UCLA College | Physical Sciences Chemistry & Biochemistry

Chem 218: Student Exit Seminar

Secondary Coordination Effects in Artificial Biotin-Streptavidin Metalloenzymes

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Designing artificial metalloenzymes is of interest because they combine the catalytic activity of possibly non-physiological but highly catalytically potent metals and the selectivity and mild operational conditions enabled by the protein. This talk will focus on joint theory-experiment efforts to design Rh and Ir artificial metalloenzymes, catalyzing the formation of 5-membered and 6-membered N-heterocycles. The biotin-streptavidin system has been used as a relatively simple and robust platform to create metalloenzymes by embedding organometallic catalysts in the protein. The monomeric streptavidin is known to retain the fold upon many different mutations, thus enabling the control over the second coordination sphere of the metal and fine-tuning of the metal electronic properties in a variety of ways without losing the entire structure. Biotin-Sav artificial metalloenzymes prepared in this way and containing Rh/Ir(Cp*) have shown improved reactivity and selectivity over simpler organometallic catalysts. We aimed to both explain the improved activity and to enhance it further by strategic mutagenesis. We have analyzed the secondary coordination effects using quantum mechanistic calculations, bonding analysis, and hybrid quantum mechanical/molecular mechanical simulations. In collaboration with experiment, we probed a library of mutants. In particular, we show that the pi-pi interaction between the catalyst and a tyrosine sidechain decreases rate-determining barriers. Additional residues in the vicinity of Tyr contribute to the quality of the pi-pi contact and the reactivity tuning. More remote mutations within the protein scaffold affect the protein structure and dynamics slightly, and thus affect the pi-pi contact indirectly, also impacting the activity. Successful and failed strategic and accidental mutations were made with the goal of improving the pi-pi contact, and will be discussed. Finally, we demonstrated that the activity correlates the most with the properties of the ensemble of states within the protein dynamics, showcasing the need for rapid QM/MM sampling in this work.

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12:00 p.m.
Via Zoom

For questions, please contact: jzabala@chem.ucla.edu