Computational Investigation of the Catalytic and Structural Roles of Metals in Metalloenzymes

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ABSTRACT:

Metalloenzymes capitalize on the unique roles of metal co-factors and protein scaffolds in catalyzing crucial chemical transformations at ambient conditions with exquisite selectivity. Some metalloenzymes exploit the redox properties of metal cofactors to catalyze challenging reactions, while others recruit metals for structural roles in stabilizing enzyme-substrate complexes. Although crystallography and spectroscopy provide foundational knowledge of the structure and reactivity of metalloenzymes, critical gaps remain in our understanding of the catalytic and structural role of metals in enzymes. Therefore, the use of novel computational tools to understand the role of metals and protein environment in dynamically promoting the reactivity and selectivity of metalloenzymes is of fundamental importance.

In this thesis, we study the catalytic and structural roles of metals in metalloenzymes using quantum mechanics (QM), classical molecular mechanics (MM), and hybrid, multi-scale (QM/MM) atomistic simulations. To address the unique challenges in QM/MM simulations of metalloenzymes, we study the relative magnitude of configurational and QM-region sensitivity of energetic and electronic properties in a representative structural metal (Zn^{2+}) binding site of a DNA methyltransferase. Next, we develop a protocol using spectroscopically-guided molecular dynamics (MD) simulations augmented with large-scale QM/MM calculations to unearth the role of protein-substrate dynamics in governing selective halogenation catalyzed by non-heme iron halogenases. Demonstrating the utility of this protocol, our simulations provide essential insights on the interplay between strategic substrate positioning, active-site configurational isomerization, and protein dynamics in halogenases SyrB2, WelO5 and BesD. We also investigate the use of vanadyl as a mimic of experimentally-elusive ferryl catalytic intermediates of non-heme iron halogenase. Additionally, we employ long-time MD simulations to investigate the conformational dynamics of ScoE, a non-heme iron dioxygenase, by connecting the contrasting crystal structures obtained thus far. In this thesis, we also provide computational evidence for the mechanical interlocking of proteins in hydrogels, a phenomenon that is difficult to visualize experimentally. We expect that insights from this work can directly guide efforts on enzyme engineering, biomimetic chemistry and therapeutic drug development.