Hybrid Car-Parrinello/Molecular Mechanics Modelling of Transition Metal Complexes: Structure, Dynamics and Reactivity

Leonardo Guidoni, Patrick Maurer, Stefano Piana and Ursula Rothlisberger[a]

[a] Prof. Dr. U. Rothlisberger, Tel.: +41 1 632 7460, Fax: +41 1 632 1090, E-mail: uro@inorg.chem.ethz.ch, Department of Chemistry, ETH Zürich, Wolfgang Pauli Str. 10, CH-8093 Zürich

Abstract

The theoretical modelling of chemically active transition metal (TM) centres is a notoriously difficult task. The metal-ligand interactions in these complexes are often highly directional and the concoction of suitable analytic interaction potentials can be far from trivial. The situation is rendered even more difficult by the fact that at finite temperature, the system might switch dynamically between different bonding situations or exhibit several energetically close-lying spin states which are all characterized by different coordination numbers and geometries. In this article, we describe the structural, dynamical and reactive properties of complex TM-containing systems with the help of a mixed quantum mechanical/molecular mechanical (QM/MM) molecular dynamics approach, in which the TM centre is described with generalized gradient corrected density functional theory embedded in a classical force field description. The power of such a combined Car-Parrinello/molecular mechanics approach is illustrated with a number of representative examples ranging from enantioselective TM catalysts to radiopharmaceuticals and metalloenzymes.

1 Introduction

A vast number of catalytic processes in chemical and in biological systems rely on the powerful reactive properties of transition metal ions. However, due to the pronounced importance of correlation effects, an accurate description of these centres is a highly demanding task even for quantum mechanical electronic structure approaches.

Density functional (DFT) methods [1] 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 [2]. Furthermore, DFT calculations can be incorporated into mixed quantum mechanical/molecular mechanical (QM/MM) hybrid schemes [3], in which only the immediate reactive region of the system is treated within the electronic structure approach and the effects of the surroundings are taken into account on the basis of a mechanical force field description. These DFT/MM calculations enable a realistic description of chemical reactions that occur in complex heterogeneous environments, such as homogeneous catalytic processes in solution and enzymatic reaction cycles in explicit protein environment. QM/MM methods also come in as a handy analytic tool, as they allow for an easy dissection of electronic and steric effects of different parts of the reactive system.

An additional difficulty in the theoretical description of systems containing transition metals lies in the fact, that these centres can also exhibit a highly dynamical behaviour, in which the coordination sphere undergoes continuos changes both in the number and in the geometric arrangements of the ligands. It is therefore advantageous to use a method that can take the molecular dynamics of the system at finite temperature explicitly into account.

In 1985, a unified approach of DFT and classical molecular dynamics (MD) has been introduced by Car- and Parrinello (first-principles MD, *ab initio* MD or Car-Parrinello MD) [4] (see the chapter in this special issue by Roberto Car).

We have recently developed a QM/MM extension of a Car-Parrinello scheme [5]. These hybrid Car-Parrinello simulations paired with enhanced sampling techniques [6] are especially attractive for the *in situ* investigation of complex chemical and biochemical reactions and are thus

Key words: transition metals, density functional theory, Car-Parrinello first-principles molecular dynamics, QM/MM simulations, enantioselective catalysis, radiopharmaceuticals, biomimetic compounds

our method of choice for the treatment of transition metal centres embedded in heterogeneous environments.

In this article, we shortly summarise some of the pertinent features of our hybrid implementation and review some recent applications of this technique to chemical and biochemical systems involving transition metals as illustrative examples of the current potential and limitations.

