Coupling of Computational Methods for the Prediction of NMR Signatures in CWAs

Todd M. Alam, Janelle E. Jenkins, Charles J. Pearce, Tiawna L. Cayton, Emily Baldwin, and Catherine F. M. Clewett

Sandia National Laboratories, Albuquerque, NM 87185

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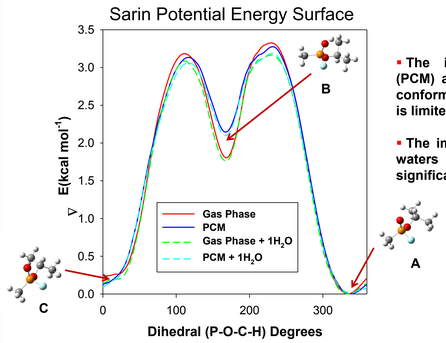
ABSTRACT

NMR spectroscopy continues to be one of the most important tools for identification, purity determination and characterization of chemical warfare agents (CWA). Moreover, NMR analysis can easily be performed on unknown or new agents developed in the future. For organophosphate CWA, phosphorous (^{31}P) and fluorine (^{19}F) NMR spectroscopy has proven to be very specific in identifying different agent, plus show remarkable spectral response to surface interactions and/or hydration state. While there has been extensive literature of using *ab initio* methods for the prediction of NMR spectra in phosphates [1,2], the application to predicting CWA NMR signatures is limited. In this presentation, we review our recent efforts involving *ab initio* simulations of the ^{31}P and ^{19}F NMR spectra of Sarin and DMMP under different environmental conditions. These calculations explore the use and relative importance of Boltzmann averaging over different molecular conformations, the inclusion of a continuum solvent field (using the PCM method) during NMR shielding calculations, and the role of explicit solvent shells in the NMR shielding calculations. We have used these results to explore the role of micro-hydration, and the impact of surface binding on the NMR shielding calculations. In addition, it is demonstrated that it is possible to correctly calculate the ^{31}P-^{19}F J coupling in CWA. It is shown that this experimentally observable NMR J coupling is a function of both molecular conformation and substituent ligand identity. More recently, this group has been developing a tool that allows the coupling of the time trajectories from either classical or *ab initio* molecular dynamic (AIMD) simulations directly with the NMR calculations. Results from MD simulation of a DMMP in water are used to demonstrate and emphasize the importance of time averaging over local molecular fluctuations, ensemble averaging over multiple DMMP molecules in the MD simulations cell, and including explicit solvent molecules in the NMR calculation. The development of this coupling tool will allow the prediction of NMR signatures for any proposed compound under different environments and surface binding conditions. Future development will allow interfacing of these NMR calculation capabilities to any MD simulations available within the chemical agent community.

Methods NMR Calculations

Specific questions concerning these type of NMR shielding calculations:

- **Is a simple gas phase structure sufficient?**
- **Does a Polarizable Continuum Model (PCM) solvent need to be incorporated?**
- **PCM for structure or NMR calculations of both?**
- **What is the role of explicit waters?**
- **Can a combined cluster/PCM model improve the NMR shielding calculations?**
- **What is the influence of conformational fluctuations?**
- **Can these calculations be coupled to MD simulations?**



- **The impact of both implicit (PCM) and explicit waters on the conformational structure of Sarin is limited.**
- **The impact of PCM and explicit waters on DMMP is more significant.**

PES evaluated using DFT B3LYP 6311++(2d,2p) basis set in Gaussian09 unless otherwise noted.

- NMR parameters given by second derivatives with respect to moments or external magnetic field.

$$\sigma_{\mathrm{NMR}} = \left(\frac{\partial^2 E_{\mathrm{Electronic}}}{\partial \mathrm{B}_i \partial m_i} \right) \qquad J_{i,j} = \left(\frac{\partial^2 E_{\mathrm{Electronic}}}{\partial m_i \partial m_j} \right)$$

