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Hybrid QM/MM Car-Parrinello Simulations of Catalytic and Enzymatic Reactions

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Abstract: First-principles molecular dynamics (Car-Parrinello) simulations based on density functional theory have emerged as a powerful tool for the study of physical, chemical and biological systems. At present, using parallel computers, systems of a few hundreds of atoms can be routinely investigated. By extending this method to a mixed quantum mechanical – molecular mechanical (QM/MM) hybrid scheme, the system size can be enlarged further. Such an approach is especially attractive for the *in situ* investigation of chemical reactions that occur in a complex and heterogeneous environment. Here, we review some recent applications of hybrid Car-Parrinello simulations of chemical and biological systems as illustrative examples of the current potential and limitations of this promising novel technique.

Keywords: Car-Parrinello first-principles molecular dynamics · Computational chemistry · Enantioselective catalysis · Enzymatic reactions · QM/MM simulations

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1. Introduction

During the last decade the field of computational chemistry has experienced enormous progress. Due to the exponential increase in computer power and the development of new computational methods it has now become possible to treat many complex chemical and biological problems on an accurate and realistic level.

First-principles molecular dynamics (MD) simulations [1] based on density functional theory (DFT) [2] and mixed quantum mechanical/molecular mechanical (QM/MM) approaches [3] are among the most powerful of these new computational tools. We have recently developed a combination of these two techniques into a hybrid QM/MM Car-Parrinello scheme [4]. This approach enables efficient and robust hybrid Car-Parrinello simulations of extended systems in which the chemically relevant part is treated at the quantum mechanical level while the effects of the surroundings are taken explicitly into account through the embedding in a classical environment.

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Hybrid QM/MM Car-Parrinello simulations paired with enhanced sampling techniques [5] are especially attractive for the *in situ* investigation of complex chemical and biochemical reactions that occur in a heterogeneous environment.

In this article, we shortly summarize some of the pertinent features of our hybrid implementation and review some recent applications of this technique to chemical and biochemical systems as representative examples of the type of problems that can be tackled with this method.

2. Computational Method

The computer simulation of chemical reactions in realistic environments is a particularly challenging task. The fact that chemical bonds are broken and formed during this process necessitates the use of a quantum mechanical method which can take explicit account of the instantaneous changes in the electronic structure. Furthermore, electronic correlation effects are known to be important for an accurate description of reaction barriers and consequently, only relatively elaborate electronic structure approaches can be applied. However, traditionally correlated quantum chemical methods are restricted to the treatment of relatively small systems in the gas phase whereas complex chemical and biochemical processes usually occur in heterogeneous condensed phase environments consisting of thousands of atoms.

One possible solution for the modelling of such systems is the choice of a hierarchical hybrid approach in which the whole system is partitioned into a localized chemically active region (treated with a quantum mechanical method) and its environment (treated with empirical potentials). This is the so-called quantum mechanical/molecular mechanics (QM/MM) method, in which the computational effort can be concentrated on the part of the system where it is most needed whereas the effects of the surroundings are taken into account with a more expedient model.

The particular QM/MM Car-Parrinello method [4] that has been used in this paper is based on a mixed Hamiltonian of the form (Eqn. (1)) in which the quantum part H_{QM} is described with the extended Car-Parrinello Lagrangian (Eqn. (2)) where M_I and $\vec{R}_I$ are the nuclear mass and position, $\psi_i(\vec{r})$ are one-particle wavefunctions, μ is the mass associated with the fictitious classical kinetic energy of the

$$H = H_{QM} + H_{MM} + H_{QM/MM} \quad (1)$$

$$L = \frac{1}{2}\mu\sum_i \int d\vec{r}\,\dot{\psi}_i^*(\vec{r})\,\dot{\psi}(\vec{r}) + \frac{1}{2}\sum_I M_I \dot{\vec{R}}_I^2 - E_{KS}\left[\psi_i;\vec{R}_I\right] - \sum_{ij}\Lambda_{i,j}\left(\int d\vec{r}\,\psi_i^*(\vec{r})\psi_j(\vec{r}) - \delta_{i,j}\right) \quad (2)$$

$$E_{KS}\left[\psi_i;\vec{R}_I\right] = -\frac{1}{2}\sum_i \int d\vec{r}\,\psi_i^*(\vec{r})\nabla\psi_i(\vec{r}) + \int d\vec{r}\,V_N(\vec{r})\rho(\vec{r}) + \frac{1}{2}\int d\vec{r}\,d\vec{r}'\,\rho(\vec{r})\frac{1}{|\vec{r}-\vec{r}'|}\rho(\vec{r}') + E_{xc}[\rho(\vec{r})] \quad (3)$$

