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Atomistic Approaches in Modern Biology

From Quantum Chemistry to Molecular Simulations

Springer

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Volume Editor: Markus Reiher

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Preface

This volume of *Topics in Current Chemistry* presents an overview of atomistic theoretical methods applied to molecular biological systems. It thus repesents a bottom-up view of chemistry on biology from a theoretical perspective. The chapters are arranged such that important issues are considered starting from a quantum mechanical perspective and proceeding to a molecular mechanics and molecular dynamics description of the motion of the elementary particles involved (i.e., of electrons and atomic nuclei and then of atoms and molecules), which are responsible for the properties and function of biomolecules.

Depending on the length and time scales relevant for a given phenomenon to be investigated, tailored theoretical methods are required to account for these. If one is interested in large scale motions of molecules, a molecular-mechnanics-based description will be appropriate. If, however, chemical reactions at local active sites within extended supramolecular ensembles such as metalloproteins shall be described, a quantum chemical descriptions of electrons and atomic nuclei is most appropriate as such a type of modelling does automatically adjust to any given chemical situation.

While the emphasis in each chapter is on the applicability and usefulness of the various theoretical approaches for a given biological system, the authors made an effort to also provide brief introductions to the foundations of these approaches. It is hoped that each introduction helps to understand the origin of the particular method under consideration. For instance, the first chapter provides a brief introduction to density functional theory and time-dependent density functional theory in the appendix.

This volume is organized in a bottom-up spirit and starts with a review by De Gioia *et al.* on how chemical reactions at the active site of the hydrogenase metalloenzyme can be analyzed with quantum chemical methods, i.e., with those based on the fundamental laws of quantum mechanics.

Quantum chemistry can also provide detailed knowledge on molecular properties as probed by various spectroscopic techniques. These options are discussed in the following two chapters. The first of these by Sinnacker and Neese deals with theoretical prediction and interpretation of resonance spectra obtained, for instance, from electron spin resonance (ESR), nuclear magnetic resonance (NMR), electron–nuclear double resonance (ENDOR) as employed in studies on active sites of metalloenzymes.

The second one by Herrmann and Reiher discusses techniques of vibrational spectroscopy with a focus on how information on local structures within large aggregates of molecules such as proteins can be extracted selectively based on local vibrations or through the selective process of intensity uptake in different vibrational spectroscopy techniques.

While the first three chapters deal with the basic quantities provided by quantum chemistry, namely (stationary) structures, properties and energetics in the electronic ground and excited states, the fourth chapter by Kirchner and collaborators introduces the reader to concepts of how to add the time-dimension to quantum chemical studies. *First-principles* dynamics is introduced in order to describe the Newtonian motion of atomic nuclei on a potential energy surface, which is available on the fly from the electronic structure.

The coupling of quantum chemical and Newtonian mechanics methods is subject of chapter 5 by Senn and Thiel. These so-called QM/MM methods aim at a combination of the best of both worlds. Of course, since the elements of both theories are by and large incompatible (compare the notions of orbitals and positions) a coupling of both can be achieved via the general concept of energy defined in both worlds.

A notorious problem of molecular dynamics is, however, the fact that the simulation time of a single reactive aggregate is usually much too small to observe spontaneous events that require a nonnegligible activation barrier. To overcome this problem, simulation techniques for rare events have been developed. The sixth chapter by Dellago and Bulthuis concentrates on one of these techniques called transition path sampling.

Then, chapter 7 by Schulten and collaborators focuses on molecular mechanics only. Here, the entities described are atoms, united atoms or functional groups. This reduces the number of degrees of freedom and allows one to study the dynamical behaviour of huge protein complexes like ATPase.

Finally, I would like to thank R. Mastalerz for his help concerning formating issues of this volume.