2 Computational Method

The system is divided into a localised chemically active region (QM region) and its environment (MM region). Through this partitioning, 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 [5] that has been used in this paper is based on a mixed Lagrangian of the form

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

where M_I and $\vec{R}_I$ are the nuclear mass and position, $\psi_i(\vec{r})$ are Kohn-Sham one-particle wavefunctions, μ is the mass associated with the fictitious classical kinetic energy of the electronic degrees of freedom , and the Lagrange parameters $\Lambda_{i,j}$ enforce orthogonality of the electronic wave functions. The potential energy terms E_{MM}, $E_{QM/MM}$, and E_{QM} refer respectively to the classical part, the interaction between QM and MM part and the energy of the QM system given by the Kohn-Sham energy density functional. The latter is given by

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

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 the sum of the densities of the occupied one-particle states.

$$\rho(\vec{r}) = 2\sum_i \psi_i^*(\vec{r})\psi_i(\vec{r}) \quad (3)$$

In our hybrid QM/MM simulations, we use a standard Car-Parrinello implementation [7], 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 [8].

The purely classical part E_{MM} of Eq. 1, is described by a standard biomolecular force field

$$E_{MM} = E_{MM}^{bonded} + E_{MM}^{non-bonded} \quad (4)$$

where E_{MM}^{bonded} and $E_{MM}^{non-bonded}$ are of the general form

$$E_{MM}^{bonded} = \sum_b \frac{1}{2}k_b(r_{ij} - b_0)^2 + \sum_\theta \frac{1}{2}k_\theta(\theta_{ijk} - \theta_0)^2 + \sum_\varphi \sum_n k_n\left[1 + \cos(n\varphi_{ijkl} - \varphi_n)\right] \quad (5)$$

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

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

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 $E_{QM/MM}$. 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 [9, 10, 11]. In the fully Hamiltonian coupling scheme developed in our group [5], 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. On the other hand, the electrostatic effects of the classical environment, are taken into account in the quantum mechanical description as additional contribution to the external field of the quantum system

$$E_{QM/MM}^{ele} = \sum_{i\in MM} q_i \int dr\rho(r)v_i(|r - r_i|) \quad (7)$$

where q_i is the classical point charge located at r_i and $v_i \times (|r - r_i|)$ 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 Eq. (7) 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 10000 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 [5] establishes an interface between the Car-Parrinello code CPMD [12] and the classical force fields GROMOS96 [13] and AMBER95 [14] in combination with a particle-particle-particle mesh (P3M) treatment of the long-range electrostatic interactions [15].

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 surroundings are taken explicitly into account.

3 Applications

In the following Sections, we present a few selected examples of hybrid QM/MM Car-Parrinello applications of transition metal systems of chemical and/or biochemical interest.

3.1 Modelling of Homogeneous Enantioselective Catalysis

The identification of the factors that govern specificity and selectivity of enantioselective catalytic processes is a particularly challenging task for a theoretical description. In this chapter, we present two examples of this type of applications. (1) is concerned with Pd(II) based enantioselective hydrosilylation catalysts and (2) is an investigation of the mechanism of enantioselective fluorination. In the former, the QM/MM approach is used to characterise the reactive properties of an enantioselective transition metal catalyst in gas phase, in particular for the identification of the specific electronic and steric effects that determine its structure and reactivity. In this piece of work, the QM/MM approach is mainly used as an analysis tool, whereas in the second study, it is employed to treat an extended system and to create a realistic chemical reaction environment.

3.1.1 Reactions in Apolar Media: The Gas Phase Properties of Chiral Palladium(II)-Bis(trichlorosilyl) Complexes

We have recently performed a QM/MM Car-Parrinello study of the chiral bis(trichlorosilyl)-palladium(II) complex shown in Figure 1 [16].

This complex is a catalyst precursor for the highly enantioselective hydrosilylation of norbornene, styrene and other olefins with $HSiCl_3$ [17]. As shown in Table 1, it presents some remarkable structural features, such as a 'world – record' Pd-P bond length of as much as 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(1)-Pd-Si(2) planes of 34°.

