THEORETICAL STUDY OF MICROHYDRATION OF CHEMICAL WARFARE AGENT VX

Karanveer Singh Gadiock [1], Sangeetha S [2*], Taniya M [3], M Sundaram K [4] and Lavanya Prathap [5]

[1,2,3,4,5] Department of Anatomy, Saveetha Dental College and Hospital,
Saveetha Institute of Medical and Technical science (SIMATS),
Saveetha University, Poonamalle High Road, Velappanchavadi, Chennai.
*Corresponding Author Email: sangeethas.sdc@saveetha.com

Abstract

Introduction: Nerve agent VX is a chemical warfare agent that has been used in many wars and assassinations including the assassination of the former north korean president, in this research we did a microhydration study of the chemical warfare agent VX, the study was done at the PW6B95D3/ 6-311+g(d) theoretical method. During the course of study, we observed a large number of changes in the structure of VX as it combined with the water molecules. **Materials and Methods:** Theoretical study is by hydrating VX with 1-5 water molecules and understanding the most stable configuration, for each water molecules combination we took upto 15 isomers each, and further found the most stable isomer according to the various thermodynamic parameters. In order to do this theoretical study, we used many computational tools, which included Gaussian G16, version C.03 for coordinates and all the DFT calculations. Further for Visualisation we used Chemcraft, in order to plot the diagrams and to calculate the gibbs free energy, enthalpy, and binding energy respectively. **Result: Discussion:** Hydration of VX was studied using PW6B95D3/ 6-311+g(d) method. For identifying the stable isomers 15 structures were analyzed. The binding energy of the water increases with the number of water molecules and shows linearity. Water molecules were found to form more intermolecular hydrogen bonds due to the hydrophobicity of VX. The Gibbs free energy change for one and two water were positive implying their formation is non-facile. For higher water molecules negative Gibbs free energy change is observed and it increases with the number of water molecules. This shows the spontaneity increases with increase in water molecules. The enthalpy change is negative which indicates the reaction is exothermic. The exothermicity increases with increase in water molecules. **Conclusion:** The present study shows a large structural change is observed during the hydration of VX. Water molecules undergo clustering due to the hydrophobicity of VX. Furthermore, thermochemistry shows that VX hydration is exothermic and spontaneous at low-temperature and high water content, meaning that the VX would act more effectively in countries with lower temperatures and more humidity than the other countries.

Keywords: Isomer, Assassination, Micro Hydration, Chemical Warfare.

1. INTRODUCTION

Chemical warfare agents (CWAs) have been a persistent threat since their introduction during World War I. Among these agents, O-ethyl S-(2-diisopropylaminoethyl) methylphosphonothiolate ,commonly known as Venomous Agent X (VX), is a disreputable blister agent with delayed but long-lasting harmful effects**(Website)**. VX is easily synthesized and can infiltrate various types of fabrics, making it highly dangerous.(Love et al. 2004)**(Love et al. 2004)** Thorough theoretical studies on the microhydration of VX are critical for understanding its behavior, developing effective decontamination strategies, and alleviating its disastrous impact.**(Bandyopadhyay et al. 2006)** By investigating the interaction between VX and water molecules through calculational modeling and simulation techniques, valuable insights can be gained into its stability, reactivity, and interactions with biological systems, contributing to the advancement of defense strategies against this potent CWA.**(Piao et al. 2005)**

At present, there exist two recognized stockpiles of V-agents: VX (S-2-(diisopropylamino) ethyl O ethyl methyl phosphonothioate) in the United States, comprising thousands of tons, and R-VX (Russian-VX, S-2-(diethylamino)ethyl O-isobutyl methylphosphonothioate),**(McCann et al. 2022)** an analogue and isomer found in Russia. According to a recent study, the decontamination chemistries of these two agents exhibit remarkable similarity.

