accurate and are ready for comparison. When the measured VCD graphs are produced, the calculated and measured spectra will be analyzed to identify if the peaks match or are of opposite signs. After that, each individual peak of the spectrum can be linked to the structure of the molecule to identify which peaks and orientations cause the lethal effects.

Identifying the chirality of the stereoisomer is critical because one isomer will be much more lethal than the other so when both are tested on animals, the isomer that proved significantly more toxic will be recognized. Future research includes determining the absolute chirality of other nerve agents and essentially creating a nerve agent chirality database.

References