Effects of Protein Environments on the Mechanism of Metalloenzymatic Reactions

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The mechanism of reactions of metalloenzymes have often been studied using the "active-site QM-only" model. The reaction on metalloenzymes usually occurs in a relatively localized region around the metal center of protein, and the active site model is considered to be a more reasonable approximation in metalloenzymatic reactions than in more delocalized enzymatic reactions such as general acid-base type catalysis. In order to take the effects of protein environments into consideration for reaction mechanism and rate and to assess the importance of particular protein residues, we have been using the ONIOM approaches in QM:MM and QM:QM:MM versions to optimize the structure of intermediates and transition states of some metalloenzymatic reactions, adopting DFT methods as the high level QM part. We have also been using the free energy perturbation (FEP) method to evaluate the free-energy contributions to critical reaction barriers by combination of pure MM dynamics with a "frozen core" QM region.

In the present presentation, we will discuss in detail the reaction mechanism of the non-heme iron enzyme isopenicillin N synthase (IPNS). IPNS catalyzes a key step in the biosynthesis of antibiotics and is a potential target in the development of novel antibiotic compounds. We will also discuss those of the iron-heme enzyme indoleamine 2,3-Dioxygenase (IDO) and others. Comparing "active-site QM only", QM:MM and FEP approaches separates the catalytic effect of the metal center from the catalytic effect of the surrounding protein. Important protein effects on structures and relative energies of reaction will be discussed by comparing ONIOM studies on these enzymes on other metal enzymes we have studied previously, e.g. methane monooxygenase (MMO), ribonucleotide reductase (RNR) and glutathione peroxidase (GPx).