By constructing a systematic series of different QM and QM/MM models (also shown in Figure 1) the nature of the Pd-P bond elongation and the origin of the non-square-

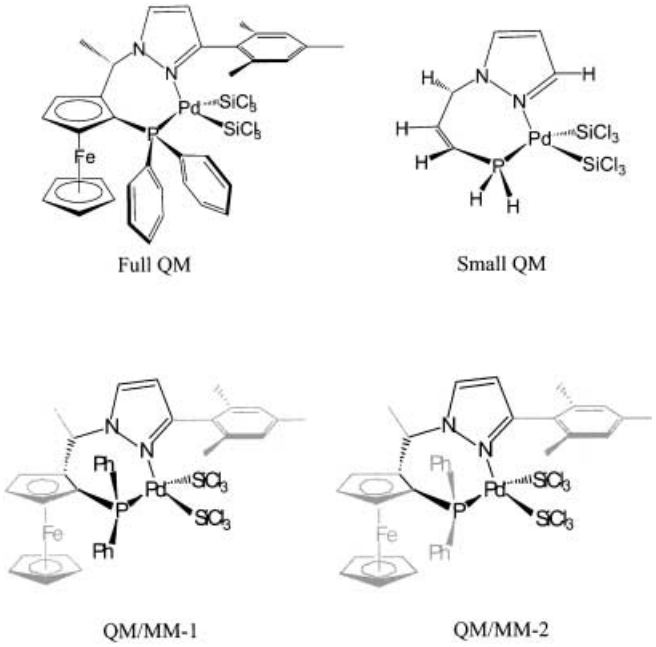


Figure 1. Different computational models of a chiral palladium-(II)-bis(trichlorosilyl) complex. "Full QM": full quantum model (DFT with BP86 gradient corrections [34]); "Small QM": minimal quantum model; "QM/MM-1": QM/MM model in which the effects of the phenyl groups of the phosphine ligand are treated on the molecular mechanics level; "QM/MM-2": QM/MM model in which the effects of the phenyl groups of the phosphine ligand are described at the DFT level. The parts that are shown in light grey lines constitute the MM part. Only steric contributions of the MM fragment are allowed to contribute [16].

planar coordination geometry of the Pd center can be traced back to specific molecular components. Moreover, 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 1) demonstrates that much of the extreme lengthening of the Pd-P bond is due to the steric interaction between the phenyl groups of the phosphine ligand and the trimethylphenyl group of the pyrazole ring [16].

Similar QM/MM calculations as the one described here 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, a QM/MM approach also constitutes a computationally highly efficient and realistic route for the detailed investigation of entire catalytic reactions cycles. QM/MM models make the calculation of comprehensive sets of different adduct structures and reactive pathways feasible, which is of paramount importance for a reliable modelling of such processes. Detailed QM/MM Car-Parrinello simulations of the enantioselective palladium catalyzed hydrosilylation of styrene [19] and the mechanism of catalytic enantioselective

Table 1. Comparison of selected geometric parameters derived from the experimental X-ray structure and those of various computational models (see Figure 1). In these QM/MM models only steric contributions of the MM fragment are allowed to contribute [16]. Distances are reported in Å and angles in deg. Si^P refers to the silicon atom in *trans* position to P; Si^N to the silicon atom in *trans* position to N.

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^N	2.31	2.33	2.33	2.32	2.32
Pd-Si^P	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

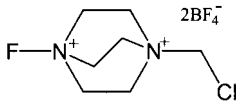
fluorination [20] in gas phase and acetonitrile solution described in the next Section are recent examples of this type of applications.

3.1.2 Solvent Effects: QM/MM Study of the Mechanism of Catalytic Enantioselective Fluorination

Some fluorinated compounds are of interest in medicinal chemistry. As most of these pharmacologically active molecules are chiral, the development of methods to achieve catalytic enantioselective fluorination are of considerable interest [21].

Amongst the most commonly employed fluorinating agents are compounds that contain an N–F bond [22]. One of these reagents is F-Triethylendiammine (F-TEDA, Scheme 1).

This reagent is able to fluorinate β-ketoesters in acetonitrile solution with good yields. In many cases the reaction is slow and can be efficiently catalyzed by a Lewis acid such as $TiCl_4$. The compounds of the [$TiCl_2$(R,R-TADDOLato)] family are enantiomerically pure Lewis acid titanium complexes. When these compounds are used as catalysts, it is possible to control the stereochemistry of the fluorination reaction and to obtain β-fluoro ketoesters with enantiomeric excesses of up to 90% from the racemic mixture (Scheme 2) [23].



