QBIC SOCIETY

The 6th Quantum Bio-Inorganic Chemistry Conference

Book of abstracts

29 August - 1 September 2023

Warsaw, Poland

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Welcome to QBIC VI!

Dear Colleagues,

We welcome you in Warsaw for the 6^{th} Quantum Bio-inorganic Chemistry Conference (QBIC VI).

The field of quantum (bio)inorganic chemistry continues to evolve as new theoretical methods make an impact, new metalloproteins are discovered, and new avenues of bioinspired chemistry are uncovered. These developments will be covered in our extensive program. Keeping our theoretical field grounded by a close connection to the experiment, we continue the QBIC tradition of inviting experimental scientists. Emerging methodologies, such as quantum computing or machine learning, may change our field completely one day, and you will hear talks on these topics during the conference as well.

QBIC VI takes place in the capital city of Poland, at the Institute of Physical Chemistry, Polish Academy of Sciences (IChF). IChF, located in the Wola district of Warsaw, is the leading research institution dealing with various aspects of chemistry. Funded in 1955, it is among the best scientific units in Poland. The interdisciplinary nature of QBIC meetings aligns very well with the Institute's profile, and IChF supported us at every step in the conference preparation. Moreover, the participants from all around the world, the international scientific committee, and Polish-French-Icelandic organizing team make this conference a truly international experience.

In organizing the program of QBIC VI we followed in the footsteps of the recent successful meetings in Bath (QBIC IV, 2018) and Marseille (QBIC V, 2019). The program features two plenary talks, 6 keynotes, 16 invited talks and 17 contributed oral presentations. In addition, 27 posters will be presented during the poster session.

We hope you will have a great time here discussing the latest ongoing research in our field, starting new collaborations, meeting up with old friends, and making new ones.

On behalf of the scientific and organizing committees,

Ragnar Björnsson

Adam Kubas

Organization of QBIC VI

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Ragnar Björnsson - CNRS, CEA, LCBM, Grenoble, France
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Conference schedule

Lectures: (P)-plenary, (K)-keynote, (I)-invited, (C)-contributed

Tuesday, 29.08

10:00	11:00	**Registration**
11:00	11:10	**Opening**
11:10	12:00	Pavel Jungwirth (P)
12:00	12:40	Elżbieta Gumienna-Kontecka (K)
12:40	13:00	Luca Bertini (C)
13:00	13:20	Agnieszka Stańczak (C)
13:20	14:40	**Lunch**
14:40	15:10	Matthias Stein (I)
15:10	15:40	Martin Srnec (I)
15:40	16:00	Gunasekaran Velmurugan (C)
16:00	16:20	Josep María Luis (C)
16:20	16:40	Erna K. Wieduwilt (C)
16:40	17:10	Dimitrios Pantazis (I)
17:10		**BBQ**

Wednesday, 30.08

08:30	09:10	Martin Kaupp (K)
09:10	09:40	Mariusz Radoń (I)
09:40	10:00	Katharina Bogusławski (I)
10:10	10:40	**Coffee break**
10:40	11:00	Justin Joyce (C)
11:00	11:20	Bettina Lier (C)
11:20	11:50	Marcel Swart (I)
11:50	12:30	Robert Izsak (K)
12:30	13:50	**Lunch**
13:50	14:20	Maylis Orio (I)
14:20	14:40	Erik Donovan Hedegård (C)
14:40	15:00	Esma Birsen Boydas (C)
15:00	15:30	Hélène Jamet (I)
15:30	15:50	Rongzhen Liao (C)
15:50	16:20	**Coffee break**
16:20	16:50	Tomasz Borowski (I)
16:50	17:10	Per Siegbahn (C)
17:10	19:30	**Poster session**

Thursday, 31.08

08:30	09:20	Jochen Blumberger (P)
09:20	10:00	Christophe Léger (K)
10:00	10:20	Maria Drosou (C)
10:20	10:50	**Coffee break**
10:50	11:20	Maren Podewitz (I)
11:20	11:40	Kyung-Bin Cho (C)
11:40	12:00	Ravi Kumar (C)
12:00	12:30	Vijay Gopal Chilkuri (I)
12:30	13:50	**Lunch**
13:50	14:30	Karin Fink (K)
14:30	15:00	Nuno Bandeira (I)
15:00	15:30	Zdenek Futera (I)
15:30	16:30	Hossein Jooya (I-Sponsor)
16:30	17:30	**QBIC Soc. meeting**
19:30		**Dinner**

Friday, 01.09

08:30	09:10	Ulf Ryde (K)
09:30	09:40	Vera Krewald (I)
09:40	10:10	Joanna Kargul (I)
10:10	10:40	**Coffee break**
10:40	11:10	Michael Roemelt (I)
11:10	11:30	Cina Foroutan-Nejad (C)
11:30	11:50	Marc Reimann (C)
11:50	12:10	Adam Šrut (C)
12:10	13:00	**Closing remarks**

Abstracts - Plenary lectures

Probing Currents of Bacterial Life with Photochemistry, Scanning Tunneling Microscopy and Computation

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Nature has evolved remarkable biological structures that shuttle electrons over length scales of more than 10 micrometers. An intriguing example are multiheme cytochromes (MHCs) which arrange a large number of densely spaced redox-active c-type Fe-heme groups in wire-like chains within their protein frame. MHCs have attracted much interest due to their involvement in bacterial extracellular respiration and their potential use in novel bio-electronic devices(1,2). From a theoretical perspective, MHCs continue to challenge our fundamental understanding of electron flow in thermally fluctuating biological structures. In my talk I will present recent pump probe transient absorption measurements on Ru-labeled decaheme cytochrome MtrC in aqueous solution(3). These experiments and their interpretation by DFT and molecular dynamics simulations (4) give strong support that electron transfer occurs via thermally activated heme-to-heme electron hopping with hopping rates of up to ~ 1 n^{-1} placing them amongst the fastest ground state electron transfer reactions in proteins. By contrast, once MHCs are removed from their native environment, and sandwiched between two electrodes (5,6), the voltage-driven electron flow (now called conduction) is close to temperature independent, and is thought to occur via 1-step tunneling with a very small decay coefficient $\beta \sim 0.2$ Å^{-1})(7,8). (7,8). Calculations show that in this case electronic transport is mediated by many protein valence band states beyond the redox active Fe-heme orbitals (7,8). Thus, photo-excited and voltage driven current flow probe different electronic orbitals of MHCs resulting in different mechanisms and flow rates. Implications for their use in bionanoelectronic devices will be discussed.

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Keywords: multiheme cytochromes, electron transfer, DFT, molecular dynamics

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Electrons in Polar Solvents: Birch Reduction, Blue Electrolytes, and Golden Metals

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Liquid ammonia is well-known as a solvent that sustains long-lived solvated electrons formed by the dissolution of alkali metals. Solvated electrons act as powerful chemical reducing agents and, as such, find applications in numerous reduction processes both in organic chemistry and biochemistry. Probably the best-known example is the Birch reduction of benzene in the environment of liquid ammonia with the addition of an alkali metal (as a source of solvated electrons) an aliphatic alcohol. Here we discuss how we have characterized the electronic structure of alkali metal – liquid ammonia mixtures at concentrations spanning from blue electrolytes to bronze colored metallic solutions by means of photoelectron spectroscopy in liquid microjets aided by ab initio molecular dynamics simulations and quantum chemical calculations.

The above alkali metal solutions of liquid ammonia with electrolyte or metallic properties have been known for centuries now. But how about water as a solvent? It it is a textbook knowledge that dissolution of alkali metals in water leads to an explosive chemical reaction, thus only low (sub-metallic) electron concentrations have been prepared so far. Here we show that we have now found a way around the explosive chemistry by adsorbing water vapor at a pressure of about 10^{-4} mbar onto a train of liquid sodium-potassium alloy drops ejected from a nozzle into a vacuum chamber. This leads to a formation of a transient gold-colored layer of water doped with $\approx 5\text{x}10^{21}$ electrons/cm^3, the metallic character of which is demonstrated by a combination of optical reflection and synchrotron x-ray photoelectron spectroscopies.

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Keywords: solvated electron, alkali metal solutions of liquid ammonia, water doped with electrons, quantum chemical calculations

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Abstracts - Keynote lectures

Calculations on the magnetic properties of transition metal and lanthanide compounds

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The description of the magnetic properties of transition metal and lanthanide compounds requires an adequate treatment of the open shell electronic structure. This includes the multireference character of the wave functions, the influence of spin orbit coupling (SOC), and the coupling of different magnetic centres. Over the last years, we have developed a complete active space configuration interaction (CASOCI) program tailored for a routine treatment of magnetic properties of such systems. (1) In the CASOCI program, spin orbit coupling is directly included in the determinant based CI and the lowest states are then obtained by a multi-state Davidson procedure. The Zeeman interaction can be included directly in the CI step.

For systems with more than one spin centre, we developed and tested a start-vector construction method based on tensor multiplication of CI subspaces of the individual sites of a multinuclear compound. For this purpose, we use orbitals localized on the different spin centres in the active space. Dynamic correlation is not explicitly considered but the energetic effects of orbital relaxation in the charge-transfer states can be mimicked by a diagonal shift of selected determinants in the MCAS-CI approach (2). From the results (energies and wave functions) of the CASSOCI calculations, properties such as magnetic susceptibilities or transition moments can be calculated. Additionally, spin-Hamiltonians are used to extract the magnetic main axes and zero field tensors.

Applications will be shown for complexes with one to three spin centres (3d-centres, 4f-centres, or organic radicals). For mononuclear compounds the interplay of SOC and ligand field is discussed for Co(II) and Ni(II) compounds. Furthermore, the magnetic properties of three different Dy(III) compounds will be compared.

The coupling of several spin centres in the 3d-compounds is usually dominated by super exchange which will be discussed for a trinuclear Co-V-Co complex and for the coupling of Co(II) with organic radicals. In 4f-compounds, the interaction of the spin centres is an order of magnitude smaller. Here, the magnetic dipolar interaction is the leading term. In the susceptibility calculations, the latter is added as an additional magnetic field in calculations where only one magnetic centre is explicitly treated.

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Keywords: quantum chemistry, spin orbit coupling, lanthanides, transition metals, magnetism

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Harnessing the power of siderophore mimics for molecular imaging applications

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Under iron-deficient conditions most aerobic microorganisms secret low molecular-weight, highly specific iron(III) chelating compounds – siderophores, which actively transport ferric ions into the cells via specific receptors in the microbial membranes (1). The difficulties in synthesis of structurally complicated natural siderophores has directed the siderophore research towards biomimetic chemistry, aiming at mimicking or reproducing the function of the natural product rather than its detailed structure. This approach allowed us to diversify the arsenal of biologically active siderophore-type molecules, introduce additional desired chemical and/or physical properties, and provide means to identify general motifs governing an interplay between structure and function in biological activity (1-4).

Taking into account, that siderophores are absent in the host cells, they are tempting targets for microbial imaging; Ga-68 is positron emitters that that is well recognised for molecular imaging applications using positron emission tomography (PET) (5). Of the evaluated siderophores, ferrioxamine E-Ga-68 (FOXE) and its close biomimetic analogues were shown as the most promising for possible applications in PET imaging of *S. aureus* (4). Currently we are working on other bacterial (*P. aeruginosa*) and fungal (*A. fumigatus*) species, to better understand the *in vivo* speciation and differences in the biological recognition and uptake of these artificial siderophores.

On the other hand, desferrioxamine B (DFO) is currently the most commonly used chelator to radiolabel biomolecules with Zr-89 (5). However, its *in vivo* stability has proven insufficient, and transchelation has been observed. Our Zr(IV) – DFO solution studies provided information on the actual chemical form of the complex in biological media, and this can contribute to a better understanding of the *in vivo* speciation and differences in the biological activity of this and other chelators (6, 7).

Overall, proposed derivatives may hold potential as inert and stable carriers for Fe(III), Ga(III) and Zr(IV) ions for diagnostic medical applications. They could also allow identifying critical microbial compartments in which siderophores accumulate and thus illuminate key targets for specific drugs against bacterial/fungal diseases.

Acknowledgements

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Keywords: siderophores, Fe(III), Ga(III) and Zr(IV) complexes, biomimetics, imaging

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Prospects of Quantum Computational Chemistry

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Chemistry, and especially the chemistry of transition metal compounds (1), is expected to be one of the first areas in which quantum computers may be beneficially applied. While the algorithmic developments have made significant progress towards this goal in recent years, the chemical problems that can be addressed using current hardware remain limited. Based on our current research and other developments in the field, I will try to draw a balanced picture of the current state of quantum computational chemistry and its hopes for the future. Our work in the field includes embedding approaches (2), cost estimation of pharmaceutical problems (3), solid state applications using translational symmetry (4), testing hardware using pharmaceutical model compounds (5) and addressing the data loading problem (6). A key issue discussed in some of these papers is the problem of quantum error correction which needs to be addressed by anyone who hopes to perform routine calculations on such complicated systems as FeMoco (7). I will illustrate some of these problems on much smaller systems before trying to estimate the cost of calculations of bioinorganic relevance.