$$\rho(\vec{r}) = 2\sum_{iocc}\psi_i^*(\vec{r})\psi_i(\vec{r}) \quad (4)$$

$$H_{MM} = H_{MM}^{bonded} + H_{MM}^{non-bonded} \quad (5)$$

$$H_{MM}^{bonded} = \sum_b \frac{1}{2}k_b(r_{ij}-b_0)^2 + \sum_\theta \frac{1}{2}k_\theta(\theta_{ijk}-\theta_0)^2 + \sum_\varphi\sum_n k_n\left[1+\cos(n\varphi_{ijkl}-\varphi_0)\right] \quad (6)$$

$$H_{MM}^{non-bonded} = \sum_{lm}\frac{q_l q_m}{4\pi\varepsilon_0 r_{lm}} + \sum_{op} 4\varepsilon_{op}\left(\left(\frac{\sigma_{op}}{r_{op}}\right)^{12} - \left(\frac{\sigma_{op}}{r_{op}}\right)^{6}\right) \quad (7)$$

electronic degrees of freedom, and the Lagrange parameters $\Lambda_{i,j}$ enforce orthogonality of the electronic wave functions. The potential energy term $E_{KS}\left[\psi_i,\vec{R}_I\right]$ is given by the Kohn-Sham energy density functional (Eqn. (3)) where $V_N(\vec{r})$ is the external potential, $E_{xc}[\rho(\vec{r})]$ the exchange-correlation functional and the electron density $\rho(\vec{r})$ is given by Eqn. (4).

In our hybrid QM/MM simulations, we use a standard Car-Parrinello implementation [6], in which the one-electron wave functions are expanded in a basis set of plane waves and only the valence electrons are treated explicitly whereas the ionic cores are integrated out using norm-conserving non-local pseudo potentials [7].

The purely classical part of the Hamiltonian in Eqn. (1), H_{MM}, is described by a standard biomolecular force field (Eqn. (5)) where H_{MM}^{bonded} and $H_{MM}^{non-bonded}$ are of the general form (Eqn. (6) and (Eqn. (7)).

The terms in H_{MM}^{bonded} take harmonic bond, angle and dihedral terms and the ones in $H_{MM}^{non-bonded}$ electrostatic point charge and van der Waals interactions into account.

The intricacies of QM/MM methods lie in the challenge of finding an appropriate treatment for the coupling between QM and MM regions as described by the interaction Hamiltonian $H_{QM/MM}$. Special care has to be taken that the QM/MM interface is described in an accurate and consistent way, in particular in combination with a plane wave based Car-Parrinello scheme. Several mixed QM/MM Car-Parrinello methods have recently been implemented [8][9]. In the fully Hamiltonian coupling scheme developed in our group [4], bonds between QM and MM part of the system are treated with specifically designed monovalent pseudo potentials whereas the remaining bonding interactions of the interface region, *i.e.* angle bending and dihedral distortions, are described on the level of the classical force field. The same holds for the van der Waals interactions between QM and MM parts of the system. The electrostatic effects of the classical environment on the other hand, are taken into account in the quantum mechanical description as additional contribution to the external field of the quantum system

$$H_{QM-MM}^{ele} = \sum_{i\in MM} q_i \int dr\,\rho(r)v_i(|r-r_i|) \quad (8)$$

where q_i is the classical point charge located at r_i and $v_i(|r-r_i|)$ is a Coulombic interaction potential modified at short-range in such a way as to avoid spill-out of the electron density to nearby positively charged classical point charges. In the context of a plane wave based Car-Parrinello scheme, a direct evaluation of Eqn. (8) is prohibitive as it involves of the order of $N_r x N_{MM}$ operations, where N_r is the number of real space grid points (typically *ca.* 100^3) and N_{MM} is the number of classical atoms (usually of the order of 10,000 or more in systems of biochemical relevance). Therefore, the interaction between the QM system and the more distant MM atoms is included *via* a Hamiltonian term explicitly coupling the multipole moments of the quantum charge distribution with the classical

point charges. This QM/MM Car-Parrinello implementation [4] establishes an interface between the Car-Parrinello code CPMD [10] and the classical force fields GROMOS96 [11] and AMBER95 [12] in combination with a particle-particle-particle-particle mesh (P3M) treatment of the long-range electrostatic interactions [13].