Scheme 1.

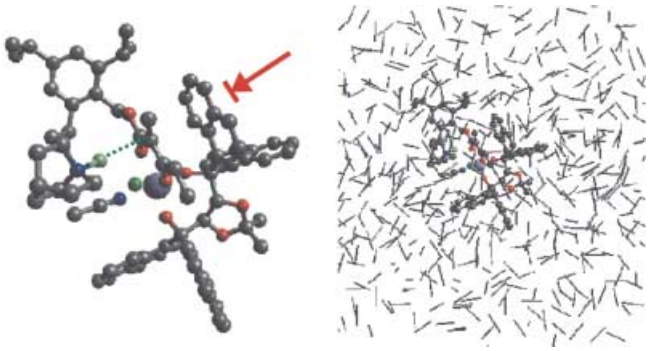
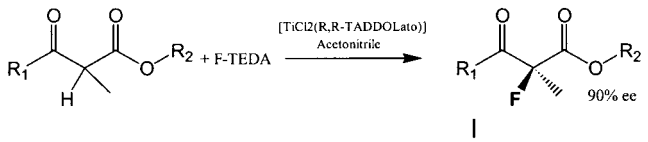


Figure 2. QM/MM simulation of the enantioselective fluorination reaction in vacuo and in acetontrile solution. The C-F distance chosen as a reaction coordinate is indicated as a dotted green line. The face of the β-ketoester shielded by the TADDOL naphtyl ring is indicated by a red arrow. The QM part of the system is shown in color and the MM part is drawn in grey.



Scheme 2.

The detailed reaction steps, which lead to the enantiomeric formation of the β-fluoro ketoester from a non-chiral compound, are still unknown although a mechanistic understanding of the catalyzed reaction would be very helpful for the rational design of more efficient and selective catalysts.

It is generally assumed that [$TiCl_2$(R,R-TADDOLato)] coordinates the β-ketoester and triggers the enolization reaction and that in fact the titanium-coordinated enolate constitutes the actual reactive species that is then fluorinated by F-TEDA in a subsequent step [23].

We have recently performed a QM/MM-DFT based study of the 8 possible isomers of the [TiCl(R,R-TADDOLato)]-enolate complex [20]. From these calculations, it turns out that the bulky side chains of the catalyst effectively shield one side of the enolate, in such a way that only one face is available for fluorination (Figure 2).

In agreement with experiment, the calculations predict that the most stable complexes are those that lead to the formation of the *R* stereo isomer of the β-fluoro ketoester. This indicates that the coordination of the enol is indeed the step responsible for enantioselectivity. Furthermore, this picture allows to rationalize the experimental observations that the stereochemistry of the reaction is dominated by the catalyst and that its steric bulk tends to enhance enantioselectivity [23].

The mechanism of the electrophilic fluorination reaction is still a subject of debate. As a special feature, the formation

of a chlorinated byproduct has been observed experimentally [23]. This side reaction could likely be explained by assuming a radical mechanism for the electrophilic fluorination. However, experimental evidence for the presence of radical intermediates in this type of reaction is highly controversial [24]. To shed light on this issue we have performed DFT/MM-based Car Parrinello molecular dynamics simulations to characterize the fluorination reaction catalyzed by Ti(TADDOL). These simulations were carried out in vacuo as well as in acetonitrile solution [20] (Fig. 2).

In the simulations in vacuo, an electron is transferred immediately from the Ti(TADDOL) complex to F-TEDA and two radical species are formed. These radicals are stable on the time scale investigated and no further spontaneous reaction is observed.

On the other hand, in the simulation in acetonitrile, the solvent stabilizes the positive charge on F-TEDA and no electron transfer is observed in the early stages of the MD simulation. In order to drive the reaction within the limited time scale of *ab initio* MD, the C-F distance was chosen as a constrained reaction coordinate and progressively reduced during $\sim$10 ps of MD simulation. When the transition state is reached, as indicated by an inversion of the sign of the constraint force, an electron is transferred from Ti(TADDOL) to F-TEDA and two metastable radical species are formed. As soon as the constraint is released the N-F bond is broken and the C-F bond forms immediately.

