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Catalytic and Electronic Properties of Redox-Active Metalloenzymes and Transition-Metal Complexes: Insights from the Computational Chemistry

Dissertation Thesis Abstract

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Introduction

Metals and their ions play a key role in maintaining life. They frequently promote protein folding, the stabilization of protein scaffolds, enzymatic activity, energy conversion, intra- and intercellular signals etc. Several decades ago, metalloproteins were considered as a rather small group of proteins. Nowadays, one-third of enzymes are estimated to contain one or more metal ions, whose presence is crucial for their enzymatic functionality. Metalloenzymes participate most often in the catalysis of difficult chemical reactions (e.g. the hydroxylation of methane, decomposition of H₂ into protons and electrons, N₂ and O₂ bond cleavage and many other examples), in oxidation-reduction and electron-transfer reactions, and in the catalysis of spin-forbidden reactions, where relativistic effects (i.e. spin-orbit coupling) are necessary.

Nowadays, the biochemical role of enzymes is well-known. They work as very effective and more or less substrate-specific biocatalysts of many reactions which are otherwise kinetically forbidden. It is very tempting to investigate catalytic processes and their reaction mechanisms occurring naturally in organisms and look for their connections not only in order to understand the principles of life but also for the very practical reason that we can benefit from nature to make the chemical industry more efficient. Undoubtedly, studies of (metallo)enzymatic catalysis may allow the design of rational new biomimetic/bioinspired catalysts, which would in addition be more robust in the laboratory or under industrial conditions. On the other hand, small transition-metal complexes are often used to mimic the active sites of metalloenzymes. However, these simplified systems provide limited information on the properties of the enzymatic active-site pockets.

Despite the availability of many experimental studies concerning the structure and function of metalloenzymes, which provide insight into biochemical processes at the atomistic and electronic level, many questions are difficult or impossible to explain without theoretical simulations, interpretation and predictions. In the presented thesis, the QM and QM/MM methods are combined with experimental measurements, which have been carried out mostly by our collaborators (the group of Prof. Edward I. Solomon, the group of Dr. Sergey Shleev and the group of doc. Michal Hocek), for studying the catalytic and electronic properties of selected polynuclear metalloenzymes and transition-metal complexes.

Methods

Owing to the size and complexity of the bioinorganic species studied in this thesis, the delicate balance between the accuracy and computational demand of the method to be employed is necessary. In the majority of the problems, a reasonable compromise is obtained using the DFT methods.

However, conventional DFT approaches suffer from several drawbacks (e.g. lack of static correlation energy). For this reason, the more sophisticated multiconfiguration methods (such as multireferent second-order perturbation theory or multireferent configuration-interaction methods) were used.

The main part of the thesis concerns modeling of the metalloenzymatic catalysis. In the presented studies, the models typically comprise several tens of thousands of atoms; It is hence necessary to use combined quantum and molecular mechanical approximation. While the QM methods must be applied to the active site, where bonds break and form, the complexity of surrounding region can be reduced to molecular-mechanical (MM) descriptions of the intra- and intermolecular interactions.

Results

The aim of the presented thesis was to extend our understanding of the catalytic and electronic properties of selected redox-active metalloenzymes and transition-metal complexes. Despite significant progress in spectroscopic techniques and theoretical methodology, the complicated electronic structure (and the complex protein environment) of these bioinorganic systems make accurate theoretical modeling of their physicochemical properties a challenging task.

In the first part of the thesis, we used mostly the QM(DFT)/MM methods for an investigation of various aspects of metalloenzymatic reactivity. In the first two sections, concerning manganese superoxide dismutase and stearyl-ACP Δ^9 desaturase, we attempted to address the relevance of several reaction pathways proposed on the basis of the known experimental data. Although the density functional theory represents the approach of the first choice for describing the reactivity of these enzymes, it was demonstrated that the energies of the open-shell spin-coupled electronic structures of some intermediates and transition states are accurately predicted only by using advanced multireference calculations. In the two following sections, the investigation of two different catalytic aspects of multicopper oxidases (MCOs) was presented. These enzymes are unique in that they consist of mononuclear and trinuclear copper sites connected via a long-distance internal electron-transfer channel (in the mononuclear copper site, the substrate undergoes oxidation, whereas O_2 is concomitantly reduced to a water molecule in the trinuclear copper site). First, we complemented an electrochemical study of our collaborators by estimating the reorganization energies of MCOs based on our QM/MM model in an attempt to elucidate the kinetics of the internal electron transfer in these redox-active enzymes. Second, we studied the key step in the conversion of O_2 to H_2O in MCOs - the cleavage of the O-O bond in O_2 . We demonstrated the significant effect of the protein environment on the predicted barriers and reaction energies. In all of the above-mentioned studies, we found the QM/MM calculations to provide useful insight (at both the electronic and atomistic level) into the experimental data obtained for the biochemically relevant systems.

In the second part of the thesis, we focused our attention on the prediction of the physicochemical properties of redox-active octahedral ruthenium- and osmium-containing complexes as representatives of medicinally interesting systems. The first section dealt with the influence of the inclusion of the explicit spin-orbit coupling (SOC) on the accuracy of the electronic-structure calculations and the prediction of reduction potentials. The importance of this prominent relativistic effect is amplified in the Ru(II/III) and Os(II/III) hexacoordinate complexes since the oxidized forms possess unpaired *d* electrons and a degenerate electronic ground state (large SOC effect), whereas the electronic structures of the reduced forms are closed-shell (small SOC effect). Consequently, this fact manifests itself in lowering the reduction potentials by several hundreds of mV for Os(II/III) complexes. In the second section, we demonstrated how the solvation effects represented by the polarized continuum model influence the electronic structures of octahedral ruthenium-containing complexes, especially $[\text{RuCl}_6]^{4-}$. Based on the results, new solvatomagnetic and solvatochromic properties of this complex were predicted.

The final aim of the presented thesis was to show that the realm of (theoretically) bioinorganic chemistry is the exciting sub-branch of chemistry. Owing to the remarkable catalytic and electronic properties of bioinorganic complexes, the author of this thesis believes in the continuously growing wave of interest in their physical and chemical properties, which would eventually lead to the progress in theoretical modeling and new bioinspired technologies.