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Keywords: quantum computing

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New DFT approaches beyond the zero-sum game

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I want to give an overview over some of the recent, exciting progress we have made in the field of local hybrid functionals(1) (LHs) and beyond, which I think opens a new era in the field. Position-dependent exact-exchange admixture of LHs like LH20t(2) allows a flexible treatment of properties depending on different spatial regions, e.g. in the core, valence or far away from the nuclei. This has been explored, e.g., for NMR and EPR parameters, including the setup of new benchmark sets of unprecedented scope for NMR shifts for main-group and transition-metal nuclei.(3) We recently extended the efficient implementation of LHs in Turbomole to range-separated LHs(4) and reported the wLH22t long-range corrected RSLH,(4) which rivals the optimally-tuned RSH approach for quasiparticle energies in molecular electronics, without the need for system-dependent tuning.(5) The most exciting progress is the introduction of strong-correlation factors into LHs(6) and RSLHs that allows us to escape the usual zero-sum game between reducing fractional charge errors (self-interaction errors) and fractional spin errors (static correlation errors). This provides powerful new DFT approaches and opens a wide range of possible applications, including in particular for transition-metal systems. I will also talk about spin-state splittings of 3d complexes, where the new CASPT2+dMRCI composite benchmark method(7) has been used to challenge interpretation of the spectra of aqueous Fe^{3+}, but also to benchmark different DFT, coupled-cluster and further methods for adiabatic energy differences.(8)

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Keywords: New density functionals, local hybrids, spin state splittings, NMR parameters

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Outer-sphere effects in hydrogenase catalysis: a challenge for theoretical chemists?

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Hydrogenases, the bacterial enzymes that oxidize and produce H2, come in two flavors, "NiFe hydrogenases" and "FeFe hydrogenases", depending on the structure of their active site. In each of these two families of enzymes, the active site and its immediate environment are fully conserved, and yet the investigations of these enzymes using direct electrochemistry have shown that their catalytic properties vary greatly: this is true regarding catalytic bias and reversibility (1), resistance to oxygen (3-4), and other properties which define whether or not a particular hydrogenase could be used under the operating conditions of a particular device. These functional variations within each family also tell us that structural features that are remote from the active site, the so-called "outer-sphere" effects, define, at least in part, the catalytic properties (2).

I will discuss two recent examples where the characterization of engineered protein helped us identify structural determinants of function that are distant from the active site.

In the FeFe hydrogenase from *Clostridium beijerinckii*, we have shown that oxygen resistance is related to a conformational change that depends on non-conserved residues that are up to 18 Å away from the active site. This conformational change occurs in two steps that can be resolved by combining site-directed mutagenesis and detailed protein film voltammetry experiments (3).

In an effort to understand which subunit of NiFe hydrogenase makes some enzymes unidirectional and resistant to O_2, we have characterized a new chimeric dimer produced by assembling the catalytic subunit of an O_2-tolerant NiFe hydrogenase and the electron transfer subunit of an O_2-sensitive hydrogenase. The results challenge the current hypotheses about the influence of the accessory FeS clusters (4).

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4. A. Fasano et al, submitted.

Keywords: hydrogenase, catalysis, enzyme

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Computational studies of nitrogenase

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Nitrogenase is the only enzyme in nature that can cleave the triple bond in N_2 to form ammonia and make nitrogen available for cell metabolism.[1] The MoFe protein of nitrogenase contains two unusual metal clusters, the P cluster, which is a Fe_8S_7 cluster that transfers electrons and the catalytic FeMo cluster, a $MoFe_7S_9C$(homocitrate) complex, bound to the protein by a cysteine and a histidine residue.[2] It performs the reaction: N_2 + 8 e^- + 8 H^+ + 16 ATP ® 2 NH_3 + H_2 + 16 ADP + 16 Pi. The mechanism is normally described as sequence of eight E0–E7 states, differing in the number of delivered electrons and protons. It is believed that N_2 binds to the E4 state, concomitant with the release of H_2.1 Many groups have employed density-functional theory (DFT) calculations to understand the mechanism, but this has not led to any consensus.[3] Instead, different groups have suggested totally different mechanisms and even diverging models of E4.

We have performed systematic studies of nitrogenase with the combined quantum mechanics and molecular mechanics (QM/MM) approach. We have studied the electronic structure and protonation state of the FeMo and P clusters,[4,5] suggested the most stable protonation of the E0–E4 states,[6–8] showing that the results depend heavily on the DFT method,[9] studied the binding of N_2 and N_2H_2 to the cluster,[10,11] calculated redox potentials of the cluster,[12] and suggested putative reaction mechanisms of the cluster with or without one of the sulfide ligands dissociated.[13–15] We have also used quantum refinement to determine what is really seen in various crystal structures of nitrogenase, both of the native enzymes and of inhibited states.[16–19] I will present some of these findings.

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Keywords: nitrogenase, QM/MM, protonation, quantum refinement, DFT, broken, symmetry state

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Abstracts - Invited lectures

Assessing charge transfer and non-innocent ligand character in a low valent nickel complex

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Redox tautomerism or charge transfer complexes(1, 2) have opened up new avenues of research and have found a variety of applications as magnetic and photo-sensitive materials.

A new (Ni(Br)(L)) complex (L=N,N-diazabutadiene derivative) was identified and characterised(3) with an unusually low coordinate environment driven by a steric congestion with bulky substituents. Based on structural comparisons and spin densities obtained from DFT calculations, the original authors concluded a formal oxidation state assignment of +1 ($3d^9$, doublet ground state) to the nickel site.

In this work we provide a re-examination of this complex through an integrated spectroscopic/computational approach whereby the more nuanced aspects of chemical bonding between the nickel site and the non-innocent ligand come to the fore, which make it inconsistent with such a clear-cut assignment. An array of computational experiments will be shown ranging from DFT all the way to top of the range wavefunction methods such as MS-CASPT2, QD-NEVPT2 and CAS+DDCI.

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Keywords: Redox, active ligand, Valence tautomerism, Redox tautomerism, Nickel, charge, transfer complexes

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Alternative wave function ansätze for (in)organic chemistry

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Quantum-mechanical modeling can assist experimental studies in efficiently devising novel compounds that feature desired properties. However, the computational models are also difficult primarily because conventional highly-accurate quantum chemistry approaches are technically limited to small-and to some extent rather simplified- model compounds and demand user control on an expert level. Thus, innovative new electronic structure tools are desirable that do not suffer from the technical bottlenecks and shortcomings of conventional machineries and that open up new frontiers for ab initio computational chemistry. To this end, we will discuss alternative wave-function-based approaches which represent computationally inexpensive, robust, and black-box-like electronic structure methods. Specifically, we will focus on electron-pair theories, where two-electron functions are the fundamental building blocks of the electronic wave function, and how they can be extended to obtain a balanced description of static/nondynamic and dynamic correlation. Furthermore, we will scrutinize their performance to describe the electronic structures of both closed- and open-shell molecules in electronic ground and excited states.

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Keywords: coupled cluster, electron correlation, large, scale modeling, organic electronics, electron, pair theories

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Computational and experimental studies on selected non-heme iron enzymes

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In this contribution, we present our recent results for non-heme iron-dependent enzymes, mainly ectoine synthase (EctC) and hyoscyamine 6β-hydroxylase (H6H). In our attempts to elucidate reaction mechanisms catalyzed by these enzymes, we combine experimental and computational approaches, encompassing X-ray diffraction, UV-vis and Mössbauer spectroscopy, molecular dynamics simulations, computational spectroscopy, and ONIOM computations for reaction pathways. The results will be presented with a focus on computational methods.

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Keywords: ectoine synthase, hyoscyamine hydroxylase, molecular dynamics, ONIOM, XRD, Mössbauer spectroscopy

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Discussion of the electronic structure of Iron-Sulfur molecules: ab initio study and model Hamiltonians

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In this talk, we present a discussion of the electronic structure of Iron-Sulfur molecules from a wavefunction based ab initio and model Hamiltonian perspective. Emphasis will be given to ease of interpretation and understanding of the electronic structure using tools such as ligand field theory and angular overlap model(1,2).

After a brief review of the wavefunction based methods used to investigate the electronic structure of transition metal dimers, we proceed to a discussion of the representation of the wavefunction. It will be shown how the different many-particle representations, such as determinants, configurations, and configuration state functions, can influence the interpretation of the electronic structure(3). This is followed by a short discussion about the single- and multi-configurational characters of the low energy states of diferric and mixed-valent dimers and the need (or not) for the use of multi-reference based methods to obtain energy differences.

In conclusion, we present some challenges in the study of Iron-Sulfur molecules going beyond dimers and towards larger molecules such as trimer and cubanes, and recent advances towards their resolution.

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Keywords: iron, sulfur dimers, model hamiltonian, ab inito, multi reference methods, ligand field theory

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Electron Tunneling or Hopping? Transport Mechanisms in Protein Junctions Investigated by DFT

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Electron transfer facilitated by redox-active proteins is utilized in various biological processes, including photosynthesis, respiration cycle, or denitrification reactions. Blue copper proteins such as Plastocyanin or Azurin and the heme-containing cytochromes often participate in these redox cascades. Recently, these proteins started to be utilized in nanobioelectronic devices due to their suitable electron-transfer properties. However, non-expected physical phenomena were observed when the proteins were incorporated between metal contacts or electrodes. While in a native aqueous environment, the electron flow through the system of redox sites proceeds by the thermally activated hopping mechanism, the temperature-independent currents of relatively high magnitudes were detected on protein/metal junctions. These data suggest that the electrons on the bio/metallic interfaces and junctions are transferred by the coherent tunneling mechanism, independently of the redox-active states. We investigate these electron-transport phenomena by means of computer simulations based on classical molecular dynamics (MD) as well as the first-principles description within the framework of density functional theory (DFT). While the incoherent hopping could be studied by combined quantum-mechanical/molecular-mechanical (QM/MM) techniques, the coherent tunneling requires a quantum description of the whole interface models. Recently, we applied these methodologies on Azurin blue-copper protein and on small tetraheme cytochrome (STC), which were previously studied experimentally. We showed that the transport mechanism in both Azurin and STC junctions between gold electrodes is the coherent tunneling facilitated by valence-band states of the proteins. In contrast to their redox properties in solution, the presence of the metal cations in the protein structures is not essential for their conductivity on the metal interfaces. The reason for this drastically different behavior in solution and on the metal interfaces is the significant electronic-level misalignment between the protein and metallic states.

Keywords: electron transport, nanobioelectronics, protein junctions, density functional theory

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Theoretical studies of reactive copper-oxygen species

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The activation of C-H bonds by energy-efficient, environmentally benign and cost-effective catalytic devices is a formidable challenge for our near-future society.(1) To achieve strong C-H bond activation, inspiration can be taken from several copper enzymes such as the particulate Methane Mono-Oxygenase (pMMO).(2)This enzyme is able to activate the strong C-H bond of methane. High-valent copper oxygen adducts have been proposed as key oxidizing intermediates, although very few of them have been experimentally detected and characterized. In this context, the use of synthetic bioinspired copper complexes was shown to be very promising for C-H oxidation and theoretical calculations an essential reinforcement to characterize these species.

In this communication, we will describe different DFT calculations we have done to understand the electronic and redox properties of reactive copper-oxygen species.(3,4) Then investigation of a mechanistic pathways for H-atom abstraction will be presented on a di-copper complex. With this complex, the activation of a toluene C-H bond was observed at room temperature and the mechanism becomes catalytic in the presence of a base.(5) Our theoretical study reproduces the reaction in both cases and Intrinsic Bond Orbital (IBO) studies show that the mechanism is characterized as either a hydrogen atom transfer (HAT) or a concerted proton-coupled electron transfer (cPCET).

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Keywords: DFT, di, copper complex, reactivity, thermodynamic properties

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Nanoengineering electron transfer pathways in biomolecular systems for efficient solar conversion

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A major bottleneck in the fabrication of efficient bio-organic nanoelectronic devices resides in the strong charge recombination that is present at the different interfaces forming the complex system. An efficient way to overcome this bottleneck is to add an optimized self-assembled monolayer (SAM) of molecules between the biological material and the electrode that promotes an efficient direct electron transfer whilst minimising wasteful processes of charge recombination. Another approach is to include plasmonic nanoarchitectures that interact with photoactive components often leading to an improved photocurrent density obtained from biophotoelectrodes.