Zürich, July 2006 M. Reiher

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Quantum Chemical Investigations of Reaction Paths of Metalloenzymes and Biomimetic Models – The Hydrogenase Example

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Abstract Quantum chemical methods allow one to investigate chemical aspects that are often difficult to evaluate using only experimental approaches. In particular, the continuous increase in reliability and speed of quantum chemical methods has recently allowed

the investigation of very complex molecular systems, such as biological macromolecules. In this contribution, we present applications of quantum chemical methods to the investigation of reaction paths of metalloenzymes and related biomimetic models, using hydrogenase models as a reference case. In particular, we discuss several examples from the literature, emphasizing the possibilities (and limitations) offered by present theoretical approaches to study structures, electronic properties and reactivity of metalloenzyme models. Some relevant aspects which have not yet been fully explored using theoretical methods, such as the role of antiferromagnetic coupling and photochemical reactions in [Fe] hydrogenases, are treated in more detail, with presentation and discussion of original data recently obtained in our laboratory.

Keywords Coordination compounds · DFT · Hydrogenases · Metalloenzymes · Quantum chemistry

Abbreviations

B3LYP	Becke3-Lee-Yang-Parr DFT functional
BP86	Becke-Perdew 1986 DFT functional
CI	Configuration interaction
CIS	Configuration interaction singles
DFT	Density functional theory
dppe	1,2-bis(diphenylphosphino)ethane)
DTMA	Di(thiomethyl)amine
EDT	1,2 Ethanedithiolate
EPR	Electron paramagnetic resonance
Fe_p	Iron atom of the binuclear cluster proximal to the $[Fe_4S_4]$ cluster in [Fe] hydrogenases
Fe_d	Iron atom of the binuclear cluster distal to the $[Fe_4S_4]$ cluster in [Fe] hydrogenases
G2	Gaussian-2 molecules set
GGA	Generalized gradient approximation
HF	Hartree–Fock
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
KS	Kohn–Sham
LDA	Local density approximation
MP2	Møller–Plesset second order perturbation method
MOs	Molecular orbitals
CT	Charge transfer
o-xyldt	Orto-xylenedithiolate
PBE	Perdew–Burke–Ernzerhof DFT functional
PDT	1,3-Propanedithiolate
RI	Resolution of identity
TDA	Tamm–Dancoff approximation
TDDFT	Time-Dependent density functional theory
TDHF	Time-dependent Hartree–Fock
TZVP	A triple-zeta basis set
VWN	Vosko–Wilk–Nusair DFT functional
ZORA	Zero-order regular approximation
BS	Broken symmetry

HS High spin
COSMO Conductor-like screening model

1 Investigation of Metalloenzymes with Quantum Chemical Methods

Enzymes are interesting molecules not only due to their crucial biochemical and medical relevance, but also because the elucidation of the molecular properties responsible of their often remarkable catalytic activity can drive the design and synthesis of bio-inspired catalysts with potential technological applications. Several enzymes are known to bind one or more transition metal ions, which often play a key role in the catalytic mechanism. The biological role of transition metals has, in turn, stimulated the synthesis and characterization of coordination compounds featuring structural and/or functional features related to metalloenzymes and several examples are known in which the investigation of biomimetic complexes has complemented the elucidation of the properties of the corresponding metalloenzymes [1].

The tremendous increase in computer power, coupled to the refinement of theories and algorithms, has allowed in recent years the application of quantum chemical methods to the investigation of complex molecular systems containing atoms from almost all the periodic table, thereby disclosing the possibility to investigate the reactivity of metalloenzymes and biomimetic models using theoretical methods [2–7].

Present quantum chemical methods are suited to compute structures and relative energies of reactants, products and intermediate species, as well as transition states, allowing the dissection of reaction paths. Moreover, the possibility to characterize structural and electronic properties of both ground and excited states gives the opportunity to investigate photochemical reactions and spectroscopic properties, which can often be directly compared with experimental data.

In this contribution, the possibilities offered by quantum chemical methods to the investigation of reaction paths of metalloenzymes and related biomimetic models are presented using hydrogenases as reference example. In fact, almost all theoretical investigations of coordination compounds related to the active site of hydrogenases have been carried out using quantum chemical approaches based on Density Functional Theory (DFT) [8–11], which is based on the fundamental theorem that proves the existence of a functional of the electron density that contains all energy contributions, including the so-called correlation contributions, which are related to the mutual interaction of groups of electrons [12]. For a thorough description of DFT, the reader is referred to the seminal book of Parr and Yang [13], whereas a short primer can be found here in Appendix I.

