The Synergy Between Molecular Theory and Solid-State NMR Spectroscopy

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Understanding DNA repair proteins is important to linking environmental impact to biological health effects.

Research evaluating the local electronic environment of zinc that affects the structural or chemical function in proteins has been accelerated by the use of two key long-term capability investments at EMSL. The first is implementation of a NWChem module that provides *ab initio* quantum mechanical calculations using molecular mechanics (QM/MM) constraints; the NWChem code was developed at EMSL. The second is the successful development and implementation of low-temperature solid-state nuclear magnetic resonance (NMR) capabilities at high magnetic fields. The latter is designed to allow direct observation of NMR resonances of metals such as zinc and magnesium in metalloproteins that, under ambient conditions, would be arduous if not impossible to accomplish. Both the NWChem software development and the capability suite to perform low-temperature, solid-state NMR experiments at 18.8T were funded by the DOE Office of Biological and Environmental Research. A study employing the converged methodologies is summarized in a paper in press (Lipton et al. 2008), authored by EMSL staff (M. Valiev and W. A. De Jong) in collaboration with staff from Pacific Northwest National Laboratory's Biological Sciences Division (A. S. Lipton, R. W. Heck, and P. D. Ellis) and a Science Undergraduate Laboratory Internship student G. R. Staeheli. The publication discusses how QM/MM methods help elucidate the NMR spectra of zinc in a pivotal type of zinc metalloprotein, in which zinc is coordinated by four cysteines (Figure 1). In this case, the zinc plays an essential structural role. Based on knowledge gained from these investigations, the authors are now primed to investigate zinc sites (again fully coordinated by cysteine residues) where one of the cysteines has been activated by the zinc, allowing it to serve as a reactive center in DNA repair. This powerful combination of theory and experiment will be utilized to probe the means by which coordination geometry differentiates between a structural site and a reactive site, allowing a deeper understanding of DNA repair mechanisms.

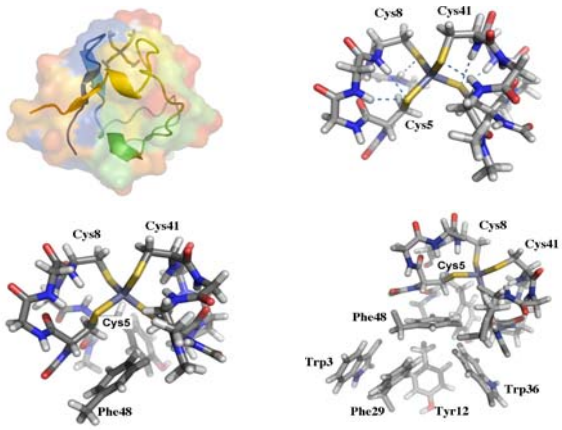

Figure 1. *Optimized quantum regions of Pf-rubredoxin, a zinc-containing DNA repair protein. Combined QM/MM calculations were performed on Pf-rubredoxin with increasing complexity in the quantum region. The research demonstrated sensitivity of the predicted NMR parameters to not only hydrogen bonding, but lone pair (LP)-π interactions. The research team achieved good agreement between theory and experimental values of both the electric field gradient and anisotropic shielding tensors.*

Citation:

Lipton AS, RW Heck, M Valiev, WA De Jong, and PD Ellis. "A QM/MM Approach to Interpreting ^{67}Zn Solid-state NMR Data in Zinc Proteins." *Journal of the American Chemical Society* (in press).