In this lecture, I will overview the concept of the biomolecular artificial photosynthesis devices and show how their bottom-up rational design can yield the increased solar conversion efficiency and stability. The biocatalysts in these devices are the robust photosystem I (PSI) complex and cytochrome *c*553 that are interfaced with various transparent electrode materials for production of green electricity and fuel. I will show that the performance of such biomolecular devices can be greatly improved by tailoring the structure of the organic conductive interface to ensure the generation of unidirectional electron transfer and minimisation of wasteful back reactions. Specifically, incorporating specific transitional metal redox centres together with plasmonic nanoparticles in the bio-organic interface significantly improves not only the light-harvesting functionality of the PSI photoenzyme but also increases photostability and the overall photoconversion performance of the biomolecular devices. The QM/MM modelling of direct electron transfer (DET) in cytochrome/single layer graphene (SLG) nanodevices confirms the possibility of fine-tuning the electronic communication within complex bio-organic nanoarchitectures and interfaces due to optimization of the tilt angle of the haem group, its distance from the SLG surface and optimal HOMO/LUMO levels of the interacting redox centres. Such comprehensive analyses based on combined experimental and theoretical investigation paves the way for the rational design of viable biomolecular technologies for solar energy conversion into fuel and other carbon-neutral chemicals.

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Keywords: artificial photosynthesis, direct electron transfer, biomolecular systems

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The Photochemistry of Azides

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The irradiation of azides to liberate dinitrogen is a long-established route towards nitrides and nitrenes, generating for instance high-valent metal complexes. The photophysical and photochemical processes can now be studied in great detail with computational chemistry approaches.

We showcase here the photochemistry of 1,1'-diazidoferrocene, where irradiation leads to release of dinitrogen and formation of a ferrocenyl nitrene. Experimentally, the photoprocesses have been studied with femtosecond ultraviolet-pump/mid-IR probe spectroscopy. With complementary calculations, we evaluate the importance of spin-orbit coupling and demonstrate the formation of a metastable intermediate, which rapidly forms the nitrene product. The electronic structure analysis of the photochemical path sheds light on the photochemistry of azides in general, and the conclusions drawn appear transferrable to other photoinduced bond splitting processes.

Keywords: iron, azide, photochemistry, excited states, TD, DFT, spin, orbit coupling

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Decoding LPMO structures by Theoretical EPR Spectroscopy

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A prerequisite for understanding the structure and function of Lytic polysaccharide monooxygenases (LPMO) is the reliable interpretation, at the atomic scale, of electron paramagnetic resonance (EPR) spectroscopic data of the copper center present in the active site. Among the various LPMO families reported in the literature, the *Pl*AA10 enzyme presents an intriguing spectroscopic phenomenology that depends on the experimental pH conditions. We have combined spectroscopic techniques and theoretical methods to rationalize experimental observations and uncover the structural origin of their unusual EPR signals. Since the precise calculation of EPR parameters of copper centers remains a challenging task for quantum chemistry, we first addressed this issue through extensive calibration studies using a series of mononuclear copper complexes to define a computational method to obtain an accurate and reliable prediction of copper EPR parameters. We then constructed large models of the active site of the *Pl*AA10 LPMO by considering features of the metal second coordination sphere. Comparison of the experimental EPR parameters with those from the computations enabled us to identify the structural elements of the active site at at the origin of the variation of the EPR signal experimentally observed. Our approach provides a solid framework for establishing correlations between structural features and spectroscopic information about LPMO enzymes.

Keywords: Quantum chemistry, EPR spectroscopy, copper enzymes, reactivity

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Computational Insights into Ascorbate Peroxidase Compound II

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Oxygen-activating heme enzymes catalyze a plethora of biological redox transformations, often involving transient high-valent iron species known as Compound I and II. Both contain Fe(IV) (ferryl) oxo species, differing in the redox state of the porphyrin, which is further oxidized to a π-cation radical in Compound I compared to Compound II. The case of ascorbate peroxidase has created continuing debate because different studies have supported either a Fe(IV)=O or a Fe(IV)-OH formulation for Compound II: the former appears more consistent with a range of spectroscopic data, whereas the latter is suggested to be more consistent with crystallographically reported iron-oxygen distances (1-2). Here we use structural models of ascorbate peroxidase Compound II, obtained from X-ray free electron laser crystallography (1) to construct reliable multilevel computational models of the enzyme that take into account possible hydrogen-bond-network configurations around the active site. On this basis, we explore correlations between different formulations of the ferryl species and all available observations from diverse spectroscopies, using a range of density functional and wave function approaches. The results allow us to establish how protonation, hydrogen bonding, and the orientation of specific amino acid residues close to the active site affect the spectroscopic properties of Compound II in ascorbate peroxidase, thereby elucidating the identity of this intermediate and explaining the spectroscopic observations.

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Keywords: peroxidases, iron, spectroscopy, quantum chemistry

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Catalysis in Confinement: Reaction Mechanism of C-X Coupling with a Cu-calix(8)arene Catalyst

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Encapsulation of molecular complexes is an attractive strategy to confine the reaction site. It has been used for developing highly efficient catalysts based on Earth-abundant metals that would otherwise suffer from deactivation. One example of such a catalyst is the Cu-calix(8)arene complex that facilitates C-X (X=N, S) coupling reactions.(1) However, the lack of adequate computational protocols has hindered the rational design of these systems. To investigate this large supramolecular catalyst, it is essential to consider the inherent flexibility of the calixarene cage, which can significantly influence the way the reaction proceeds.

Thus, we developed a multistep protocol to model this class of homogeneous, supramolecular catalysts. The first steps involved investigating the reaction mechanism with quantum chemistry. We used classical MD simulations of the educts, products, and reaction intermediates in explicit solvent to approximately describe the conformational diversity and flexibility of the calixarene macrocycle.(2) While this static picture already revealed some features that explain the high catalytic activity,(2, 3) we next turned to developing a full QM/MM MD scheme to study the dynamic nature of the bond formations in solution. The downside of this strategy is the large number of computational resources needed for an evaluation of the reaction pathway.

To reduce computational costs, we utilized semi-empirical quantum mechanical methods (GFN2-xTB) to describe the QM zone. This approach reduced computational costs by orders of magnitudes while yielding results remarkably similar to full DFT. Consequently, we were able to perform massive sampling of the reaction pathway, allowing us to perform statistical analyses of the reaction energetics, the response of the macrocyclic ligand during bond formation, and the dynamic nature of the transition states in explicit solvent.

Our detailed molecular picture of the reaction dynamics provides new design strategies for supramolecular catalysts.

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Keywords: DFT, MD, transition, metal complexes, reaction dynamics

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Experiment-Derived Benchmark Set of Transition Metal Spin-State Energetics for Assessment of Quantum Chemistry Methods

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Reliable prediction of spin-state energetics (energy differences between alternative spin states) for transition metal complexes is a compelling problem in computational chemistry. Different methods often lead to contradictory results and credible reference data are scarce. In this work, we present a new benchmark set for transition metal spin-state energetics (TMSSE16), which is based on the experimental data for 16 complexes of Fe(II), Fe(III), Co(II), Co(III), Mn(II), and Ni(II) with chemically diverse ligands. The new benchmark is a significant extension of our previous studies for iron complexes (1) and metallocenes (2). The reference data are derived from experimental spin-crossover enthalpies or maxima of spin-forbidden absorption bands, and carefully back-corrected for relevant vibrational and environmental effects (due to solvation or crystal lattice) to enable direct comparison with computed electronic energy differences. The new benchmark set makes it possible to assess the accuracy of spin-state energetics computed using both DFT and wave function theory methods. For the latter ones, we use explicitly-correlated (F12) approach to efficiently minimize the basis set incompleteness error. The results of benchmarking confirm high-accuracy of single-reference CCSD(T) calculations, which significantly outperform the CASPT2, CASPT2/CC and MRCI+Q ones. The best performing DFT methods are double-hybrids (PWPB95-D3(BJ), B2PLYP-D3(BJ)), whereas DFT methods previously recommended for spin states (e.g., B3LYP*-D3(BJ) and TPSSh-D3(BJ)) do not perform well across the whole benchmark set.

Our study not only provides new data for the assessment of computational methods, but also enhances the interpretation of spectroscopic data (e.g., through the concept of vibronic correction to band maximum) and contributes to the understanding of experimental data measured in condensed phases. In this context, we reexamine the particularly interesting case of the lowest sextet-quartet excitation for aqueous $(Fe(H_2O)_6)^{3+}$, which we presented already a few years ago as a challenging benchmark for theory (3). Recently, however, Reimann and Kaupp (4) put in doubt the traditional interpretation of the electronic spectrum of $(Fe(H_2O)_6)^{3+}$ by suggesting that all the low energy d-d bands observed in the experiment originate from trace amounts of the hydrolysis product. We disprove this hypothesis though a carefully designed experiment, and show how the "mysterious" sextet-quartet band of $(Fe(H_2O)_6)^{3+}$ can be consistently interpreted in solution and in the crystal.

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Keywords: spin states, spin state energetics, spin state splittings, benchmark, wave function methods, CCSD(T), CASPT2, MRCI, DFT, electronic spectra, spin crossover

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Revealing Complex Electronic Distributions in Transition Metal Compounds with Multireference Electronic Structure Methods

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An accurate description of transition metal complexes poses a formidable challenge to quantum chemical methods. Complexes with multiple transition metals or redox-active ligands further aggravate the problem as charge-relocalized states might be readily accessible and other subtle phenomena such as exchange coupling of local spins influence the spectroscopic and chemical properties. In the language of quantum chemistry the aforementioned aspects of electronic complexity in transition metal compounds translate to the presence of static (or strong) and dynamic correlation effects. Modern wavefunction-based multireference (MR) methods, as they are implemented in our MOLBLOCK program(1) and in many other programs, provide a formally correct and systematically improvable approach to deal with this problem even in cases with many strongly correlated electrons.(2)

In this contribution, two computational studies of transition metal complexes with multiple open shells using MR methods are presented. The first example concerns two interconvertible, high-valent Co-oxygen TAML intermediates that have been characterized by multiple spectroscopic techniques including X-band EPR, ENDOR, XAS/EXAFS, and MCD.(3) Interestingly, a consistent interpretation of the spectroscopic results was only able with the aid of MR electronic structure methods. In the second example, MR methods are used to predict the unusual electronic distribution in the $Mn_2O_3^+$ ion in the gas-phase. The obtained results are in line with results from soft X-ray absorption spectroscopy whereas most DFT functionals fail to provide results that agree with the experimental findings.(4) Importantly, however, the MR calculations depend crucially on the size of the used active space.

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Keywords: transition metal complexes, multireference methods, spectroscopy

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Off-diagonal thermodynamics and its effect on reactivity

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We formulated an original and unique theoretical framework aiming at the prediction of C-H bond activation reactivity. In its current form, it features two thermodynamic factors that we named asynchronicity and frustration that together modulate coupled proton-electron transfer reactivity. Only after addition of these two factors to the classical well-documented effect known as linear free energy relationship (LFER) a complete thermodynamic basis for the control of reactivity is formed. In principle, each of the two factors and their combination enable changing the preference of which C-H-bond is likely to be activated that would be otherwise driven by LFER, which favors the weakest C-H bonds in molecules. To demonstrate the power of the approach, we will show and discuss H-atom abstraction reactivity of several transition-metal complexes and organic radicals. Finally, we also discuss the generalization of the approach to reactions with radical group transfer.

Keywords: asynchronicity, frustration, offdiagonal thermodynamics, reactivity, hydrogen atom abstraction, radical transfer

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Bio-inspired Catalysis and Therapeutics

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When elucidating the design principles of metalloenzymes, advanced spectroscopic studies need to be combined with computational chemistry in order to allow a definite assignment of spectral data.

When abstracting the structure-function relationship from biological systems, the realm of bio-mimetic models can be explored. Incorporation of different metals, systematic variations of ligands in the first and second coordination shell spheres are possible.

With a focus on hydrogen evolving enzymes and model complexes, the strenght of combinding experiment and theory will be demonstrated.

The use of flexible synthetic DNA-binding Cu(II)-peptides in the treatment of cancer will be demonstrated. Systematic searching the conformational space and reduction to unsual Cu(I) gives results in excellent agreement with experiment.

Keywords: enzyme, transition metal, catalysis

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Pushing the Limits of Quantum Mechanics in Predicting BioInorganic Reactivity

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In recent years, the field of bioinorganic chemistry has seen a growing interest in the use of quantum mechanics to predict and understand the reactivity of metalloenzymes and other bioinorganic systems. However, the accurate modeling of complex bioinorganic reactions using quantum mechanical methods is a significant challenge due to the size and complexity of these systems.

In this talk, I will discuss our recent efforts to push the limits of quantum mechanics in predicting bioinorganic reactivity. Specifically, I will focus on our development and application of novel computational methods that can handle large, complex bioinorganic systems with high accuracy.

I will present several case studies that demonstrate the power of these methods, including the study of the mechanism of oxidation chemistry with hydrogen-atom transfer, oxygen-atom transfer, proton-coupled electron transfer as competing pathways.

