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Averaged Molecular Dynamics Trajectories in Frozen-Density Embedding Theory

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Frozen-Density Embedding (FDE) Theory has become one of the most popular approaches for accounting environmental effects within the Density Functional Theory (DFT) framework[1-4]. In FDE, a presence of solvent is taken into account through the inclusion of averaged embedding potential into the Kohn-Sham equations. The averaged embedding potential is evaluated at a fictitious electron density of the solvent by virtue of «dressing up» with electrons the classical site distributions derived from the statistical-mechanical 3D molecular theory of solvation known as 3D-RISM method[3].

In this work we evaluate the performance of FDE method using statistical averaging of the molecular dynamics trajectories instead of 3D-RISM approach[5].

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Effect of Mixed Organic Cations on the Phase Stability of Hybrid Organic/Inorganic Lead Perovskites for Solar Cell Applications

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Due to their high power conversion efficiency, mixed organic/inorganic lead halide perovskites have emerged as promising materials for next-generation solar devices. However, the long-term stability of this kind of devices is an open question because various different crystalline phases exist in a narrow temperature range. The main phases that are observed are a trigonal structure called *α* phase or black phase and a hexagonal structure called *δ* phase or yellow phase. The latter however is not suitable for solar cell applications. Therefore, one of the main questions is how one can differentially stabilize the 3D perovskite-phases. Recently, it has been reported that mixing formamidinium lead iodide ($FAPbI_3$) with methylammonium lead iodide leads to a stability increase of the *α* phase.[1,2] Here we investigate the reasons for this effect computationally by combining the relatively unstable formamidinium lead iodide ($FAPbI_3$) with Cs cations and examining the phase stability, as well as the morphology of the mixed perovskites.

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Computational Investigations of a β-Class Carbonic Anhydrase from Desulfovibrio vulgaris

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There has been a widespread research, both experimental and computational, to develop efficient (bio)catalysts for the assimilation of atmospheric carbon dioxide. Although, a remarkable progress has been made in recent decades, some systems clearly suffer from the poor catalytic efficiency.[1] Herein, we focus on a β-carbonic anhydrase from *Desulfovibrio vulgaris*. The properties of this β-CA has been optimized by directed evolution and tested at pilot scale.[2] The mature enzyme is predicted to be a β-class CA homologous of the CA from *Mycobacterium tuberculosis* (MtCA) which can switch between dimer and tetramer states through a carboxylate shift mechanism.[34] The metal binding site of the dimer and tetramer forms of the enzyme have been parametrized. Details of the carboxylate shift mechanism and carbon dioxide binding properties are under investigation in our lab. The results of this study will enrich our perspective for protein-CO_2 interactions to develop biotechnological approaches.

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Intramolecular symmetry-adapted perturbation theory - a tool for elucidating the weak intramolecular interactions

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During the last two decades it has been firmly established that the description of the non-covalent inter- and intramolecular interactions is essential for understanding numerous chemical, photochemical processes, the behaviour of systems of biological importance (e.g. DNA) and designing new materials. Consequently, the theoretical chemistry community has put a large effort into developing methods for calculating and decomposing those interactions into physically interpretable parts. Amongst those methods, the most prominent is the symmetry-adapted perturbation theory (SAPT), which is able to accurately calculate and partition the interaction energies of dimers into physically meaningful components (e.g. electrostatics, exchange, induction dispersion).

Until now, no counterpart of SAPT for the intramolecular interactions has been developed. Here, we propose such a method, based on the previously introduced by Gonthier and Corminboeuf [1] zeroth-order wavefunction and the notion of Chemical Hamiltonian introduced by I. Mayer [2]. In this “intramolecular SAPT” approach the interaction between the two weakly interacting fragments is in the first step removed by projection operators and then brought back as a perturbation. The arising perturbation terms have clear physical interpretation as Coulomb-exchange, charge-transfer and dispersion interaction.
The method is validated on examples of some prototypical systems and applied to a number of problems involving intramolecular interactions, e.g. to elucidate the nature of the interaction between chains of folded unbranched hydrocarbons ("hairpin alkanes").

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Visualizing and quantifying molecular excited state interactions with scalar fields.

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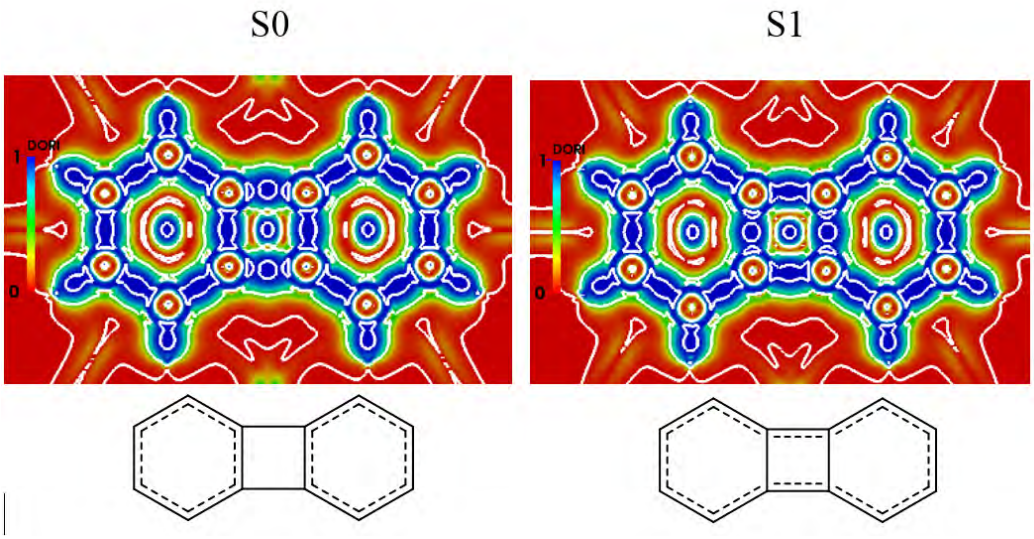
Molecular scalar fields offers an intuitive representation of electronic structures[1]. Yet, most functions are not suitable for analysing bonding in the excited state due to the orbital dependency of the kinetic energy density. De Silva et al. recently introduced an orbital-free scalar field that is capable of revealing both covalent bonding patterns and intermolecular interactions. We here use the Density Overlap Region Indicator (DORI)[2] to capture various excited state phenomena such as the formation of excimer, charge transfer excitations as well as intramolecular electronic rearrangement. The DORI function provides a clear visual and numerical signature of these excited state processes.



