Medicinal Chemistry   **85**

New C-glucosylxanthones from the leaves of *Arrabidaea patellifera* (Bignoniaceae)

F. Martin[a], A.E. Hay[a], S. Vargas[a], L. Vivas[b], M.P. Gupta[c] and
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[b]London School of Hygiene and Tropical Medicine, Department of Infectious and Tropical Diseases, Keppel Street, London WC1E 7HT, UK
[c]Center for Pharmacognostic Research on Panamanian Flora (CIFLORPAN), College of Pharmacy, University of Panama, Panama

As a part of our ongoing investigations on Panamanian Bignoniaceae [1], seven methanolic extracts from six plants were submitted to a β-hematin polymerization inhibition test [2]. This reaction is one of the possible targets in the fight against parasites of the genus *Plasmodium*, responsible for malaria. The extract from the leaves of *Arrabidaea patellifera* (Schlecht) Sandw., a liana which grows from lowlands to mountain forest, was selected because of its good activity, corroborated by an *in vitro* test against *Plasmodium falciparum*. Moreover, this plant has never been investigated before.

The extract was first fractionated by vacuum liquid chromatography (VLC) and then by medium pressure liquid chromatography (MPLC). It afforded directly mangiferin and four of its derivatives, new C-glucosylxanthones, all active *in vitro* against *P. falciparum*. Further chromatographic separations gave other compounds, of which the identification is underway.

The structures were determined by means of spectrometric methods, including 1D and 2D NMR experiments and MS analysis.

[1] F. Martin, A.E. Hay, L. Corno, M. P. Gupta, K. Hostettmann, *Phytochemistry*. **2007**, in press
[2] K. K. Ncokazi, T. J. Egan, *Anal. Biochem.* **2005**, *338*, 306-319

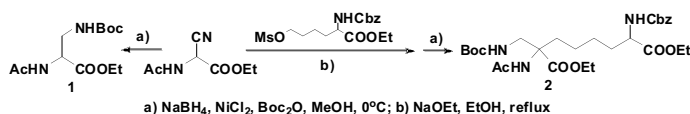Medicinal Chemistry   **87**

A New Protocol to the Syntheses of α,β-Diamino Acids

Y. Liu[1], P. Schmutz[1], M. Bauwens[2], J. Mertens[2], R. Alberto[1]

[1]Institute of Inorganic Chemistry, University of Zurich Winterthurerstr. 190, CH-8057 Zurich, Switzerland [2]Radiopharmaceutical Chemistry, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussel, Belgium

α,β-Diamino Acids have attracted the interests from both organic chemists and biochemists through years, because of its unique structural and ubiquitous role playing in biologically active compounds. Moreover, it has been demonstrated that the α,β-diamino acid can be used as efficient tripodal ligand for the labelling of Re(I)/Tc(I) tricarbonyl, the corresponding hydrophilic compound of which is stable to air and competition from cysteine or histidine. However, in the radiopharmaceutical context, only after being coupled to other biomolecules, could α,β-diamino acids be feasible for the further application [1].

Here we report a new method for the preparation of α,β-diamino acid, which entails also the convenient syntheses of α,β-diamino acids derivatized at α-position. The deprotected **2** formed stable Re(I)/Tc(I) tricarbonyl complex, which can be recognized and transported into a cell by LAT1 [2].

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Medicinal Chemistry   **86**

Analyses and bioactivities of wild populations of *Rhodiola rosea* L. (Crassulaceae) from Switzerland

D. van Diermen, A. Marston, K. Ndjoko and K. Hostettmann

Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland

Rhodiola rosea L., also known as "Golden root", has been used for centuries in the traditional medicine of Eastern Europe and Asia. It has been classed as an adaptogen by Russian researchers due to its ability to increase resistance in humans to a variety of stressors.

According to the Soviet Pharmacopoeia (RFMHMI 1983), extracts of *Rhodiola rosea* L. are now standardized in both rosavin (min. 3%) and salidroside (min. 1%) content [1].

The efficacy observed in clinical studies is due to the synergistic activity of these two metabolites and other active ingredients.

An efficient analytical method by HPLC-UV/DAD was developed to quantify rosavin and salidroside in the roots of four wild populations of *R. rosea* L. coming from the same area in Switzerland. The analyses were performed in order to observe the variability in the populations, and to establish the dynamics of their rosavin and salidroside content over a one year period. The results obtained after the analysis of 20 samples will be useful in the selection of the most appropriate population for large scale cultivation.

Acetylcholinesterase-inhibitory activity was observed due to the presence in the plant of linoleic acid and cinnamic alcohol.

Further investigations on *R. rosea* are underway in order to discover new biological activities, especially in the area of depression (inhibition of monoamine-oxidase).

[1] Khanum F., Bawa A. S., Singh B*., Comp Rev Food Sci Food Safety*, **2005**, *4*, 55-62.