In this way, efficient and consistent QM/MM Car-Parrinello simulations of complex extended systems of several 10'000–100'000 atoms can be performed in which the steric and electrostatic effects of the environment are taken explicitly into account.

3. Applications

In the following sections, we present a few selected examples of hybrid QM/MM Car-Parrinello applications in order to illustrate the type of problems that can be treated with this method.

3.1. *Organometallic Transition Metal Complexes and Enantioselective Catalysis*

Due to the importance of correlation effects, an accurate description of transition metals is a highly demanding task for quantum mechanical electronic structure approaches. Density functional methods [2] have a long tradition in the treatment of such systems and constitute an attractive compromise between accuracy and computational cost. Nowadays, organometallic transition metal complexes of the size of a few hundreds of atoms can be treated entirely at the quantum mechanical level [14]. Nevertheless, QM/MM methods are a handy tool also for these systems as they allow for an easy dissection of electronic and steric effects of different parts of the molecule. An example for the use of combined QM/MM calculations as such an analytic tool has recently been performed [15] for the chiral bis(trichlorosilyl)-palladium(II) complex shown in Fig. 1.

This complex is a catalyst precursor for the highly enantioselective hydrosilylation of norbornene, styrene and other olefins with $HSiCl_3$ [17]. As shown in the Table, it presents such remarkable structural features as a 'world-record' Pd–P bond length of as much 2.50 Å and a rather pronounced deviation from ideal square planar geometry as indicated by the angle between the P-Pd-N and Si-Pd-Si planes of 34°.

By constructing a systematic series of different QM and QM/MM models (also shown in Fig. 1) the nature of the Pd–P bond elongation and the origin of the non-square-planar coordination geometry of the Pd center can be traced back to the different molecular components. Steric *versus* electronic effects can be separated clearly by allowing only for steric contributions of the MM fragments while the electrostatic coupling is explicitly suppressed. A comparison of the structural features of the different computational models (Table) demonstrates that much of the extreme lengthening of the Pd–P bond is due to the steric interaction between the phenyl groups of the

