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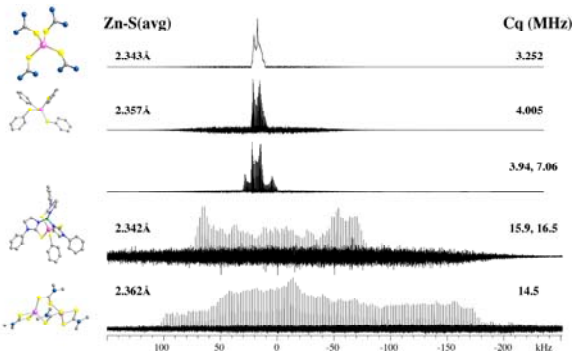
EMSL In Brief
Environmental Molecular Sciences Laboratory

NMR/Theoretical Method Being Developed to Characterize Proteins

Both computational and experimental resources at the Environmental Molecular Sciences Laboratory were employed by researchers from the Pacific Northwest National Laboratory to develop a method to understand the structure-function relationships in proteins. For example, a recent discovery showed a metal-amino acid motif once thought to only play a structural role in proteins can, in special cases, be reactive. The researchers' method is helping them understand what determines when a site such as this—zinc (Zn) metal coordinated to four cysteines (Cys), which are sulfur-donating amino acids—plays a structural or reactive role.



EMSL users are developing a method to understand proteins better, merging NMR experiments and theory to study compounds containing Zn (pink) and sulfur (yellow).

One example of a protein with this metal environment is Ada—a DNA-repair protein that demonstrates an adaptive response to alkylation (typically, the addition of a methyl group, $-CH_3$). In Ada, zinc is thought to activate a cysteine sulfur such that an alkylated piece of DNA will transfer its lesion to the sulfur. The mechanism of this transfer is in question: Does the sulfur dissociate from the Zn, or is there an electrostatic interaction that activates it? These questions can be addressed by a solid-state ^{67}Zn nuclear magnetic resonance (NMR) experiment.

To this end, the research team used EMSL's suite of NMR capabilities, including the 900-MHz NMR spectrometer, as well as EMSL's supercomputer and NWChem—computational chemistry software developed at EMSL and PNNL—to perform experimental measurements and apply computational models to five known compounds in which one Zn is coordinated to four sulfurs, including one compound that is a synthetic analogue of Ada.

The team employed a two-step process, such that they first observed the solid-state ^{67}Zn NMR spectroscopy at multiple magnetic field strengths to correlate known structural details about each complex to its NMR parameters. The team then compared their experimental findings with molecular theory performed at varying levels of detail to determine what method best predicted the NMR characteristics. Their results, published in the *Journal of the American Chemical Society* [129(29):9192-9200], show the Zn-Cys system to be sensitive to both the electronic environment and, to a lesser extent, small structural changes. In addition, the results illustrate the level of theory adequate for predicting NMR results. In the future, the team's approach could be used to model and characterize proteins whose structure-function relationship is not well understood, such as Ada.

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