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Empirical valence bond simulations of the hydride transfer step in the monoamine oxidase B

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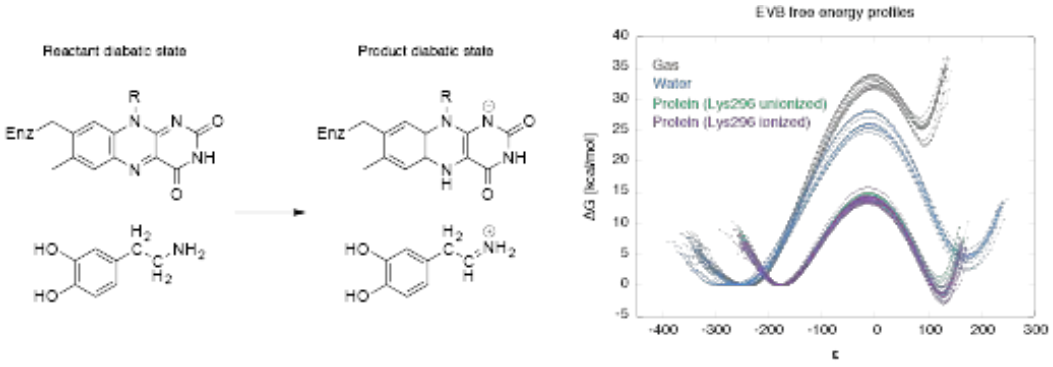
Monoamine oxidases (MAOs) A and B are flavoenzymes involved in the metabolism of biogenic amines that include the monoamine neurotransmitters dopamine, serotonin and some histamine metabolites. MAOs regulate the concentrations of neurotransmitters in the central and peripheral nervous systems, having a major impact on cardiac output, blood pressure, sleep, mood, cognition, and movement.[1]

By using the Empirical Valence Bond method of Warshel and coworkers[2] we studied the degradation of dopamine by MAO B. The relative speed of the method allowed us to obtain reactive trajectories in excess of 1 ns, thereby ensuring the free energy profiles are well converged. Moreover, this enabled us to study the effect of the protonation state of a lysine residue in the vicinity of the active site.



We showed that MAO B is specifically tuned to catalyze the hydride transfer step from the substrate to the flavin moiety of the FAD prosthetic group and that it lowers the activation barrier by 12.3 kcal mol-1 compared to the same reaction in aqueous solution, a rate enhancement of more than nine orders of magnitude. Taking into account the deprotonation of the substrate prior to the hydride transfer reaction, the activation barrier in the enzyme is calculated to be 16.1 kcal mol-1, in excellent agreement with the experimental value of 16.5 kcal mol-1. Additionally, we demonstrate that the protonation state of the active site residue Lys296 does not have an influence on the hydride transfer reaction.[3]

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A TD-DFT-based Approach to Describe Electron Dynamics of Molecules in Intense Laser Fields

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A combination of Time-Dependent Density Functional Theory (TD-DFT) and Ab-initio Molecular Dynamics (MD) is used to study the ultrafast electron dynamics triggered by high intensity laser sources.

In particular, we describe the electron dynamics occurring in the high harmonic generation (HHG) of oriented molecules [1] using TD-DFT Ehrenfest-based MD simulations [2]. Taking the iodoacetylene molecule (I-C≡C-H) as a test case, our aim is to rationalize the electronic movement triggered by the external pulse and monitor the dynamics of the hole created during the process [3]. For that purpose, we have compared the relaxation of the molecule after a single ionization from selected molecular orbitals to that occurring in the presence of an external field. We show that results in the relaxation of $I\text{-}C{\equiv}C\text{-}H^+$ generated by ionization from a HOMO/HOMO-1 superposition of molecular orbitals, are in a good agreement with the experimentally observed characteristic 2 fs period of electronic oscillations [4]. Applying the laser field, the oscillation period is shifted up reflecting a much more complex electron dynamics. In fact, when the vector potential is of the order of $|\mathbf{A}/c| = 1$ a.u., both σ- and π-symmetries are broken leading to charge oscillations of 2.85 fs located along the polarization and perpendicular axis.

Additionally, we investigate the excited-state deactivation of the N(5)-Ethyl-4a-hydroxyflavin molecule, a model system used to study bacterial luminescence [5]. Preliminary nonadiabatic MD simulations using a linear response-TDDFT based formulation of Tully's Fewest Switches Trajectory Surface Hopping method [6] show that the S2 - › S1 transition occurs in the first 10-20 fs of simulation, while the relaxation to the ground state (S1 - › S0) takes longer time (~100 fs). The latter also shows certain probability of having a C4a-N5 bond break.

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Computational Rationalization of the selectivity of Ru(II) and Os(II) anticancer agents in HIS/HER binding to the histone components of the Nucleosome Core Particle

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Cancer is a widespread disease in developed countries. Over the last twenty years, metal-based antitumor drugs have emerged as effective chemotherapeutic agents.[1] Indeed, the success of platinum complexes (i.e., cisplatin and carboplatin) paved the way for exploiting the unique physico-chemical properties of organometallic complexes in medicinal chemistry.[2] The resistance and the severe side effects of cisplatin, prompted for the development of alternative metal-based anticancer agents, such as ruthenium(II) and osmium(II) based compounds that exhibit low toxicity and selective activity against specific cancer cells types.[3,4] In collaboration with the group of Prof. P. J. Dyson at EPFL and Prof. C. Davey at Nanyang Technological University, we are working on the design of novel potential Ru(II) and Os(II) anticancer drugs acting at the Nucleosome Core particle (NCP) level.[5] X-ray crysrallographic structures show that these compounds bind to the histone components of the NCP, which is the basic repeating unit of chromatin. By looking at the binding of a series of Ru(II) and Os(II) compounds in crystals of the NCP,we found that these compounds bind either exclusively to His side chains (i.e., HIS sites) or to highly electronegative regions (i.e., HER sites), which are characterized by the presence of at least one negatively charged side chain (Glu/Asp). Understanding and determining the binding selectivity of Ru(II) and Os(II) compounds for either HIS or HER sites of the NCP is of great interest to rationalize the design of future potential anticancer drugs. Here, classical molecular dyanmics (MD) and hybrid quantum mechanics/molecular mechanics (QM/MM) simulations are used to unravel the selection mechanism at molecular level. Thermodynamic Integration (TI) is used to determine the binding free energies, thus allowing the discrimination of the HIS vs. HER preferred binding site. Overall, our computational and experimental efforts could provide novel insights for the discovery of new anticancer drugs targeting the NCP.

