QM/MM analysis of catalytic promiscuity and proton pumping in enzymes

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Abstract

I'll discuss the application of QM/MM methods developed in our lab to two fascinating problems in biochemistry: catalytic promiscuity and redox driven proton pumping. The first problem focuses on enzymes in the alkaline phosphatase (AP) superfamily, which exhibit remarkable catalytic promiscuity toward a broad class of phosphates and sulfates. Our QM/MM studies with a series of substrates in two members of the AP enzymes provide explicit support to the model that these enzymes are able to recognize and stabilize different types of transition states in a single active site. Analysis of the structural features of computed transition states indicates that the plastic nature of the bi-metallic site plays a minor role in accommodating multiple types of transition states, and that the high degree of solvent accessibility of the AP active site also contributes to its ability to stabilize diverse transition state structures without causing large structural distortions in the bimetallic motif. The second problem concerns proton pumping in Cytochrome c Oxidase (CcO). By judiciously combining QM/MM calculations and continuum electrostatic models, we demonstrate that a key element is the change of hydration level for the hydrophobic cavity that bridges the proton input channel, the binuclear center and the candidate proton loading site. The trigger of the hydration level change is the protonation of the candidate proton loading site, an event that calls for a novel proton transfer mechanism that involves an additional proton in the input channel. Together, the two research topics highlight the advantage of an efficient QM/MM framework based on SCC-DFTB and the diverse roles of water molecules in enzyme functions.