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Computational Chemistry, Lecture **143**

A Computational Approach to Direct the Biosynthesis of Target Molecules

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Recent efforts in metabolic engineering offer sustainable alternatives for the production and degradation of industrial feedstocks. Considering microbial production of organic compounds provides an efficient framework based on renewable energy resources. An approach has been developed to postulate and evaluate novel biochemical networks to further the production of high-value target molecules. An evaluation of the feasibility of a network requires a detailed modeling of the molecular mechanisms involved in the reaction. The present study incorporates ab initio and classical molecular dynamics methods to assess the response of an engineered pathway. As a test case, this approach has been developed for the production of 3-hydroxypropanoate (3HP) from pyruvate. All-atom molecular dynamics simulations of the enzyme in complex with its natural substrate and with a non-natural substrate are examined to evaluate binding free energy differences and to identify the main molecular contributions responsible for deviations in the binding affinities. An examination of the catalytic cycle considers hybrid Car-Parrinello QM/MM dynamics to model the novel step of the reaction pathway producing the target molecule. Analysis from simulation is then used to guide the re-design of the enzyme target to enhance and optimize the catalytic efficiency of the novel reaction pathway.

Computational Chemistry, Lecture **144**

Modeling of Rod/Stack Supramolecular Zipper Architecture

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The unique zipper architecture [1] can be accessed *via* supramolecular assemblies of appropriate diads, where substituted naphthalenediimides (NDIs) assemble into π-stacks and *p*-oligophenyls (POPs) or oligophenylethynyls (OPEs) are used as rods. This so-called rod/stack architecture paves the way for long lived photoinduced charge separation and an efficient photocurrent generation [2].

We report quantum chemical investigations of substituted NDIs and their π-π dimeric complexes as the essential building blocks for rod/stack architecture. Geometry optimizations and property calculations with *ab initio*, DFT, and DFT-D methods will be compared.

MD simulations of rod/stack supramolecular architecture revealed highly ordered zipper assembly of NDIs stacks along OPE rods, where the repeat distance in the rigid-rod scaffold provides the optimal NDI-NDI interplanar distance in agreement with QM modeling. According to MD simulations, in addition to π-π interactions, multiple hydrogen bonding contributes in a significant way to the cohesion of the zipper assemblies. In contrast, MD simulations of NDI π-stacks along the POP rods result in a highly disordered supramolecular architecture due to the topological mismatch.

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Computational Chemistry, Lecture **145**

Exploring the trigger sequence of the GCN4 coiled-coil using molecular dynamics simulations

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The leucine zipper of the yeast transcriptional activator GCN4 exhibits a two-stranded, parallel coiled-coil motif, in which two α-helices are wound around each other. Its folding is proposed to proceed via an autonomous helical 33-residue folding unit. Biophysical analyses of two monomeric 16-residue peptides belonging to the folding unit suggest that the C-terminal half has a propensity to form a stable helix and constitutes the trigger sequence of GCN4. The C-terminal peptide has been investigated using NMR techniques including Nuclear Overhauser Enancement (NOE) intensities and $^3J(H_N,H_{C\alpha})$-coupling constants [1]. However, the proposed NMR model structures do not reproduce all the $^3J(H_N,H_{C\alpha})$-coupling constants. We show that molecular dynamics simulations incorporating time-averaged NOE distance restraints and instantaneous or local elevation ^3J-value restraints can satisfy the entire set of the experimental data. The analyses of the simulated ensembles indicate an essential role of the salt bridge between 22Glu and 25Arg, which is complemented by networks of hydrogen bonds and polar contacts involving 17Tyr and 18His. The networks formed around these residues are complex and involve not only interactions between side chains discussed before [1]; hydrogen bonds and polar interactions between main chain and between main and side chains are equally prominent.

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Computational Chemistry, Lecture **146**

Endocleavage Promotion in Pyranosides with Locked Conformation

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Pyranosides carrying 2,3-*trans*-carbamate undergo endocleavage-induced anomerization from the β-form to the α-form in the presence of a weak Lewis acid [1]. Transition state energies of these ring-fused pyranosides in the course of the anomerization reaction were found to be notably lower than those of typical pyranosides[2]. Here we report further theoretical and experimental investigations on a typical pyranoside (**1**), pyranosides with 2,3-*trans*-carbamate (**2**, **3**, **4**), with a 6-membered ring (**5**, **6**), with 2,3-*trans*- or 2,3-*cis*-carbonate (**7**, **8**), suggesting that the predominant factor to promote the anomerization is bending energy caused by the ring that fuses the pyranose ring at 2,3-*trans*. The position and the orientation of the carbonyl group of the substituent at a nitrogen atom of carbamate as well as high polarity solvents *e.g.* CH_3CN were identified to be responsible for strongly accelerating the anomerization reaction.

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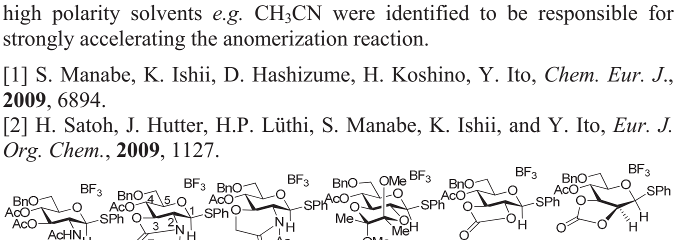

Computational Chemistry, Lecture **147**

The Role of Ligand Compound Space and Protein Environment in Dioxygen Induced Inhibition of [FeFe]-Hydrogenase

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The promising application of [FeFe] hydrogenases for sustainable hydrogen production is severly hampered by a high intrinsic sensitivity of these enzymes against molecular oxygen [1,2]. Interestingly, monoiron hydrogenase does not suffer from this limitation, but has a lower catalytic activity in the concentration regime relevant for H2 formation [4]. In a detailed quantum chemical study we analyzed the main differences in the coordination and reaction behaviour of these two classes of enzymes with respect to dioxygen attack and studied the influence of the different ligand spheres of the active sites. This was facilitated by first establishing the striking similarity of the overall ligand arrangement around the reactive Fe atom in [FeFe] and Hmd hydrogenase [5] that allowed us to systematically swap the coordination spheres. Along with this exploration of the ligand compound space in both active sites we extend our previous work [6] on the dioxygen induced inhibition of [FeFe] hydrogenase by considering the protein environment in a QM/MM approach and possibilities for protein engineering that could result in more oxygen tolerant enzyme variants [7].

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Computational Chemistry, Lecture **148**

Dynamics and Structural Studies of a Peptide Dendrimer Cobalamin Complex

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Dendrimer **B1** (AcGluSer)$_8$(*Dap*GluAla)$_4$(*Lys*AmbTyr)$_2$*Dap*CysAspNH$_2$ (*Dap* = branching (*S*)-2,3-diaminopropanoic acid, *Lys* = branching lysine, Amb = 4-aminomethyl benzoic acid) binds strongly ($K_a = 5.0\ 10^6\ M^{-1}$) and rapidly ($k_2 = 21,000\ M^{-1}min^{-1}$) to cobalamin by coordination of cobalt to the cysteine residue at the dendrimer core, featuring a prototypical model of a dendrimer ligand interaction. Diffusion NMR shows that the hydrodynamic radius of the dendrimer remains constant upon cobalamin binding or even contracts in the case of the 2nd generation peptide dendrimer **B2** (AcGluAla)$_4$(*Lys*AmbTyr)$_2$*Dap*CysAspNH$_2$, suggesting a preorganized binding pocket despite of the conformational flexibility and random coil structure indicated by NMR and CD-spectroscopy [1-2].