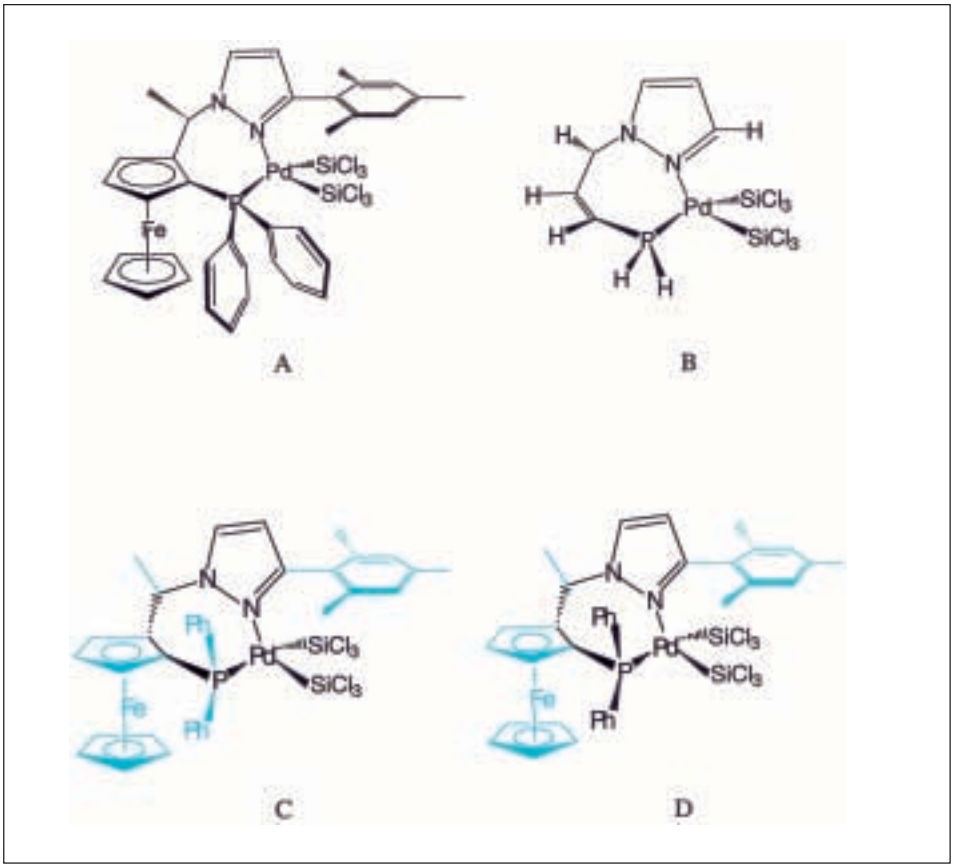


Fig. 1. Different computational models of a chiral palladium(II)-bis(trichlorosilyl) complex. A: full quantum model (DFT with BP86 gradient corrections [16]); B: minimal quantum model; C: QM/MM model 1 and D: QM/MM model 2. The parts that are shown in light blue lines constitute the MM part. Only steric contributions of the MM fragment are allowed to contribute [15].

parameter	X-ray	Full QM	Small QM	QM/MM-1	QM/MM-2
Pd-P	2.50	2.53	2.39	2.46	2.50
Pd-N	2.21	2.25	2.18	2.20	2.21
Pd-Si(1)	2.31	2.33	2.33	2.32	2.32
Pd-Si(2)	2.26	2.29	2.29	2.28	2.28
N-Pd-Si	154	159	167	158	154
P-Pd-Si	157	154	165	159	157

Table. Comparison of selected geometric parameters derived from the experimental X-ray structure and those of various computational models (see Fig. 1). In the QM/MM models only steric contributions of the MM fragment are allowed to contribute [15]. Distances are reported in Å and angles in deg. Si(1): silicon atom in *trans* position to P; Si(2): silicon atom in *trans* position to N.

phosphine and the trimethylphenyl group of the pyrazole ring [15].

Similar QM/MM calculations as the one described have also proven to be useful in evaluating the structural effects of π–π stacking interactions in organometallic complexes [18]. Besides serving as an analytic tool, QM/MM models provide also computationally highly efficient, realistic models that make the detailed investigation of entire catalytic reactions cycles, in which many different adduct structures and reactive pathways have to be considered, feasible. Detailed QM/MM Car-Parrinello simulations of the enantioselective palladium catalyzed hydrosilylation of styrene [19] and the mechanism of catalytic enantioselective fluorination [20] in gas phase and acetonitrile solution are recent example of this type of applications.

3.2. *Design of Biomimetic Compounds*

During millions of years of evolution, nature has developed its own mild and efficient way of doing chemistry. Enzymes, the cell's chemical laboratories, are able to catalyze a large variety of biologically relevant chemical reactions with high efficiency and selectivity. In many cases, laboratory experiments have to resort to extreme pressures and temperatures to perform reactions that are easily carried out in living cells at ambient conditions. The idea of synthesizing enzyme mimics therefore emerges quite naturally. Many research groups throughout the world are working on reaction schemes that adopt biochemical strategies with the goal of finding 'green chemistry' routes with higher efficiency and/or selectivity. One especially attractive strategy is to map the essential catalytic properties of the natural system on to relatively simple synthetic compounds that can easily be handled and modified for specific purposes. However, due to the large complexity of biological systems, the development of functionally equivalent biomimetic compounds has met with great difficulties.

In this field, computer simulations, in which the role of different active site residues can be probed systematically, can make important contributions in trying to pinpoint the essential catalytic features of an enzymatic process, as well as in the subsequent design of simplified biomimetic analogues.

We have recently performed a parallel study of the copper enzyme galactose oxidase (GOase) and existing low-efficiency mimics [21] (Fig. 2). GOase oxidizes primary alcohols selectively to the corresponding aldehydes and is therefore of interest as a potential (stereo)selective, mild oxidation catalyst. This is of special importance in view of the fact that even though selective oxidation is of key importance for many industrial applications (*e.g.* in the preparation of perfumes and UV-stabilizers), to date relatively expensive and hazardous chemicals (such as *e.g.* RuO_4^- or $KMnO_4$) are used for this purpose [23].

By applying mixed QM/MM Car-Parrinello simulations, the natural and a low-efficient synthetic system (shown in Fig. 2) were confronted step by step throughout the catalytic cycle, and mutual differences were identified [21]. This comparative study showed that the overall features of the mimetic compound are qualitatively remarkably similar to the ones of its natural target. However, important differences exist in the activation energy of the rate-determining step of the reaction, which involves the abstraction of a hydrogen atom in an antiferromagnetically coupled diradical species. The overall geometric features of the corresponding transition states are very similar. However, a detailed characterization of their electronic structure provides a possible *rationale* for the decreased efficiency of the synthetic system. In fact, our calculations show that in the natural system, the unpaired electron density of the intermediate ketyl radical is in part delocalized over an equatorial ligand of the copper coordination sphere. Due to an unfavorable geometric orientation, the analogous effect is not present in the synthetic compound resulting in a difference in the corresponding activation energies of 5 kcal/mol.