Computational Chemistry   **88**

DFT Study of Jahn-Teller Effect in Cobaltocene

Matija Zlatar[1,2], Emmanuel Penka Fowe[1], Carl-Wilhelm Schlapfer[1], Claude Daul[1*]

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[2]Center for Chemistry, IHTM, University of Belgrade, Njegoševa 12, P.O. Box 815, 11001 Belgrade, Serbia

The detailed analysis of Jahn-Teller (JT) effect in bis - cyclopentadyenyl-cobalt(II) - cobaltocene (CoCp₂), is given. Descent in symmetry goes from D_{5h} (eclipsed conformation of the two rings) to C_{2v}. The electronic ground state, $^2E_1''$, splits into $^2A_2$ and $^2B_1$. We have used the method developed by Daul et al. [1] for the calculation of the ground-state JT stabilization energy (E_{JT}) and the resulting properties of a JT-active molecules by DFT. The adiabatic potential energy surface is described by three parameters (E_{JT}, Δ and R_{JT}) which are related to the Bersuker's description [2] of $E \otimes e$ problem (K_E, F_E, G_E - force constant, first and second order vibronic coupling constants respectively). We obtained $E_{JT} = 750 - 850 \ cm^{-1}$ (depending on the basis set and functional used) which is in agreement with experimentally estimated value of $1010 \ cm^{-1}$ [3]. There is no second order JT effect. The geometry changed mainly in the Cp rings. The results are interpreted by group theory, in both, the high, D_{5h}, and the low, C_{2v}, symmetry. In D_{5h}, the problem was considered as a multimode $E \otimes (\sum_i e_i)$ and in a C_{2v} as a multimode $(^2A_2 + ^2B_1) \otimes (\sum_i a_i)$ vibronic interactions. The contribution of the totally symmetrical vibrations in C_{2v} to the E_{JT} was analysed.

[1] R. Bruyndockx, C. Daul, P. T. Manoharan, E. Deiss, *Inorg. Chem.*, **1997**, *36*, 4251-4256.
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Medicinal Chemistry   85

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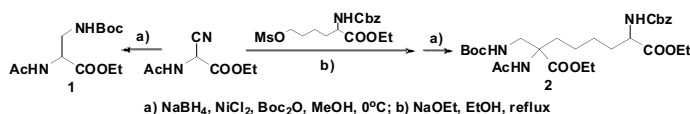
Medicinal Chemistry   86

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Medicinal Chemistry   87

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Computational Chemistry   88

DFT Study of Jahn-Teller Effect in Cobaltocene

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[3] R. Bucher, *ESR-Untersuchungen an Jahn-Teller-Aktiven Sandwitchkomplexen*, PhD Thesis, ETH Zuerich, **1977**.

Computational Chemistry **89**

Electronic Structure of the Ni/γ-Al₂O₃ Catalyst: DFT Cluster Model Study

Izabela Czekaj, Jörg Wambach, Alexander Wokaun

Paul Scherrer Institute, CH-5232 Villigen PSI, Switzerland

The molecular structure of Ni/γ-Al₂O₃ catalyst used during methanation of synthesis gas was investigated using DFT method with a non-local functional [1]. The several Ni-compounds such as Ni, NiO and Ni₃C as well as γ-Al₂O₃ surfaces were considered. Furthermore, the geometric and the electronic structures of Ni deposited on γ-Al₂O₃ system were studied in details. The theoretical studies are presently used to help with understanding more detailed surface modifications during methanation and reasons of a nickel particles detachment together with a carbon whiskers formation in specific fixed bed conditions.The Ni/γ-Al₂O₃ catalyst in different state of methanation consists of several Ni-compounds such as Ni, NiO and Ni₃C, which was suggested by previous experimental studies [2, 3]. Our findings about electronic structure suggest that the nickel carbide is supposed to be less reactive then pure nickel or nickel oxide. The nickel adsorbs at Al₂O₃ (100) surface in the hole position between surface oxygen centers. The nickel deposition influences electronic properties of the Al₂O₃ surface by modification of both oxygen and aluminum centers. The Ni dopes electrons to the system, which leads to increase of a negative charge of oxygen centers. The visible asymmetry in Ni deposition at Al₂O₃ (100) surface suggests that the Ni would prefer localization at AlO₄ tetrahedrons.