However, preferential dynamic and structural basis for strong and rapid binding of dendritic over non-dendritic ligands remained inconclusive by experimental studies. Molecular dynamics simulations based analysis suggests that such a preorganized binding pocket is present in dendrimer **B1**. Complexation of cobalamin results in burial of a large and mostly hydrophobic surface (695 Å^2) from the solvent, which probably contributes to the enhanced binding of **B1** compared with non-dendritic cobalamin ligands

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Computational Chemistry, Lecture **149**

Ab initio Molecular Dynamics Study of Li_2O_2, Li_2O and LiO_2 in propylene carbonate.

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Of the various metal-air battery chemical couples, the Li-air battery is the most attractive due to the high voltage of the electrochemical discharge reaction and to the low density of the element involved. Upon discharge Li and O_2 may form, depending on the conditions, lithium peroxide (Li_2O_2), lithium oxide (Li_2O) and lithium superperoxide (LiO_2).

Although the increasing interest, it is a matter of fact that the practical performance of nowadays prototypes is far from being comparable to the theoretical one. Several studies, both experimental and theoretical[1,2] have tried to rationalize the source of such discrepancy, leading to a unanymous consensus of the need of understanding deeper the nature of the possible products of the discharge reaction (Li_2O_2, Li_2O and LiO_2) in aprotic solvents such as propylene carbonate (PC).

In this talk, we will present ab initio molecular dynamics simulation of lithium peroxide (Li_2O_2), lithium oxide (Li_2O) and lithium superperoxide (LiO_2) in propylene carbonate, in order to investigate the nature of these species in promising electrolytes (PC with LiPF6, PC with LiTFSI). Emphasis is put on understanding the nature of the lithium-oxygen species in solution: i.e. on the possibility of forming tight ion pairs (like $Li^+ + LiO_2^-$), or of being entirely dissociated.

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Computational Chemistry, Poster Talk **150**

A Revisited Picture of the Mechanism of Glycerol Dehydration

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In this talk we present a revisited picture [1] of the dehydration mechanism of neutral glycerol in gas phase. The high temperature decomposition reaction was investigated theoretically by means of metadynamics at the PBE/DFT level. Barriers have been further refined at the PBE0 level.

Optimized geometries, transition states, and the theoretical rate constants at 800K have been computed for the different steps involved in the pyrolytic process.

We provide a new picture for the pyrolytic process where the neutral glycerol dehydration proceeds with formation of glycidol with a barrier of 56.2 kcal/mol [2]. The formation of the glycidol is the rate determining step of the overall decomposition process.

Once formed, glycidol converts into 3-hydroxypropanal with a barrier of 39.7 kcal/mol. 3-hydroxypropanal can decompose further into either acrolein or formaldehyde and acetaldehyde, with barriers of 45.9 kcal/mol and 29.0 kcal/mol, respectively. The theoretical findings offer new insights to available experimental data based on glycerol pyrolysis studies performed with isotopic labelling.

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Computational Chemistry, Poster Talk **151**

Molecular structure calculations without clamping the nuclei

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The clamped nuclei or Born–Oppenheimer approximation is one of the most important approximations in chemistry. Clamping the nuclei provides a mathematical basis to such notions as the potential energy surface, equilibrium structure, and the phenomenon of chemical isomerism, all central to the classical way of chemical thinking [1]. From a physical aspect however molecules are assemblies of particles with specific mass, electric charge, and spin. At specific ranges of these parameters the expectation values of interparticle distances, mass-densities, *etc.,* can be very different indicating the emergence of qualitatively different structures [2]. In order to be able to address such questions as well as to calculate accurate rovibronic energy levels of molecular systems within the nonrelativistic framework a variational algorithm was implemented for the solution of the Schrödinger equation without invoking the Born–Oppenheimer approximation, *i.e.,* without making any *a priori* assumptions on the structure [3]. Our approach starts out on the pioneering works in the field by Suzuki and Varga [4] and Adamowicz *et al.* [5]. In this contribution after presenting the methodological developments, numerical results calculated for many-particle systems—including energy levels, wave functions, and related properties—are discussed.

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Computational Chemistry, Poster Talk **153**

The hydrolysis of isocyanic acid: theoretical catalyst screening

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The catalytic hydrolysis of isocyanic acid – an important reaction step in the urea-SCR process – was studied on the anatase TiO_2 (101), γ-Al_2O_3 (100) and SiO_2 (111) surfaces with DFT calculations using a cluster model and compared with in situ DRIFTS investigations and kinetic experiments. In our previous DFT studies [1,2] we presented two possible reaction mechanisms for the hydrolysis of isocyanic acid over TiO_2 anatase (101). The objective of the present work was to extend our theoretical study to other metal oxide catalysts. We have chosen γ-Al_2O_3 and SiO_2, because these materials show a clear stepped reactivity for HNCO hydrolysis in the order anatase $TiO_2 > \gamma$-$Al_2O_3 > SiO_2$ [3].

The co-adsorption of isocyanic acid and water and their reaction to ammonia and carbon dioxide on catalysts surfaces were studied with ab initio density functional theory (DFT) calculations using a cluster model as well as with in situ DRIFTS investigations. The reaction pathway proceeds as follows: A water molecule attacks the –NCO group at an early stage, thereby forming carbamic acid at the surface. In a further step this compound is transformed to a carbamate complex, which leads to CO_2 desorption and consequently NH_3 formation. Since water is always present in diesel exhaust gas, only the second mechanism is relevant under practical conditions.

Based on the computational screening of different catalysts we can confirm the experimental results, which show that TiO_2 is the best catalyst for isocyanic acid hydrolysis.

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Computational Chemistry, Poster Talk **152**

The importance of non-electrostatic terms in embedding calculations of the effect of protein-like environment to the iso-g values of Biliverdin

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The exact embedding potential in multilevel methods, such as QM/MM etc, to calculate electronic structure of embedded molecules contains two types of terms: the electrostatic and non-electrostatic ones [1,2]. The former exist also in classical methods whereas the latter reflect purely quantum mechanical effects such as electron correlation, exchange, and the non-zero kinetic energy of the electronic gas. Frequently, neglecting the non-electrostatic terms is an applicable approximation, especially if small basis sets are used for embedded species and the energy and/or geometry is the only target of the calculations. In the present work, we analyze the importance of the non-electrostatic component of the embedding potential given according to Wesolowski and Warshel [1] as a functional of two electron densities (that of the embedded system and that of the environment) on numerical values of iso-g for several systems comprising Biliverdin in a protein-like environment consisting of a few aminoacids. The Kohn-Sham results are used as the reference. It is shown that neglecting the electrostatic parts of the embedding potential leads to erratic numerical values of the environment-induced shifts in iso-g.

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Computational Chemistry, Poster Talk **154**

Mixed quantum-classical dynamics with time-dependent external fields: A TDDFT approach

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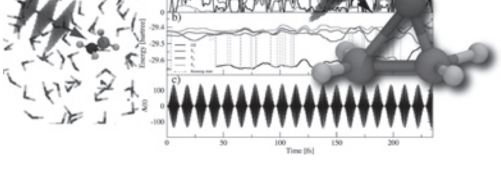
In the last years, linear-response time-dependent density functional theory (LR-TDDFT) has become widely used for the calculation of vertical excitation energies and excited state properties of medium to large size molecular systems in gas and condensed phases.

In this work [1], we present a trajectory surface hopping *ab initio* molecular dynamics (AIMD) scheme that couples nuclear and electronic degrees of freedom with an external electromagnetic field. All relevant quantities, namely ground and excited state energies, nuclear forces, nonadiabatic couplings (NACs) and transition dipole elements are expressed as a functional of the electronic density or, equivalently, of the Kohn-Sham (KS) orbitals in the framework of LR-TDDFT. The method is applied to the study of the photodissociation dynamics of some simple molecules in gas phase, and is then extended to the photochemistry of molecules in solvent within a QM/MM scheme.