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Investigation of the Posttranslational Modifications Expressed in Polyteonamide B by Molecular Dynamics Simulations

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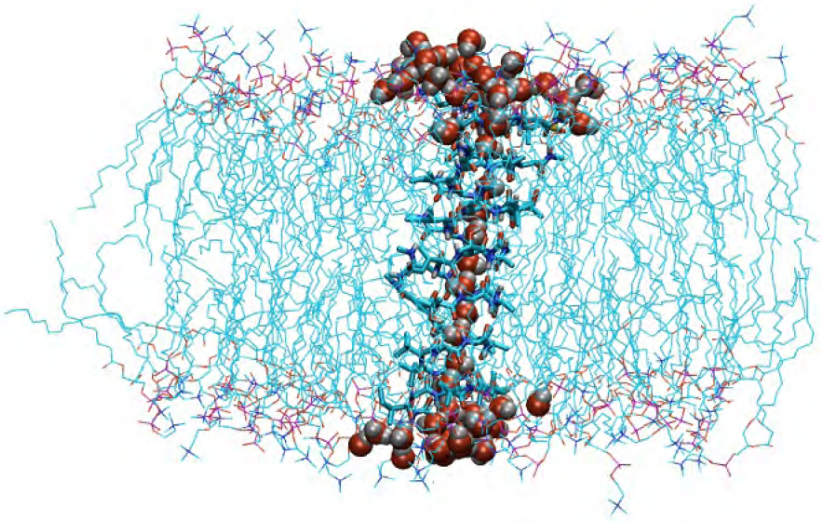
Marine sponges are a unique source for bioactive metabolites. In particular, *Theonella swinhoei* produces an exceptionally potent peptide cytotoxin, polytheonamide B (PTB)[1]. PTB is a transmembrane ion channel, where 23 of the total 48 amino acids are posttranslationally modified by symbiotic bacteria enzymes[2]. Alternating L- and D- amino acids confer to this peptide an uncommon $\beta^{6.3}$ -helical structure. Here, the effects of the posttranslational modifications are investigated by molecular dynamic simulations of models reverted back to the natural amino acids. The posttranslational modifications are grouped into sets with steric and electrostatic effect, and studied separately. In addition, mutations of the N-terminus reported experimentally to enhance or reduce the cytotoxicity, respectively, are investigated. Simulations of the modified peptides in water and in different membranes are compared to the wild-type peptide in structure, fulfillment of NMR data and channel activity to provide insights into the functional mechanism of PTB.



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Mechanistic Study of Denitrification in Truncated Hemoglobin using Adiabatic Reactive Molecular Dynamics

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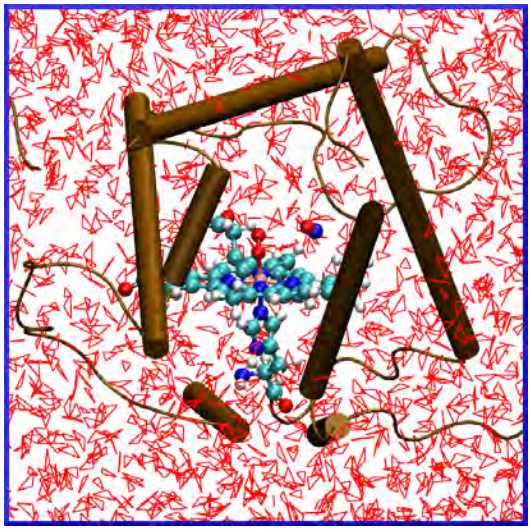
Proteins such as truncated hemoglobin (trhbN) bind oxygen cooperatively with very high affinity and a slow dissociation rate. Understanding the kinetics of binding of nitric oxide (NO) to the oxygenated hemoglobin (trHbN) gains increased interest as it plays an important role in bacterial detoxification and nitrosative stress[1,2]. Many studies have been carried out on trHbN but it is not clear how the denitrification reaction takes place in trHbN (reaction sequence shown bellow). Mechanistic details of binding of NO to the oxygenated trHbN was studied here using force field based multi surface adiabatic reactive molecular dynamics (MS-ARMD) as implemented in CHARMM[3]. Although *ab initio* MD or hybrid QM/MM can be used to such process, they do not allow to sample the phase space exhaustively because of high computational cost. On the other hand we successfully parametrized the force field for the above process with sufficient accuracy, which allow to exhaustively sample the phase space and in turn offers meaning full energetics and rate constant for the NO replacement reaction (Expt. rate constant 4.36 X 10^7 $M^{-1}S^{-1}$)[4,5].

$Fe^{II}NO + O_2 \rightarrow Fe^{II}O_2 + NO \rightarrow Fe^{III} + NO_3^-$



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Assembly of a diverse 10M GDB Fragment Set

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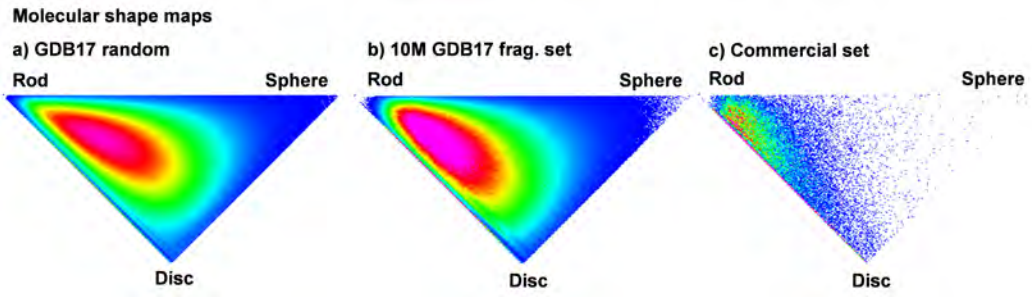
How many organic molecules are possible in total? To answer this question we have computationally enumerated all molecules that are possible following simple rules of chemical stability and synthetic feasibility with an increasing upper boundary for molecule size, resulting in the chemical universe databases GDB-11 (generated database up to 11 atoms of C, N, O, F, 26.4 million structures), GDB-13 (up to 13 atoms of C, N, O, S, Cl, 977 million structures) and GDB-17 (up to 17 atoms of C, N, O, S, halogen, 166.4 billion structures) [1]. GDB molecules are of comparable size to small molecules used in fragment based drug discovery, which typically cover the range 11-16 atoms [2]. The GDBs therefore represents an extremely large reservoir of new fragments. However only a fraction of GDB molecules have fragment properties, such as those defined by the “rule of 3” for fragment likeness [3]. Here we generated a subset of GDB-17 considering Ro3 together with additional functional group and molecular complexity criteria to define a subset of GDB-17 comprising approximately 5 billion fragment-like molecules. The subset was then sampled equally across molecular size, stereochemistry and polarity to produce a library of 10 million diverse fragments. This fragment library was then organized for fast interactive browsing in a combined mapplet/browser format [4] to enable molecular shape and pharmacophore similarity searching [5]. The GDB fragment set can be used for designing new fragments, with emphasis on 3D-shaped molecules.