[1]   I. Czekaj, J. Wambach, A. Wokaun, *Annual Report, Electrochemistry Laboratory PSI* 2006, 12.
[2]   I. Czekaj, F. Raimondi, J. Wambach, A. Wokaun, *Annual Report, Electrochemistry Laboratory PSI* 2005, 42.
[3]   F. Raimondi, M. Seemann, S. Biollaz, J. Wambach, A. Wokaun , *PSI Scientific Reports* 2003, 5, 116.
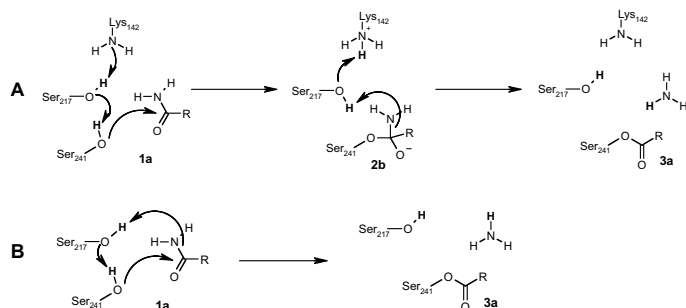
Computational Chemistry **90**

Equilibrium geometries of non-covalently bound intermolecular complexes derived from subsystem formulation of density functional theory

Marcin Dułak[a], Jakub W. Kamiński[a,b] and Tomasz A. Wesołowski[a]

[a]Université de Genève, Département de Chimie Physique 30, quai Ernest-Ansermet, CH-1211 Genève 4, Switzerland
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The equilibrium geometries of the noncovalently bound molecular complexes have been obtained using subsystem formulation of density functional[1] theory applying proposed efficient optimization algorithm. The representative set of molecules is chosen and divided into hydrogen-, dipole- and weakly-bounded spices as proposed by Truhlar[2] for a comparisions standart, where accurate ab-initio benchmark data are available. We have also tested performance of two different ways of approximating the exchange-correlation- and non-additive kinetic energy parts of total energy. The non-empirical local density approximation (LDA) leads to excellent equilibrium geometries and interaction energies with accordance to reference data in all of the studied three sets. The best results are obtained for the set of hydrogen bonded complexes where the maximal error in distance between subsystems reach 0.13 Å for NH₃-NH₃[3]. The applicability of the chosen generalized gradient approximation is limited to cases where LDA fails, which compromises molecules involving π-π stacking such as benzene dimer, which is also confirmed by our previous studies[4].

[1]   P. Cortona, *Phys. Rev.*, **1991**, *44*, 8454.
[2]   D. G. Truhlar, Y. Zhao, *J. Chem. Theory Comput.*, **2005**, *1*, 415.
[3]   M. Dułak, J. W. Kamiński, T. A. Wesołowski, *J. Chem. Theory Comput.*, in press,
[4]   T.A . Wesolowski, F. Tran, *J. Chem. Phys.*, **2003**, *5*, 2072.

Computational Chemistry **91**

Elucidation of the mechanism of hydrolysis by fatty acid amide hydrolase (FAAH) from QM/MM simulations

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[†]Auburn University; [*]Yale University.

FAAH is a serine hydrolase and a potential therapeutic target for some neurological disorders. It is remarkable for hydrolyzing amides and esters with similar rates; however, the normal preference for esters reemerges when Lys142 is mutated to alanine. To elucidate the hydrolysis mechanisms and the causes behind this variation of selectivity, QM/MM calculations using Monte Carlo simulations and free energy perturbation theory were carried out to obtain free-energy profiles for various mechanisms for the formation of the acyl intermediate from the Michaelis complex, using oleamide as the substrate. For wild-type FAAH, the results support a two-step mechanism, **A**, which involves activation of the nucleophile by indirect proton abstraction by Lys142 via Ser 217. For the mutant, a striking concerted mechanism, **B,** is proposed. Support comes from the free-energy results, which well reproduce the observation that the Lys142Ala mutation in FAAH decreases the rate of hydrolysis for oleamide significantly more than for methyl oleate.

Computational Chemistry **92**

The Concept of Protobranching and its DFT Treatments

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[a]Department of Chemistry and Center for Computational Chemistry, University of Georgia, Athens, Georgia, USA 30602
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Branched alkanes like isobutane and neopentane are more stable than their straight chain isomers, *n*-butane and *n*-pentane (by 8.6 and 21.1 kJ/mol, respectively) due to the greater number of stabilizing 1,3-interactions. There are three 1,3-interactions in isobutane but only two in *n*-butane. We call such attractive 1,3-interactions "protobranching" [1]. Protobranching also stabilizes all *n*-alkanes relative to ethane (which has none). There is one in propane, two in *n*-butane, etc. Accurate computational treatments of protobranching are essential when assessing the energies of physical organic concepts.
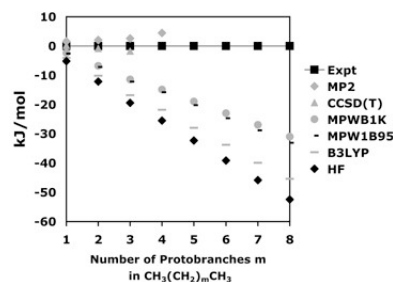
While correlated methods such as CCSD(T) do account for this stabilization, DFT methods systematically underestimate protobranching interactions for *n*-alkanes, branched alkanes, and saturated hydrocarbon cages [2].

[1] M. Wodrich, P.v.R. Schleyer *et al.* submitted to *Chem. Eur. J.*
[2] M.Wodrich, C. Corminboeuf, P.v.R. Schleyer *Org. Lett.* **2006**, *8*, 3631.