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Computational Chemistry, Invited Lecture **155**

Towards a subsystem density functional theory description of covalent bonds

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Instead of using a single quantum chemical calculation on a large system, subsystem methods split up this large system into smaller subsystems. This makes it possible to focus on those subsystems that are of particular interest. The frozen-density embedding (FDE) scheme [1] provides such a subsystem approach within the context of density functional theory (DFT). It relies on the use of approximations for the kinetic-energy component $v_T[\rho_1, \rho_2]$ of the embedding potential. While the currently available approximations are rather accurate for weak interactions such as hydrogen bonds, they break down for bonds with a covalent character.

Thus, to be able to directly apply the FDE scheme to subsystems connected by covalent bonds, improved approximations are needed. In this talk, I will give an overview of recent work towards this goal [2,3] and discuss the importance of these developments for embedding wave-function based methods into environments described by DFT [4]. As an alternative to the development of improved approximations, one can also try to circumvent the their insufficiencies. This is possible by applying a recently developed generalization of the FDE scheme [5], which introduces capping groups to describe covalent bonds between subsystems.

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Computational Chemistry, Lecture **156**

A System-Dependent Density-Based Empirical Dispersion Correction

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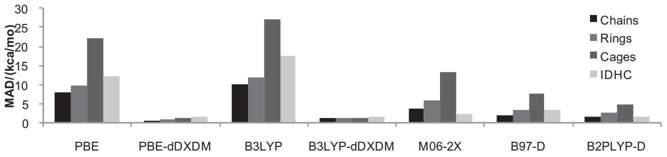
Density functional approximations fail to provide a consistent description of weak interactions. A simple remedy to correct for the missing interactions is to add *a posteriori* an attractive energy term summed over all atom pairs in the system. We showed previously that inter- and intramolecular weak interactions can be corrected jointly.[1] Now, we present a density-dependent energy correction that is available for all elements of the periodic table. Dispersion coefficients are computed according to the exchange-hole dipole moment (XDM) formalism[2] thereby depending on the chemical environment of an atom. The long-range ~R^{-6} potential is supplemented with higher-order correction terms (~R^{-8} and ~R^{-10}) through the universal damping function.[3] A genuine damping factor depending on Hirshfeld populations, atomic ionization energies and on two empirical parameters specifically adjusted to a given DFT-functional is also introduced. The new dDXDM scheme was tested on 145 systems featuring both, intra- and intermolecular interactions. The correction dramatically improves the performance of popular density functionals for both, inter- and intramolecular interactions.



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Computational Chemistry, Lecture **157**

Studying chemical reactions in complex environments with force fields

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Neuroglobin (Ngb), a relatively new member of the globin family of proteins [1], is 75 % sequence identical to myoglobin (Mb) and its crystal structure shows the same characteristic three-over-three α-helical globin fold. Despite these similarities Ngb is regarded as functionally more diverse than Mb. In the absence of an exogeneous ligand at the sixth coordinating position of the heme iron, the distal His64 of Ngb can bind in a competitive fashion to the heme with external ligands, like CO. Another discrepancy of Ngb compared to Mb is its possibility to form a disulfide bond between residues Cys46 and Cys55 [2]. In this work we first analyze the competition of His64 and CO to form a hexacoordinated heme using Reactive Molecular Dynamics Simulations [3] and compare it to the experimentally suggested two-step mechanism. Furthermore, we investigate the process of heme-sliding taking place after dissociation of the heme bound His64. Heme-sliding was found to trigger several rearrangements within the close proximity of Ngb's active site like opening and enlarging the distal side cavity of the protein. Additionally, the calculations revealed differences in the evolution and timescales of these rearrangements depending on the presence or absence of the Cys46 to Cys55 disulfide bond.

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Computational Chemistry, Lecture **158**

Defeating the efficiency of both quantum and classical simulations with accurate semiclassics [1]

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Nowadays rigorous quantum mechanical calculations for many-particle systems remain out of reach, while classical simulations, although feasible, do not include quantum effects at all. Semiclassical approximations take into account all quantum effects through interferences of classical trajectories and, unlike full quantum methods, are numerically affordable for complex systems even though challenging problems severely affects their numerical efficiency. We will show an accurate semiclassical approximation, called "dephasing representation" [2,3,4,5], which is even *much faster* than the classical calculation [1]. What about the accuracy? It is well known that, unlike in quantum dynamics, classical chaotic trajectories are sensitive to perturbations of equations of motion caused by numerical errors while it is believed that distributions are much more stable [6]. We show that also classical distributions are affected by such errors and that in general systems, even though on a much smaller scale, quantum propagation is sensitive to numerical precision too. We numerically prove that "dephasing representation" is not. The accuracy of the method will be demonstrated by comparing with the exact quantum calculation. Examples will include a special 100-dimensional system in which exact quantum dynamics is possible [1].

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Computational Chemistry, Lecture **159**

Intrinstic Distortion Path: A Novel Approach in the Analysis of the Jahn-Teller Effect

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The Jahn-Teller (JT) theorem states that a molecule with a degenerate electronic ground state distorts along non-totally symmetric vibrational coordinates. The structural instability is due to an energy stabilization of the respective chemical bonds. This chemical origin of the JT effect is often lost behind complex group theoretcal reasoning. We have analyzed it using the concept of the Intrinstic Distortion Path [1-4]. The JT distortion represents a linear combination of the displacements along all the totally symmetric normal coordinates of the energy minimum structure. Topologically it is given by the projection of the normal coordinates on the distortion.

Inspection of the path of minimal energy from the high symmetry configuration towards the low symmetry energy minimum gives the detailed information on the chemical nature of the coupling between the electron distribution and the motion of the nuclei.

Examples of our work include DFT studies of organic radicals, JT active coordination compounds, JT active metallocenes, etc.

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Computational Chemistry, Lecture **160**

Strong Correlation via Model Hamiltonians and Complete Active Space Wavefunctions

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The description of strong correlation is usually obtained by performing multiconfigurational (MC) calculations, and it is therefore limited to relatively small systems. Most MC methods available today can treat only a relatively modest number of electronic configurations (about few millions), due to the severe scaling of memory and algorithmic requirements. In real cases, like for the study of $Gd_2@C_{60}$ [1], more than a billion configurations are needed to get a result with accuracy comparable to experiment. We will describe here an approach to overcome such limitations, based on the use of Löwdin's partitioning technique [2] to complete active space (CAS) wavefunctions. We obtain a splitting of the configuration space into a principal and an extended part. This approach, that we call *SplitCAS*, has enormous computational advantages, since only the principal part needs to be solved exactly (few thousands configurations), while the effect of the external part is treated perturbatively through a model hamiltonian. The method is therefore suitable for problems where the active space required is too large to be handled by the present CAS-based implementations.

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Computational Chemistry **161**

S-poisoning of Ni/Al_2O_3 catalyst: DFT cluster studies

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Recently, surface modifications on a commercial Ni/Al_2O_3 catalyst during the production of methane from synthesis gas were investigated by *quasi in-situ* X-ray photoelectron spectroscopy (XPS) [1, 2]. Further, we studied the sulphur poisoning processes on the Ni/Al_2O_3 catalyst used for the methanation process [3]. The purpose of this study was to investigate the sulphur deactivation mechanism during an industrial methanation process, but also after catalyst regeneration.

In the present work we extended our computational investigations to study the adsorption of sulphur poisoning compounds on the Ni/Al_2O_3 catalyst. The focus was to study possible catalyst changes and the thus modified catalytical behaviour of the nickel particles, as well as to see differences in the poisoning behaviour, when sulphur adsorbs either on the Ni particle or on the support. This was done using Density Functional Theory calculations (StoBe) with cluster model and non-local functional (RPBE) approach. For modelling the catalyst, an $Al_{15}O_{40}H_{35}$ cluster has been selected representing the γ-$Al_2O_3(100)$ surface, and Ni metal particles of different sizes were cut from a Ni(100) surface and deposited on the $Al_{15}O_{40}H_{35}$ cluster. Several poisoning agents have been found to be stable on both Ni clusters and alumina support such as COS, H_2S, or hydrogen thiocarbonates.