Keywords: Oxidation chemistry, Density Functional Approximations, Spin states

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Deep Learning from Atoms in Molecules

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Accuracy and completeness are among the top challenges in data quality. We will discuss a versatile workflow that automates the generation, preparation, and prediction of atoms-in molecule properties within MATLAB platform. Molecular optimization problem is used as a benchmark to illustrate how deep learning techniques is utilized to learn from atomic features to predict molecular properties. Density functional calculations are used to enrich and complete the dataset of interest, followed by cheminformatics techniques to analyze, and prepare the data. Graph neural networks are then built to classify molecular structures using the equilibrium and non-equilibrium configurations. Atomic forces are encoded in graph vertices and the substantial suppression in the total force magnitude on the atoms in the optimized structure is learned for the graph classification task. The results are obtained using two different graph pooling layers and compare their respective performances.

Keywords: Deep Learning, Graph Neural Networks, Molecular Optimization

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Abstracts - Contributed lectures

Differences and similarities between fungal and bacterial laccases in oxidation of polycyclic aromatic hydrocarbons

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Laccases are blue multi-copper oxidases that catalyze the oxidation of a wide variety of substrates concomitantly with the reduction of molecular oxygen to water. These enzymes are widely distributed in bacteria, fungi, plants, and insects and among their numerous substrates, small phenolic molecules are the ones of choice for oxidation.The ability of laccase to process hazardous non-phenolic substrate such as polycyclic aromatic hydrocarbons (PAHs) has aroused interest in bioremediation.

Laccases are classified as high or low potential on the basis of the standard T1 Cu(II) site reduction potential values which, in turn, are finely determined by the first coordination sphere of the metal. High potential laccases are fungal while low potential laccases are bacterial, being these latter more interesting for biotechnological applications due to their greater resistance to temperature and pH variations.

The first scientific article (1) reporting the oxidation of benzo(a)pyrene (BAP) by a fungal laccase dates back to 1996 and since then many studies have been published on this particular process due to the extreme toxicity of BAP.

Regarding BAP oxidation, one of the aspects that remain unclear is the catalytic mechanism, in particular the first step which provides the monoelectronic oxidation of the substrate with the formation of an aromatic radical. (2)

To investigate the BAP oxidation mechanism we consider a strategy in two steps. We first identify two laccase XRD structures (one high potential fungal and one low potential bacterial) from a systematic molecular docking (3) screening using 2,6 dimethoxy phenol (as reference phenolic substrate) and BAP. Starting from the best poses of the ligands we built cluster models to be used for simulations at the DFT level in order to study the reaction profiles.

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Keywords: Copper, Laccase, DFT

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The Good, the Bad, and the Ugly of multiplet dominated X-ray processes

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X-ray spectroscopy is a widely used technique that harnesses the power of x-rays to explore the electronic and chemical properties of atoms, molecules, and materials, while unveiling the structure, composition, bonding, and dynamics of matter in various domains of science and technology. The observed spectra are influenced by a plethora of different interactions such as the core-hole lifetime. spin-orbit coupling, core-valence-exchange interactions, and more.

It can be argued that for transition metal compounds the L-edge, which originates from creating a core-hole in the 2p shell, is most difficult to interpret and simulate owing to strong 2p SOC effects and the occurrence of multiplet effects in the valence shell in the ground and excited states. Modelling 2p→3d excitation to the fullest extent without semi-empirical parameters necessitates a multi-configurational treatment while including many closely spaced excited state roots during simulation. The present study focuses on and tackles the final state multiplet problem in such X-ray regions (such as L-edge) via truncated configurational interaction (CI) techniques, such as complete or restricted active space (CASCI ro RASCI) manner. In addition to the traditional CAS- and RAS-formalism, the CI-space is manually truncated by 99.9% while keeping the crucial "chemistry", in an effort to pave the way to modelling a transition metal dimer whilst taking into account both metal centers simultaneously.

Keywords: x, ray absorption spectroscopy, theoretical spectroscopy, multireference quantum chemistry

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Biomimetic inorganic compounds with DFT: some examples

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Our laboratory specializes in density functional theory calculations on biomimetic inorganic compounds, mimicking enzyme reactions occurring in the nature. The simplification of enzymes into small synthetic model complexes enables us to understand the core reactions occurring in the active site of enzymes without having to consider the complications that may occur due to the interference of peripheral enzyme parts. Of special interest is metal-oxygen catalyzed reactions of organic substrates, such as C-H activation, hydroxylation or other oxygen addition reactions. In this multi-part presentation, some examples highlighting our research will be presented: the importance of spin states, C-H activation reactions by Mn(IV)O systems, Ni catalyzed NOx conversion, aldehyde deformylation reactions and more.

Keywords: biomimetic, inorganic, DFT, reaction mechanisms

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Insights into the Mechanism of NiFe-Hydrogenase Using Correlated Wavefunction Methods

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NiFe-hydrogenases are metalloenzymes that catalyse the reversible conversion of the dihydrogen molecule to protons and electrons. Following extensive computational studies, various mechanistic proposals have been put forth, but no consensus has been established (1). The widely used density functional theory (DFT) may fail spectacularly when it comes to providing the relative energies of transition metal complexes with different electronic configurations, accentuating the need for highly accurate and reliable wave function theory methods. The domain-based local pair natural orbital approach to coupled cluster theory, DLPNO-CCSD(T) (2), offers a highly efficient way to extend the applicability of the "gold standard" coupled cluster theory to large systems. In recent work we developed a robust and transferable DLPNO-CCSD(T) computational protocol for the reliable estimation of spin state energetics as well as relative energies between isomers with different numbers of unpaired electrons, based on a combined and balanced mix of extrapolation to the complete basis set and infinite pair natural orbital space limits (3). Reference-quality results can be readily achieved for the exceptionally hard problem of spin-state energetics in iron complexes (4). Herein, we present a pioneering application of this method to elucidate the mechanism of NiFe-hydrogenase. The methodology developed here has the potential to become a new computational standard in the quantum chemical simulation of metalloenzymes.

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Keywords: Hydrogenase, coupled–cluster, DLPNO, spin–states

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DFT studies of O_2 activation by iron and nickel bi-metallic sites

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A wide range of enzymes, which are natural catalysts, contains single metal ions in their active sites. However, there are also a number of them, where two metal centres are located in proximity to each other. Such bi-nuclear active sites with two iron ions are observed e.g., in soluble methane monooxygenase. Thus, there are two metal ions that are involved in the reaction and can react with various molecules – oxidants what can lead to formation of the reactive oxygen species (ROS).

In this context, we explored the reactivity of inorganic active sites in enzymes modelled by iron and nickel porphyrin (Por) dimers towards the dioxygen molecule. Our quantum chemical calculations were performed within Density Functional Theory (DFT) with def2-TZVP basis sets for all atoms. For Ni PBE and for Fe B3LYP functionals (with the dispersion correction) were employed. All calculations were done with the Turbomole program.

The series of metalloporphyrins placed face-to-face at different distances with O2 located between the metal ions were studied. This allowed us to explore the influence of the type of metal ions and their separation on the ability to split O_2 and form ROS. Our calculations show that all investigated metal ion pairs can bind the oxygen molecule located between them, what is manifested by elongation of the O-O bond. However, for the Fe(II) ions this effect is much stronger than in the case of Ni(II). Additionally, in case of Fe(II)-Por dimers the transient state of the dioxygen splitting was observed what allows to determine the energy barrier and its dependence on the distance between the ions.

Our results are consistent with the DFT studies of analogous metal ions incorporated into zeolite matrices, done in J. Heyrovský Institute of Physical Chemistry, Prague (JHI) and may be helpful in modelling new catalysts in future.

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Keywords: binuclear sites, transition metal ions, artificial enzymes, ROS formation, metalloporphyrins, DFT

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Electron in a box; a room-temperature-stable electride

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Here I present the synthesis and characterization of a highly reduced bipyridyl magnesium complexe that is the first example of a stable organic magnesium electride supported by quantum mechanical computations and X-ray diffraction.(1) The complex serves as an unconventional homogeneous reductants due to its high solubility, modular redox potentials, and formation of insoluble, non-coordinating byproducts. Unlike the majority of known electrides in which free electrons are trapped in between molecules in the crystalline form, the present case is a molecular electride in which the free electron is confined within a single complex. Here, I discuss potential application of this system beyond its chemistry. (1) *J. Am. Chem. Soc.* 2022, 144, 29, 13109–13117

Keywords: Electride, Molecular material, Topological Analysis

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Treating transition metals in solvents and proteins properly

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Transition metals in biological systems pose a formidable challenge in modern quantum chemistry. The main issues are that (i) Static and dynamic correlation effects are both crucial to include, typically demanding costly complete active space (CAS) methods. (ii) Relativistic effects can be sizable, also requiring methods that become computationally demanding. (iii) The relevant chemistry usually occurs in a surrounding solvent or within a protein environment that also needs to be taken into account, both in terms of the nuclear dynamics as well as the electronic interactions between the metal complex and the environment.

In this talk, it will be demonstrated how the challenges (i)–(iii) can be tackled efficiently and accurately: The static and dynamical correlation can efficiently and accurately be described by combining a CAS wave function with (short-range) density functional theory (srDFT), using a range-separation method (CAS-srDFT) (1). In this model, we can include environment effects through an explicit, mean-field embedding method for both electrostatic and polarization interactions. We show results for the absorption spectra of solvated transition metal complexes and show that CAS-srDFT is sufficiently efficient to allow proper sampling over many solvent configurations (2). Finally, we discuss recent developments on an explicit mean-field embedding method for four- and two-component relativistic wave functions (3,4).

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Keywords: Multiconfigurational methods, relativistic effects, QM/MM, proteins

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Electronic Structure Impact of Nitrogenase's Central Carbide: A QM/MM Study

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Nitrogenase are the only class of enzymes that can reduce nitrogen to ammonia. Our group has recently established an interstitial carbide as their unifying structural motif. The binding mode of carbide with six iron centers is not observed anywhere else in nature. The catalytic significance of the interstitial carbide remains unresolved. Herein, we develop a quantum mechanical/molecular mechanic (QM/MM) model to characterize the electronic structure of the interstitial carbide. We consider the changes in the electronic properties of the carbide with respect to nitrogenase-type in the ground state and select redox states.This informs a local spin state description of the eight metal centers in nitrogenase and their extended magnetic interactions. The relationship between carbide electronic structure and substrate binding is explored for the nitrogenase systems.

Keywords: Nitrogenase, QM/MM, Spin State Energetics, Magnetism

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Oxidizing Ni or Fe in the Glutamate Coordinated O2-Tolerant (NiFe)-Hydrogenase: Broken-Symmetry DFT Exploration

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Hydrogenase metalloenzymes catalyze the conversion of molecular hydrogen to protons and electrons and vice versa. Based on their active site compositions, they are classified into three categories, (FeFe)-, (NiFe)- and (Fe)-hydrogenases. Oxidation of molecular hydrogen is mainly performed by (NiFe)-hydrogenases, while the (FeFe)-and (Fe)-hydrogenases are in the production of molecular hydrogen. Shomura *et al.* reported the oxygen tolerance of the (NiFe)-hydrogenase from *H. thermoluteolus* and suggested its origin to come from an unusual coordination sphere of the active site nickel atom (Science **2017**, 357, 928-932, 10.1126/science.aan4497). In the fully oxidized state, bidentate coordination with a nearby Glu32 displaced a terminal cysteine residue to a μ-cysteine bridging position. Recently, Kulka-Peschke *et al.* assigned an uncommon closed-shell Ni(IV)Fe(II) to the fully oxidized state based on the spectral features (*J. Am. Chem. Soc.* **2022**, 144, 17022-17032, 10.1021/jacs.2c06400). In biological systems, such a high oxidation state of nickel with soft ligand donations is unprecedented and needs to reconsidered. Here, we provide some arguments for why we consider the assignment of the unprecedented Ni(IV) oxidation state in the soluble hydrogenase (SH) as ambiguous and not fully plausible. An energetically low-lying broken-symmetry Ni(III)Fe(III) state of the active site can also be realized. It also reproduces the spectral properties and the coordination sphere of (NiFe)-hydrogenase. The Ni(III)Fe(III) broken-symmetry open-shell singlet (S = 0) is produced via antiferromagnetic spin-coupling of Ni-d^7 and Fe-d^5 with evenly distributed spin densities over metal atoms. Finally, some suggestions are provided for experimental chemists to clarify the final assignment of redox states.

Keywords: (NiFe) Hydrogenase, Broken Symmetry DFT, Open shell singlet, Antiferromagnetic coupling, Metalloenzymes

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QM and QM/MM Studies of Selectivities in Metalloenzymes

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The understanding of the catalytic function of enzymes at an atomistic level is of both fundamental and practical interest. Quantum-chemical calculations have been shown to be a complement and alternative to experimental studies in elucidating the reaction mechanism and selectivities of metalloenzymes,(1-8) for example, benzoyl-CoA epoxidase, (2) tetrachloroethylene reductive dechlorinase,(3) quercetin 2,4-dioxygenase,(4) Benzoyl-Coenzyme A Reductase(5), B12-dependent SAM Enzyme TokK(7), and (*R*)-2-hydroxyisocaproyl-CoA dehydratase.(8) For these enzymes, the calculations can rationalize the reactivity and explain the various selectivities, including chemoselectivity, regioselectivity, stereoselectivity, and metal preference (W vs Mo).