Computational Chemistry **93**

Rebinding Molecular Dynamics Simulations of Nitric Oxide to the V68FMyoglobin Mutant

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The study and modelling of reactive processes in chemically and biologically relevant systems has been always an interesting scientific topic. Here, an atomistically detailed picture of NO rebinding from myoglobin V68F is presented. Using reactive molecular dynamics [1] the rebinding probability as a function of time after dissociation is calculated. Reactive molecular dynamics considers two intersecting potential energy manifolds which dissociate to different adiabatic states. During the simulations, crossings are detected by monitoring an energy criterion and the surfaces are mixed over a finite number of time steps. The unbound surface (Fe...NO) is a standard force field, whereas the bound surface (Fe-NO) is based on ab initio calculations. The rebinding is nonexponential in time, in agreement with experimental studies [2] and can be described using two time constants. Particular emphasis is paid to the asymptotic separation Δ between the two potential energy manifolds. An extension of the original reactive molecular dynamics approach with a conformationally varying Δ is discussed and implemented. The advantages and the results of the conformationally dependant and conformationally independent Δ - function implementations are analized and compared.

[1] D.R. Nutt and M. Meuwly, *Biophys. J.* **2006**, *90*, 1191.
[2] Y. Wang, J.S. Baskin, T. Xia and A.H. Zewail, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, *52,* 18000.

Computational Chemistry **94**

An efficient dual-topology scheme for free-energy calculations

Teodoro Laino*, Guillaume Lamoureux†, Juerg Hutter*

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Free energy perturbation simulations play a vital role in understanding chemical processes that occur in the condensed phase because they deal with thermodynamic quantities which are independent of the time scale of the studied processes.

Of particular interests are the so called *alchemical* free energy simulations in which one chemical species is transformed reversibly into another using a coupling parameter λ. Relying on the fact that free energy differences are independent of the coupling path, many methodological approaches have been proposed to solve this problem[1]. All of them make assumptions on specific kind of Hamiltonians making the scheme itself not general and often difficult to be exported to other kind of problems.

In this work we propose a combination of the standard dual-topology-dual-coordinate technique[2] with an umbrella potential[3] in order to compute free energy differences. Since no assumptions have been made about the nature of the two Hamiltonians, the method shows a general applicability going from classical molecular mechanics simulations up to fully *ab initio* simulations. The presence of the umbrella potential fixes the problems of the statistical sampling at the critical point of $\lambda = 0$ and $\lambda = 1$. The method has been implemented as a module of the CP2K[4] suite of packages and applications will be shown in the field of *ab initio* simulations.

[1] A.Pohorille, C.Chipot (Eds.),*Free Energy Calculations*, **2007**
[2] S.Boresch, M.Karplus,*J. Phys. Chem. A*, **1999**, *103*, 103-118
[3] G.M.Torrie, J.P.Valleau,*J. Comp. Phys.*, **1977**, *23*, 187-199
[4] http://cp2k.berlios.de

Computational Chemistry **95**

Ab initio molecular dynamics simulation of liquid water

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Maurício D. Coutinho-Neto[3], and Ursula Rothlisberger[1]*

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The ubiquity of water invariably leads to its important roles in most biological, chemical and environmental processes. Yet, despite extensive studies, its microscopic nature, which could be of help in understanding these processes, remains elusive. Precise knowledge of the intermolecular interactions in water will faciliate a better understanding of this ubiquitious substance.

Here, we employed Car-Parrinello molecular dynamics with DFT-BLYP to probe the structural and dynamical properties of water. The poor description of weak interactions in DFT-BLYP, which may be one of the possible causes for the overstructuring observed in DFT-BLYP water, is remedied using dispersion corrected atom centered potentials [1]. Properties such as radial distribution functions, mean square displacements, molecular dipole moments, and hydrogen bond statistics will be presented.

[1] O. A. von Lilienfeld et al., *Phys. Rev. Lett.*, **2004**, *93*, 153004.

Computational Chemistry **96**

Structural Assignment of Spectra by Characterization of Conformational Substates in MbCO.

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Residue motions of the distal heme pocket of the oxygen-storing protein Myoglobin have been shown to influence protein function, control ligand rebinding rates [1], and have been implicated in ligand recognition [2]. For carbonmonoxy Myoglobin (MbCO) both the ligand bound (MbCO, A-state) and unbound (MbCO, B-state) have been characterized by x-ray crystallography. Because ligand binding and unbinding are transient processes in nature, it is difficult to experimentally characterize both structural and dynamic properties of the system. Atomistic simulations using validated force fields provide additional insight [3,4]. In further studies [2,5], Molecular Dynamics simulations have linked theoretical motions of residues within the heme pocket to changes in observed spectroscopic A-states. The distinct A-states of the bound CO ligand were attributed to different orientations and protonation states of the adjacent HIS64 moiety. Here we characterize the bound states A0, A1 and A3 using a combination of molecular dynamics simulations and Density Functional Theory calculations. Calculated absorption bands were derived from different configurations for comparison with experimental results. The experimental data is then used to guide refinement of the original CHARMM model. Particular attention is paid to the charge model of the bound CO ligand, key to representing interaction with the local binding site.