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Computational Chemistry **162**

Dynamics of solvated biomolecules investigated by magnetic linear response properties with the GAPW method

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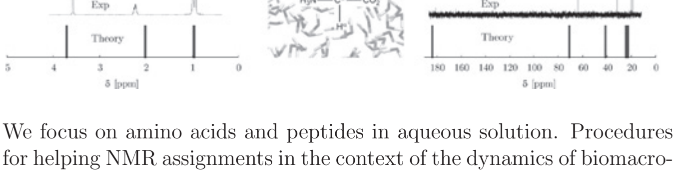
An approach for calculating Nuclear Magnetic Resonance (NMR) chemical shifts based on Density Functional Perturbation Theory [1] combined with the Gaussian and augmented-plane wave method (GAPW) has been recently introduced [2]. For this type of spectroscopy, the core electronic structure plays a crucial role and has to be appropriately modeled. GAPW allows for efficient DFT all–electron calculations of extended systems, thus making the proposed methodology appealing for applications in condensed phase.



We focus on amino acids and peptides in aqueous solution. Procedures for helping NMR assignments in the context of the dynamics of biomacromolecules are still challenging, improvements on this respect would provide insight in phenomena such as ligand binding, enzyme catalysis and protein folding.

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Computational Chemistry **163**

Boron Nitride Nanomesh Interacting with Water and Atomic Hydrogen

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The boron nitride nanomesh is a periodic corrugated structure with a periodicity of 3.22 nm, which is formed by self-assembly through decomposition of borazine on a Rh(111) surface at high temperature[1][2][3]. With DFT structure optimization applied to a slab of four layers of 12×12 Rh(111) and one h-BN layer (13×13 units), we are able to reproduce the corrugation of the nanomesh. STM images and projected DOS also confirm the agreement of our results with the experiment. In close contact to experiment[4], we study water clusters and nano-ice crystals that formed in the pore after dosing different amount of water on the surface at low temperature. The simulation gives insight into the properties of the hydrogen bond network and the role of corrugation in trapping molecules that makes the nanomesh a suitable template for self-assembly.

The interaction of hydrogen with the nanomesh is also reported, showing that intercalation of H can lead to partial or complete flattening of the corrugation. This can be relevant for applications, like hydrogen storage or switching of surface properties. The agreement of our results with the experimental findings [5] demonstrates that our model can be further used to study interactions with more complex molecular systems.

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Computational Chemistry **164**

Tree Monte Carlo

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The development of high performance computers makes more and more computing power available. To use this potential, novel algorithms have to be adopted that display increasing potential for parallelization. In the case of molecular simulations, the scalability of Molecular Dynamics (MD) is ultimately limited, and the step by step integration essentially serializes the procedure. Here, we present a Tree Monte Carlo (TMC) algorithm which allows for calculating many molecular configurations simultaneously. Using a speculative approach, various pathways, accounting for both rejectance and acceptance of proposed moves, can be computed in parallel. Key to this approach is the fact that generating configurations for the Monte Carlo algorithm is cheap and can be performed without computing forces. The TMC procedure respects detailed balance[1], and in fact the sequence of used Monte Carlo moves is independent of the number of simultaneously computed tasks. The parallel efficiency of the TMC algorithm depends on the acceptance probabilities of the moves. Various configurational changes such as atom and molecule translation or molecule rotation have been implemented, and extensions of the scheme to hybrid Monte Carlo and parallel tempering will be explored. Further efficiency gains will come through dynamic process termination and acceptance estimation. Finally, the algorithm is well suited to be implemented in a Fault Tolerant context, which might become essential on future architectures.

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Computational Chemistry **165**

Parallel Sparse Matrix Library for Enabling Quantum Chemical Calculations of Large Systems

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Quantum chemical calculations can be practical for large systems only if the computational time increases at most linearly with the number of atoms in the system.

Sparse matrices are an essential data structure for these calculations because the number of non-zero elements and therefore their storage size is linearly proportional to the number of atoms. These matrices then enable linear algebra operations such as multiplication of two sparse matrices to be performed in linear time. In addition, all operations should run efficiently on massively parallel computers. For this, a balance must be found between memory usage, load balancing, and minimizing the communication cost.

We present a library [1] for sparse matrix storage, manipulation, and the operations needed for quantum chemical calculations on distributed-memory parallel computers. The library also supports contemporary hybrid architectures featuring shared memory nodes. The library has been developed to support linear scaling in the CP2K [2] quantum chemistry program.

We present an efficient way to construct sparse preconditioners that are important in electronic structure minimization algorithms. We also present several quantum chemical calculations that are possible using the sparse matrix library and its applications.

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Computational Chemistry **166**

Evaluation of the nondiabaticity of the quantum molecular dynamics using the dephasing representation of quantum fidelity [1]

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We propose an approximate method for evaluating the importance of non-Born-Oppenheimer effects on the quantum dynamics of nuclei. The method uses a generalization of the dephasing representation (DR) [2,3] of quantum fidelity to several diabatic potential energy surfaces and its computational cost is the cost of the dynamics of classical phase space distributions. It can be implemented easily into any molecular dynamics program and also can utilize on-the-fly *ab initio* electronic structure information. We test the methodology on several model problems including three model problems introduced by Tully and the photodissociation of NaI. The results show that for dynamics close to the diabatic regime the decay of fidelity due to nondiabatic effects is described accurately by the DR. In the nearly diabatic regime, unlike "classical" methods such as surface hopping or Ehrenfest dynamics, the DR can capture more subtle quantum effects than transitions between potential energy surfaces. Hence we propose using the DR to estimate the importance of diabatic coupling elements, spin-orbit interaction terms, or other terms that couple potential energy surfaces. The acquired information can help reduce the complexity of a studied system without affecting the accuracy of the quantum simulation.

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Computational Chemistry **167**

Efficient evaluation of the accuracy of molecular quantum dynamics on an approximate analytical or interpolated *ab initio* potential energy surface [1]

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Ab initio electronic structure methods have reached a satisfactory accuracy for the calculation of static properties, but remain too expensive for quantum dynamical calculations. Recently, an efficient semiclassical method [2,3,4] was proposed to evaluate the accuracy of quantum dynamics on an approximate potential without having to perform the expensive quantum dynamics on the accurate potential [5]. Here, this method is applied for the first time to evaluate the accuracy of quantum dynamics on an approximate analytical or interpolated potential in comparison to the quantum dynamics on an accurate potential obtained by an *ab initio* electronic structure method. Specifically, the vibrational dynamics of H_2 on a Morse potential is compared with that on the full CI potential, and the photodissociation dynamics of CO_2 on a LEPS potential with that on the excited $^1\Pi$ surface computed at the EOM-CCSD/aug-cc-pVDZ level of theory. Finally, the effect of discretization of a potential energy surface on the quantum dynamics is evaluated.

