Hybrid DFT/DFT study of Cu(II) binding to prion protein

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Hybrid DFT/DFT method[1] is a computational approach that combines Kohn-Sham DFT with orbital-free DFT and is suitable calculating properties of systems containing solvated biological molecules. Within this method the biological molecules and their first solvation shells are treated with full Kohn-Sham DFT, while an approximate orbital-free DFT based on Thomas-Fermi theory is used for the rest of solvent. This approach allows for an efficient inclusion of full solvation within the DFT calculations: Our tests show that the orbital-free DFT treatment of the solvent takes 10 % or less of the total calculation time even when the solvent outnumbers the solute by 100:1.

The DFT/DFT method was used to study binding of copper ions to the prion protein. This protein plays an important role in several neurodegenerative diseases, including the mad cow disease in cattle and the Creutzfeldt-Jakob disease in humans. Experiments show that the prion protein can bind copper in three distinct modes depending on its concentration. We determined the detailed geometries and copper ion binding energies for all three cases. The results explain the surprise found experimentally, namely that with increasing copper concentration the copper binding mode changes from a stronger to a weaker one. Our findings also lend strong support to the hypothesis that the role of the prion protein is to act as a copper buffer, protecting cells from the effects of uncomplexed copper.

[1] M. Hodak, W. Lu and J. Bernholc, J Chem Phys. **128** 014101 (2008).