These results indicate that the electrophilic fluorination reaction can indeed proceed through the formation of radical intermediates. However, even a moderately polar solvent like acetonitrile is able to stabilize the reactants in such a way that electron abstraction is observed only at the transition state. As a consequence most of the radical species that are formed immediately recombine to yield the reaction products.

It is possible however that due to thermal fluctuations, some of the radicals do not recombine instantaneously and are released into the solvent. These free radicals can react with chloride anions that are present in solution to yield $Cl^{\cdot}$ radicals that finally generate the chlorinated byproducts observed experimentally.

$$^{\cdot}F + Cl^{-} \rightarrow F^{-} + Cl^{\cdot} \qquad (8)$$

This theoretical hypothesis has received strong confirmation by subsequent experiments in which a small amount of radical scavenger was added to the reaction medium. While the presence of the scavenger had no effect on the fluorination reaction, it drastically decreased the amount of chlorination [20].

3.2 Characterization of Radiopharmaceuticals

Metal complexes with radioactive nuclei are widely used in medicine as they enable the monitoring of biological functions and constitute tools for the imaging of tissues, organs and tumors [25]. Radioactive imaging techniques have therefore become an indispensable tool in cancer diagnosis. Furthermore, radiopharmaceuticals are now also used in a therapeutic manner for an *in situ* treatment of cancerous tissues.

Over 90% of all diagnostic nuclear medicine studies are carried out with technetium-99m. This is mainly due to the favourable properties of this radio isotope (^{99m}Tc is a γ-emitter with a half life of 6 h and an emission energy of only 141 keV) and its ready generator availability. Since ^{99m}Tc can only be used as an imaging agent, a wider range of radioactive metal nuclei is being tested with regard to a potential use as therapeutic agents. Among these are rhenium compounds with ^{186}Re and ^{188}Re as β-emitting isotopes for the targeted *in situ* irradiation of cancerous tissues [25].

Different classes of radiopharmaceuticals are being distinguished according to the applied design strategy. 'Metal essential or first generation agents' are typically relatively small complexes in which the radioactive metal center is chelated with oxygen, sulfur, nitrogen or phosphorus atoms containing ligands that can be further functionalized with additional groups. An example is Cardiolite® (^{99m}TcMIBI$_6^+$; MIBI: 2-methoxy isobutyl isonitrile) which serves as a tissue selective heart imaging agent [26]. First generation agents of this type have been very successful in the selective imaging of organs such as the heart, the brain, the kidneys, the liver and the bones. Although tissue-specific accumulation of first generation agents is not well understood, few key factors governing this process are starting to emerge. Among these are molecular parameters such as size, charge state and solvation properties (hydrophilicity/lipophilicity). Heart specific agents are e.g. thought to be characterized by lipophilicity and unipositive charge, whereas brain specific agents are mostly neutral and moderately lipophilic.

Growing demand in more specificity led to the development of 'conjugate or second generation agents' in which the complex containing the radioactive nucleus is covalently linked to a monoclonal antibody or a biologically active molecule that binds to specific receptor sites. A similar approach leads to the development of 'integrated or third generation agents' in which the outer sphere of the chelating ligand contains the sites for receptor binding, i.e. the ligand itself mimics a biologically active molecule, e.g. a steroid hormone such as estradiole or testosterone.

In general, upon injection, radiopharmaceuticals encounter a variety of chemical environments with different pH or redox power. The agent's pathway and final destination is crucially determined by its chemical transformation under these varying external conditions. In most cases however, the physicochemical properties of the radiopharmaceuticals, such as pKas and redox potentials, are not well characterized. Clearly, a thorough determination of these properties would be extremely desirable as such knowledge is likely to assist efforts towards a rational design of highly selective radiopharmaceuticals.