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Computational Chemistry **169**

Predicting heats of formations of highly branched alkanes

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Detailed knowledge of molecular interactions within simple hydrocarbons has profound implications in all aspects of organic chemistry. Within this context, significant advancements have been made in the understanding of hydrocarbon thermochemistry since Rossini's and Nenitzescu's pioneering works of the 1930s.[1,2] The recent concept of protobranching[3] proposes that linear *n*-alkanes are stabilized with similar (although fewer) 1,3-alkyl-alkyl interactions than those present in their more stable branched counterparts. The purpose of this work is two-fold: first, to identify a methodology for computing accurate heats of formations of highly branched alkanes and, second, to use these computed values to probe the energetic effects of various substitution patterns on 1,3-alkyl-alkyl stabilities. A scheme based on computing heats of formation using hyperhomodesmotic reactions is found to perform most satisfactorily, giving an average deviation from experiment of less than 1 kcal/mol for 14 highly branched alkanes. In singly-methylated and permethylated alkanes, all 1,3-alkyl-alkyl interactions (those involving both carbon and hydrogen atoms) are found to be stabilizing, in contrast to the strongly unfavorable $C(CH_3)_3{\bullet}{\bullet}{\bullet}C(CH_3)_3$ interaction found in permethylated alkanes. These values explain the diverging trends seen in total alkane stability.

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Computational Chemistry **168**

A Novel Approach Clarifying the Electronic and Magnetic Anomalies of Norbornene

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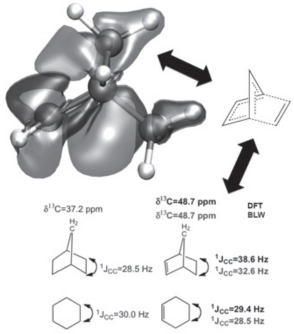
The long-standing mystery surrounding the peculiar electronic structure of norbornene and its derivatives is revealed by the direct comparisons of their properties with those of reference analogues with localized double bonds (i.e. Lewis structures). The latter provide unperturbed reference properties, which can be used directly to probe the effect of pi-conjugation. Our block-localized wave function analysis coupled with the computations of NMR parameters (e.g. chemical shift and $^1J_{cc}$ coupling constants) evidently supports the manifestation of a density redistribution toward an incipient retro-Diels-Alder reaction position.



Computational Chemistry **170**

Synthesis, Characterization, Structure and Theoretical Investigation of Uranium Oxide Material

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Uranyl complex compound, which is stable under normal conditions, was synthesized as convenient single-source precursor for the preparation of uranium oxide material (U3O8). Quantum chemical calculation was performed using Wien2k package based on DFT. The bulk and electronic properties of U3O8 material was calculated using method involving full potential linearized and augmented plane waves (FP-LAPW) in the Generalized Gradient Approximation (GGA). The theory was applied to explain the analytical observations of U3O8. The agreement between theory and experimental results is quite satisfactory.

Computational Chemistry **171**

Calculations of the atomic and electronic structure for YVO4 (001) surface

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We present and discuss results of the calculations for YVO4 (001) surface relaxation with different terminations (YO_8 and VO_4) using ab initio method based on Density Functional Theory (DFT) formalism with different exchange–correlation functionals, including the LDA and GGA. We modeled the surface with a slab of 13 layers thickness. The vacuum spacing between tow repeated slabs are 10 A to ensure no significant interaction between the slabs. The positions of atoms near-surface layers placed atop a slab are optimized. This permits us determination of surface energies and surface electronic structures for different terminations.

Computational Chemistry **172**

A Nonradial Coarse-Grained Potential for Proteins Produces Naturally Stable Secondary Structure Elements

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We introduce a nonradial potential term for coarse-grained (CG) molecular simulations of proteins. This term mimics the backbone dipole−dipole interactions and accounts for the needed directionality to form stable folded secondary structure elements. We show that α-helical and β-sheet peptide chains are correctly described in dynamics without the need of introducing any a priori bias potentials or ad hoc parametrizations, which limit broader applicability of CG simulations for proteins. Moreover, our model is able to catch the formation of supersecondary structural motifs, like transitions from long single α-helices to helix−coil−helix or β-hairpin assemblies. This novel scheme requires the structural information of C_α beads only; it does not introduce any additional degrees of freedom to the system and has a general formulation, which allows it to be used in synergy with various CG protocols, leading to an improved description of the structural and dynamic properties of protein assemblies and networks.

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Computational Chemistry **173**

Can DFT accurately predict the spin-density distributions in iron nitrosyl complexes?

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Transition metal complexes play an important role in catalysis and bioinorganic chemistry. For a detailed understanding of their functions and catalytic mechanisms theoretical analysis has become indispensable. Especially, nitric oxide as an open-shell molecule and noninnocent ligand endows a corresponding transition metal nitrosyl complex with a complicated electronic structure which is difficult to describe by quantum chemical methods. Recently, Conradie and Ghosh have identified a particularly difficult case [1]; salen- and heme-containing iron nitrosyl complexes show remarkable differences in their spin density distributions for different exchange–correlation functionals. To address this problem, we study various density functionals to calculate the spin-density distributions of two iron nitrosyl complexes: Fe(salen)(NO) and Fe(porphyrin)(NO). The origin of these differences can be explained and understood by analyzing the corresponding DFT orbitals. We find that the FeNO fragment represents the most important structural unit in these molecules, and investigate $[Fe(NO)]^{2+}$ as a model system to compare the DFT and CASSCF spin densities. Analysis of the CASSCF wave function with respect to configurations, CI coefficients and natural orbitals allows us to comprehend the distribution of α- and β-electron density, and the CASSCF spin-density profiles yield insights into the reliability of selected density functionals in reproducing accurate spin-densities and describing open-shell systems.

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Computational Chemistry **174**

Computational studies of the binding affinities of Vitamin E to Alpha-Tocopherol Transport Protein

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Vitamin E is a group of 8 different highly lipophilic molecules, 4 tocopherol and 4 tocotrienol molecules. They differ at the substitution of the chromanol ring (Fig.1).

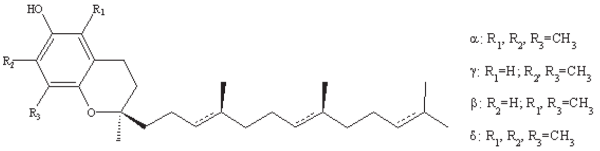

Fig.1: Chemical structure of Vitamin E species.

α-tocopherol transport protein (α-TTP, PDB entries: 1OIZ/1OIP [1]), shows high selectivity for the α-tocopherol molecule with an α/γ ratio higher than 11, where γ is the third best binder tocopherol type [2]. Recent experimental studies show an inverse selectivity when α and γ-tocopherol are bound to a mutant α-TTP, thus, linking selectivity to specific structural features of the binding pocket. Here, we compute the binding affinities of α and γ tocopherol types in the native α-TTP, and the mutated protein, using Free Energy Perturbation (FEP) methods in classical MD simulations.

Our studies allow for the identification of the structural motifs in the binding pocket responsible for the natural selectivity of the two forms of tocopherols.

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Computational Chemistry **175**

Reconstructing the Exact Embedding Potential in Frozen-Density Embedding

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Frozen-density embedding (FDE) [1] strongly relies on the use of approximations for the kinetic-energy component $v_\mathrm{T}[\rho_1, \rho_2]$ of the embedding potential. In the case of weakly interacting subsystems such as hydrogen bonds, an acceptable description is obtained by employing approximations derived from generalized-gradient approximation density functionals. With increasing strength of the interaction, the quality of the approximation decreases and in case of bonds with a covalent character, it entirely breaks down. In order to directly apply the FDE scheme to subsystems connected by covalent bonds, improved approximations to v_T are required. As a first step toward this goal, we have implemented a scheme, proposed by Wu *et al.* [2] and Bulat *et al.* [3], for the numerical calculation of accurate references for v_T. We present accurate embedding potentials for a selected set of model systems, in which the subsystems are connected by hydrogen bonds of various strength (water dimer and F–H–F$^-$), a coordination bond (ammonia borane), and a prototypical covalent bond (ethane). These potentials are analyzed and compared to those obtained from popular kinetic-energy density functionals [4].