In February 2017, Kim Jong-Nam, half-brother of North Korea's leader, Kim Jong-Un, was allegedly assassinated at Kuala Lumpur airport. Two women smeared a mysterious chemical on Nam's face as he transited through the airport. Despite seeking emergency care, Nam's condition worsened and he died. An autopsy revealed the presence of the nerve agent VX on his face and eyes**(Chai et al. 2017).**

2. COMPUTATIONAL METHODS

All calculations were conducted using Gaussian 16 C.03 at 40−43 44 298 K and 1 ATM running on SEAGrid. To visualize the outcomes, GaussView 05 and Chemcraft 1.745 software were employed. The reported conformers of VX were reexamined using the PW6B95D3 functional in conjunction with the 6-311++G(d) basis set for all atoms. The most secure conformer of VX, as illustrated in Figure 2, was identified as A. The other lowest energy structures are denoted alphabetically based on their relative stability and are provided in the Supporting Information in Table S1.Hydrated VX clusters derived from A were optimized using the PW6B95D3 computational method along with the 6-311++G(d) basis set. In the case of monohydrated complexes, a solitary water molecule was introduced to A at various positions and orientations. For the di- and tri hydrated clusters, a collection of structures was taken into account, wherein the water dimer and trimer were added to A. All complexes containing n water molecules (where n = 1−5) are reorganized and denoted as Gn (Generation n), a term introduced by Michaux and co-workers. Each complex is labeled as An-m, where A represents the A conformer of VX, n signifies the number of water molecules, and m is an increasing integer representing the relative stability of the complex within the considered generation.

The results obtained from M06-2X/6-311++G(d) computations are reported, as this method performs well for systems involving organic molecules and noncovalent interactions. The results obtained from the other three methods are provided as part of the Supporting Information.

The binding energies (BEs) were calculated using the equations

$$\Delta E_{ZPE+BSSE} = E(VX \cdot nH_2O) - [E(VX) + n \times E(H_2O)] \quad BE \ 2 \ 2 \quad (1)$$

$$\Delta G_{BE} = G(VX \cdot nH_2O) - [G(VX) + n \times G(H_2O)] \quad (2)$$

$\Delta E_{ZPE} + BSSE$ is the binding electronic energy of the complex BE

corrected for zero-point energy (ZPE) and basis set super- position error (BSSE). The BSSE correctional value was obtained using the counterpoise method. The ΔG_{BE} is the binding free energy of the hydrated complexes, and $E(VX \cdot nH_2O)$ and $G(VX \cdot nH_2O)$ are the electronic and free energies of the hydrated VX, respectively. The $E(VX)$ and $G(VX)$ and the $E(H_2O)_n$ and $G(H_2O)_n$ are the electronic and free energies of isolated VX and isolated n water molecules, respectively.

3. RESULTS

3.1. Conformational Search
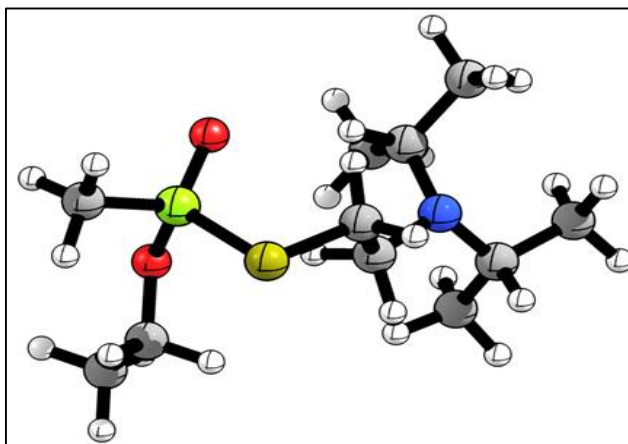
Figure 1: VX molecule in the lowest energy state computed in the gas phase using PW6B95D3/6-311++G(d) method

Twenty-two conformers of VX were located using the PW6B95D3/6-311++G(d) method. Conformer A which is shown in **Figure 1,** is the most stable one, and this is in agreement with previous studies. A was used as the free VX molecule to which discrete water molecules were subsequently added. The structure of all the conformers of VX along with their relative stability was acquired using PW6B95D3/6-311+ +G(d)