This is a clear example of the fact that a subtle electronic effect can play a decisive role in determining the catalytic properties of a system. This electronic influence can only be detected with an electronic structure calculation and cannot be captured by a design strategy that is merely based on geometric parameters. The crucial (electronic) factors that determine the height of the activation barrier in the rate-determining catalytic step that

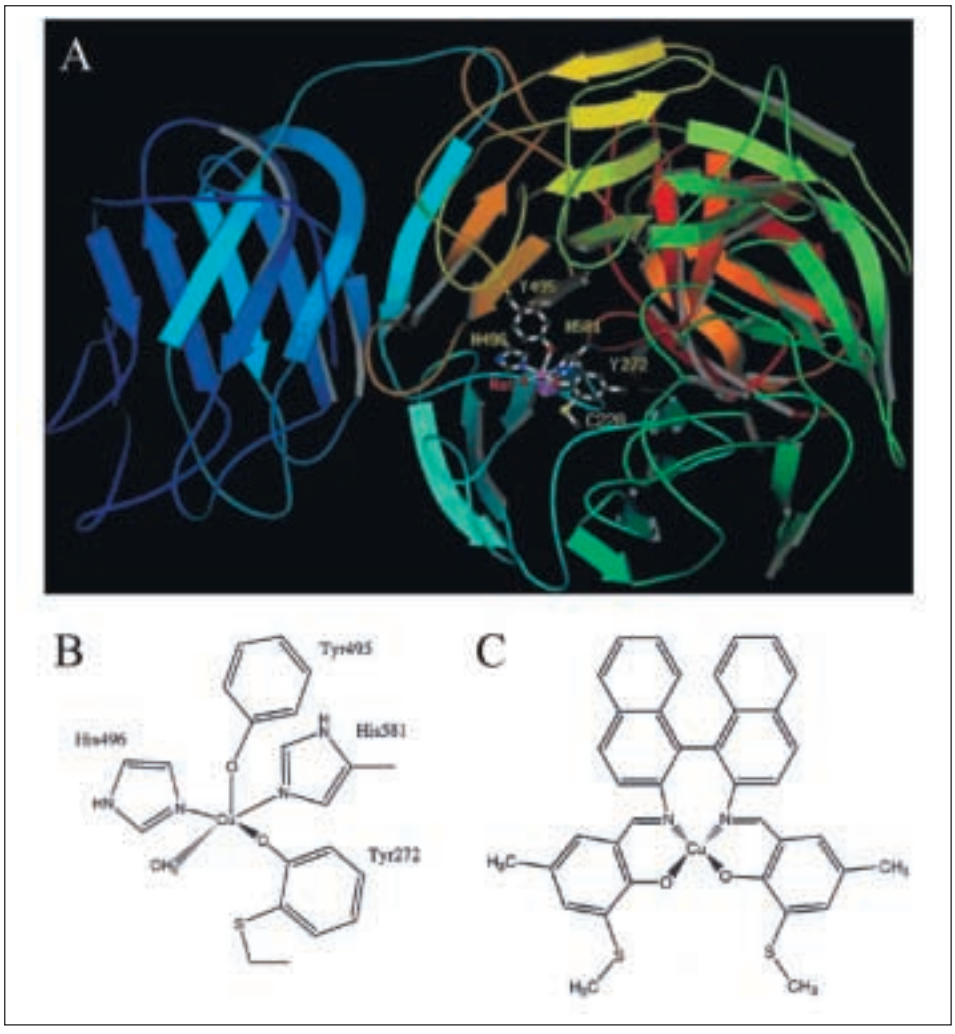


Fig. 2. The copper enzyme galactose oxidase (GOase) (A) and its active site (B) in comparison with a functional biomimetic compound (C) [22].

have been identified in this study were subsequently used to design a new generation of synthetic compounds. QM/MM Car-Parrinello calculations performed on these newly designed models predict an improvement of several orders of magnitude in the catalytic efficiency, making it similar to (or higher than) that of the natural system.