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Computational Chemistry **176**

A Quantum Chemical Study of the Mechanism of Dioxygen Induced Inhibition of [FeFe]-Hydrogenase

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Because of [FeFe]-hydrogenase's high activity for catalyzing the formation of molecular hydrogen, this enzyme is attractive for technical hydrogen-based energy production. However, application of [FeFe]-hydrogenases in the field of renewable energies is challenged by their extreme sensitivity against molecular oxygen that irreversibly inhibits these enzymes [1]. We address this key problem of [FeFe]-hydrogenases with density functional theory (DFT) calculations on several experimentally inspired [2] O_2 addition and decomposition reactions at the catalytic center. The presented work is a continuation of the research recently published by our group [3] and discusses also possible decomposition pathways of the [4Fe-4S] cubane cluster upon oxygen attack. Coordination energetics of dioxygen adducts of [FeFe]-hydrogenase, transition state structures and activation barriers for the oxygen induced destruction of the active center, and the role of different spin-coupling schemes at iron centers are considered. The discussion of DFT-error margins for the calculations is also undertaken in order to judge the accuracy of the obtained results. Theoretical investigation of the inhibition pathway of the [FeFe]-hydrogenase active center allows us to identify the crucial steps of the reaction and offers explanation for its, experimentally observed, irreversibility [4].

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Computational Chemistry **177**

Computation of hydrogenation reactions with a VALBOND TRANS force field

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Efficient calculation of transition metal complexes, used as asymmetric catalyst e.g, in hydrogenation reactions, is of major interest in the field of organic chemistry. The creation of a catalyst requires an accurate way to predict relative energies and activation barriers for multiple diastereomers. This can be done either by DFT calculations or, for more efficiency, by the VALBOND TRANS force field,[1] because geometry optimizations can be done in seconds, even in explicit solvent. The progress is, compared to the VALDOND force field of Landis and coworkers[2] that there the trans influence of ligands on bond lengths and relative energies is part of the computations. In the present contribution, the VALBOND TRANS force field is parameterized for model octahedral complexes containing Ir, so that DFT relative energies for different diastereomers can be reproduced. For this, the mulliken charges and the vdW parameters[3] of the Ir-complexes were fitted with INolls[4] to scrutinize the method and the parameters obtained are then used for chemically related compounds to examine their transferability.

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Computational Chemistry **178**

Towards Automated Parameterization of Classical Force Fields from Density Functional Theory/Molecular Mechanics Simulations

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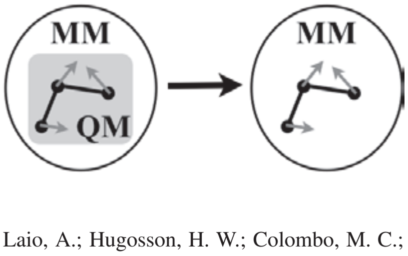
Molecular dynamics (MD) simulations using empirical molecular mechanics (MM) force fields (FFs) have become a standard tool to investigate biochemical systems, because of their computational efficiency compared to full quantum mechanical or hybrid quantum mechanical/molecular mechanical (QM/MM) methods. Protocols to derive FF parameters are usually based on a mixture of calculated quantities determined at different level of theory and experimental values and involve a considerable amount of human effort.

In our protocol [1], based on the force matching algorithm [2], we derive FF parameters from QM/MM simulations in a consistent and automated procedure to reproduce the steric, electrostatic, and dynamic properties of the QM subsystem, allowing simulations with QM/MM accuracy at the computational cost of classical MD. In this contribution the implementation within the CPMD software package and its application to current biochemical problems is presented.



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Computational Chemistry **179**

Combined classical and quantum molecular dynamics simulations shed light into structure and signaling of the rhodopsin photoreceptor.

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Rhodopsin is a prototypical G protein coupled receptor responsible for dim-light vision. Upon photoexcitation, the bound inverse agonist 11-cis-retinal isomerizes inside the binding pocket leading to a cascade of events ultimately causing G-protein activation. The different steps of this activation pathway have been characterized by spectroscoscopic techniques up to milliseconds, showing the presence of several distinct well-characterized photointermediates[1]. However, an atomistic description of the associated conformational changes occurring in the protein has turned out to be elusive and only few structures are available. Combining classical and quantum molecular dynamics simulations, we can follow the conformational changes of rhodopsin up to microseconds, identyfing the distinct photointermediates through their absorption spectra using semiempirical excited states methods[2,3]. Our simulations reveal the structural conformational changes associated to light-induced activation of rhodopsin and shed light into the fascinating mechanism of vision.

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Computational Chemistry **180**

Using Quantum Chemical and Molecular Dynamics Methods to Study Highly Charged Spacies in Solution

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The hydration of transition metals, lanthanides and actinides in aqueous solution is a topic that attracts the attention of many chemist, as this process is of relevance to environmental problems and medicinal applications. By using the NEMO approach [1] have performed molecular dynamics simulations in order to examine structural and dynamical behavior of highly charged ions in aqueous solutions. We try to understand how the coordination of Lanthanides and Actinides depends on the salt concentration. To our knowledge this is the first molecular dynamics simulation study using fully ab-initio potentials of a system containing not only a cation in water, but also the counter-ion.
We present the results of simulations study of solutions containing chloride salts of La^{3+}, Gd^{3+} and Er^{3+} at various concentrations (from 0.05 to 2M). In the $LaCl_3$ case, nine water molecules surround the central La^{3+} cation in the first solvation shell and chloride is present only in the second shell. In the Gd^{3+} case the coordination number is about 8.6 for the lowest concentrations (0.05 and 0.1 M) and then it decreases rapidly. In the Er^{3+} case, the coordination number is 7.4 for the lowest concentrations and then it decreases. The counter-ion Cl^- is not present in the first solvation shell in the La^{3+} case for most of the solutions, while it becomes progressively more present in the Gd^{3+} and Er^{3+} case, even at low concentrations.

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Computational Chemistry **181**

Shielding tensor σ of $^{59}CoCl_xBr_{6-x}]^{3-}$ complexes - a theoretical study

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σ_{iso} in $^{195}PtCl_xBr_{6-x}]^{2-}$ shows a linear behaviour for δ_{iso} vs x. DFT calculations can reproduce this ligand substitution effect and are in excellent agreement with experimental results [1]. Using Ramsey equations [2], Dean and Green [3] showed that the orbital energy gap contributes in PtX_4 platinum halogenides to the platinum chemical shift less than did the covalence of the platinum-ligands bonds.

In this work we are interested in $^{59}CoCl_xBr_{6-x}]^{3-}$ complexes and their behaviour for δ_{iso} vs x. We expect a much smaller contribution of the transitionmetal-ligands bonds for the ^{59}Co σ_{iso} and therefore apply our on LF-DFT [4] based model for the calculation of the shielding tensor σ [5], gaining an insight concerning the importance of the multiplett interaction.

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Computational Chemistry **182**

Molecular Dynamics simulation of the polarity of collagen fibrils

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Collagen fibrils are responsible for piezo- and pyroelectrical properties of connective tissues. Up to date, no structural mechanisms can provide explanation at a molecular level of such peculiar electric features. The structure of collagen is a triple-helix, characterized by the repetition of X-Y-Gly triplets, where X and Y positions are mostly occupied by Prolines (Pro). Hydroxylation of Pro at Y (Hyp) position often occurs in collagen fibrils and this seems to be connected to stabilization of the structure. In our study two models were considered: 1) with all Pro residues in X, Y positions; and 2) with Hyp residues in a central X, Y repeat. Internal fibril regions were modeled by adding N-methyl and Acetyl caps to the termini (neutral systems), while systems without the caps were used to model the whole collagen molecule in general. In total, four systems were generated for both the models. We performed a classical NPT ensemble MD simulations for all the systems considered. Piezoelectricity is investigated by inducing a stresses (shrinking and elongating the fibrils) and pyroelectricity by increasing and decreasing the temperature of the systems. The induced dipole moments will be calculated with careful structural analysis. This information will allow us to find a correlation between electric properties and structural conformations, and a molecular model for the electrical feature of collagen fibrils.