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DFT study of the influence of guest-host interactions on the high-spin/low-spin energy difference in $Co(bpy)_3^{2+}$@Y

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In a previous DFT study of the zeolite-Y encapsulated $[Fe(bpy)_3]^{2+}$ complex ($[Fe(bpy)_3]^{2+}$ @Y, bpy=2,2'-bispridine)[1], the guest-host interaction has been shown to have a dramatic influence on the high-spin/low-spin energy difference for the complex.

With the present study, we are extending the analysis of the influence of encapsulation to $[Co(bpy)_3]^{2+}$.

[Co(bpy)3]2+is usually a high-spin complex. However, when located in a constraining environment, such as the one provided by the supercage of zeolite Y, it is turned into a spin-crossover species [2,3,4].

For our study, we have optimized the low-spin and high-spin geometries of the complex in the gas phase and in the supercage, showing that the encapsulation leads to a destabilization of the high-spin state with respect to the low-spin state. Additionally, the low-spin state shows a substantial Jahn-Teller distortion. For our calcualations we used DZP and TZP basis sets and the PBE functional with and without the Grimme-3 dispersion correction.

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Accounting for electronic polarization in subsystem DFT calculations

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Within Frozen-Density Embedding Theory[1], concepts like polarization areambiguous. This ambiguity takes its source in the partitioning of the total density, which is not unique. One common way to take into account the polarization of the environment is to optimise the environment density ρ B in ”freeze-and-thaw” calculation[2]. However, previous works[3] demonstrated that theoptimization of the environment density ρ B with the ”freeze-and-thaw” procedure enhances the polarization effect to an unreasonable extend: In ”freezeand-thaw” calculation, the effect of the polarization of the environment by theembedded species and the effect due to the approximation in the non-additivedensity functional can not be distinguished.

The purpose of this study[4] is to distinguish the two effects. The environmentinduced shifts in the energies of local excitations of the investigated chromophore demonstrate that, in ”freeze-and-thaw”, the effect due to the approximation in the non-additive density functional is actually higher than theeffect of the polarization of the environment by the embedded species.

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Study of Excited State Geometries of Organic Chromophores

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The deformation a chromophore encounters upon electronic excitation can be crucial to understand its absorption (and emission) spectrum. Accounting for the environment effect on the excitation energies is sometimes necessary, but this can be a very expensive task.
FDET [1-3] is a multilevel method of choice when it comes to simulate local excitations of various chromophores. It has been shown that the environment density (ρ_B) in such calculations can be generated with a lower level of theory [4] without loosing accuracy on the excitation energies and environment induced shifts.
Having this in mind, the excited state properties of several experimentally relevant organic chromophores are evaluated and analysed[5,6].

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Pyrphyrin Adsorption on Au(111) Surface: Influence of Herringbone Reconstruction

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We study adsorption of Porphyrin derived heterocyclic molecule with cyanide (CN) groups, which will be called as Pyrphyrin on ideal and reconstructed Au(111) surfaces and compare favorable adsorption geometries of the molecule on both surfaces by DFT simulations. Experimentally the geometries of self assembly monolayers of Pyrphyrin has been observed. In order to classify the role of molecule/metal and molecule/molecule interactions as in the assembling process we consider the structure and electronic properties of adsorbed monomer and dimer.

Our calculations show that the most stable adsorption state is the one with adsorption of CN links along Au axis with adsorption energy of -82.97 kcal/mol. The interaction to the surface is dominated by van der waals with contribution of -79.31 kcal/mol, but the orientation and deformation of the molecule are determined by the attraction between the CN groups and the closest Au atoms (-1.84 kcal/mol for each CN links). Adsorbed dimer calculations show that there are repulsive interactions between CN links of the molecules which results in rotation of Pyrphyrin cores to opposite directions on Au surface. Results suggest that adsorption geometries of both monomer and dimer show differences with respect to the modeled Au surface whether is ideal or reconstructed.

We plan to further investigate the electronic structure of Pyrphyrin/Au by calculating molecular energy states, N1s XPS Spectra and STM images which can be directly compared to experimental results in order to assess the obtained adsorbed structures.

Exploiting dispersion-driven aggregators as a route to new one-dimensional organic nanowires

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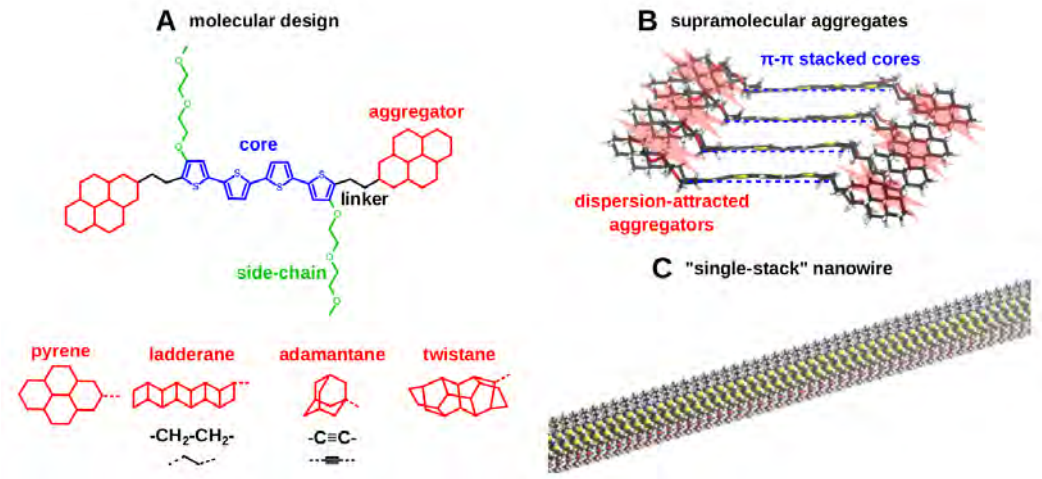
Quaterthiophene dominates the field of organic semiconducting materials due to its fine-tunable structural features. The efficiency of charge carrier mobility in organic semiconductors is heavily dependent on the long-range ordering and on the relative arrangement of the thiophene cores. At a molecular level, the charge hopping between adjacent quaterthiophene molecules will strongly depend on their π-orbital overlap. Therefore, constructing tightly packed 1D nanowires could improve the charge mobility along the π-stacking direction [1].

Inspired by natural membranes [2], we here exploit London dispersion forces to construct 1-D assemblies of quatertiophene cores. We identify hydrogenated pyrene and [n]ladderane substructures as ideal aggregator candidates that lead to well-ordered 1-D nanowires. Despite their different shapes, our MM and QM/MM simulations demonstrate that the two types of aggregators leads to similar structural and electronic characteristics. In particular, the computed DORI-based electronic compactness that was shown to correlate with charge mobility [3], is in line with that found in quaterthiophene crystals. Tighter stacking arrangements can be achieved by inserting linkers such as -CH_2-CH_2- and -C≡C- between the quaterthiophene cores and dispersion-aggregators. For instance, the insertion of -C≡C- linkers increases the electronic compactness by 50% as compared to simpler assemblies. Our computational predictions are established based on several criteria such as the structural stability of the assemblies and improved electronic properties. Our findings provide a route to the rational design of new 1-D nanowires.