3.2. Effect of Distinct Solvent Molecules and Bulk Solvation on the Properties of VX
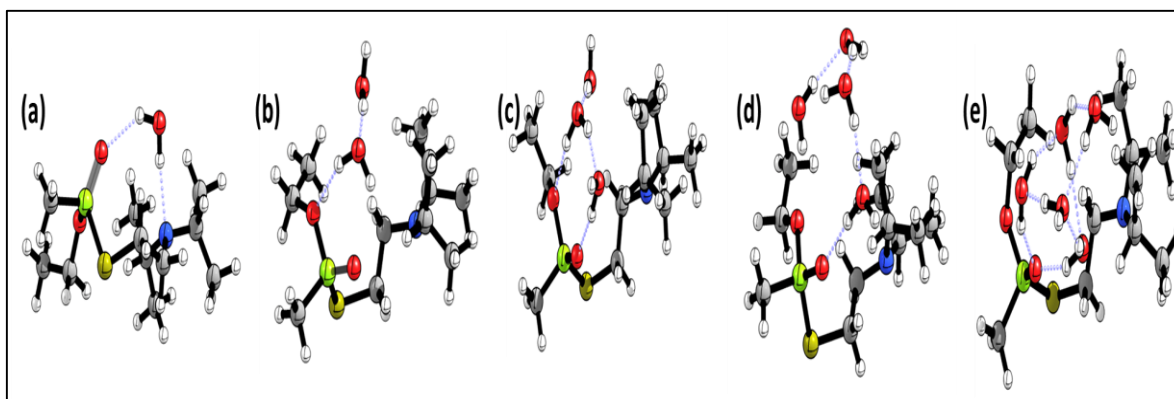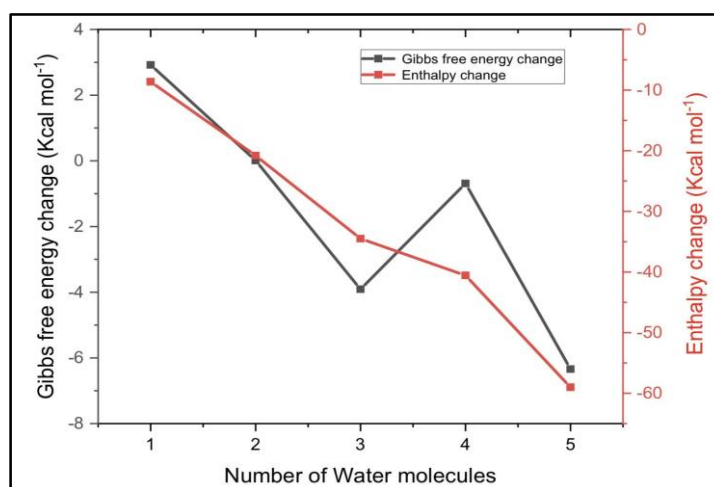

Figure 2: Optimized structure of VX with 1-5 water molecules in the gas phase using PW6B95D3/6-311++G(d) method

The addition of discrete water molecules to A gave rise to three monohydrated, seven dehydrated, and nine trihydrated complexes when the PW6B95D3/6-311++G(d) method was used. The VX·nH2O (for n = 1−5) complexes at the most stable state obtained are shown in Figure 2, and their binding energy, enthalpy, entropy, and free energy values are condensed in Table 1.

Table 1: Computed Binding energy, Gibbs free energy and Enthalpy change for the hydration of VX with 1-5 water molecules

| Number of water molecules	Binding energy (Kcal mol-1)	Gibbs Free energy change (Kcal mol-1)	Enthalpy Change (Kcal mol-1)
-	-10.69	2.92	-8.61
2	-24.57	0.01	-20.80
3	-40.28	-3.91	-34.49
4	-48.59	-0.69	-40.56
5	-69.11	-6.34	-59.01

Figure 3: Relation between gibbs free energy (black) and enthalpy change (red) with the number of water molecules

We have computed the Gibb's free energy change as a function of water molecule and diagram is shown in Figure 3. From the graph we can see that there is a continuous decrease in the enthalpy with an exception at 4 water molecules where it slightly increases . The enthalpy change shows a linear decrease with the increase in water molecules.
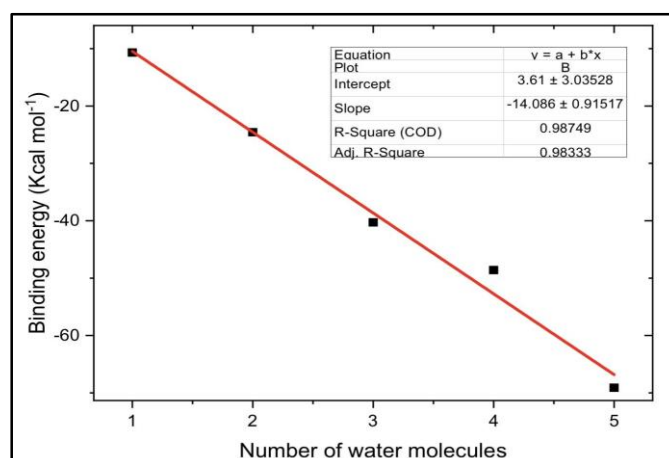