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Keywords: DFT, QM/MM, metalloenzymes, reaction mechanism, selectivity

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BuRNN: Machine Learning for Polarizable QM/MM Simulations

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The field of computational chemistry has been significantly advanced by the development of hybrid Quantum Mechanics/Molecular Mechanics (QM/MM). It is a powerful approach that combines the accuracy of QM with the efficiency of MM to study complex systems. However, partitioning the system into two regions treated at different levels of theory may lead to various artifacts at the interface. We have therefore developed the Buffer Region Neural Network (BuRNN) approach as an alternative to existing QM/MM schemes. BuRNN introduces an additional buffer region between the QM and MM region treated at both levels of theory. However, performing a second QM calculation at every time step of a simulation significantly increases the computational costs. Instead, we employ atomistic neural networks (NN) and train them directly on the energy difference between two QM calculations. The trained NNs are capable of reproducing the interactions within the QM region itself, as well as its interactions with the surrounding buffer. They also capture the polarization of the buffer due to the presence of the QM region. Besides, training on interaction energies achieves outstanding accuracies. A second NN derives charges to account for mutual polarization even at longer distances. Thus, the BuRNN approach enables efficient and accurate polarizable QM/MM simulations.

Keywords: QM/MM, Machine Learning, BuRNN, Buffer Region, Atomistic Neural Networks, Mutual Polarization

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Carboxylic Acid Directed γ-Lactonization of Unactivated Primary C–H Bonds Catalyzed by Mn Complexes

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Reactions that enable selective functionalization of strong aliphatic C–H bonds open new synthetic paths to rapidly increase molecular complexity and expand chemical space. Particularly valuable are reactions where site-selectivity can be directed toward a specific C–H bond by catalyst control. We have studied the catalytic site- and stereoselective γ-lactonization of unactivated primary C–H bonds in carboxylic acid substrates.(1) The system relies on a chiral Mn catalyst that activates aqueous hydrogen peroxide to promote intramolecular lactonization under mild conditions, via carboxylate binding to the metal center. The system exhibits high site-selectivity and enables the oxidation of unactivated primary γ-C–H bonds even in the presence of intrinsically weaker and a priori more reactive secondary and tertiary ones at α- and β-carbons. With substrates bearing nonequivalent γ-C–H bonds, the factors governing site-selectivity have been uncovered. DFT study of the mechanism points toward a rebound-type mechanism initiated by intramolecular 1,7-HAT from a primary γ-C–H bond of the bound substrate to a highly reactive MnIV-oxyl intermediate, to deliver a carbon radical that rapidly lactonizes through carboxylate transfer. Intramolecular kinetic deuterium isotope effect and 18O labeling experiments provide strong support to this mechanistic picture. Unlike existing and popularized primary C–H bond oxidation processes, by a judicious choice of catalyst structure and absolute configuration, γ-lactonization at the gem-dimethyl unit of rigid cyclic and bicyclic carboxylic acids can be achieved with unprecedented levels of diastereoselectivity, that can be rationalized with a simple computational model.

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Keywords: DFT study, functionalization of C, H bonds, catalysis, γ, lactonization

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Optical Excitations of 3d Transition Metal Hexaaqua Complexes - A Challenge for Theory

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Aqua complexes of 3d metal ions are encountered by first year chemistry students and yet the calculation of their optical spectra requires state-of-the-art techniques of computational chemistry. While CASPT2 and NEVPT2 can reach mean absolute errors of around 0.15 eV,(1) results for specific excitations can deviate by up to 0.4 eV. In a recent study,(2) we have supplemented CASPT2 results by a MRCI-based high-level correction, which reduces the mean and maximum errors for our test set of 6 metal ions with non-degenerate ground states (V^{2+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{3+}, Ni^{2+}). At this level, we observed a significantly higher deviation from experimental data for the Fe^{3+} case compared to all other complexes. Especially large deviations for Fe^{3+} have been observed by many others and have created a discussion in the field. Using our approach, we argue that the optically active species of this spectrum is not the hexaaqua complex but its singly deprotonated analog, for which we find significantly improved agreement with the experimental spectra.

Going forward, we have also used our new composite scheme to obtain high-level spin-crossover energies for Fe(II) test systems that we used to evaluate different lower-cost approaches.(3)

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Keywords: Spin, Crossover, Spin, flip, Multireference Method, Composite Scheme

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Important redox reactions in nature

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The mechanisms for the two most important enzymes in nature are presented. Nitrogenase is the only enzyme in nature that can transform nitrogen in the air to products that can be used making amino acids, for example. It has a complicated cofactor consisting of seven irons and one molybdenum linked by sulfides. It is known that catalysis goes through a process of four steps before nitrogen can be activated. It is here shown that an additional four steps are needed before the catalytic cycling. The second enzyme discussed here is Photosystem II, which can form oxygen molecules from water by using sunlight. Catalysis goes through four S-states, where O_2 is formed in S4 . The mechanism for O_2 formation has been shown to proceed by forming an oxygen radical (oxyl) which attacks a bridging oxo group in the manganese cluster, in the so called oxyl-oxo mechanism. Recent suggestions for alternative mechanisms are discussed and shown to be either impossible or just be a less favorable variant of the oxyl-oxo mechanism.

Keywords: nitrogenase, photosystem II

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Unraveling tyrosinase ortho-hydroxylation reaction mechanism: Interplay between experiment and theory

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Tyrosinase (Ty), the coupled binuclear copper (CBC) enzyme, is the ubiquitous enzyme responsible for O_2-dependent *ortho*-hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), as well as the subsequent two-electron oxidation of L-DOPA to L-dopaquinone. These elementary reactions are the initial and rate-limiting steps in melanogenesis (1).

Due to its key catalytic role in the biosynthesis of melanin, Ty is of an interest in the early detection, prevention, and treatment of complex human diseases, including skin cancer (2) as well as Parkinson's disease (3). Until now the mechanism of this critical monooxygenation reaction was very poorly understood despite extensive efforts.

By combining theoretical and experimental methods we investigated H-bonding interactions in oxy-Ty (Ty/O_2) active site (4), and have trapped and characterized the elusive catalytic ternary intermediate (Ty/O_2/monophenol) intermediate (5).

Next, we examined monooxygenation reaction of Ty with the analogue of native substrate, that is with methyl 4-hydroxybenzoate. Subsequently, we investigated the *ortho*-hydroxylation step employing series of substrates with different electron donating/withdrawing group in phenol *para*-position revealing biphasic substrate dependence of the monophenol monooxygenation reaction of tyrosinase. This biphasic nature is ascertained mainly by correlating experimental and theoretical energy barrier/k2, and solvent KIE (6).

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Keywords: Tyrosinase, binuclear copper, monooxygenase, oxygen activation, dicopper, oxygen complexes, DFT, QM/MM

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Quantification of the nuclear coordinates for electron transfer: the antisymmetric and symmetric dimensions of the Marcus–Hush model

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The Marcus–Hush model forms the foundation for all modern discussions of electron transfer (ET) in strongly coupled systems. In this model, ET results in a change in diabatic potential energy surfaces, separated along an ET nuclear coordinate. This coordinate accounts for all nuclear motion that promotes electron transfer. It is usually assumed to be dominated by a collective asymmetric vibrational motion of the redox sites involved in the ET. However, this coordinate is rarely quantitatively specified. Instead, it remains a nebulous concept, rather than a tool for gaining true insight into the ET pathway. Herein, we describe an approach based on *ab initio* calculations for quantifying the ET coordinate assuming only the validity of the Marcus–Hush model. As a proof of concept, we identify the ET dimension for strongly coupled dinitroradical anions where only two electronic states are involved in the ET. For delocalised viologene radicals, where a third diabatic state (the bridge state) comes into play, we expanded the methodology to identify an additional symmetric motion involved in the ET, in accord with previously proposed models. A study of the prototypical Creutz-Taube ion uncovered a symmetric and antisymmetric dimension but also revealed some shortcomings of the Marcus–Hush model. We propose a modification that leads to qualitative agreement with the *ab initio* data.

Keywords: Electron transfer, density functional theory, vibronic coupling

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A dicopper(II)-based carbonic anhydrase model – quantum-chemical evaluation of the mechanistic pathway

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Ascidians of the Pacific and Indian Oceans produce a variety of cyclic peptides. The patellamide-derived macrocycles lead to relatively stable dicopper(II) complexes, and these are extremely efficient carbonic anhydrase mimics, the most active model systems known so far. Importantly, we have already established that copper(II) is coordinated to patellamide derivatives in Prochloron cells. The interesting question therefore is, whether or not the biological function of ascidiacyclamide and/or patellamides is related to the catalytic activity of their Cu^{II} complexes in CO_2 hydration or its reverse. Here, we present a computational study to evaluate the energetics of the catalytic cycle to answer these questions and compare the computed energy barriers with the experimentally obtained kinetic data.

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Keywords: carbonic anhydrase, reaction modelling, dicopper(II) complexes, catalytic activity, CO2 hydration

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Exploring off-path reactions of lytic polysaccharide monooxygenases

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Lytic polysaccharide monooxygenases (LPMOs) are a new key ingredient of industrial enzyme cocktails used to produce biofuels from biomass (1). In industry as well as in nature, LPMOs significantly boost the degradation of several different polysaccharides (2). To this end, LPMOs employ a unique oxidative mechanism. However, this mechanism remains elusive.

One issue complicating especially experimental studies is that the copper-dependent LPMOs perform many different reactions: Their main reactivity is to oxidatively cleave one of the C-H bonds next to the glycosidic bond in their polysaccharide substrate. The required oxygen could either be provided by molecular oxygen or hydrogen peroxide (3). The true nature of the co-substrate is challenging to clarify, especially since LPMOs can use oxygen to produce hydrogen peroxide in the absence of substrate (4).

Moreover, LPMOs are prone to self-oxidative damage, which inactivates the enzyme (3). Understanding the mechanism of self-oxidative damage is thus an important step for exploiting the full industrial potential of LPMOs.

However, theoretical studies on LPMOs have so far mostly focused on the mechanism of substrate degradation (5). Therefore, we performed quantum mechanics / molecular mechanics (QM/MM) calculations on different LPMOs, exploring the mechanisms of off-path reactions. In the talk, I will particularly focus on how we obtained a new mechanism for peroxide formation (6).

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Keywords: Lytic polysaccharide monooxygenases, LPMOs, QM/MM

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Abstracts - Poster presentations

Computational Study of Non-Heme Iron Enzymes with Taurine and Hyoscyamine

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Mono-nuclear non-heme oxygenase enzymes catalyze oxidative transformation reactions, such as hydroxylation, epoxidation, halogenation, ring expansion, desaturation, epimerization, and ring closure (1). The reactive species is Fe(IV)-Oxo which is formed from Fe(II) by incorporation of 2-oxoglutarate (2OG) and their reactivity with oxygen. The rate determining step is usually the C-H activation of the substrate. Here, we used quantum chemical methods to get insight into the mechanism underlying the reactivity of different mono-nuclear non-heme iron enzymes and to probe the role of different residues in the active site. We examined the reactivity of alpha-ketoglutarate-dependent taurine dioxygenase (TauD) and hyoscyamine 6β-hydoxylase (H6H) enzymes with their natural substrate, but also tested their reactivity towards other substrates. For example, while TauD enzymes only perform the hydroxylation of taurine (2), H6H catalyzes a subsequent dehydrogenation step leading to the epoxidation of hyoscyamine (3). Thus, we investigated what happens if we used taurine as the substrate of H6H and hyoscyamine as the substrate of TauD.

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Keywords: Non heme iron enzymes, Fe(IV) Oxo, Hydroxylation, Epoxidation

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Improving the precision of quantum-chemical calculations by novel embedding scheme including Friedel oscillations

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We developed the new embedding scheme that allows "gold-standard" coupled-cluster approach application to metallic surface chemistry. The system is divided into two regions: high-level "quantum" cluster and the semi-classical surroundings. This multilevel scheme improves the description of high-level quantum region (active site) with a singlepoint DLPNO-CCSD(T) calculations. The key to reaching high accuracy was an embedding scheme that was performed by including large number of repulsive core-less effective core potentials (cECPs) that prevented the electrons to leak outside of the high-level region. The charges were derived both from calculations on a large semi-spherical model with adsorbate and from our original analytical approach based on the Green functions, Tamm surface states and Kronig-Penney model of the metal.

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Keywords: surface charge oscillations, green function, embedding

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DFT studies of chemical and biological reactivities of complexes of copper and cobalt with paracetamol as ligand

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Mineral complexes can consist of important minerals in the human body and its vital functions, notably the minerals of the first transition group of the periodic table.