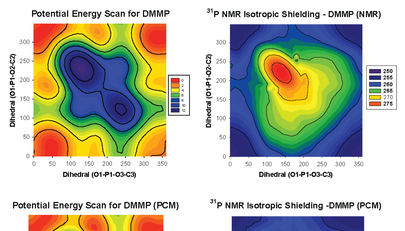
$$\delta(\mathrm{NMR}) = \sigma_{\mathrm{ref}} - \sigma \qquad J = J_{\mathrm{DSO}} + J_{\mathrm{PSO}} + J_{\mathrm{FC}} + J_{\mathrm{SD}}$$

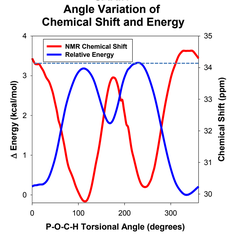
Diamagnetic spin-orbit; Paramagnetic spin-orbit; Fermi contact; Spin-Dipole

- All NMR shielding and J calculations performed in Gaussian 09 on the REDSKY cluster.

Ab Initio Calculations of ^{31}P NMR Chemical Shift

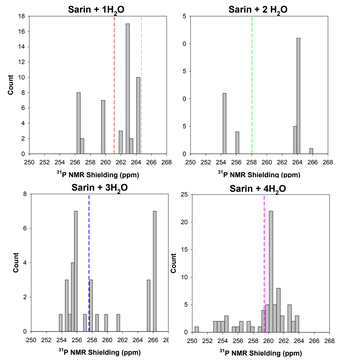
Role of Conformational Averaging





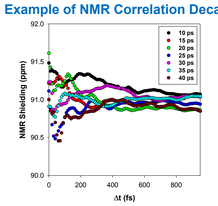
- Have predicted the ^{31}P NMR chemical shift for Sarin and DMMP across their torsional conformational space.
- Surprisingly, the Boltzmann averaged NMR chemical shift does not shift the dramatically from the gas phase optimized minimum.
- There potential energy surfaces still represent partially "optimized" structures.

Role of Micro-Hydration

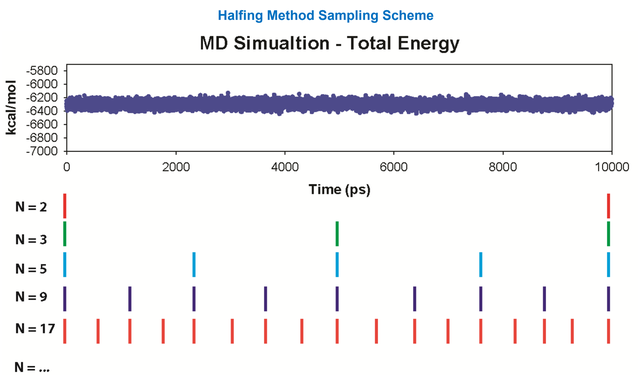


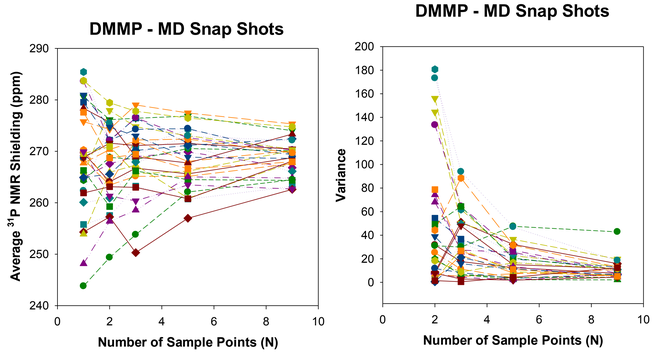
- Have predicted the ^{31}P NMR for Sarin and DMMP across these micro-hydrated clusters. Example for Sarin up to 4 explicit waters shown (left).
- With increasing number of waters the complexity of the clusters is reflected in the NMR shielding.
- There is an increasing number of micro-hydration states with increasing waters.
- The Boltzmann weighted averages do not significantly vary above n > 1 explicit water, arguing that at least 2 waters need to be included in the P=O hydration sphere for accurate NMR shielding calculations.
- The decrease in the NMR shielding (increased chemical shift) of approximately 2 ppm is consistent with experimental NMR studies.
- *These results also demonstrate that a cluster model must include explicit waters to obtain consistent results.*