3.3. *Locating Copper-Binding Sites in Prion Proteins*

Prions are infectious agents that play a central role for a group of invariably fatal, neurodegenerative diseases affecting animals such as sheep (scrapie), cattle (BSE), and humans (*e.g.* variants of the Creutzfeldt-Jacob disease) [24]. It is now widely established that these diseases are caused by an abnormal isoform PrP^{Sc} of the normal cellular prion protein PrP^{C} [25]. Recent experiments, both *in vivo* and *in vitro*, indicate that prions are able to bind metal ions, in particular Cu^{2+} [26]. It has generally been assumed that Cu^{2+} ions bind to the histidine-rich unstructured part [27]. However, recent pulse EPR and ENDOR experiments [28] suggest that copper binds with higher affinity in the structured part (amino acids residues 125–228). Three pH-dependent copper binding sites have been identified together with some information about the nature of the immediate copper coordination sphere. The exact position of the metal binding sites within the protein, however, could not be localized experimentally.

An identification of the copper binding sites in the structured part of prion proteins and a detailed characterization of the metal protein interactions are of great interest, as it has been suggested that metal ions could influence the structural stability and, potentially, also the transition to the infectious scrapie form. Moreover, the interplay with metal ions is a common denominator for several other neurodegenerative disorders such as Alzheimer's, Parkinson's and amylotrophic sclerosis [25].

Starting from the available NMR structure of the metal-free mouse PrP^{C} [30], we have performed mixed QM/MM Car-Parrinello simulations with the aim of identifying likely locations for Cu^{2+} binding [31].

Locating (transition) metal ions in a protein structure is a particularly cumbersome task, since the intricate nature of the bonding properties of the metal necessitates the use of a quantum mechanical electronic structure approach. At the same time the protein environment and solvent have to be taken into account, as well as dynamical finite temperature effects. A QM/MM approach appears therefore as the method of choice. However, since it is *a priori* not known which ligands are involved in binding, the necessary partitioning of the system into QM and MM regions is far from trivial. To circumvent this problem, we first performed a statistical analysis of all available high resolution (≤2 Å) crystal structures of copper proteins, to determine the relative propensity of different amino acids for copper ligation. Using this probability map, we scanned the structure of the mouse prion protein for the most likely Cu^{2+} binding regions. The resulting candidate structures were ranked by increasing probability and their stability was subsequently tested in QM/MM Car-Parrinello simulations of several picoseconds around room temperature. The starting point of all simulations was the experimentally determined NMR structure, which was immersed in a box of water and equilibrated by classical molecular dynamics simulations. Subsequently, a Cu^{2+} ion was placed in the vicinity of selected residues included in the QM region, and the exact location of the Cu^{2+}