The different description of correlation effects is one of the fundamental differences between DFT and the conventional Hartree–Fock (HF) theory. In fact, the HF method neglects correlation effects because each electron is supposed to move in the mean field provided by all other N-1 electrons, even though the HF energy expression includes an exact term for the exchange energy, which could be considered as a sort of correlation for electrons of equal spin. In the past, several methods have been proposed and used to introduce correlation effects via post-HF corrections, all of them including to different extent the configuration interaction (CI) [14], which, in turn, is based on the idea of approximating the exact wavefunction (in the limit of the adopted basis set) building up a combination of N-electron configuration state functions.

The HF method, among the so-called "ab initio" approaches, provides the cheapest way to obtain a molecular wave function, whereas the CI expansion (in all possible variants) is usually extremely time consuming. On the contrary, the computational time required by DFT calculations is only slightly longer than for HF, giving at the same time a one-electron structure similar to HF, thus offering a straightforward interpretation of the results while incorporating the correlation effects. Moreover, the description of open-shell systems is more balanced in DFT than in the HF, which generally enhances the importance of high-spin configurations (that are characterized by the highest exchange contributions). Finally, when open-shell systems are treated at the "unrestricted" level (different MOs for different spin) the DFT solution is generally less contaminated by high multiplicity contributions than the HF one. DFT methods can also give excellent results for molecular systems characterized by near-degenerate states, which are generally not adequately described by ab initio mono-determinantal perturbation theories (for example MP2). However, limitations affect also DFT methods. The accuracy of DFT results cannot be increased systematically, as it occurs with ab initio approaches based on variational principle, which ensures that large CI expansions on large basis sets of N-electron state functions can be arbitrarily close to the (non-relativistic) exact solution. Other limitations of the DFT approach are related to the adopted exchange-correlation functional, for which the exact form is unknown. As a consequence, functional reliability can be only established in a heuristic way by comparing DFT results with experiments or extremely accurate results obtained from highly correlated ab initio methods. In this context, coordination compounds represent a challenging case because very accurate ab initio results are often unavailable and also experimental results may be scarce. In spite of the above limitations, DFT has become a very useful tool for the investigation of models of metal-containing proteins. In fact, functionals based on GGA and so called hybrid methods, in which a portion of Hartree–Fock exchange energy is added to the exchange-correlation energy, give accuracies similar or higher than ab initio MP2 methods. In add-

ition, efficient approaches developed to calculate the Coulomb energy, such as the RI approximation [15–18], have further improved the computational efficiency.

The hybrid three parameter B3LYP and the pure BP86 functionals have been widely used in computational studies of models of the active site of enzymes. The hybrid B3LYP functional [19–22], which was originally calibrated on the G2 database of organic molecules, is now extensively used to study also metal-containing molecules, due to increasing evidence that B3LYP can predict accurately properties like bond dissociation energies and molecular geometries when coupled to an appropriate basis set. Similar considerations hold true for BP86 [23, 24]. Reaction energies can be generally evaluated with a reasonable accuracy, even if they can be affected by the choice of the exchange-correlation functional and basis sets [2, 25]. Other relevant experimental observables such as spin densities, EPR hyperfine coupling constants, g-tensors and vibrational frequencies can be presently computed within the DFT framework with a sufficient accuracy to allow comparison with the corresponding experimental data [2–6].

2
The Hydrogenase Example

Hydrogenases, which are widespread in prokaryotes and found also in some unicellular eukaryotes, are enzymes that catalyze the reversible oxidation of dihydrogen and therefore play a fundamental role in energy metabolism [26]. Most hydrogenases can catalyze the reaction in both directions in vitro, although in vivo they are usually involved either in H_2 uptake or H_2 evolution, depending on the metabolic state of the organism. Studies of isotope exchange led to the conclusion that dihydrogen cleavage catalyzed by hydrogenases follows an heterolytic reaction path, which implies formation of intermediate hydride species [27].

