

3D3b Protein Effects on the Redox Reactions in Isopenicillin N Synthase - Insights from ONIOM QM/MM Calculations

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Redox-active metal enzymes play a critical part in many fundamental biochemical reactions, e.g. photosynthesis (photosystem II) and cell respiration (cytochrome *c* oxidase). An improved understanding of these enzymes not only gives an insight into nature's most fascinating molecular machines, but could also help to develop efficient biomimetic catalysts, e.g. for solar energy collection.

The function of a metal enzyme primarily depends on the nature of the metal center. Density functional theory (DFT) can treat transition-metal systems with reasonable accuracy and has become a widely used tool in the modeling of enzymatic reactions. However, very little is known about the function of the surrounding protein matrix. Does it mainly increase the stability of the active site and protect it from unwanted side reactions, or does it directly affect the catalytic reaction?

To increase the understanding of metal enzymes, and how to properly model their catalytic activity, the non-heme iron enzyme isopenicillin N synthase (IPNS) has been investigated using both active-site (B3LYP) and ONIOM QM/MM (B3LYP/Amber) models. IPNS is an oxygen-activated enzyme that uses dioxygen to catalyze a key step in the biosynthesis of the β -lactam antibiotics penicillin and cephalosporin.

The ONIOM QM/MM modeling has been performed using novel optimization algorithms. The increased stability of the optimization scheme leads to fewer problems with artificial geometry changes in the large protein part and therefore more reliable relative energies. Further, full optimizations of QM/MM transition states are possible with the use of a novel coupled Hessian algorithm.

In the present system, the reaction mechanism is mainly determined by the electronic structure of the active site. The long-range effects of the surrounding protein are relatively small. However, the use of a QM/MM model significantly improves geometries and relative energies, and largely removes problems from truncations of the computational model. This feature becomes more and more important as the size of the active-site model increases.

It is further shown that the active-site model fails to describe O₂ binding and product release. There are two important reasons for this failure. First, the active-site model does not accurately describe coordinatively unsaturated iron centers, e.g. five-coordinate sites. Second, non-bonded interactions, e.g. van der Waals interactions, are important in binding processes but are neglected when using active-site models. In total, the binding energy of O₂ increases by 8 kcal/mol when the surrounding protein is included.

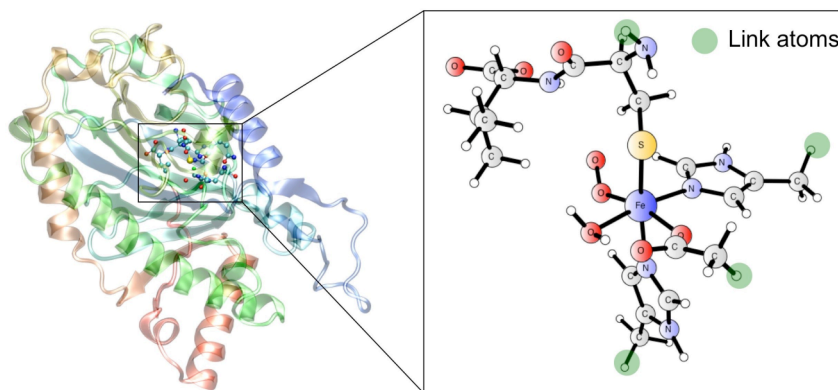


Figure 1. ONIOM QM/MM model of isopenicillin N synthase.