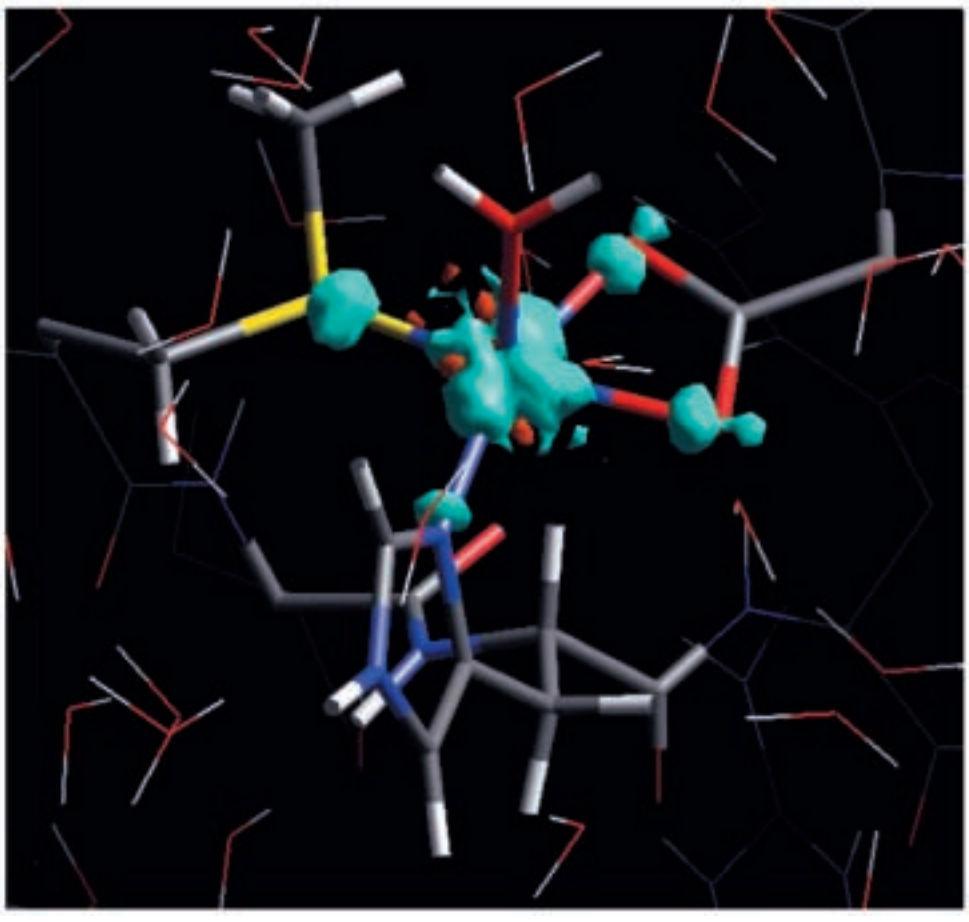


Fig. 3. Potential copper binding site in the structured part of the murine prion protein. Atoms that constitute the quantum part are indicated in thick cylinders, the classical environment with thin sticks. A contour plot of the unpaired spin density is shown in cyan.

ion and its coordination were determined in mixed QM/MM Car-Parrinello simulations. We have performed calculations on several binding sites, one of which is shown in Fig. 3. This possible binding site is approximately axial square planar and involves Met138, His140, and Asp147 as equatorial and a water molecule as axial ligand. The detailed coordination spheres that have been determined in the simulations can now be tested *via* site-directed mutagenesis experiments.

3.4. *Investigation of the First Step of Human Vision*

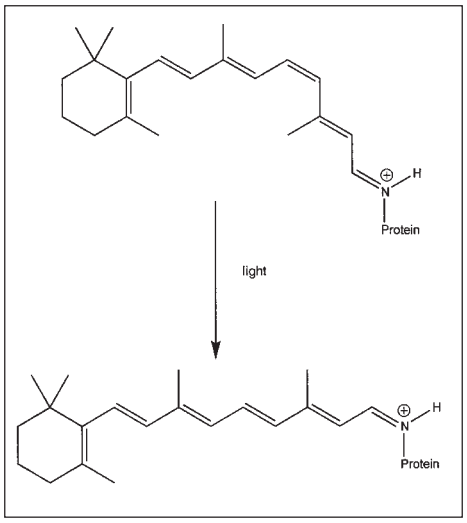
Human vision is a highly efficient process in which light is transformed into a neuronal signal that is detected in the brain. In the first step of this biochemical reaction chain, the transmembrane protein rhodopsin, which is located in the retina, plays the predominant role [32]. Rhodopsin consists of seven transmembrane helices accommodating in their middle the covalently bound chromophore, the protonated Schiff base of 11-*cis* retinal. Upon exposure to light, retinal isomerizes from 11-*cis* to all-*trans* in an extremely fast and efficient process, which is completed within 200 fs with a quantum yield of 0.67 (Scheme 1).

This induces a structural change of the intracellular part of the protein and triggers the signal transduction to another receptor protein of the signal cascade. A mechanistic understanding of this primary reaction is not only essential with regard to the cure of some eye diseases, but also of great interest for the development of optical switches.

The recent X-ray structure of rhodopsin [33] has paved the way to a molecular investigation of the activation mechanism. However, a detailed mechanistic understanding is still lacking. The role of the protein environment that promotes the isomerization reaction is not well understood. Also, the conformational changes that accompany the accommodation of all-*trans* retinal within the tight binding pocket are unknown. From a theoretical point of view, the investigation of these questions requires a mixed quantum/classical approach, because the excited state dynamics of retinal (50 atoms) is a quantum chemical process, while the description of the whole protein (about 5600 atoms) is only feasible within a classical framework.

We have recently combined our mixed QM/MM Car-Parrinello approach [4] with the restricted-open shell Kohn-Sham (ROKS) [34] method for describing the dynamics in the first excited singlet state. This combination allows the investigation of photochemical processes in complex biological systems. As a first test case study, we are currently investigating the *cis-trans* photo-isomerization in rhodopsin. Our model system (24000 atoms, see Fig. 4) contains the protein, a hydrophobic membrane-mimetic environment consisting of octane, and a saline solution. This setup is based on the most recent crystal structure of rhodopsin and results in a stable classical MD of several nanoseconds without imposing any type of structural constraint [35].