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[2] A. Loccisano, O. Acevedo, et al., *J. Mol. Graph. Model.*, **2004**, *22*, 369.
[3] D. Nutt, M. Meuwly, *PNAS*, **2004**, *101*, 5998.
[4] M. Meuwly, *Chem. Phys. Chem.*, **2006**, *7*, 2061.
[5] C. Rovira, B. Schulze et al., *Biophys. J.*, **2001**, *81*, 435.

Computational Chemistry

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Ab Initio Surface-Hopping Dynamics of Ethyl Radical

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Ethyl radical is an important intermediate in hydrocarbon crackers and combustion processes, playing a central role as the principal precursor to ethylene through loss of a hydrogen atom. Two recent studies[1,2] of the dissociation dynamics of ethyl have found that highly excited radicals can dissociate with a fast and a slow component, with the slower component decaying four to five orders of magnitude more slowly than predicted by Rice–Ramsperger–Kassel–Marcus RRKM theory, even though the 5-eV excitation energy far exceeds the 1.6-eV barrier to dissociation.
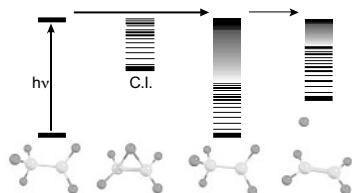
The anomalous and unexpected kinetic behaviour is investigated by on-the-fly CASSCF nonadiabatic dynamics[3] to model the fast decay of the first excited state through a conical intersection. The simulations result in an excited state lifetime of 27 fs, bimodal product energy distributions and show no isotopic scrambling of the reaction products. These results stand in good agreement with experimental findings.[1,2]

Further simulations apply MRCI values to incorporate effects of dynamical correlation.

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Computational Chemistry

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Ab-initio dynamics of the adsorption and reactivity of ketones on Pt(111)

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Heterogeneous catalysis occurs at the interface between a surface and a gas or a liquid, and very often the mechanisms at the base of such chemical transformations are not known. Experimental techniques for the analysis of surface phenomena exist but often fail to yield critical details of the reaction pathway. One very important class of heterogeneous reactions for which detailed mechanistic insight is not available are hydrogenations on transition metals, broadly used in both industrial and fine chemical synthesis. In this contribution an *ab-initio* molecular dynamics study of the adsorption and reactivity of differently substituted ketones is presented, which aims at clarifying surface reaction intermediates, transition states of the reaction, together with the effect of α-substitution on reaction parameters.

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Computational Chemistry

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Solid-Solid Phase Transitions: Nanointerface Reactivity and Formation of Metastable Phases

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Finding new pathways to novel materials is an open challenge in modern solid state chemistry. Metastable phases are in this respect a powerful point of access to new materials. Thus a precise atomistic understanding of the reactivity in the solid state, in its many facets (critical processes with phase coexistence, reactivity of interfaces, nucleation patterns), is mandatory. Recently we have started a systematic theoretical study of phase transitions with first order thermodynamics [1-3] to reach a firm understanding of the atomistic mechanisms behind polymorphism in solid state. A clear picture is emerging of the interplay between nucleation patterns, domain interface reactivity and final material morphology [4]. Therein intermediate metastable phases with distinct atomic patterns are identified. CdSe, CaF$_2$ and AgI are three different examples of reactivity governed by nanointerfaces. We have investigated CdSe in a set of simulations and experiments [5,6]. TEM experiments combined with computer simulations unfold the composite nature of the material after application of pressure. Low dimensional nanosurfaces formed under pressure are responsible for the recrystallization of the fluoride sublattice in CaF$_2$ [6]. Metastable phases are formed at interfaces in AgI during pressure or temperature induced phase transitions [6]. Therein stacking disorder enhances the mobility of silver ions.

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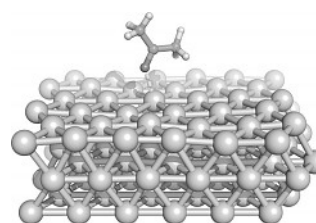[6] S.Leoni, *in preparation*.