Experimental and theoretical studies of hydrogenases are not only driven by the biological relevance of these enzymes [28, 29], but also by the possibility to cheaply produce large amount of hydrogen gas, which is a very promising future energy carrier [30].

2.1
[NiFe] and [Fe] Hydrogenases

The two hydrogenase families more thoroughly investigated so far are [NiFe] and [Fe] hydrogenases, which are phylogenetically distinct and named according to the metal ions bound in their active site [31–39]. Remarkably, another evolutionary distinct family of hydrogenases has been recently found to contain an iron cofactor of functional importance [40].

The structural organization of [NiFe] and [Fe] hydrogenases, as well as several peculiar features of the metal cofactors involved in H_2 activation, have been disclosed by X-ray diffraction and spectroscopic studies [41–48]. In the active site of [NiFe] hydrogenases a nickel ion is bound to the protein by four cysteine residues, two of which are also coordinated to an iron ion (Fig. 1). IR spectroscopy studies revealed that the iron ion binds also two CN^- and one CO ligands [49]. In the catalytically inactive form of the enzyme an additional oxygen-containing ligand, which has been recently characterized as a hydroperoxide moiety, bridges the two metal ions [50]. Several redox states for [NiFe] hydrogenases have been characterized by kinetic and spectroscopic studies. Four correspond to paramagnetic forms (usually referred to as Ni-A, Ni-B, Ni-C, Ni-L). The Ni-A form is slowly activated in the presence of H_2, whereas Ni-B undergoes quick activation. The Ni-C form, which is two electrons more reduced than Ni-B, is catalytically active and upon illumination forms the Ni-L species, which is stable at temperature below 100 K. EPR silent forms (Ni-SU, Ni-SI and Ni-R) have also been identified and might be involved in the catalytic cycle [51].

An unusual $[Fe_6S_6]$ cluster, referred to as H-cluster and formed by a classical $[Fe_4S_4]$ cluster bridged by a cysteine residue to a binuclear subcluster ($[2Fe]_H$), is bound in the active site of [Fe] hydrogenases (Fig. 2).

The two iron atoms of the $[2Fe]_H$ subcluster are coordinated by CO and CN^- ligands and by a chelating $S-X_3-S$ moiety, which has been proposed to be either di(thiomethyl)amine (DTMA) or 1,3-propanedithiolate (PDT). Spectroscopic investigations of [Fe] hydrogenases are consistent with a +2 oxidation state for the $[Fe_4S_4]$ cluster, both in the oxidized and reduced forms

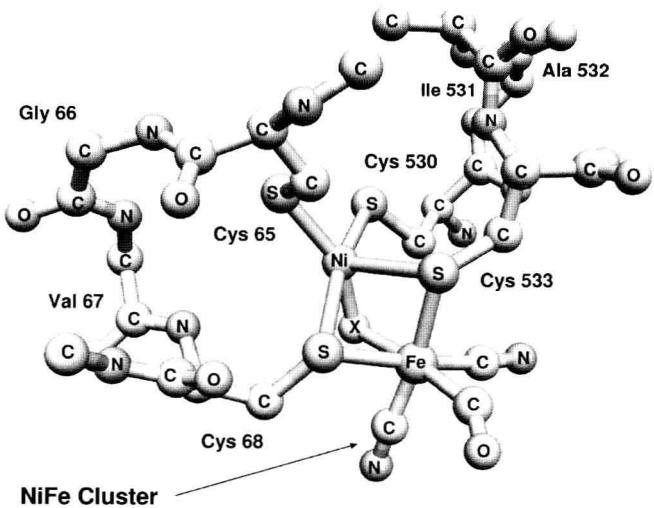

Fig. 1 Structure of the bimetallic cluster found in the active site of [NiFe] hydrogenases