In this work the complexes of cobalt and copper have been studied .These complexes contain metals which are important for many biological and medical characteristics, and were the subject of several experimental international researches .

In this study, we have used paracetamol as main ligand and various amino acids (Proline and valine) as secondary ligand. The studied complexes were synthesized at the level of the coordination chemistry laboratory.

These complexes have also been studied theoretically using density functional theory (DFT) for the aim to define geometric structures, calculate energetic properties, reactivity descriptors, and spectral properties.

Keywords: Complexes, copper, cobalt, paracetamol, DFT, reactivity descriptors

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Reactivity factors in catalytic methanogenesis and their tuning upon coenzyme F430 biosynthesis

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Methyl-coenzyme M reductase, responsible for the biological production of methane by catalyzing the reaction between coenzymes B (CoBS-H) and M (H3C-SCoM), hosts in its core an F430 cofactor with the low-valent NiI ion (1-4). The critical methanogenic step involves F430-assisted reductive cleavage of the H_3C-S bond in coenzyme M, yielding the transient CH_3 radical capable of hydrogen atom abstraction from the S-H bond in coenzyme B (5). Here, we computationally explored whether and why F430 is unique for methanogenesis in comparison to four identified precursors formed consecutively during its biosynthesis. Indeed, all precursors are less proficient than the native F430, and catalytic competence improves at each biosynthetic step toward F430. Against the expectation that F430 is tuned to be the strongest possible reductant to expedite the rate-determining reductive cleavage of H_3C-S by NiI, we discovered the opposite. The unfavorable increase in reduction potential along the F430 biosynthetic pathway is outweighed by strengthening of the Ni-S bond formed upon reductive cleavage of the H_3C-S bond. We found that F430 is the weakest electron donor, compared to its precursors, giving rise to the most covalent Ni-S bond, which stabilizes the transition state and hence reduces the rate-determining barrier. In addition, the transition state displays high pro-reactive motion of the transient CH_3 fragment toward the H-S bond, superior to its biosynthetic ancestors and likely preventing the formation of a deleterious radical intermediate. Thus, we show a plausible view of how the evolutionary driving force shaped the biocatalytic proficiency of F430 toward CH4 formation.

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Keywords: Methanogenesis, Methyl coenzyme M reductase, F430

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Studying the molecular basics of TLR8 Z-loop proteolytic cleavage by furin protease with an emphasis on the role of water molecules in the system

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Toll-like receptors (TLRs) are transmembrane proteins which trigger a proinflammatory response. TLRs contain three domains: leucine-rich repeats (LRR), transmembrane helix, and cytoplasmic Toll/IL1 receptor (TIR). The general mechanism of TLR signalling involves ligand interaction with the LRR domain, leading to receptor dimer formation or conformational changes in the preexisting dimer. In certain TLRs, the proteolytic cleavage of the Z-loop within the LRRs is required for proper dimer formation and ligand recognition (1). In TLR8, it is considered that furin protease might be involved in the proteolytic cleavage reaction, however, the molecular basis of this process remains unclear.

In our work, we implemented state-of-the-art in silico methods including AI-supported protein structure prediction together with molecular dynamics (MD) simulations, a small-molecule tracking approach, quantum mechanics (QM) and quantum mechanics/molecular mechanics (QM/MM) calculations to get insight into the molecular basis for the TLR8 functioning and proteolytic cleavage reaction. Specifically, we focused on the role of water molecules within this complex system. AI-supported protein structure prediction allowed us to obtain a TLR8 LRR - furin complex oriented towards each other in such a way that residues from the furin's catalytic site were in close proximity to the proteolytic cleavage site. Results from MD simulations combined with those from the small-molecule tracking approach provided us with starting point for QM and QM/MM calculations, necessary to investigate the possible reaction mechanism of furin protease. Thus, we have made the first attempt to describe the reaction profile of Z-loop proteolytic cleavage by furin protease. Also, we showed that QM and MD methods can support each other while studying complex biological systems.

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Keywords: Toll like receptors, furin protease, proteolytic cleavage, molecular dynamics simulations, small molecules tracking, quantum mechanics calculations

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Revealing Catalyst's Secrets: the Impact of Substituents in Zinc(II) Complexes with N4-donor ligands on their catalytic performance

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A crucial aspect in using CO_2 as a raw material lies in designing an efficient, selective, and sustainable catalyst which allows its conversion into valuable products. One promising approach is the catalyzed non-reducing coupling reaction of CO_2 with propylene oxide to produce cyclic carbonates in the presence of tetrabutylammonium bromide (TBAB) as a nucleophile.(1)(2)

We have computationally studied the above mentioned reaction, considering Zinc(II) complexes with tetra-aza donor ligands bearing phenanthroline bis(aniline) skeleton as catalyst. Experiments show that different substituents at the *ortho*-aniline position influence the catalytic activity and reaction yield. Using methods based on Density Functional Theory (DFT) various reaction mechanisms have been considered, and free energy profiles obtained. Furthermore, a microkinetic model has been built taking into account the different experimental concentrations of the species involved in the reaction. With this model, we have elucidated the most likely mechanism and the rate determining step of the reaction. The results agree satisfactorily with the experimental observations. Analyzing several structural and energetic aspects of the considered catalysts, the crucial factors that determine their effectiveness have been revealed. These findings pave the way for designing more effective and sustainable catalysts to harness the potential of CO_2 in producing valuable chemical products.

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Keywords: Zinc complexes, Carbon dioxide, Cyclic carbonates, DFT calculations, Computational catalysis

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Understanding Substrate Binding and Reactivity of Stearoyl-CoA Desaturase (SCD1) through Classical and Multiscale Molecular Dynamics Simulations

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Stearoyl-CoA desaturase (SCD1) plays an important role in the metabolism of fatty acids and is a promising therapeutic target. However, the underlying mechanism of SCD1, as well as other transmembrane non-heme diiron enzymes, remains poorly understood. This study builds upon a previous DFT cluster model study which proposed a potential reactive intermediate of SCD1. We assessed its dynamical properties by employing classical and multiscale molecular dynamics (MD) simulations. Our classical MD simulations revealed that the proposed intermediate lacks the ability to form a favourable reactive complex with stearoyl-CoA, highlighting the significance of a conserved asparagine residue in controlling the substrate's orientation. Motivated by these observations, we proposed a new intermediate in which a water molecule is strategically placed to stabilize the conserved asparagine residue. Subsequent classical MD simulations showed that the new intermediate is able to form a reactive complex with the substrate, consistent with the experimentally observed selectivity of SCD1. The free energy barrier for the first hydrogen atom abstraction (HAA) step on C9 by the new intermediate was estimated to be accessible. The estimate is based on a hybrid quantum mechanics/molecular mechanics (QM/MM) approach utilizing the efficient semiempirical GFN2-xTB method in combination with B3LYP energy corrections. Considering its computational efficiency, GFN2-xTB seems to be a promising tool for the study of complex transition metal systems. Overall, our findings provide valuable insights into the mechanism of SCD1, thereby advancing the understanding of the entire class of transmembrane non-heme diiron enzymes. Furthermore, the findings can potentially help in the design of new inhibitors.

Keywords: stearoyl–CoA desaturase, SCD1, non–heme diiron enzymes, transmembrane enzymes, transition metals, enzyme mechanisms, classical MD simulations, QM/MM, GFN2–xTB, umbrella sampling

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Theoretical Study of Selectivities in Sequential Methylations Catalyzed by the B12-dependent SAM radical enzyme TokK

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The B12-dependent radical SAM enzyme, TokK, plays a vital role in the biosynthesis of asparenomycin A, an antibacterial carbapenem compound.TokK selectively constructs isopropyl groups on the β-lactam ring by three sequential methylations of the substrate (2*R*,3*R*,5*R*)-pantetheinylated carbapenem (PCPM). We used the quantum chemical cluster approach to study this reaction to investigate the selectivity and mechanism of this reaction involving three C-H methylations. DFT calculations show that during the first methylation, TokK utilizes a 5'-deoxyadenosyl radical in the active region to selectively grab a *pro*-*S* hydrogen atom at the Cα site of the lactam ring in PCPM, resulting in the formation of the substrate radical intermediate. Then, methylcobalamin in the active site donates a methyl group, which transfers from the *Re* plane of the substrate-based radical intermediate to the Cα radical site of the radical intermediate involving a homolytic Co-C bond cleavage, obtaining (*R*)-Me-PCPM, the product of the first methylation process. For the two subsequent methylation reactions, various possibilities of 5'-deoxyadenosine radical to capture hydrogen atoms from different sites were considered, and the full energy profiles of different reaction pathways were obtained. Finally, the internal reasons for the selective synthesis of isopropyl in (*R*)-iPr-PCPM catalyzed by TokK enzyme were deciphered.(3) This theoretical study will help us understand other B12-dependent SAM enzymes that can catalyze multiple continuous methylations. It also has potential applications for the design and modification of asparenomycin A.

Keywords: DFT, SAM radical enzyme, reaction mechanism, selectivity

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Reactivity of platinum anticancer complexes - theoretical results of QC computations

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The reactivity (and thus toxicity) of anticancer platinum drugs in the human cells is mainly governed by the rate of the aquation reaction, i.e. the substitution of the complex's chloride anion by a water molecule. As we have shown previously, the kinetics of this activation reaction can be fine-tuned by the nature of the non-leaving ligand present in the trans- position with respect to the leaving Cl anion (1,2).

In our present contribution we have studied the gas phase and water environment reactivity of cis isomers of the previously studied complexes - cis orientation of the non-leaving and leaving moieties is historically and experimentally preferred orientation in platinum drugs. Our results show very similar substituent effects in comparison with the trans- oriented complexes - the electron-donating (NH_2) and withdrawing (NO_2) groups led to a faster and slower reactions, respectively.

Next, we compared the reactivity in the neutrally charged, doubly chlorinated complexes, one of which is currently under the clinical consideration as the prospective drug picoplatin. In our computations the first hydrolysis did preferentially take place in the trans- position in the gas phase. On the other hand, both cis- and trans- chlorides showed the same lability in water environment.

Finally, we present the results for another promising drug - doubly chlorinated Pt complex with quinoline as the non-leaving ligand, which adds to the line of our previously studied molecules a larger aromatic moiety.

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Keywords: platinum, reactivity, aquation reaction, trans effect, cis effect

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Molecular agregate structures determined by repulsive rather than attractive interactions

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We demonstrate that repulsive rather than attractive interactions between molecules are frequently responsible for the structure that is obtained for their aggregates or crystals. This is caused by the strongly anisotropic character of the repulsive exchange-repulsion forces which can be understood by rewriting this contribution to the interaction energy as a sum of orbital-orbital contributions. The latter contain one orbital of each of the two molecules and are strongly repulsive if the overlap of these orbitals differs significantly from zero.

The attractive induction, dispersion and electrostatic interactions are much more isotropic than the exchange repulsion and they depend less strongly on the distance between the molecules. Thus, molecular arrangements with small molecular overlap give rise to reduced repulsion and thus to shorter distances between the molecules which are associated with increased attractive interactions. We demonstrate that such a mechanism explains the parallel displaced arrangement of benzene dimers as well as the on top position of an alkaline cation upon a benzene molecule.

We show that the orbital-orbital contributions to the exchange repulsion energy can be deduced from the respective energy contribution in symmetry adapted perturbation theory in SAPT0(S^2) approximation. The examples discussed above are used to gain insight to the exchange-repulsion energy and to explain the aggregate structures. Attractive contributions to the interaction energy are also presented to complete the picture of these noncovalent interactions.

Keywords: Molecular aggregate and crystal structures, pi, pi and cation, pi interactions, SAPT, exchange, repulsion energy

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Does the localized state exists? Multiconfigurational study of the charge transfer process in a simple diamine cation.

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Charge transfer processes are crucial in biological reactions like photosynthesis and modern technological applications like photovoltaics. Investigating these processes in complex systems can be challenging due to the interplay of multiple reactions. To gain insight, simpler molecules like diamine cations can be used as models to elucidate charge migration. Modern experimental techniques have made it possible to study charge transfer (CT) processes occurring on extremely short timescales, ranging from picoseconds (10^{-12} s) to femtoseconds (10^{-15} s). Recent advancements in photoelectron spectroscopy have allowed the observation of CT between two Rydberg states in a simple diamine molecule, N,N'-dimethylpiperazine (DMP), a perfect test case for investigating the charge transfer process.[1] The higher energy state was identified as localized, with a single charge localized on one of the nitrogen atoms, while the lower energy state was found to be delocalized, with the hole spread over the two nitrogen centers

Initial theoretical investigations revealed that commonly used density functional approximations (DFA) failed to accurately describe the localized state of DMP^+.[2] This result sparked a heated debate within the quantum chemistry community,[3-8] as these DFAs exhibited similar performance to the *gold standard* of quantum chemistry—CCSD(T) (coupled cluster singles doubles with perturbative triples).