Extraction of Chemical Shift from MD Simulations

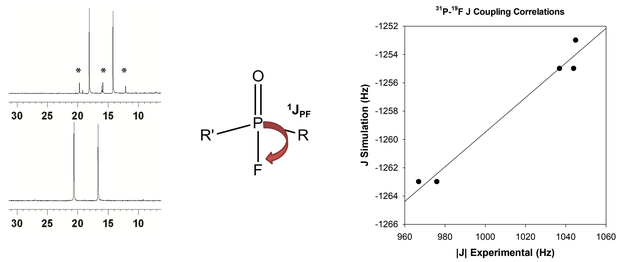


- Time and ensemble averaging over the configurations obtained during a MD simulations can provide a more accurate result in calculation of the NMR chemical shift (and J coupling).
- Typically, need to average the NMR shielding over a n "appropriate" time scale (auto correlation time) for the NMR observable. See example (above).
- This time scale is NOT know *a priori.*
- NMR time scale is NOT the same as the decay time for the energy auto correlation function.
- May require thousands of calculations to simply determine the appropriate NMR time scale.
- Long term fluctuations may not be captures in a simple auto correlation averaging. This may not be an issue for small molecules, but could represent a issue for large complexes or surface adsorption.
- We have implemented a "halfing" sampling method to improve the speed and performance of the time and ensemble averaging of the NMR chemical shifts.
- By monitoring the variation of the standard deviation it is possible to determine when enough sampling points have been averaged.
- Sample over the entire time series, incorporates long term fluctuations.
- The averaged NMR shielding results are close to experimental, and suggest this sampling method is promising.
- Continue to develop this interface to improve the speed and compatibility with MD simulations from different sources.

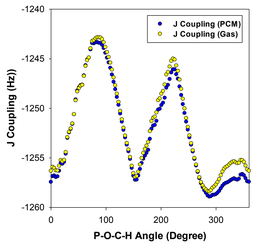




Calculation of ^{19}F-^{31}P J Couplings



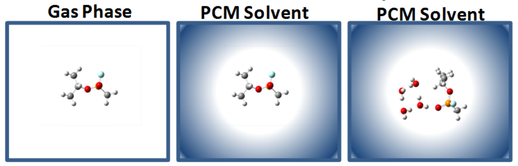
Role of Conformation



- In addition to the ^{31}P AND ^{19}F NMR chemical shifts it is also possible to calculate ^{19}F-^{31}P and ^{1}H-^{31}P through bond J couplings as a tool for identification of compounds and binding states.
- ^{1}H-^{31}P J coupling have been previously used in HMQC identification and quantification. Involves a 2-bond coupling, but is a direct identifier of the CWA substituents.
- It has been proposed that ^{19}F-^{31}P can be used to filter only those F containing compounds, and may provide additional details on binding to other molecules and surfaces.
- Initial correlations between theory and experiment exist, but predictions are offset by some constant.
- *What is needed to get the experiment and theory to agree!*
- ^{31}P and ^{19}F are known to be electron rich systems, need to explore what impact theory, conformational space and micro-hydration play on this offset.

Table J-1: Theory and Basis Set Effects on Calculation of ^{31}P-^{19}F NMR J Couplings in Sarin.

Basis Set	HF	HF Mixed	DFT B3LYP	DFT B3LYP Mixed
6-21G	-865		-1160	
6-31G	-848		-1350	
6-31++G	-824		-1128	
6-31++G(2d,2p)	-691		-1039	
6-311++G(d,2p)	-878		-1271	
6-311++G(2d,2p)	-859		-1255	
6-311++G(2df,2p)	-841		-1242	
6-311++G(3df,2p)	-842		-1242	
6-311++G(3df,2pd)	-842		-1243	
6-311++G(3df,3pd)	-842		-1242	



Conclusions

- Calculation of the ^{31}P NMR chemical shifts for CWAs with individual clusters needs to include both explicit micro-hydration and a PCM solvent to improve the results.
- Torsional conformational averaging produces a small (1-2 ppm) change.
- Time and Boltzmann averaging over non-optimal configurations is possible from MD simulations.
- Have introduced a "halfing" sampling scheme to reduce the number of shielding calculations that are required.
- In the MD simulations it is also required to include water and other CWA interactions out to 4 Å to get accurate results.
- Still exploring the reason for the shift between experiment and theory in the J coupling experiments.

References

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