Computational Chemistry

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Theoretical investigation of infrared spectra and pocket Dynamics of Photodissociated Cabonmonoxy Neuroglobin

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Neuroglobin (Ngb) is a small globular protein, expressed in the brain of man and mouse. which can bind ligands such as oxygen, carbon monoxide (CO) and nitric oxide at a heme prostetic group. The X-ray structure, which was solved in 2003 [1], shows some particular features which distinguish Ngb from other members of the globin family [2]: The proximal histidin (His-96) can bind to the heme-iron atom in two conformations and the heme group appears to be considerably more mobile. Spectroscopically, carbonmonoxide as a ligand was characterized in its unbound (Ngb $\cdots$ CO) state using IR spectroscopy [3]. Using molecular dynamics and a fluctuating charge model for CO [4] the infrared spectrum was calculated. Two different docking sites within the active site of Ngb were found which confirms results from FTIR experiments. Barriers for the migration between these two pockets were calculated and compared to results from TDS measurements. Furthermore, the simulations confirm the experimental observation for the higher flexibility of the heme plane compared to other globins such as myoglobin and give insight into its dynamical behaviour after CO dissociation.

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Computational Chemistry **101**

LFDFT calculations of Zeeman and zero-field splitting tensors for high-spin transition metal complexes

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LFDFT has been proposed over the past few years as a systematic method for the study of ground and excited multiplet states of transition metal compounds, where the ligand-field approach is reformulated within the framework of density-functional theory. The method allows the determination of all d-d [1] or f-f [2] excitation energies for a given system, and was used to calculate the magnetic properties of low-spin molecules [3]. This work extends the latter method to the case of high-spin complexes.
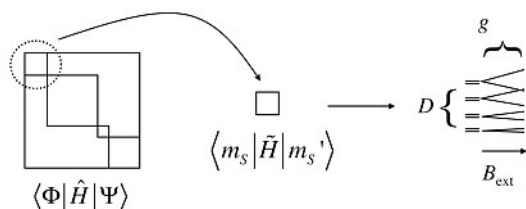
By showing how one can relate the LFDFT and effective spin Hamiltonians for such systems, a meaningful comparison with experimental data or other theoretical methods becomes possible, as demonstrated for a few selected examples.

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Computational Chemistry **102**

Microsolvation Effects on the Excited-State Dynamics of Protonated Tryptophan

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To better understand the complex photophysics of the amino acid tryptophan, which is widely used as a probe of protein structure and dynamics, we have measured electronic spectra of protonated, gas-phase tryptophan solvated with a controlled number of water molecules and cooled to ~10 K. We observe that, even at this temperature, the bare molecule exhibits a broad electronic spectrum, implying ultrafast, nonradiative decay of the excited state. Surprisingly, the addition of two water molecules sufficiently lengthens the excited-state lifetime that we obtain a fully vibrationally resolved electronic spectrum. Quantum chemical calculations at the RI-CC2/aug-cc-pVDZ level, together with TDDFT/pw based first-principles MD simulations of the excited-state dynamics, clearly demonstrate how interactions with water destabilize the photodissociative states and increase the excited-state lifetime.

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Computational Chemistry **103**

Virtual Exploration of Chemical Space by Guided Travel between Reference Structures

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The chemical space of organic structures up to a MW-range of 500 Da is of particular interest for new structures with therapeutic applications. In previous work chemical space below MW of 160 Da was exhaustively listed with a total number of more than 26 Mio. possible structures, showing how vast chemical space can be [1]. We herewith present *Chemical Space Travel* as a new type structure generator to explore chemical space beyond MW of 160 Da. The program travels from a start to a target molecule that both are proven to be therapeutically active and therefore define favourable regions in chemical space for the chosen target. Chemical Space Travel combines structural point mutations as propulsion device and a selection module that holds track on the target by measuring similarity [2]. The principle is demonstrated and analysed by travelling from methane, the smallest structure in the organic chemical space, to different targets and by travelling between two structures.

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Computational Chemistry **104**

DFT Modeling of HNCO Hydrolysis over the TiO$_2$ (101) Surface

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Decreasing NO_x emission limits for diesel engines impel the further development of existing DeNOx technologies, particularly the selective catalytic reduction of nitrogen oxides with urea (urea-SCR). In this process a urea solution is injected into the exhaust gas and thermolyzed to ammonia and isocyanic acid (HNCO), which is further hydrolyzed to ammonia and carbon dioxide. This reaction was found to be catalyzed by TiO_2 in the anatase modification, which is, therefore, used as hydrolysis catalyst in the urea-SCR process. The mechanism of the hydrolysis of isocyanic acid (HNCO) was studied on the ideal TiO_2 anatase (101) surface using the ab-initio density functional theory (DFT) method with a cluster model. Based on the energy levels of different possible transition states and intermediates two mechanistic pathways have been identified to be feasible for this reaction. In one mechanism HNCO is molecularily adsorbed and an intermediate surface complex is formed by NCO skeleton modification [1]. Whereas water is absent at the beginning of reaction in this mechanism, water is included at an early stage in the second scenario [2]. In this pathway a water molecule attacks the –NCO group, thereby forming carbamic acid at the surface. In a further step this compound is transformed to a carbamate complex, from which CO_2 desorbs and NH_3 is finally formed.