This study investigates these states through a multiconfigurational approach, progressively incorporating electron correlation by expanding the active space from CAS(3,2) with 3 electrons in 2 orbitals to CAS(19,20) with 19 electrons in 20 orbitals. The study highlights the necessity of including all relevant bonds, such as N-C, C-C, and nitrogen pairs and corresponding virtual orbitals in the active space, to accurately predict the energetic difference between the experimentally observed localized and delocalized DMP^+ states. Furthermore, a deeper understanding of the delocalized state's complexity is revealed, emphasizing the importance of additional correlations to describe its multiconfigurational character comprehensively.

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Keywords: Charge transfer, DMP cation, correlation effects

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Quantum chemical study of an Ir-catalyzed dehydrogenation reaction

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Alkenes are counted to the most crucial compound families in various synthetic endeavors, ranging from the synthesis of pharmaceuticals and fine chemicals to simple but central compounds like acetone.(1) Conversely, alkenes and aromatic compounds are not as readily available as their hydrogenated counterparts, the alkanes. Addressing this imbalance, Ir-based dehydrogenation catalysts offer the possibility to selectively convert alkanes into alkenes without the requirement of high temperature and pressure. However, the majority of homogeneous dehydrogenation catalysts necessitate an acceptor compound that undergoes hydrogenation to recover the catalytically active species. Often, the hydrogenation reaction is undesired but deemed a necessary compromise due to the limited availability of acceptorless dehydrogenation catalysts.(2)

Recently, Thomas and coworkers have immobilized {p-KO-C_6H_2-2,6-(OP(t-Bu)$_2$)$_2$}IrH_2 in a hydrophobic microporous polymer and successfully applied it in a continuous-flow solid-gas catalysis with cyclohexane as the substrate.(3) Anchoring the catalyst in a polymer allows higher reaction temperatures, thereby resulting in increased catalytic activity. Despite the overall good performance of the catalytic setup, there are open questions such as the identification of the rate-determining step, the influence of the ligand system, why no cyclohexene or cyclohexadiene is observed and why the catalyst does not exhibit activity towards n-hexane. In this work we have investigated these questions as well as the reaction mechanism that takes place in the catalysis. These key insights are currently used to design more efficient catalyst candidates.

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Keywords: Iridium, dehydrogenation, catalysis, pincer, acceptorless

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Simulation and analysis of the relaxation dynamics of a photochromic furylfulgide

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Furylfulgides, a class of photochromic organic compounds, show a complex system of photoinduced reactions.(1)(2) In the present study, the excited-state dynamics of the Eα and Eβ isomers of a representative furylfulgide is modelled with the use of nonadiabatic molecular dynamics simulations. A pattern recognition algorithm is employed in order to automatically identify relaxation pathways, and to quantify the photoproduct distributions. The simulation results indicate that, despite differing only in the orientation of the furyl group, the two isomers show markedly different photochemical behaviour. The predominant Eα isomer undergoes photocyclisation with a quantum yield (QY) of 0.27$\pm$0.10. For this isomer, the undesired E $\rightarrow$ Z photoisomerisation around the central double bond represents a minor side reaction, with a QY of 0.09$\pm$0.07. In contrast, the minority Eβ isomer, which is incapable of photocyclisation, undergoes efficient E $\rightarrow$ Z photoisomerisation, with a QY as high as 0.56$\pm$0.14. The relaxation kinetics and photoproduct distributions are interpreted in the light of the available experimental data.(3)(4)(5)(6)

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Keywords: photochemistry, fulgides, molecular dynamics, quantum yield

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DFT studies of potassium clusters in Algerian groundwater

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Within the scope of this study, the primary waters that originate in the hydrographic bassin area are given extensive consideration. This investigation is being done with the intention of making a contribution to the quantification of water coming from recovered sources at various locations. The physicochemical parameters taken into account when characterizing its waters are: Conductivity, temperature, hydrogen potential, Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}, Zn^{2+}, NH_4^{+} cations and NO_3^{-}, NO_2^{-}, Cl^{-}, HCO_3^{-}, SO_4^{2-}, PO_4^{3-} anions.

We have noted that some samples have plus or mine exceed of potassium ions which can influence the quality of water and alter the human health.

The scope of this study is to suggest a solution for the reduction of the concentration of the potassium ions by forming clusters with water molecules.

The interest of these cluster is to minimize the exceed of concentration of potassium ions. These clusters were realized and studied at the level of DFT theory using the Gaussian software.

Keywords: groundwater, DFT, clusters, potassium.

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Comparison of oxidative damage and protection mechanisms for two members of the AA9 LPMO family

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Lytic polysaccharide monooxygenases (LPMOs) are copper-dependant metalloenzymes that use oxidative chemistry to break down polysaccharides. A major focus in LPMOs' research has been the investigation of the substrate oxidation mechanism.(1) Yet, the potent oxidative species can also cause oxidative damage to LPMOs in the absence of a substrate.(2) This self-oxidation renders LPMOs inactive, but the underlying mechanism remains poorly understood.

Proteomics techniques have demonstrated that oxidative damage is primarily confined to the two histidine residues coordinating the copper ion.(2) We recently employed QM/MM in combination with density functional theory to show that the oxidation of the histidine brace can be initiated by the hydrogen abstraction from either of the two histidines by a Cu(II)-oxyl, forming histidyl radicals.(3) Both experimental and theoretical investigations have revealed the potential involvement of a second-sphere tyrosyl intermediate in a protective pathway mitigating this self-oxidation process.(4, 5)

Previous QM/MM calculations involving the tyrosyl and histidyl radicals were focused exclusively on a single enzyme (*Ls*AA9). For the first time, we employ QM/MM calculations to directly compare two enzymes (*Ls*AA9 and *Ta*AA9) to offer insights into potential variations in the mechanisms and to contribute to a better understanding of the formation of radical intermediates in the process of oxidative damage.

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Keywords: lytic polysaccharide monooxygenase, LPMO, QM/MM, oxidative damage, copper

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Protonation of Homocitrate and the E1 State of Fe-Nitrogenase Studied by QM/MM Calculations

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Nitrogenase is the only enzyme that can cleave the strong triple bond in N2, making nitrogen available for biological life. There are three isozymes of nitrogenase, differing in the composition of the active site, viz. Mo, V and Fe-nitrogenase. Recently, the first crystal structure of Fe-nitrogenase was presented. We have performed the first combined quantum mechanical and molecular mechanical (QM/MM) study of Fe-nitrogenase. We show with quantum-refinement calculations that the homocitrate ligand is most likely protonated on the alcohol oxygen in the resting E0 state. The most stable broken-symmetry (BS) states are the same as for Mo-nitrogenase, i.e. the three Noodleman BS7 states, which maximise the number of nearby antiferromagnetically coupled Fe–Fe pairs (with a surplus of b spin on the eight Fe ion). For the E1 state, we find that protonation of the S2B μ2 belt sulfide ion is most favourable (like Mo-nitrogenase). However, protonation of the Fe2 ion is close in energy (4 or 16 kJ/mol less stable with the r^{2}SCAN and TPSSh density-functional theory methods, respectively), which may explain the recent ENDOR observations that the E1 state of Fe-nitrogenase should contain a photolysable hydride ion. For the E1 state, we find that many BS states are close in energy and that the preferred BS state differs depending on the position of the extra proton.

Keywords: Fe nitrogenase, QM/MM, Protonation, Broken, symmetry state, Quantum refinement, Density functional theory

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Simulating the photophysics of DMABN: what have we learned, and where do we go from here?

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4-(N,N-dimethylamino)-benzonitrile (DMABN) is a model compound for dual fluorescence – in solvents of sufficiently high polarity, it exhibits two distinct fluorescence bands, of which one (the so-called "normal" band) has a small Stokes shift, and the "anomalous" second band is strongly red-shifted. Many aspects of its photophysics, and especially the structure of the species which is responsible for the anomalous band, have been the subject of long-standing controversy. In my presentation, I will outline my efforts to clarify the dual fluorescence mechanism of DMABN with the use of computer simulations. In particular, I will show how the calculation of time-resolved fluorescence and transient absorption (TA) spectra provides a direct connection between simulation results and spectroscopic data. Moreover, I will discuss the implications of this research for the study of larger donor-acceptor compounds with applications in organic optoelectronics.

Keywords: photochemistry, DMBN, dual fluorescence, time-resolved fluorescence spectra, transient absorption spectra

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Study of the Streptomyces tyrosinase reaction mechanism: a dynamic QM/MM approach

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During the biosynthesis of melanin, the conversion of tyrosine into dopaquinone is catalysed by tyrosinase, a di-copper enzyme, that contains a peroxide ion in the active form. As a dysfunction in the production of melanin can lead to health issues (1), tyrosinase reaction mechanism is actively studied. To do that, the *Streptomyces* tyrosinase is often used as a model and has recently been characterised by crystallographic approach (2,3). To get a better understanding of this system, a QM/MM metadynamic approach was used, which lead us to model both the deprotonation of the tyrosine and the movement of one of the coppers, such as described by experiment. We also witnessed an opening of the peroxo group following the deprotonation, which was observed as well by a previous QM/MM study performed using a static approach (4). The next reaction step, a formation of a bond between one of the oxygen of the peroxo group and a carbon of the tyrosinase, was also described. However, due to a complex spin state configuration, the systems are not trivial to describe. The coupling between the two coppers in the active site of the tyrosinase is described to be antiferromagnetic which requires the use of a broken symmetry approach. This coupling is also evolving through the reaction, especially after the opening of the peroxo group. Our study will thus now focus on getting a better understanding of the electronic structure in later reaction steps by using diverse QM/MM interfaces. Another objective will be to obtain a better estimate of the different energy barriers by using methods such as NEB (nudged elastic band) performed on model systems, and thermodynamic integrations.

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Keywords: Tyrosinase, Metadynamics, QM/MM, Broken symmetry approach, Enzymatic mechanisms

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Investigating Metal-Metal Bonding in Heterometallic Iron-Sulfur Clusters with XAS and DFT

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Heterometallic iron-sulfur clusters serve as the catalytic sites for difficult biochemical transformations, including N_2 and CO_2 reduction in the M-cluster of nitrogenase and the C-cluster of CO dehydrogenase. The unique geometric and electronic structures that facilitate this reactivity have been the subject of intense spectroscopic and computational study for decades, but open questions remain due to difficulties inherent in the characterization of these systems. For example, the number of iron sites in the M-cluster results in multiple plausible oxidation state and spin topologies for each catalytic state, and C-cluster preparations are notoriously heterogeneous. Thus, investigations with well-defined model systems are needed to understand the interactions underlying enzymatic catalysis. Here, iron-sulfur clusters incorporating nickel and tungsten, including the first cluster isolated with a three-coordinate nickel, are characterized using X-ray absorption spectroscopy (XAS), magnetism and density functional theory (DFT). The heterometallic nature of the clusters allows the unambiguous assignment of all local oxidation and spin states using XAS at the Fe and Ni K-edges and W L3 edge. Spectroscopically validated DFT analysis reveals the importance of metal-metal bonding in the clusters' electronic structures, including covalent Ni-W bonds and a non-Hund configuration at W. The electronic interactions and spectroscopic signatures described are of particular relevance to the debated nickel oxidation state and possible Ni-Fe bonding in the C-cluster of CO dehydrogenase.

Keywords: Spectroscopy, X, ray spectroscopy, XAS, DFT, Iron, Sulfur clusters

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Evaluation of competing models for the high-spin forms of the S2 state of the oxygen-evolving complex

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The oxygen-evolving complex (OEC) of photosystem II (PSII) contains an oxo-bridged Mn4Ca cluster that oxidizes water through a sunlight-powered pathway. This pathway is a four-electron catalytic cycle composed of five intermediates (Si, i = 0-4), where the Mn ions of the OEC are in different oxidation states. The S2 intermediate is the most extensively studied by electron paramagnetic resonance (EPR) spectroscopy. Two main EPR signals are observed depending on experimental conditions. The first is a multiline signal at $g \approx 2$, attributed to a low-spin state with total spin $S = 1/2$, where the Mn ions are antiferromagnetically exchange-coupled. The second signal is detected at $g \geq 4$ and arises from a higher-spin state $S \geq 5/2$. There is little disagreement regarding the structural model behind the low-spin signal, but the structural model for the high-spin signal is debated.(1) Three main ideas are proposed in the literature: **a**) *Valence Isomerism*,(2) where there is a different distribution of the Mn oxidation states, **b**) *Protonation Change*,(3) where an oxo bridge is protonated but the Mn oxidation state distribution is the same as in the low-spin model, and **c**) *Coordination Change*,(4) where an extra hydroxide is added to one Mn. In this work, all possible ideas are evaluated computationally using large models of the OEC (_~350 atoms). These models are examined with broken-symmetry DFT calculations of their magnetic and spectroscopic properties. Our results show that models **a** and **c** produce the correct ground spin state, but model **b** does not lead to a high spin ground state, in contradiction to past claims in the literature. Furthermore, model **c** has a much larger energy gap and a different excited state sequence compared to model **a**, which is therefore the preferred model for the high-spin form of the S2 state.