Figure 4: The relation of binding energy with the number of the water molecules

The binding energy change as a function of water molecule is shown in Figure 4. We can see from the graph that there is a linear decrease in the binding energy with the increase in the number of water molecules.
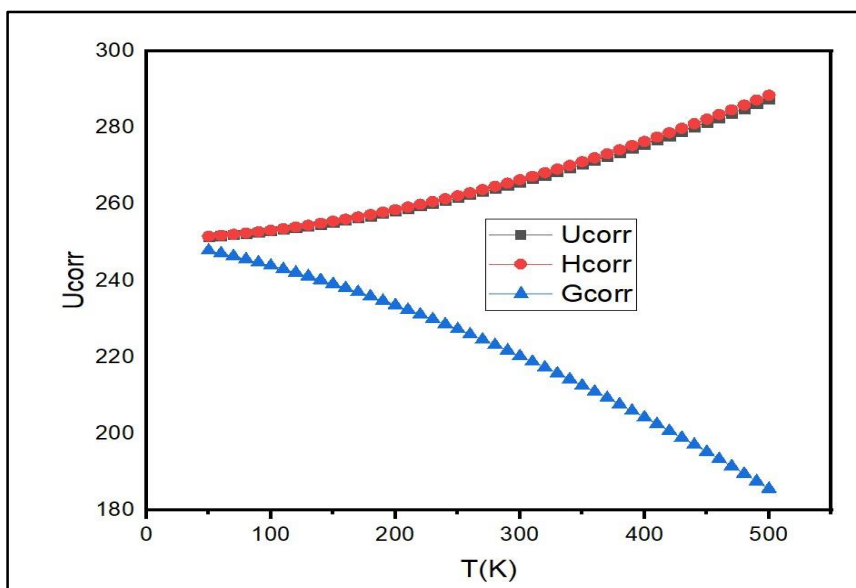
Figure 5: Relation between internal energy with temperature of the water molecules

In Figure 5, we have given the change in internal energy, enthalpy and free energy change fo the hydration of one water molecule as various temperature. We can see that the gibbs free energy decreases with the increase in temperature of the water molecules.On the other hand, the enthalpy increases with the increase in the temperature of the water molecules.
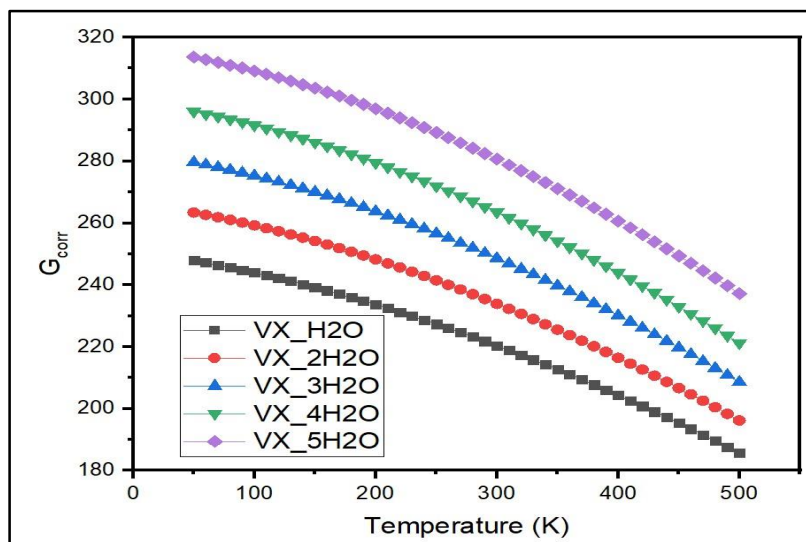
Figure 6: Relation of Gibbs free energy with the temperature of the water molecules

In Figure 6, we have plotted the change in Free energy as function of temperature for the hydration of water from 1-5 molecules. From the graph it can be evaluated that the gibbs free energy is highest for 5 water molecules followed by 4,3,2,1 water molecules at a particular given temperature.