The key configurations of these classical pre-equilibration runs are currently used for mixed QM/MM simulations of



Scheme 1

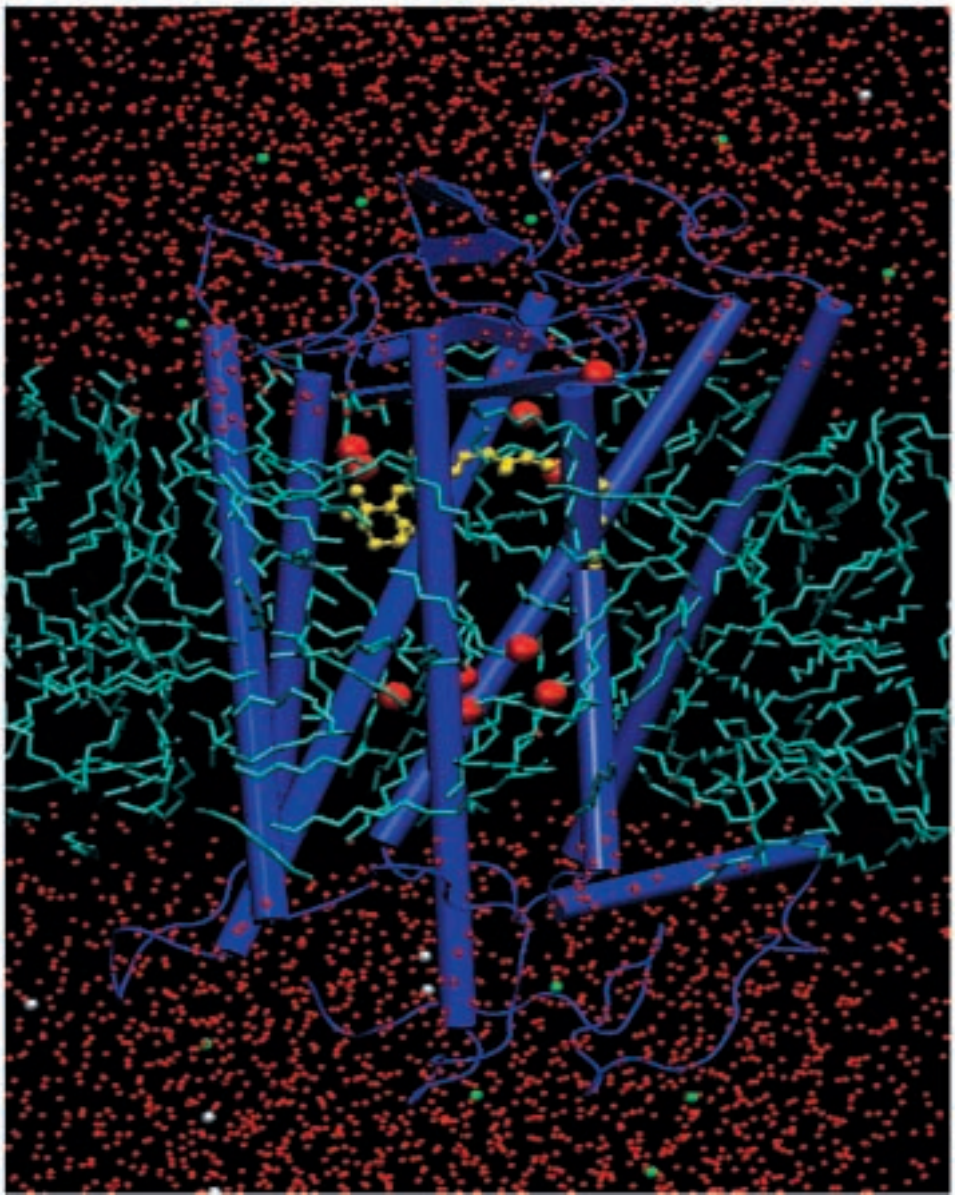


Fig. 4. Simulation system for rhodopsin. The protein (blue) contains seven transmembrane helices which accommodate the chromophore (yellow) in the middle. The membrane is mimicked by an octane solution (turquoise) surrounded by water (red sticks). Internal water molecules are indicated as red balls.

the initial reactant state and the ROKS-QM/MM Car-Parrinello simulations of the isomerization in the excited state.

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