We are currently applying *first-principles* molecular dynamics and mixed QM/MM techniques to characterize

structural, electronic and dynamic properties of different radiopharmaceuticals [27] in close collaboration with experimental groups. In these calculations, essential physicochemical parameters can be determined, e.g. the most favourable protonation and/or oxidation states of the system, as well as the effect that different substituents have on these properties. In this way, possible reasons for e.g. chemical instabilities of the systems in different chemical environments (water, saline solutions) can be identified on the atomic and electronic level. Such knowledge is likely to provide some help in the rational redesign of existing radiopharmaceutical compounds.

As a first part of this project, we have investigated crown thioether complexes of rhenium, technetium and ruthenium in different redox environments [27]. The large overall structural similarity of these complexes with thioether chelated first generation agents and the availability of a considerable amount of experimental data make these compounds ideal test cases to validate our computational approach.

Hexathioether compounds $[M(9S3)_2]^{n+}$ (where M are metals from Group 7–12 of first, second and third row transition elements, 9S3 = 1,4,7-trithiacyclononane and n = 1–3) have been synthesized and characterized [28]. These systems exhibit interesting redox properties: Treatment of the doubly charged hexathioether complexes containing M = Tc or Re with mild reducing agents such as ascorbic acid, Zn or $SnCl_2$ results in immediate carbon-sulfur bond cleavage and release of ethene. This bond fission does not occur for any of the other transition metals that have been investigated. This observation has been explained in terms of the fact that Tc and Re exhibit a stronger π-back donation from metal d-orbitals into empty C–S σ* ligand orbitals. Several experimental studies including solution experiments, crystallographic data and electro spray mass spectrometry show the same trend [29].

The results of our calculations on these hexathioether compounds with Re, Tc and Ru as metal centres show that our computational scheme is capable of providing excellent structural descriptions for all three transition metal compounds. The experimentally observed C–S bond lenghts are very well reproduced and analysis of the electronic structure of the three compounds clearly supports the hypothesis of π-back donation (Figure 3).

Our calculations show that the C–S bond fission occurs as a subsequent reaction step after reduction of the doubly charged complexes to their unipositive analogues. In the Re and Tc compounds the additional electron leads to a lowering of the activation energy by about 10 kcal/mol, to a level that thermal fluctuations at room temperature are sufficient to induce loss of an ethene molecule.

These results are thus very encouraging and show that our computational approach is appropriate for the description of metal complexes containing the radioactive nuclei used in radiopharmaceutical applications. This type of computational studies might support experimental groups in the rational design of new radiopharmaceutical compounds or in the improvement of existing agents. Moreover, through the application of a QM/MM-DFT technique, 2nd or 3rd generation agents and their interaction with possible target sites can be investigated as well.

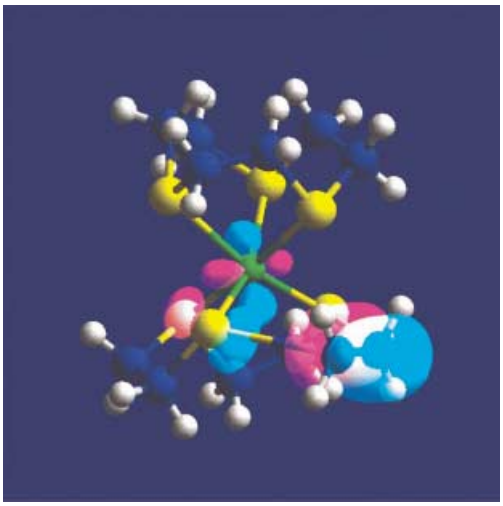


Figure 3. HOMO-2 of the transition state for dissociation of ethene from $[Re(9S3)_2]^+$ (9S3 = 1,4,7-trithiacyclononane). The interaction of the metal d-orbital with the antibonding C–S σ* orbital emerges clearly.

3.3 Design of Biomimetic Compounds

Enzymes are able to catalyze a large variety of biologically relevant chemical reactions with high efficiency and selectivity while laboratory experiments often have to resort to extreme pressures and temperatures to accomplish the same chemical transformations. It is therefore natural to adopt enzyme chemistry as a model for the development of synthetic analogues. 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 possible approach is to map the essential catalytic properties of the natural system onto 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 [30] (Figure 4). GOase oxidizes primary alcohols selectively to the corresponding aldehydes and is therefore of interest as a potential (stereo) selective, mild oxidation catalyst.