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Statistical Averaging over Molecular DynamicsEnsembles in Frozen-Density Embedding Theory

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Frozen-Density Embedding (FDE) Theory has become one of the most popular approaches for accounting environmental effects in Density Functional Theory (DFT) [1-4]. In FDE, a presence of a solvent is taken into account through an inclusion of an averaged embedding potential into the Kohn-Sham equations. The averaged embedding potential is evaluated at a fictitious electron density of the solvent by virtue of «dressing up» with electrons the classical site distributions derived from the statistical-mechanical 3D molecular theory of solvation known as 3D-RISM method[3].

In this work we evaluate a performance of the FDE method in which the 3D-RISM approach is replaced by the averaging over molecular dynamics trajectories[5].

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Molecular binding mechanism of a potent ruthenium-arene anticancer agent to the nucleosome core particle (NCP)

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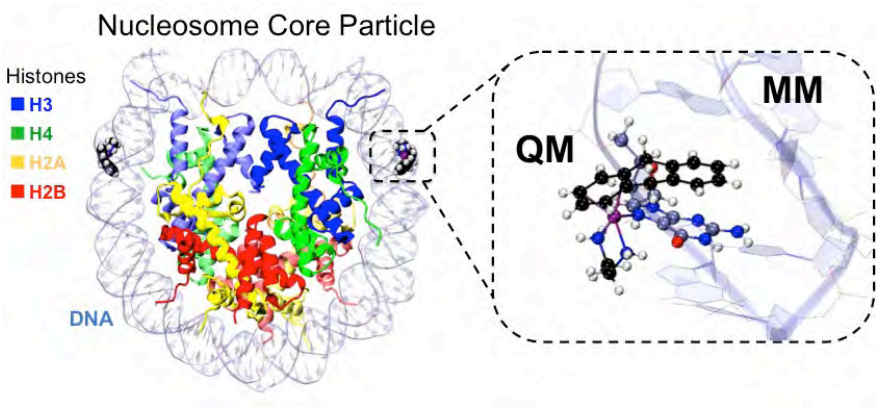
Ruthenium compounds have become promising alternatives to platinum drugs by displaying specific activities against different cancers and favorable toxicity and clearance properties.[1] At the molecular level, these compounds have been shown to target both constituents of chromatin, chromosomal DNA and the associated histone proteins.[2] Here, we focus on the novel Ru(II) organometallic arene complex [(η^6-tetrahydroanthracene) Ru(ethylenediamine)Cl]PF6 (RAED-tha), which inhibits the growth of human ovarian cancer cells with a potency comparable to that of cisplatin (IC_{50} ~0.6 mM).[3] By combining x-ray crystallography and molecular simulations, we reveal the molecular mechanism of binding of RAED-tha at the level of the nucleosome core particle (NCP), which is the basic repeating unit of chromatin. Long time-scale molecular dynamics (MD) and hybrid quantum mechanics/molecular mechanics (QM/MM) simulations show that RAED-tha binds at the nucleosomal DNA via a peculiar mechanism of *"mono base-stacking"*. Thanks to the distinct coordination geometry of the Ru(II) center and to the presence of a tetrahydroanthracene ligand, RAED-tha is simultaneously engaged in ligand coordination and stacking interactions with a nucleosomal guanine. Due to the structural characteristics of the nucleosomal DNA[4], RAED-tha circumvents the typical intercalative binding modes of DNA binders, resulting instead in a selective *semi-intercalation* mechanism. At contrast, RAED-tha does not assume this specific binding mode in canonical double-stranded DNA exemplifying the difference in molecular action of anticancer compounds for free versus compacted DNA. Overall, our collaborative efforts pose the basis for understanding the mode of association of Ru(II) compounds at the nucleosome level, while also crucially contributing to the design and development of novel ruthenium-based chemotherapeutic agents.



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EVOLVE: a new genetic algorithm toolbox for protein engineering

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[1]EPF Lausanne, [2]Joint BioEnergy Institute Emeryville

The structure and function of a protein is affected by the amino acid (AA) sequence. Therefore, the ability to evaluate the effect of AA mutations in a protein opens up the door for protein engineering. We present a new evolutionary algorithm toolbox, EVOLVE, which enables the systematic evaluation of AA mutations in proteins. EVOLVE, similarly to other genetic algorithms (GAs), provides a heuristic search inspired by processes in evolutionary biology such as inheritance mutation, selection and crossover. EVOLVE possesses a distinctive toolset for protein engineering that consists of an extensive library of 177 amino acid rotamers based on the Richardson rotamer library [1] and a user-definable fitness function (*f*). As a proof-of-principle case study, we report the application of EVOLVE to the sequence optimization of an ideal 20 AA long homo-alanine alpha-helix (A_{20}) for which the central 8 AA were optimized in different chemical environments [2]. In this case *f* evaluates the relative stability of each new sequence with respect to A_{20} at the molecular mechanics level making use of the coupling with the AMBER [3] suite of programs, (benchmarking studies proved that *f* accurately describes the helical stability [2]). Our results showed that EVOLVE is achieving fast optimization through utilizing a form of genetic memory, is converging and is proficient in finding low energy sequences. The low-energy sequences provided insight into the various amino acids combinations that affect helical stability in a specific environment. EVOLVE can be easily adapted to new problems whether they be different proteins, additional fitness functions, the coupling with other software packages. Currently we are using EVOLVE to screen for thermostable mutants.

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The role of dispersion-correction in the description of metal-ligand bonds in density functional theory

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With the considerable increase in sampling efficiency of Kohn-Sham density functional theory (DFT) based first-principles molecular dynamics, the availability and computational feasibility of more accurate exchange-correlation functionals has become of central importance to the field.

First-principles molecular dynamics are typically limited to the use of generalised-gradient approximation (GGA) exchange-correlation functionals. GGA are either unable to predict the highly nonlocal electron dispersion effects that govern the weak interactions *e.g.* between π-stacking species or rare gas atoms, or they yield highly spurious results. Employing an appropriate dispersion-correction scheme that is not associated to a large computational overhead is therefore of vital importance for the first principles simulation of many (bio)chemical systems. The inclusion of non-local atom-centred corrections to the Kohn-Sham effective Hamiltonian is referred to as the dispersion-correction atom-centred potential (DCACP) scheme. In contrast to other approaches that emulate electron dispersion, DCACP take the form of parametrised Gaussian projectors that act directly on the non-interacting single particle orbitals; the ground-state density of the effective DCACP Kohn-Sham Hamiltonian is therefore variational.

