**Contract W911NF-15-1-0624**

A computational protocol to model organophosph(on)ate chemical warfare agents and their simulants

**Project summary:** A computational protocol to predict the infrared spectra and binding behavior of organophosph(on)ates has been developed. Sarin (GB) was used to benchmark the method through gas phase simulations with progressively more sophisticated models. Computed spectra were compared to examples in the literature and those provided by Dstl. Density functional theory using the EDF2 functional and diffuse 6-311++G\*\* basis set was found to give the closest match. Using the same method and functional the 6-31G (2df, 2p) basis set was found to be superior when hydrated sarin was modelled.

GA, GB, GD, GF, VG and VX, together with 11 simulants, were modeled using the gas phase protocol and the G-series was additionally modeled using the protocol for hydrates. The results for the gas phase simulations were in good agreement with calculated asymmetric P-O-R stretches in the literature and more accurate for the P=O stretches. The hydrated simulations exhibited shifts for the P-O-R and P=O bond stretches as would be expected from the effects of hydrogen bonding to water. The shift to lower wave numbers for the P=O stretch on organophosphonates is consistent with literature data for the simulant DMMP.

Complexation of GB, GD, GF and simulants with cyclodextrins reproduced the binding preference for GD over simulants by β-cyclodextrin in agreement with experimental data from Dstl. Calculations indicated that DIFP was the best simulant to mimic the binding behavior of GD. It was correctly predicted that the isomers of GD known to have the highest toxicities, due to weak binding to enzymes, should also bind less strongly to β-cyclodextrin.

**Data deposited:** Files deposited are those used in calculations of molecular energies and binding affinities produced during the project using Spartan software (available from Wavefunction, Inc., Irvine, CA) and are in the native .spartan format.

There are no restrictions on the deposited files, however, a Non-Disclosure Agreement exists between the University of Brighton and partners the Defence Science and Technology Laboratory covering unpublished spectroscopic data files and for that reason they have not been deposited. Where data data have been published, as noted below, it can be found either in the main text or the accompanying Electronic Supplementary Data.

**Publications arising:**

1. Experimental and computational study of the inclusion complexes of β-cyclodextrin with the chemical warfare agent soman (GD) and commonly used simulants, MR Sambrook, JC Vincent, JA Ede, IA Gass and PJ Cragg, *RSC Adv.*, **2017**, *7*, 38069-38076.
2. Spectroscopic and inclusion properties of G-series chemical warfare agents and their simulants: A DFT study, MR Sambrook, IA Gass and PJ Cragg, *Supramol. Chem.*, **2018**, *30*, 206-217.
3. Comparison of binding affinities of water-soluble calixarenes with the organophosphorus nerve agent Soman (GD) and commonly-used nerve agent simulants, JA Ede, PJ Cragg and MR Sambrook, *Molecules*, **2018**, *23*, 207.
4. Hydrogen-bonding interactions in crown-(thio)urea complexes with anions, chemical warfare agents and simulants, H Cave, JA Ede, MR Sambrook, H Dodd, F Fucassi, AS Cragg, AH Lansley, PJ Cragg, *Supramol. Chem.*, **2019**, *31*, 703-712.

**Spartan files deposited for the following compounds/complexes:** VX, VG, GA, GB, GD, GF, DMMP, DIFP, DEMP, DIMP, DCP, DCyP, TMP, TEP, TiPP, TnPP, TnBP, α-cyclodextrin·2H2O, (H2O)2, α-cyclodextrin·GB, α-cyclodextrin·DMMP, α-cyclodextrin·DIFP, α-cyclodextrin·DEMP, α-cyclodextrin·DIMP, α-cyclodextrin·DCP, α-cyclodextrin·DCyP; GD·4H2O, β-cyclodextrin·10H2O, (H2O)14, β-cyclodextrin·GD[(*S*)-C (*R*)-P], β-cyclodextrin·GD[(*R*)-C (*R*)-P], β-cyclodextrin·GD[(*R*)-C (*S*)-P], β-cyclodextrin·GD[(*S*)-C (*S*)-P]; TEP·4H2O, TnPP·4H2O, TiPP·4H2O, DEMP·4H2O, DIMP·4H2O, PMP·4H2O, GD·4H2O, DIFP·4H2O, DCP·4H2O, GF·4H2O, β-cyclodextrin·TEP, β-cyclodextrin·TnPP, β-cyclodextrin·TiPP, β-cyclodextrin·DEMP, β-cyclodextrin·DIMP, β-cyclodextrin·PMP, β-cyclodextrin·DIFP, β-cyclodextrin·DCP, β-cyclodextrin·GF