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Computational Chemistry **105**

Photoinduced ring opening of oxirane: a non-adiabatic molecular dynamics study

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The modeling of non-adiabatic excited state reactions constitute one of the major challenges of modern computational chemistry. Time-dependent density functional theory (TDDFT) [1] in the linear response (LR) formulation [2] allows the computation of electronic spectra, excited state nuclear forces [3] and non-adiabatic couplings [4,5,6]. Theory and implementation of a surface hopping molecular dynamics [7] scheme using LR-TDDFT [6] is presented. The scheme is applied to study photoinduced ring-opening of oxirane.

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Computational Chemistry **106**

Development of Hybrid-Quantum Chemical Methods for Modeling Ligand-Protein Interactions

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Quantum chemical methods enable calculation of chemical reactions using highly accurate algorithms. Despite advances, however, it remains difficult to model complex systems such as biomolecules. In this work, we investigate the possibilities of a hybrid quantum mechanics and adaptive Poisson-Boltzmann (GAMESS[1] /APBS[2]) method for investigations involving ligand-protein interactions. The results have been in part obtained using modern grid computing. The algorithm involves the embedding of the field generated by the APBS method into the quantum mechanical Hamiltonian operator, and the resulting self-consistent field computation on the complex of interest. The algorithm will be demonstrated on a key ligand-protein system of interest.

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Computational Chemistry **107**

Farming for a 5-HT$_{2A}$ Pharmacophore.

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The 5-HT$_{2A}$ receptor is the target of many atypical antipsychotic drugs used to treat psychological conditions such as schizophrenia. The exact mechanism by which the this receptor mediates the action of this class of drugs is unknown. There is no experimental data for the 3D structure of this particular receptor subtype, and many attempts at deriving a quantitative structure activity model of drugs that interact with this receptor are based on binding a number of ligands to a homology model of the receptor. The approach presented here focuses instead on identifying and testing quantum mechanical descriptors that seem to be predictive of binding specificity and affinity as well as biological activity. Particular emphasis is placed on properties (such as the sigma profile and the partition coefficient) that can be calculated from GAMESS-COSab quantum mechanical implementation of a dielectric continuum solvation model . These findings are used to present a quantum mechanically based pharmacophore model for the mechanism of antipsycotic drugs acting at the 5-HT$_{2A}$ receptor. In order to better understand the pharmacophore and validate the data, the same set of molecules is also tested using a commercialy available QSAR software package. The results of the QSAR test and the quantum mechanically based pharmacore model are used to outline a schema and interface for for a high-throughput methodology for screening drugs that act at this receptor.

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Computational Chemistry **108**

Core Electron Spectroscopy of Glycine and Glycine-Based Polypeptides in Aqueous Solution

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Recently, an approach for calculating X-ray absorption spectra based on the transition potential method combined with the Gaussian and augmented-plane wave method (GAPW) has been introduced [1]. For this type of spectroscopy, the promotion of a core electron to an unoccupied orbital and the resulting relaxation of the electronic structure has to be appropriately modeled. The GAPW formalism allows for efficient DFT all-electron calculations of extended systems, making this framework appealing for condensed phase X-ray spectroscopy.

We focus on excitation spectra of glycine and glycine-based oligomers in aqueous solution. The calculations were performed along classical MD trajectories and compared with reported experimental spectra [2]. The analysis of conformation–dependent signal patterns of absorption leads to the interpretation of the transitions in therms of the dynamical reorientation of hydrogen bonds between donor–acceptor partners. This technique opens new perspectives towards the characterization of the nature of the H–bonds, clarifying how the number and the strength of the local coordination sphere affects the spectra.

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Computational Chemistry   **109**

Expanding the small-molecule GDB with focused libraries of ligands for ionotropic glutamate receptors

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We have recently reported the so-called Generated Database (GDB) [1] consists of 26.4 millions small organic molecules up to 11 C, N, O, F atoms. This database is an abundant source of numerous synthetically feasible small-molecule ligands for various drug targets. Herein we report the further expanding of the GDB database with the generated focused-libraries of aspartic acid and glutamic acid's analogs targeting the human ionotropic glutamate receptors. Advanced molecular modeling and chemoinformatic methods were also implemented to predict the bioactivity and to analyze the structure-activity relationships among compounds in those focused libraries *in silico*. The hit-list from virtual screening of the generated focused libraries offers a set of drug-like new structures which are very interesting in term of synthesis.

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Computational Chemistry   **110**

Multiway PLS calibration model based on Molecular Lipophilicity Potential and GRID Molecular Interaction Fields with artificial membrane PAMPA-skin experimental data

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Multiway calibration methods (such as PARAFAC, Tucker and N-PLS) have been shown to be powerful tools to extract relevant chemical information from Molecular Interactions Fields (MIF) in the context of CoMFA [1]. A multiway N-PLS model was proposed to investigate artificial membrane PAMPA-skin experimental data [2] from a set of 53 compounds and their permeation profiles evaluated by 3D descriptors based on GRID probes and Molecular Lipophilicity Potential (MLP) [3]. Low energy conformation was calculated for each compound and molecules were aligned in the same coordinate system using conventional alignment methods. Molecular Interactions Fields were generated using an in-house MLP routine and GRID software with commonly-used probes. Multiway pretreatment and calibration were performed with Matlab and a N-PLS model was calibrated on the 5D hypercube (molecules * MIF * X * Y * Z). The final model was validated using Leave-One-Out crossvalidation. This study showed that multilinear N-PLS modelling is a suitable tool for the evaluation and the comparison of MIF descriptors as it provided valuable information to better characterize the structural properties of the compounds.