We have recently extended the library of DCACP-parameters, which now includes metals for the first time. Although the importance of a proper description of electron dispersion is obvious in metal complexes *e.g.* for stacking in between ligands, or for the interaction between neutral metal atoms, the significance of dispersion is less evident for metal-ligand interactions that comprise a charged metal centre. We are currently investigating the influence of electron dispersion on various transition metal complexes and compare the result against data reported in the literature and to force-field like dispersion-correction schemes. The assessment includes, but is not limited to, both static and dynamic structural properties.

The role of Mg^{2+} ions in adenylate cyclase

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The Human Brain Project (HBP) is a European project that aims at getting a better understanding of how the brain works. As part of HBP we are collaborating with four other groups to uncover which important steps need to be taken in order to regulate signal transduction by G-protein-coupled-receptor (GPCR) activation at the membrane surface of cells. Every group is studying a part of the pathway. The segment that we investigate is the reaction mechanism that adenylate cyclase (AC) performs during GPCR activation. The active site of the enzyme is heavily water solvated and ions are able to move in and out. Hence, the active-site environment does not only consist of protein residues, but also includes water molecules and Mg^{2+} ions, which are proposed to be crucial during catalysis. However, how these Mg^{2+} ions help catalyse the conversion from adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) and what the role of the large number of water molecules is close to the ligand binding site remain unclear. The main focus of our study is to get a better understanding of the effect of the environment on AC's ATP conversion.

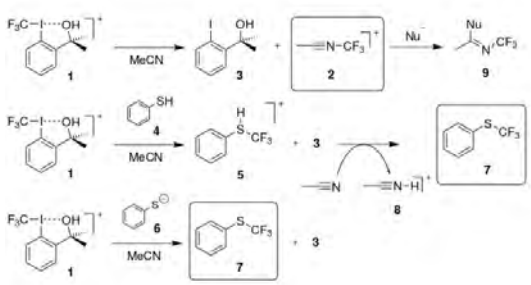
Understanding AC's enzymatic reaction could also have an impact on the understanding of other enzymes. This is because the S_N2 reaction that takes place is not unique, but is also present in other enzymes such as: DNA polymerase η, ribonuclease H and RNA polymerase II. In order to study the enzymatic reaction, classical molecular dynamics and quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) are employed. In combination with QM/MM MD, thermodynamic integration is used to investigate the reaction mechanism and to uncover the role of the environment as the reaction takes place.

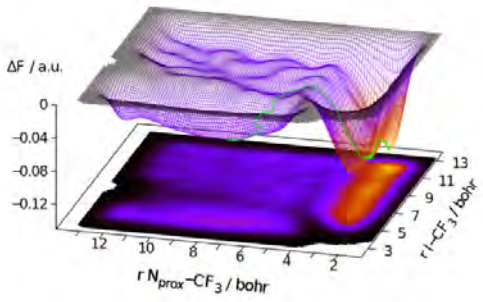
The reactivity of hypervalent $\lambda^{3,4}$-iodanes explored using ab initio (meta-)dynamics

O. Sala[1], H. P. Lüthi[1], M. Iannuzzi[2], A. Togni[1]*, J. Hutter[2]*

[1]ETH Zurich, [2]University of Zurich

Hypervalent iodine reagents (**1** in Fig.) are widely used in organic syntheses for trifluoromethylation of a vast array of nucleophiles [1]. Their reactivity is reminiscent of transition metal compounds, and the reactions may occur via different mechanisms, depending on the conditions and the nucleophile involved. The electrophilic *N*-trifluoromethylation of MeCN with a λ^3-iodane reagent to form a nitrilium ion, that is rapidly trapped by an azole nucleophile, is thought to occur via reductive elimination (RE) [2]. A recent study based on stationary calculations showed that, depending on the solvent representation, the S_N2 is favoured to a different extent over the RE [3]. However, there is a discriminative solvent effect present, which calls for a statistical mechanics approach to fully account for the entropic contributions. We perform metadynamic simulations (AIMD) for two trifluoromethylation reactions (with *N*- and *S* -nucleophiles), showing that the RE mechanism is always favoured in MeCN solution [4]. These computations also indicate that a radical mechanism (single electron transfer - SET) may play an important role [5].





We show that radical reaction mechanisms compete with polar ones involving the *S*-nucleophile thiophenol, the free energies of activation $\Delta F^{\ddagger}$ lying between 17 and 21 kcal mol^{-1}. Due to the higher nucleophilicity of thiophenolate, configurational ligand isomerization of the resulting λ^4-iodane reagent occurs, leading to the formation of side products by reductive elimination. The formation of a CF_3 radical can be thermally induced by internal dissociative electron transfer. The computational protocol based on accelerated molecular dynamics for the exploration of the free energy surface (FES), in particular the choice of collective variables (CVs) to construct the FES, is transferable and will be applied to similar reactions to investigate other electrophiles on the reagent. This approach gives insight into mechanistic details of the trifluoromethylation and shows that these commonly known mechanisms mark the limits within which the reaction proceeds. These details are obtained by the activation parameters.

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The new second-generation ETH DMRG program for quantum chemical applications

S. Knecht[1], S. Keller[1], Y. Ma[1], E. D. Hedegård[1], M. Reiher[1]*

[1]ETH Zurich

The density matrix renormalization group algorithm (DMRG) [1] employs a new wavefunction parametrization, tackling the problem of exponential scaling and thus facilitating calculations on larger systems than accessible for standard complete-active-space (CAS)-type methods which allows an efficient description of static electron correlation. In our software [2] we combine the matrix-product-state formulation of second-quantized operators in DMRG with the incorporation of non-abelian spin symmetry to yield the first spin-adapted *second-generation* DMRG implementation, where the Hamiltonian is represented as a matrix-product operator [3]. In this approach, the Hamiltonian effectively becomes an input parameter of the method, which greatly facilitates the implementation of other models, e.g. from relativistic quantum chemistry [4].

Taking advantage of an interface [5] to the quantum chemical software package *MOLCAS*, large-scale (e.g. 30 electrons in 30 orbitals) DMRG self-consistent field (DMRG-SCF) calculations for state-specific and state-averaged cases along with the calculation of analytical nuclear gradients become thus routinely feasible. We elucidate the potential of the DMRG-SCF approach in a theoretical study of a bioluminescence process, where many (near-)degenerate electronic states have to be considered simultaneously during the bond-breaking process while gradients for each state are indispensable to further analyze the light-emitting state.

For the remaining dynamical correlation problem, we pursue an *ansatz* that couples wavefunction and density functional theories (DFT), using range separation. Here we describe a range-separated short-range DFT method with a long-range wave function based on DMRG (DMRG-srDFT) [6]. First applications to dissociation reactions of transition metal complexes where accurate experimental gas-phase data is available demonstrate the potential of the new DMRG-srDFT approach.