Keywords: oxygen evolving complex, S2 state, EPR, high spin forms, DFT, broken symmetry

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Theoretical insights into tuning the enantioselectivity for anion-binding organocatalysis

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Asymmetric anion-binding catalysis(1) has become a powerful synthetic tool in recent years. However, only a limited number of catalyst's motifs are available i.e. based on chiral bidentate N-H and, more recently, O-H hydrogen-donor catalysts such as thioureas(2) and silanediols,(3) respectively. Additionally, while anion-binding offers high flexibility and tunability, the non-covalent interactions involved are experimentally more difficult to control compared to the covalent approaches, especially looking at the C-H binding.(4) Therefore, theoretical approaches are necessary to tune the many-body reactions in a way to strengthens or activates the given type of binding mode.(5) The first example of enantioselective (*ee*) activity of the Iodo-TetrakisTriazoles was recently shown.(6) In the next step, we have investigated the possibility of tuning the *ee* introducing additional halogen bond (XB) interactions between the reactants and catalyst. An extensive analysis of the transition state structures, energetics, and wave function analysis of the catalytic systems has been performed based on quantum chemical calculations for the two enantioselective routes ((*S*) and (*R*)). We found cooperative XB interactions with additional stabilization effects that drove the reaction pathway towards the (*S*)-product formation with a very good 66% *ee*. Excellent agreement with the experiments has been found and further optimization of the reaction allows us to achieve the exceptional 90% *ee*.(7)

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Keywords: anion binding organocatalysis, enantioselectivity transfer, halogen bonds, quantum chemical calculations

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MP2-based correction scheme to approach the limit of a complete pair natural orbitals space in DLPNO-CCSD(T) calculations

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The domain-based local (DL) pair natural orbital (PNO) coupled-cluster (DLPNO-CCSD(T)) is an accurate and computationally efficient approximation to the canonical CCSD(T) method. The latter is famous for its high accuracy and has long been applied as the "gold standard". However, in case of DLPNO-CCSD(T) the "chemical accuracy" w.r.t the CCSD(T) may only be achieved using large basis set and PNO space.

Herein, we present a simple and accurate perturbation theory-based correction scheme that significantly increases the accuracy of the DLPNO-CCSD(T) method (J. Pogrebetsky, A. Siklitskaya, A. Kubas, J. Chem. Theory Comput. 2023, 19, 4023). This approach requires one to calculate canonical MP2 correlation energy and DLPNO-MP2 correlation energy within the same PNO space and orbital basis as the preceding DLPNO-CCSD(T) calculation. The difference between the canonical MP2 and DLPNO-MP2 correlation energies may be used as a correction term to add to the DLPNO-CCSD(T) correlation energy. This approach allows to obtain total correlation energy that is close to the limit of the complete PNO space. The proposed procedure can bring the error of the DLPNO-CCSD(T) w.r.t the CCSD(T) to the "chemical accuracy" level with a miniscule increase in computation cost. Unlike the recently developed PNO-extrapolation technique by Bistoni and co-workers (J. Chem. Theory Comput. 2020, 16, 10, 6142), the presented correction scheme does not result in sufficient increase in computation time even in case of open-shell systems.

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Keywords: complete PNO space, local correlation methods, coupled cluster, DLPNO, CCSD(T)

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Second sphere residue effects on K-edge X-ray absorption spectroscopy and reactivity in Lytic Polysaccharide Monooxygenases.

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Lytic polysaccharide monooxygenases (LPMOs) are monocopper enzymes which activate strong C–H bonds through a mechanism that remains a matter of debate. The LPMO active site is largely conserved and features a "histidine brace" motif as the primary coordination sphere ligating a mononuclear copper center. However, the secondary sphere around the copper site has large scale variations through the LPMO subfamilies, which may allow for tailoring of the copper site and substrate binding pockets. In this study, we investigated the role of a conserved glutamine residue (Q164) in the second coordination sphere of *Nc*AA9C LPMO on the reactivity with H_2O_2 (co-substrate) in the absence of polysaccharide substrate (reoxidation) by mutating this residue.

Experimental reaction rates showed that the nature of the headgroup of the second-sphere residue, Q164 fine tunes LPMO functionality and copper reactivity. X-ray absorption spectroscopic (XAS) studies gave virtually identical Cu K-edge spectra for all *Nc*AA9C variants, showing that the mutation did not directly perturb the Cu(II) ligand field, but showed differences in the rising edge features for the Cu(I) LPMO mutant. Mutation of the residue 164 lowered the reduction potential and decreased the ratio between reduction and reoxidation rates. Mutant LPMO demonstrated abnormalities in a protective hole-hopping pathway and displayed increased enzyme inactivation, which was likely caused by changes in the confinement of radical intermediates.

Our QM calculations suggested mechanistic differences between the wild type (WT) and mutant LPMO. Furthermore, TD-DFT calculations also captured the K edge modulation for the mutant with varying protonation states. Calculations using DFT suggested that varying protonation states of the mutant residue might explain the differences in the experimental reoxidation rate. We also discovered a Cu(III)-hydroxide species which was produced on the H_2O_2 splitting pathway in a single step, thus indicating an altered reaction mechanism. This is in contrast to the Cu(II)-hydroxide and hydroxyl intermediates followed by Cu(II)-oxyl which are predicted for the WT. These findings indicate that this second sphere residue plays a crucial role in the catalytic functioning of the LPMO through modulating copper reactivity and provide information that may help in understanding LPMOs, the production of LPMO-inspired synthetic catalysts to target a wider range of C-H bond activation reactions.

Keywords: LPMO, XAS, TD, DFT, Second sphere mutation, Cu(III) hydroxide, H2O2

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Static WFT-in-DFT embedding with the pair coupled cluster doubles-based methods

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Reliable quantum-chemical modeling of large molecular systems still remains an elusive question. Wave function theory (WFT) based methods, although highly accurate, are limited by very high computational scaling. Quantum embedding methods have shown promising results to address this challenge.[1,2] In this approach, the molecular structure is partitioned into a system part studied by more reliable WFT methods and the environment part modeled by low-level methods. We propose a novel embedding scheme, augmenting pair-coupled cluster doubles (pCCD)-based methods [3] as the WFT-based component for the system fragment with density functional theory (DFT) approximations for the environment. The pCCD method produces reliable results for strongly correlated systems with mean-field computational scaling. [4] We also use a posteriori linearized coupled cluster (LCC) corrections on pCCD wave-function to account for the large extent of dynamic correlation, missing in pCCD ansatz and its extension to excited states.[5]

All codes have been implemented in the developer version of the PyBEST software package.[6] We have tested our embedding methods for the water–ammonia complex and for the more challenging uranyl halides (fluorine, chlorine, and bromine). The accuracy of the proposed model is assessed against the vertical excitation energies and orbital correlation analysis.[7] Our work serves as a starting point for further development of pCCD-based embedding schemes.

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Keywords: embedding, pair-coupled cluster doubles method, pCCD

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Role of Three-Component Thermodynamics in Reactivity and Mechanism of Radical Transfer Reactions

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Radical transfer reactions play a major role in a variety in biological transformations, such as neutralisation of toxins or biosynthesis of natural products, as well as open the way in organic synthesis to obtain novel useful compounds. The prominent example of radical transfer is hydroxylation (OH rebound); the reaction is initiated by hydrogen atom abstraction (HAA) by the high-valent metal-oxo species. This leads to formation of a substrate radical and Fe(III)-bound hydroxide, the two moieties subsequently recombine to yield a hydroxylated product.

From the thermodynamic perspective OH radical transfer can be perceived as electron transfer (ET) coupled to an ion transfer (IT, and together termed electron-coupled ion transfer, ECIT) and thus be subject to a three component thermodynamic description as previously developed for HAA (Proc. Natl. Acad. Sci. U.S.A. 2018, 115, E10287-E10294, Inorg. Chem. 2022, 61, 18811–18822). Within this model OH rebound, a diagonal (concerted ECIT) path, is strongly affected by two off-diagonal (sequential) ones: one initiated by ET, which is followed by IT, and the other, which begins with IT and is completed by ET.

Therein we present that the changes of ECIT reactivity in a series of model Fe(III)-OH systems can be effectively captured by the canonical linear free energy relationship together with the off-diagonal contributions: asynchronicity, which describes to what extent ET is independent from IT, and frustration, measuring the overall accessibility of the two off-diagonal pathways. Moreover, for OH rebound two mechanisms are feasible and they differ by the direction of ET (from substrate to Fe(III) or from Fe(III) to substrate). We demonstrate that the off-diagonal contributions allow to distinguish between the two pathways as these correlate with the electronic structure evolution of the systems along the reaction coordinate (charges and volumes of the OH moiety).

Keywords: radical transfer, computational chemistry, thermodynamics, reactivity

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Experiment and theory cooperation in studies of structurally similar biomimeitc Cu(II) and Co(II) cationic-anionic N-scorpionate ligand complexes with different catalytic activity

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This work is focused on the structural and spectroscopic characterization supported by quantum chemical studies of two novel Cu(II): **(CuLCl)$_2$(CuCl$_4$)** (**1**) and Co(II): **(CoLCl)(CoL1Cl$_3$)** (**2**) cationic-anionic complexes with N-scorpionate type ligand: N, N, N-tris(3,5-dimethylpyrazol-1-ylmethyl)amine (L).

The obtained complexes are the first reported examples of cationic-anionic coordination compounds tested on catecholase activity. Interestingly, from the tested Cu(II) and Co(II) complexes, only Cu(II) one (**1**) possesses catalytic activity in the oxidation of 3,5-di-*tert*-butylcatechol (3,5-DTBC). Moreover, catalytic results obtained for **1** revealed that the solvent's nature significantly affects the catecholase activity of the Cu(II) complex.

Experimental UV-Vis spectroscopy of **1** shows that essential features of the solid-state spectrum are maintained in DMSO and MeOH solvents. On the contrary, the build-up of a new, well-resolved feature around 475 nm for **1** in ACN was noted, along with negligible catalytic activity. Using high-level quantum chemical methods at single- and multireference levels, we found that this feature should be attributed to ligand-to-metal charge-transfer (LMCT) excitations in the $CuCl_4^{2-}$ unit. LMCT excitations are shifted to lower energy as compared to isolated $CuCl_4^{2-}$. This is due to Coulomb interactions with neighbouring $(CuLCl)^{1+}$ fragment that breaks the quasi-tetrahedral symmetry of the $CuCl_4^{2-}$ unit. These excitations are presumably present in the solid-state spectrum of **1** but remain hidden in a broad peak with a maximum around 420 nm. We found that only in ACN the zwitterionic system is more stable by about 5 kcal/mol in comparison to the situation when two fragments are separately stabilized by a ACN molecules. In DMSO and MeOH, the solvent-stabilized fragments are more preferred in comparison to zwitterionic complexes. In the case of DMSO, the solvent molecule serves as an inert ligand in a $(CuLCl)^{1+}$ fragment (binding energy of ca. 19 kcal/mol) and blocks the catalytic centre disturbing the formation of the (catalyst-substrate) complex and decreasing activity. Interactions of MeOH with the $(CuLCl)^{1+}$ and $(CuCl_4)^{2-}$ fragments are weaker and mainly via hydrogen bonds. Therefore, the free coordination site is accessible for the substrate molecule to bind.

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Keywords: Copper(II) complexes, cobalt(II) complexes, cationic-anionic complexes, N-scorpionate ligand, catecholase activity

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Theoretical (DFT) and experimental studies, reactivity descriptors calculated of Natural compounds

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Volatile isolates obtained by hydrodistillation from leaves and stems of *Dittrichia viscosa* (L.) were analyzed by CG and GC-MS. Oxygenades sesquiterpene and diterpenoids are dominant in the leaves and the stems (40.7% and 69.1%) respectively. The most abundant compounds for the leaves are*: carryophyllene oxide (10.4%) ,Fokienol (9.6%),E-Nerolidol (7%), α-Eudesmol (7.6%) and γ-Eudesmol* (6.2%*).* The isolate from the stems is mainly composed of *E-totarol (18.1%), α-cedrol (16.7%) ,Ferruginol (16.6%).* The essential oils of leaves and stems have high antimicrobial activity against the bacterial strains and yeasts at a concentration of 300 μg. The functional density (DFT) has been employed in order to calculate the structural parameters, the energetic properties, as well as the descriptors of reactivity of the major compounds of *D. viscosa (L.).* We notice a good agreement between experimental and theoretical results.

Keywords: Dittrichia viscosa (L.), volatile compounds, hydrodistillation, GC and GC/MS analysis, antimicrobial activity, DFT

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