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Computational Chemistry   **111**

Application of a Quantum Mechanical solvation method for theoretical Corannulene studies

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In the development and refinement of continuum solvation models, highly accurate continuum-dielectric models that can describe subtle effects in structure and reactivity processes are a desirable endpoint. Detailed chemical treatments of molecular and electronic structure with the inclusion of the effects of the environment enable to predict molecular geometry, follow reaction paths, predict electrostatic effects in a variety of environments with an accuracy not offered by gas phase analysis [1].
Still, there are several areas of application where even refined dielectric models have difficulty in establishing reliable predictability. Solvation modeling is particularly challenging for ionic species, due to strong electrostatic effects arising from unbalanced localized charges. As well, dynamical processes, which change as a function of either solvent volume or solvent dielectric and/or change mechanistically across small ranges in dielectric, also represent a challenge for continuum models.
In this study, we show results from our general quantum mechanic solvation algorithm for the prediction pKa constants, and for modeling the dynamics of polynuclear aromatic hydrocarbon systems, in particular corannulene (C20H10) based structures [2], both applications in these difficult regimes.

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Computational Chemistry   **112**

On the DFT calculation of the adsorption energy of benzene on Pt(111)

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The heat of adsorption of benzene on Pt(111) has been extensively studied by means of temperature programmed desorption (TPD) [1], single crystal adsorption calorimetry (SACS) [2] and density functional theory calculations (DFT) [3]. Recent SACS experiments show adsorption energies almost twice as large as the ones previously published, and also in large disagreement with DFT calculations [2]. In order to understand the origin of this disagreement a detailed DFT study of the adsorption of benzene on Pt(111) surfaces is performed, using both cluster models and periodic boundary conditions to model the metal.
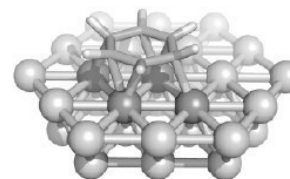
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Computational Chemistry **113**

Progress on Computation of Molecular Parity Violation Using the Coupled-Cluster Linear Response Approach

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Progress has been made in the theoretical description of molecular-parity violation over the last decade[1-4], and its possible implications for the origin of molecular chirality and biomolecular homochirality, as well as possible experiments on molecular parity violation are of fundamental interest[5-8]. Following our previous work[1,2], we report new developments to computation of molecular parity-violation potential E_{pv}. Particularly, we seek for an effective and controllable way to examine the importance of electron correlation for the parity-violating potential. Since, the coupled cluster method[9] has proved to be a most rigorous approach to account for the electron correlation in molecules, we show how the linear response function[10] of the coupled cluster wavefunction provides the contributions to E_{pv}. We discuss the algorithms and computational steps, which are being developed, to achieve the effective coding of this property. The results will be important for future accurate analyses of experimental results[7].

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Computational Chemistry **114**

Ab Initio Study of Some Persistent Nitroxide Radicals

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Stable free radicals have a variety of applications. Particularly, the aminoxyl group is frequently used in spin-labeling experiments. Nitroxides may also exhibit intriguing chiral and magnetic properties and must be of interest for studies of molecular parity violation[1,2]. Three different groups of persistent NO-radicals :i) acyclic[3-5] :dimethylaminoxyl (Me_2NO), bis(trifluoromethyl) aminoxyl ($(CF_3)_2NO$, and [$(CMe_3)_2NO$]; ii) cyclic[6-8] : aziridine-N-oxyl, azetidine-N-oxyl, pyrrolidine-N-oxyl and piperidine-N-oxyl; and iii) nitronyl nitroxides[9]. We used density functional and *ab initio* (MP2, coupled cluster) methods. The molecular structures, harmonic vibrational frequencies, and inversion barriers are reported and compared with experiment when available. The cyclic species exhibit considerable inversion barriers of ~hc 3500 cm^{-1} compared to only ~hc 500 cm^{-1} for the acyclic ones. Nitronyl nitroxides are theoretically characterized for the first time in our work. We discuss the possibilities that some of the chiral derivatives may be dominated by molecular parity violation in their dynamics.

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Inorganic and Coordination Chemistry **115**

Small Molecule Activation and Generation by Early Transition Metal Complexes

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Inorganic and Coordination Chemistry **116**

Chemistry with Aminyl Radical Complexes and Related Compounds: New Perspectives for Catalysis

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