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Bohmian Mechanics with virtual particles

O.T. Unke[1], M. Meuwly[2]*

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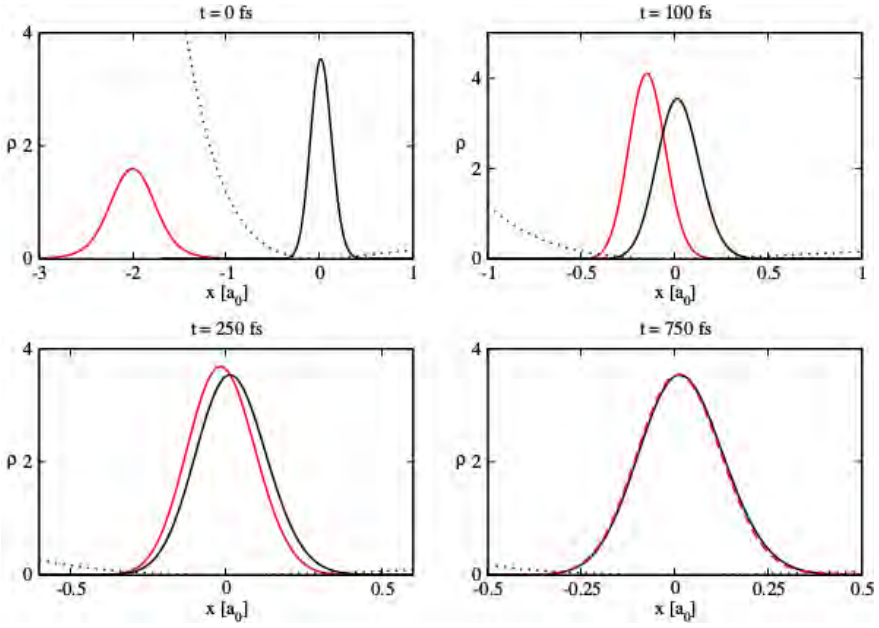
Since the introduction of the quantum trajectory method (QTM) by Lopreore and Wyatt in 1999[1], computational methods based on the de-Broglie-Bohm formulation of quantum mechanics have increased in popularity.[2] However, computational implementations of the Bohmian formalism suffer from numerical difficulties, such as the “node problem” or when fitting the hydrodynamic fields.[3]

We present a novel, computationally efficient formalism that uses an ensemble of N virtual particles instead of a wavefunction to evolve a quantum system, eliminating the aformentioned numerical problems. All particles follow classical equations of motion and quantum effects are introduced through the Bohmian quantum potential Q. The necessary derivatives to calculate Q are obtained from estimating the ”particle density” from the known N particle positions using kernel density estimation (KDE)[4,5].

The method can be used to solve the time-dependent Schrödinger equation and to calculate ground state densities and -energies. Results are in good agreement to exact quantum mechanical calculations for one- and two-dimensional model problems.



Convergence of a trial density (red) to the analytical solution (black) of the ground state of a Morse oscillator potential (dotted black) using the KDE-method with N=100.

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A Force Field Approach to Reproduce Grotthuss Mechanism in Reactive Systems

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[1]University of Basel

Theoretical studies of Grotthuss mechanism in the bulk phase, which involves a number of fundamental charge transport processes in biochemical systems, is a long-standing problem in computational and physical chemistry[3]. The MMPT force field (Molecular Mechanics with Proton Transfer), which was previously implemented in CHARMM[1], is a powerful and promising tool for simulating proton transfer processes in the gas and condensed phases. In this work, the extensive development of MMPT force field shows new advances in delocalizing the reactive sites in multi-molecular systems. By introducing global potential energies with mixed multi-surfaces[2], which correspond to combinatorial recognition of donor-proton-acceptor (DH-A) motifs, it is feasible for all hydrogen atoms to complete transfer moves in the water bulk with excess protons. Meanwhile, a transferable point charge model is employed to improve the diffusibility of the positive net charge throughout all water molecules in the system. In order to investigate the mobility of active protons, MD simulations also run in *n*-H2O-H^+ clusters in the gas phase and results are compared with semi-empirical QM-MD simulations.

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New computational approaches for liquids and energy-related compounds

S. Luber[1], J. Hutter[1]*

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Knowledge about local properties is extremely helpful for the analysis of molecular structures and interactions.Moreover, it is a valuable source of information for the characterization of dynamic processes and facilitates the interpretation of experimental data.Calculations provide additional insight allowing the targeted study of specific structures. In this way, it is possible to quantify the contributions of, e.g., solute and solvent molecules [1] or adsorbates on solids. We present novel methods for the calculation of local properties with a focus on Raman [2] and Infrared spectroscopy [3] applied, among others, to solvents used in Li-ion batteries as well as an in-depth study of artificial water oxidation catalysts [4,5].

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Physical Organic Characterisation of the Molecule-Electrode Contact in Single Molecule Junctions

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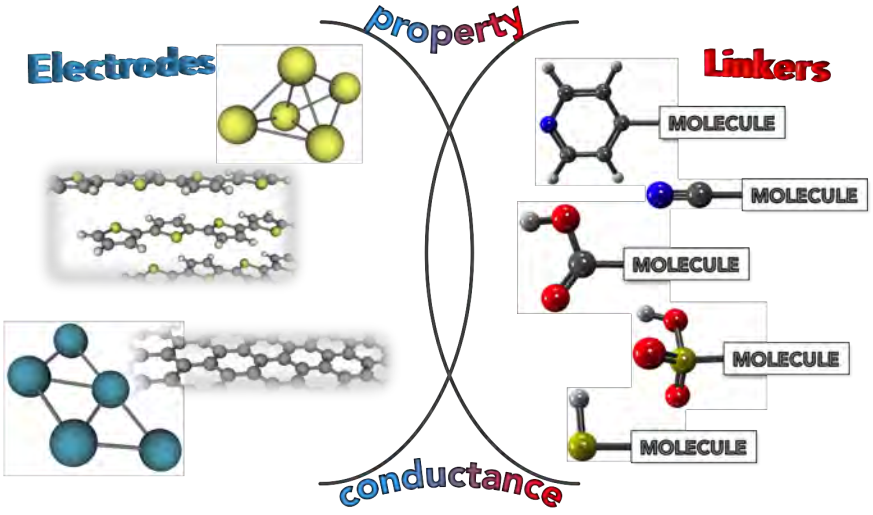
Single molecule junctions (SMJ) are molecular electronics devices that feature a single, most often organic molecule, anchored between two conducting electrodes. SMJs are invaluable in studying the molecular structure and electron transport by means of, for example, scanning tunnelling microscopy. They are also promising nanoscale components of electric circuits with sensing and switching capabilities.[1]

One of the key challenges in both the manufacturing and the characterization of the SMJs is the nature of the electrode-molecule interface, dependant on the electrode material and work function, local chemistry of the molecule's linking site, energy level alignment of the molecular orbitals in the junction, to name a few. However, research to date has focussed primarily on gold electrodes, and little attention has been devoted to the intricacies of the contact chemistry, with bigger focus on the bulk junction properties. In this presentation we employ accurate computational chemistry tools to elucidate the key contact parameters, such as geometry, type and strength of molecule-electrode bonding, its electronic compactness, polarity and degree of frontier orbital coupling.[2] These quantities will be assessed for a range of electrode materials, going beyond conventional noble metals and including non-metal electrodes, e.g. carbon nanosheets and conducting organic polymers, and various organic linking groups. The most promising combinations would ultimately be identified through transport calculations for the model junctions,[3] and the relevant experimental design criteria will be formulated.