Computational Chemistry **183**

Theoretical study on annulated donor-π-acceptor systems incorporating tetrathiafulvalene and perylenediimide units

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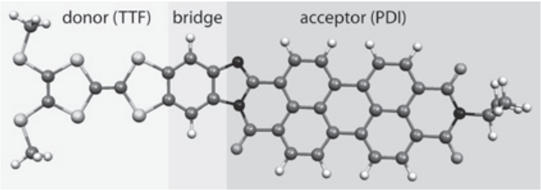
Electron donor-acceptor (D-A) molecules are of prime interest on account of their potential applications in organic (opto)electronic devices. We focus on compactly fused, conjugated D-π-A assemblies comprising tetrathiafulvalene (TTF) and perylene-tetracarboxydiimide (PDI) moieties (see Figure for one example).



We present a theoretical study of two such D-π-A molecules [1,2]. We examined ground- as well as excited-state properties such as electronic absorption spectra with density functional theory (DFT) and the second-order approximate coupled cluster singles and doubles method (CC2).

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Computational Chemistry **184**

Photoabsorption and pump-probe spectra via the dephasing representation of quantum fidelity [1]

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The usual time-dependent approach to the electronic molecular spectroscopy starts from the time autocorrelation function of the quantum dynamics on the excited potential energy surface (PES) V_2 [2]. We reinterpret the autocorrelation function as the quantum fidelity between the dynamics on the excited PES V_2 and the dynamics on the ground PES V_1. Our new interpretation reduces to the standard one for photoabsorption or photodissociation spectroscopy where the initial state is a vibrational eigenstate of V_1, but is more general and also includes, e.g., the pump-probe spectroscopy. Hence any approximation of quantum fidelity can be used to compute photoabsorption and pump-probe spectra. We use the dephasing representation (DR) [3, 4, 5] of quantum fidelity, an efficient on-the-fly semiclassical approximation, for this purpose. The problem of exponential scaling with dimensionality of quantum dynamics is avoided in the DR: It will be shown that the number of trajectories required is approximately independent of the number of degrees of freedom [4, 6]. In fact, it will be shown that the DR approach to pump-probe spectra is faster computationally than both quantum and classical calculations. The accuracy and efficiency of the method will be tested on several systems for which exact quantum calculations are possible.

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Computational Chemistry **185**

Optical properties of multisubstituted corannulene by first principles

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Corannulene is a conjugated aromatic molecule, C_{5v} symmetric, consisting in a central pentagon fused with 5 hexagonal rings. It has a bowl curvature of 0.87 Å, with a bowl-to-bowl inversion barrier of about 11.5 Kcal/mol and a permanent dipole of 2.1 db. The possibility of functionalizing the molecule by attaching different substituent groups (-alkyl, -aryl, -alkynyl) to the external rings alters the bowl-depth/barrier to interconversion, enabling tuning of the electronic properties. Recently, [1] it has been shown that various phenyl-ethynyl substituted corannulenes display high-quantum-efficiency solution luminescence and variable emission wavelengths depending on the nature of the substitution. In this work we investigate the optical properties of multisubstituted corannulene by means of state of the art electronic structure approaches based on GW-BSE theory [2]. The proper inclusion of screening and correlation effects enables to individuate the main optical transitions of the systems by the investigation of the excitonic nature of the optical spectra. The calculated spectra reproduce quite well experimental results helping in their interpretation.

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Computational Chemistry **186**

Computational determination of pKa

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Proton transfer reactions are ubiquitous in both chemistry and biochemistry. Consequently, a first principles prediction of pKa is of broad interest, and considerable efforts have been made in the last decade to achieving this and producing a generally applicable approach. The biggest hurdle for a first principle calculation of pKa is accurate determination of solvation phase energies. The first solvation shell contribution is particularly significant for proton transfer reactions and consequently Dielectric Continuum Solvation Methods (DCSM) are inherently unable to provide the desired accuracy. A hybrid solvent approach, referred to as a continuum cluster method or an implicit/explicit method, has gained increasing attention as a compromise between a full DCSM and a Moleculer Dynamics approach. The general concept is that a small number of solvent molecules (i.e n=1 – 3) are positioned around the solute to imitate the first solvation shell and then the resulting cluster is then calculated with a DCS method. However, determination of the number and positioning of the water molecules becomes challenging. In this work, we show results of a systematic cluster continuum study that enables accurate determination of pKa without the need to use a thermodynamic cycle or other error caneellation scheme, and shows patterns which offer guidance for number and placement of explicit solvent molecules in the first solvation shell.

Computational Chemistry **187**

Theoretical Modeling of Nucleobase Stacks in Solution with Dispersion-Corrected DFT

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Stacking interactions, which involve weak non-covalent dispersion interactions, are among the more challenging binding interactions to model accurately using computational methods. However, these sensitive interactions are of great importance to studying many biological systems such as DNA helical stacking, formation of RNA structures, and non-covalent protein interactions. Among the techniques to achieve an improved treatment of these sensitive interactions are density functional theory (DFT)-D methods, which include a semi-empirical correction term that is often able to capture these long-range interactions and still benefit from DFT's relatively low computational cost. In this study, calculations are conducted using the GAMESS computational suite to compare the relatively recent DFT-D approach to that of a new generation, referred to as DFT-D3, which no longer rely on a preparametrized set of coefficients to account for dispersion effects. The enhanced performance of this new DFT-D3 methodology is demonstrated via the analysis of interaction energies of stacked nucleobase systems of varying complexity. Further, these stacking interactions are compared with and without treatment of solvent effects, using a polarizable continuum model.

Computational Chemistry **188**

In silico identification of the toxic potential of drugs and chemicals

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The early recognition of the toxic potential of drugs, pharmaceuticals, industrial chemicals, food and cosmetic additives represents an important task to meet the legal safety requirements. The *VirtualToxLab*[1] developed at the Biographics Laboratory 3R and the University of Basel is a fully automated protocol for the *in silico* identification of endocrine and metabolic disruptors among drugs, chemicals and natural products.

In the *VirtualToxLab*, the toxic potential of small-molecule drugs or chemicals is evaluated based on their binding affinity calculated towards 16 protein targets known to trigger adverse effects: nine members from the nuclear receptor family (AR, ERαβ, GR, LXR, MR, PPARγ, TRαβ), the aryl hydrocarbon receptor (AhR), five enzymes of the cytochrome P-450 family (1A2, 2A13, 2C9, 2D6, 3A4) and the human ether-à-go-go related gene potassium channel (hERG).

For each target the binding mode is identified using a state-of-the art computational approach featuring pharmacophore alignment, automated flexible docking and multidimensional QSAR. The underlying algorithm allows for multiple binding modes, the simulation of induced fit and the consideration of entropic and solvent effects. The models were trained using 1,240 compounds and tested with 2,500+ compounds. Each QSAR model was validated by an external data set, y-scrambling and consensus scoring.

For a modest fee, the *VirtualToxLab* is accessible over the Internet. In contrast to other approaches in the field, it allows to verify a prediction at the molecular level by interactively inspecting the binding mode of the tested compound towards all targets in real-time 3D.