4. DISCUSSION

4.1 Microhydration : Effect on the structure.

The isolated structure of VX is not significantly affected by the addition of discrete water molecules in any of the examples examined. Studies on the aziridinium ion of mercury when it was microhydrated with one to four water molecules have previously shown similar kinds of results.**(Worek et al. 2016),** along with this microhydration of another nerve poison, Sulphur Mustard also produced similar kinds of results. **(Emambocus et al. 2020).** For mono, di and tri hydrated complexes of VX, much of bond extension and severe changes are not seen, however lengthening of the H-bonds are seen as the number of water molecules increased, in almost all of the cases H- bonding motifs are cyclic in nature and consist of five- to eight- member rings system between VX and water, this ring formation has been hinted to hydrophobic nature of the VX molecule, which increases the bond pressure and forces a ring nature in order for the structure to get stabilised, these kind of interactions are seen before in another study done by Yang **(Yang et al. 1997)**

4.2 Comparison with other nerve agents

There was one study done by Alam and his co-workers**(Ab initio investigation of Sarin micr...)**, which was done on Sarin conformers, this study was performed at B3LYP/6-311++G(2d,2p),in the comparison to the sarin structure, the addition of water molecules to VX produce more variable results and both the chemical warfare agents showed a negligible result during the microhydration procedure, the energy difference between the molecules was also analyzed and it was discovered that sarin dissolves much easily in water as compared to the VX molecule. We also compared this study with Sulphur mustard, we discovered that as the VX, the sulphur mustard did not show any great results on microhydration **(Zafrani et al. 2009)**, another interesting property of Sulphur mustard was it can be hydrolysed by the nanoparticles into TDG,and the further presence of water also accelerates the growth of the reaction. (**(Zinc peroxide nanoparticles: Surface,...)**) , The sulfonium ion is formed when the C-Cl link is broken with the help of the water molecules. Within Mann's molecular dynamics simulations,**(Mann 2010)**The binding energies of SM with DNA bases were calculated using the B3LYP/6-31+G(d) method and found to be −36 and −22 kcal/mol in the gas and aqueous phases (PCM) at the N7 of the guanine DNA base, respectively.

5. CONCLUSION

Finally, our theoretical investigation on the microhydration of chemical warfare agent VX has yielded important new information. We noticed a considerable structural shift in the VX during hydration, demonstrating the critical part water plays in the procedure. VX's hydrophobic properties caused water molecules to collect around it. Additionally, our thermochemical investigation showed that VX hydration is an exothermic, spontaneous process that is most beneficial at low temperatures and high water content. This result implies that VX would demonstrate increased efficacy in areas with lower temperatures and higher humidity. Overall, this study clarifies VX's microhydration behavior and offers helpful information for comprehending how it responds to various environmental factors. The conclusions drawn from this study may have consequences for tactical planning and defensive strategies.

Author Contrıbutıon

Karanveer Singh Gadiock**:** Data collection, manuscript writing.

Mrs.S.Sangeetha : Study design, data verification, manuscript correcting.

Acknowledgement

Conflıct Of Interest

None to declare.

References

1) Bandyopadhyay, Indrajit, Min Jeong Kim, Yoon Sup Lee, and David G. Churchill. 2006. "Favorable Pendant-Amino Metal Chelation in VX Nerve Agent Model Systems." *The Journal of Physical Chemistry. A* 110 (10): 3655–61.

2) Chai, Peter R., Edward W. Boyer, Houssam Al-Nahhas, and Timothy B. Erickson. 2017. "Toxic Chemical Weapons of Assassination and Warfare: Nerve Agents VX and Sarin." *Toxicology Communications* 1 (1): 21–23.

3) Love, Adam H., Andrew L. Vance, John G. Reynolds, and M. Lee Davisson. 2004. "Investigating the Affinities and Persistence of VX Nerve Agent in Environmental Matrices." *Chemosphere* 57 (10): 1257–64.

4) McCann, James J., Douglas H. Pike, Mia C. Brown, David T. Crouse, Vikas Nanda, and Ronald L. Koder. 2022. "Computational Design of a Sensitive, Selective Phase-Changing Sensor Protein for the VX Nerve Agent." *Science Advances* 8 (27): eabh3421.

5) Ovenden, Simon P. B., Renée L. Webster, Eva Micich, Lyndal J. McDowall, Nathan W. McGill, Jilliarne Williams, and Shannon D. Zanatta. 2020. "The Identification of Chemical Attribution Signatures of Stored VX Nerve Agents Using NMR, GC-MS, and LC-HRMS." *Talanta* 211 (May): 120753.

6) Piao, Haishan, Randall B. Marx, Steven Schneider, David A. Irvine, and John Staton. 2005. "Analysis of VX Nerve Agent Hydrolysis Products in Wastewater Effluents by Ion Chromatography with Amperometric and Conductivity Detection." *Journal of Chromatography. A* 1089 (1-2): 65–71.

7) "Website." n.d. Acc. Chem. Res. 1999, 32, 2, 109–115 Publication Date:November 4, 1998 https://doi.org/10.1021/ar970154s.