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Multicenter Bonding in Hypervalent λ^3-Iodanes: New Insight from the Analysis of Domain Averaged Fermi Holes

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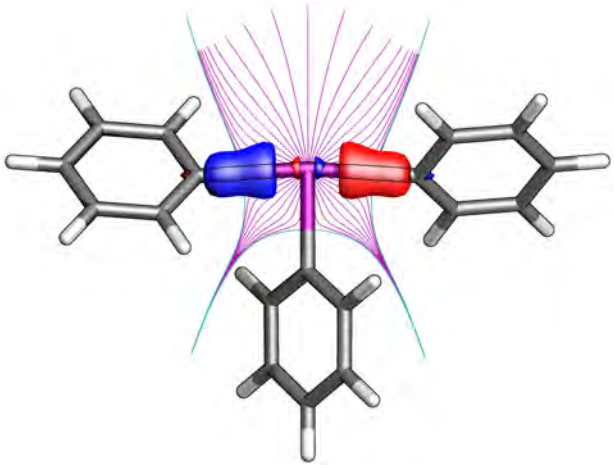
[1]ETH Zurich, Departement of Chemistry and Applied Biosciences, [2]Ghent University, Department of Inorganic and Physical Chemistry

Hypervalent iodine compounds have the ability to undergo fast reactions even with a closed shell electronic structure. The resulting reaction patterns allow for a variety of applications, e.g. the transfer of electrophilic substituents to arenes and other nucleophiles, well-known in organic synthesis. In these reactions, the hypervalent λ^3-iodane systems were shown to play a crucial role.[1] To explain the reactivity of these λ^3-iodanes, the 3-center-4-electron bond is still the most widely used model.[2]



In view of a more advanced description of bonding, the analysis of Domain Averaged Fermi Holes[3] was employed to explore the relationship between the occurrence of 3-center bonding and structural parameters. We show that the 3-center-4-electron bond model is explicitly valid for those compounds that exhibit a coupling beyond a single electron pair. However, compounds carrying electron-withdrawing ligands fall into a different category[4]: the pairing of electrons is restricted to extend over two centers only, thus challenging the 3-center bonding pattern. The analysis of domain Averaged Fermi Holes allows to further differentiate between features of the electronic structure of the λ^3-iodanes studied and to relate these to their reactivity.

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Processing Data from Quantum Chemical Calculations using Turbomole-XML-eXist

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In molecular modeling and design, the archival, analysis, and exchange of large amounts of data (results) from quantum chemical calculations on large arrays of compounds poses new challenges, and often marks the bottleneck in the process. In this work, we processed the results of the computations on a small array of biomedically active compounds. For the calculations and the processing of the data we used the Turbomole-XML-eXist infrastructure developed earlier [1]. This infrastructure had to be adapted for new tasks and finally allowed us to calculate, among other, charge autocorrelation functions as a descriptor quantity.

The charge autocorrelation functions were calculated based on atomic charges received from three different models (Mulliken, Lowdin and Natural Population Analysis (NPA)), and three different sets of structures (PDB, CORINA, quantum chemically optimized). The dependence of the autocorrelation functions on the structure, the charge model, and the way the hydrogen atomic charges are accounted for (included, omitted, projected onto nearest atom) is shown.

The data, once imported into the eXist document database, were queried using XQuery. Writing XQueries can be a rather involved task, and also constitutes a major part of this work. Indeed, this infrastructure proves to be an effective way to store quantum chemical data in a human- and machine-readable format (XML), and to process/transform the results of the queries efficiently to receive output in any desired format (ASCII text, XML, graphical, etc.) for further analysis. The figure compares the distribution of carbon-carbon bond lengths observed for two arrays.

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Thermal stability predictions as a tool for inherently safer process design

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Performing an efficient risk assessment and implementing the proper risk mitigation measures are essential to avoid or at least reduce accidents in industrial chemical processes and their potentially disastrous consequences. Differential Scanning Calorimetry (DSC) is one of the most used analytical methods employed to determine the thermal stability of compounds and mixtures. It can be considered resource efficient as an experiment can be conducted within hours using samples of few milligrams. However it becomes simply impossible to perform a measurement when an intermediate cannot be isolated, is extremely toxic or is physically unavailable. Moreover, when several tests have to be performed, the time and required resource accumulate.

Predictions would be the appropriate response to such scenario. This work aims at predicting thermograms of pure compounds, resulting from DSC experiments, using their molecular structures as input.

Prior to modeling, DSC curves are analyzed and decomposed into five key parameters (onset temperature, peak position, amplitude or maximum heat release rate, width and asymmetry). They are studied separately in order to preserve and later recover the full shape of the DSC curve by minimizing the data loss due to data abstraction. Then, predictive models are developed for a large number of structurally diverse and thermally reactive chemicals. There are mainly two structure-based approaches of data prediction: Group Contribution (GC) models and Quantitative Structure-Property Relationships (QSPR). Herein, both methods are applied in parallel and resulting models are evaluated relatively to the experimental data and compared to each other.

This procedure delivers the entire DSC thermal trail whereas usual abstractions only retain onset temperature and enthalpy. The curve’s shape encloses complementary information regarding the thermal behavior of the tested compound as the decomposition kinetics for instance and therefore should not be discarded.

Simulating the DSC thermograms from the molecular structure offers several advantageous applications in process design. Besides the previously mentioned possibility to predict DSC curves estimations which cannot be experimentally measured, there are several other benefits: predictions can be made at a very early stage of the process design; they also allow analyzing several alternatives within limited resources; finally, it is also noteworthy that predictive models help avoiding expendable handling of harmful chemicals. However, it is important to stress that predictive models are not intended to replace proper experimental investigations, but rather be a helpful tool that allows focusing the experimental work on the most critical compounds. The major benefits of such procedures within process design context are mainly to broaden the number of evaluations within given time and resources, an efficiency gain in testing phase with better strategies in resource allocation and valuable timing leading to anticipation.