[1] http://www.virtualtoxlab.org

Computational Chemistry **189**

Oxygen Dynamics and Migration Pathways in Truncated Hemoglobin

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Truncated hemoglobin (trHbN) is a protein involved in NO dioxygenation [1,2] by converting nitric oxide to harmless nitrates $(Fe(II)O_2 + NO \rightarrow Fe^+(III) + NO_3^-)$. The tunnel system of trHbN plays an important role in determining and controlling ligand entrance, migration, and rebinding.[2] Due to a greater affinity of Fe(II) for NO than for O_2, the first step of dioxygenation is expected to be the substitution of NO ligated to the heme group by free O_2 $(Fe(II)NO + O_2 \rightarrow Fe(II)O_2 + NO)$. The three-point fluctuating charge model of NO, that reproduces accurately the dipole and quadrupole moments, has proven to be necessary for the identification of docking sites.[3] A similar model for O_2 is thus devellopped and implemented in CHARMM. Molecular dynamics simulations of oxygen dynamics and migration in trHbN of *Mycobacterium tuberculosis* are studied with different models. Multiple extended trajectories are run from separate snapshots to sample efficiently all the accessible states inside the protein. From these trajectories, the structural and energetic properties of the ligand docking sites in the protein are characterized and a connectivity network for the ligand docking sites is built. Migration and exit pathways are analyzed in detail.[3]

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Computational Chemistry **190**

Gaussian Delocalized Charge Approximation for the Computation of NMR Properties

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NMR is a fundamental tool in modern science and the computation of NMR parameters can aid in reasoning experimental results as well as make predictions.

To compute NMR properties of large systems (e.g. proteins) approximations have to be used due to the atom number limitations of *ab initio* methods. Within the QM/MM scheme, parts of the molecule (or system) being studied are replaced by single point charges. However, these charges overpolarize the wavefunction and are inadequate for the computation of the shielding tensor components.

We present and discuss the implementation of a gaussian delocalized charge approximation applied to the computation of NMR chemical shifts. In this method, point charges are replaced by smeared charges, which are better approximations to the electrostatic behaviour of atoms. This improved description leads to more accurate computations of the NMR properties.

ATP is used as a benchmark system. Our approximation, along with standard QM/MM methodology using point charges, is compared to full QM computations. Significant emphasis is put on the shielding tensor components, fundamental in solid state NMR, which are innacurately described by the current QM/MM methodology.

Our approximation offers a cheap, accurate and efficient alternative to the full QM computations, too expensive for extended systems.

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Computational Chemistry **191**

Efficient use of RNA folding in microRNA target prediction: RNA-RNA recognition relies more on evolutionary pressure than on thermodynamic stability

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Among the recently discovered small RNAs that regulate gene expression through base pair complementary with their targets, miRNA in animals are characterized by an incomplete complementarity along the resulting duplex. Considering accessibility of the 3'UTR is known to reduce the false discovery rate of miRNA target predictions. Little has however been said about the correct use of such information or about the actual improvement in precision offered by using either the minimum free energy structure or the canonical ensemble of secondary structures. We show that, contrary to common belief, ranking according to the difference between the opening and hybridization energies, used in currently available algorithms [1,2], is not an efficient way to rank predictions. Instead, we introduce a miRNA target prediction algorithm which also considers only the accessible binding sites but which ranks predictions according to overrepresentation [3]. The resulting method is applied to experimentally tested predictions in the fruit fly and human: our algorithm shows considerable improvement not only in precision but also in the computational cost in comparison with the free energy based methods. Furthermore, using a common statistical framework [3] we demonstrate explicitly the advantages of using the canonical ensemble of secondary structures instead of using the minimum free energy structure alone.

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Computational Chemistry **192**

Cross-Conjugation: A Lost Case ?

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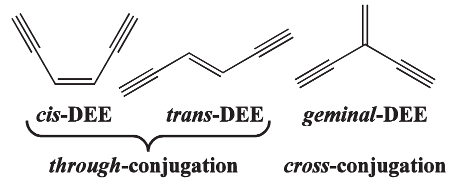
Cross-conjugation, even though very common in chemistry, has only sparsely been visited by experiment or by theory. Until very recently, this form of conjugation was considered to be much less able to promote electron delocalization than through - conjugation. Therefore, exploiting cross - conjugation to design new materials was considered difficult and not very promising.



Here we show that this view, at least for neutral molecules in their electronic ground state, is essentially correct. For cross-conjugated radical ions the situation is different: there is appreciable charge delocalization across the bifurcation point, *i.e.* the point where the two conjugated branches meet. Simple Hückel molecular orbital considerations show that the connectivity pattern encountered in cross-conjugation will lead to enhanced electron delocalization effects. This observation, confirmed by density functional calculations, also applies for electronically excited species. Therefore, cross - conjugation may be exploited to build molecular switches or may be used to design devices such as molecular transistors [1].

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Computational Chemistry **193**

Enveloping Distribution Sampling: Estimation of Multiple Free Energy Differences from a Single Simulation

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Enveloping distribution sampling (EDS) allows the estimation of multiple free energy differences from a single simulation by construction of a reference state, which envelopes the regions of phase space important to the various end states of interest. The Hamiltonian of the reference state can be adjusted using two kind of parameters, ensuring optimal sampling. The parameters are the smoothness parameter s, which decreases the barrier between the end states, and the energy offset parameters, which allow equal sampling of all end states. These parameters can be derived in an automatic iterative procedure, but convergence depends on various aspects like the number and distance between the end states, or the initial parameters chosen. Here, the relative free energies of 17 disubstituted benzene derivatives in water are calculated using different initial values for the smoothness parameters and the energy offsets and simulation conditions (NVT and NPT). The results are compared to those of thermodynamic integration (TI) simulations. A very good correlation between TI and EDS free energy differences is observed, while the EDS simulations require much lower computational time than TI simulations. It seems thus that EDS is an efficient alternative to TI simulations.

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Computational Chemistry **194**

Investigation of Blue Light Photoreceptors Using Molecular Dynamics - The AppA BLUF Domain

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The antirepressor protein AppA is present in a number of bacterial and algal species. It regulates the blue light photosynthesis gene expression in *Rhodobacter sphaeroides.* The photoactive part of the protein is formed by the BLUF (Blue Light Utilising Flavin) domain. The conformation of the dark state of the BLUF domain has been a matter of intense discussion during the past years. Two contradicting X-ray structures of the dark state have been published [1, 2], see Figures 1 and 2.
In this study we investigated the two proposed dark state conformations of the AppA BLUF domain using molecular dynamics simulations.

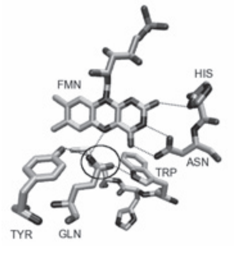

Figure 1: Binding pocket conformation proposed by Anderson et al.

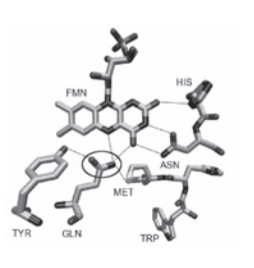

Figure 2: Binding pocket conformation proposed by Jung et al.

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Computational Chemistry **195**

Complete-Graph Tensor Network Expansion for the Electronic Wave Function of Molecules

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Over the last decade, we have witnessed the rise of the Density Matrix Renormalization Group (DMRG) algorithm which had a tremendous impact on the fields of condensed matter and quantum chemistry [1,2].
The understanding of the DMRG wave function laid the foundations for a new family of states, the tensor network states (TNS). The basic idea of tensor network states is to approximate ground-state wave functions of strongly correlated systems by breaking down the complexity of the high-dimensional coefficient tensor of a full configuration-interaction (FCI) wave function.
We present a new class of states which we denote Complete-Graph Tensor Network (CGTN) states and employ them to represent electronic wave functions of molecular systems in the framework of quantum chemistry [3]. The CGTN states provide an efficient and compact description of the ground state in terms of variational parameters compared to a FCI wave function. We assess CGTN states for the spin splitting of methylene, for the strongly correlated ozone molecule, and for a high-spin transition metal complex, $[\mathrm{Co(II)(H_2O)_4}]^{2+}$.

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