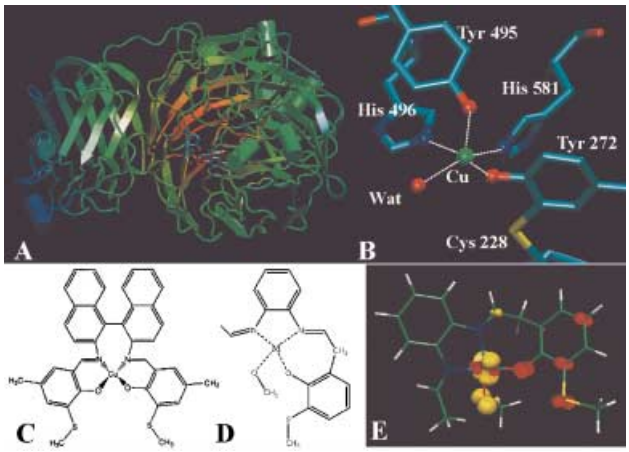


Figure 4. The copper enzyme Galactose Oxidase (GOase) (A) and its active site (B). Sketches of the functional biomimetic compound (C) [35] and of newly designed biomimetic systems (D). Spin density contour (E) at the rate-determining transition state of coumpound (D) with M = Rh.

By applying mixed QM/MM Car-Parrinello simulations, the natural and a low-efficient synthetic system (shown in Figure 4) were confronted step by step throughout the catalytic cycle [30]. 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 anti-ferromagnetically-coupled diradical species. A detailed characterization of the electronic structure at the transition state for hydrogen abstraction 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, whereas due to an unfavourable geometric orientation, the analogous effect is not present in the synthetic compound. This seemingly subtle discrepancy in the electronic properties results in a difference in the activation energies of 5 kcal/mol, i.e. a variation in reaction rate of several orders of magnitude at room temperature.

The knowledge of the electronic factors governing the rate-determining step of the biomimetic compound (Figure 4C) can also be used to model novel synthetic analogues with higher efficiency. A generation of newly-designed complexes is currently under study for which both the geometrical properties and the nature of the metal centre are varied (Figure 4D). The electronic properties of these molecules at the transition state for hydrogen abstraction closely reproduce those of the enzyme (Figure 4E), opening an avenue to the modelling of a new class of putative biomimetic compounds.

4 Outlook

In this article, we presented examples of hybrid Car-Parrinello/MM simulations of systems containing transition metals. In all cases considered, this approach provides an accurate picture of the structural and electronic properties of these compounds. In addition, it also gives access to the dynamic properties at finite temperature and enables to take solvent and environment effects directly into account.

In spite of the considerable success of this method, there are still a number of factors that restrict its current performance. One of the most important issues is the limited accuracy of present day density functional models. The pronounced relevance of correlation effects poses particularly severe challenges so that typical accuracies in predicting activation (free) energies for reactions involving TM are usually distinctly lower than those for main group elements. Hopefully, the future development of improved exchange-correlation functionals will help in treating the intricate nature of correlation effects in these systems with increased accuracy. A further issue in the modelling of reactions with TM systems is related to the large amount of possible structures, electronic states and reaction pathways that have to be considered for any conclusive treatment. The configurational sampling can be significantly increased by applying enhanced sampling techniques [6, 31] and the problem of multiple electronic states may possibly be approached within the framework of a finite temperature DFT approach with variable occupation numbers [32]. The recent progress in time-dependent density functional theory [33] will certainly also contribute to increase the number of direct connections with experiments via the calculation of various response properties such as optical and electron paramagnetic resonance spectra.

In summary, DFT and mixed DFT/MM approaches, in particular in combination with a dynamical Car-Parrinello framework, hold a great promise for the comprehensive and accurate modelling of these challenging and intriguing systems.

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