doi:10.2533/chimia.2009.407 Chimia 63 (2009) 407–412 © Schweizerische Chemische Gesellschaft

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Analysis of vibrational spectra of polypeptides in terms of localized vibrations

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While nowadays efficient quantum chemical methods allow for the calculation of vibrational spectra of large (bio-)molecules, such calculations provide a large amount of data. In particular for the vibrational spectra of polypeptides, a large number of close-lying normal modes contribute to each of the experimentally observed bands, which hampers the analysis of the calculated spectra considerably.
Here, we discuss how vibrational spectra obtained from quantum chemical calculations can be analyzed by transforming the calculated normal modes contributing to a certain band in the vibrational spectrum to a set of localized modes [1]. We demonstrate that these localized modes are more appropriate for the analysis of calculated vibrational spectra of polypeptides and proteins than the delocalized normal modes.
We apply this methodology to investigate the influence of the secondary structure on infrared and Raman spectra of polypeptides [2]. As a model system, a polypeptide consisting of twenty (S)-alanine residues in the conformation of an α-helix and of a 3_{10}-helix is considered. In particular, we show how the use of localized modes facilitates the analysis of the positions and of the total intensities of the bands in the vibrational spectra, and how the couplings between localized modes determine the observed band shapes. Finally, this analysis is applied to analyze the Raman optical activity (ROA) spectra of these helical polypeptides, which provides a detailed picture of the generation of ROA bands in proteins [3].

[1] Ch. R. Jacob and M. Reiher, *J. Chem. Phys.*, **2009**, *130*, 084106.
[2] Ch. R. Jacob, S. Luber, M. Reiher, *J. Phys. Chem. B*, **2009**, in press, DOI: 10.1021/jp900354g.
[3] Ch. R. Jacob, S. Luber, M. Reiher, *in preparation*, **2009**.

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The Effect of π conjugation on Bond Length Alternation and (Hyper)polarizability Properties of Polyacetylene Oligomer Chains

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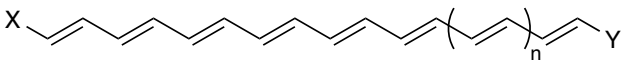
Although electron delocalization is a concept rather than a physical observable, it is used to explain a plethora of properties in π conjugated systems such as the polyacetylenes. Its presence and strength can be estimated by inspection of the carbon-carbon bond distances, especially the difference in length of a single and a double bond. Electronic properties such as the dipole polarizability and hyperpolarizabilities are also expected to depend strongly on the amount of π conjugation present in the system.[1]



However, it is known, that standard density functional theory fails in predicting accurate geometries and, more importantly, severely overestimates hyperpolarizabilities for polymers of extended size due to an incorrect electric field dependence modelled by the the commonly used exchange functionals. This led to the development of longrange corrected density functionals containing range dependent contributions of DFT and HF exchange. The CAM-B3LYP functional is shown to not only deliver accurate geometries for polyacetylenic systems but also to remove the systematic overestimation of hyperpolarizabilities known from standard DFT to large parts.[2]

[1] Bruschi, M., Limacher, P.A., Hutter, J. and Lüthi, H.P., *J. Chem. Theor. Comput.*, **2009**, *5*, 506.
[2] Limacher, P.A., Mikkelsen, K.V. and Lüthi, H.P., *J. Chem. Phys.*, in press.

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Spatial averaging: A new enhanced sampling scheme for condensed phase systems

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A new approach is tested for addressing sparse or rare-event sampling problems. The approach does not use tempering. Instead, the importance function is modified to make the sampling easier while keeping a defined relation to the original statistical distribution. For this purpose, the Monte Carlo (MC) module in CHARMM[1] is modified to allow modified Metropolis sampling.[2] Each MC move is applied to a Gaussian distribution of points around the selected atom coordinates and the average energy difference over all points as well as its variance are considered for acceptance or rejection.
The method is tested for model systems, which differ in the shape of the free energy landscape. The three test systems include carbon monoxide sampling an amorphous ice surface, sampling of the favorable positions for a hydrogen molecule inside an amorphous ice cube and sampling of CO positions in Myoglobin. Comparison of the different test systems shows that the optimal parameters for the modification of the importance function are systematically related to the steepness and height of the free energy landscape relevant to the sampling problem.

[1] Brooks *et al.*, *J. Comp. Chem.* ,**1983**, 4, 187-217.
[2] Metropolis *et al., Chem. Phys.*, **1953** , 21, 6.

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Universal Inter- and Intramolecular Empirical Correction Formula for Generalized Gradient Approximation Density Functional Theory

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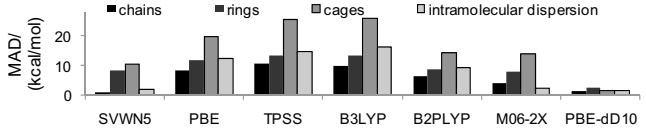
Density functional computations of alkane reaction energies suffer from systematic errors which accumulate with increasing system size.[1] An efficient way to correct the errors is to add an empirical atom pair wise interaction-correction, inspired by the Lennard-Jones potential (R^{-6} dependence).[2] The presented results show that higher order correction terms (R^{-8} and R^{-10} dependent) together with the universal damping function of Tang and Toennis[3] reduce these errors more efficiently with even less empiricism. For general applicability, the TT-damping function is augmented by a second damping function in order to have negligible corrections at covalent distances. The scope of this correction (dD10) is simultaneously expanded to intermolecular interactions. We test several combinations of first-principle functionals along with the new correction (PBE-dD10, PBEsol-dD10 and RGE2-dD10) and find that PBE-dD10 gives the most reliable results, closely followed by RGE2-dD10. The results outperform or match B2PLYP-D and M06-2X, two of the newer functionals with increased accuracy for weak interactions.



[1] M. D. Wodrich, C. Corminboeuf, P. v. R. Schleyer, *Org. Lett.* **2006**, *8*, 3631.
[2] M. D. Wodrich, D. F. Jana, P. v. R. Schleyer, C. Corminboeuf, *J. Phys. Chem. A* **2008**, *112*, 11495.
[3] K. T. Tang, J. P. Toennies, *J. Chem. Phys.* **1984**, *80*, 3726.

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COST Molecular Annotation Project: a repository for data mining of molecular information

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The availability of high-throughput computing of molecular properties is defining the need for databases of molecular structures, where each configuration can be decorated with QM-evaluated properties, data relationships, and user-generated annotations and evaluation. Sensible proof exist that this concept is solid and produces added value for the user community (for example, Wikipedia, the many bioinformatic databases and the Cambridge Structural Database). At the moment, however, the computational chemistry community is missing a standard, public access database to share scientific knowledge.
We present the COST Molecular Annotation Project (COSTMAP), a prototype database implemented in our group, soon to be integrated with the Lensfield project, developed in Peter Murray-Rust' group at Unilever Center, Cambridge, UK. COSTMAP employs a graph-based data model to store, retrieve and represent information about molecules. When fully operative, the database will allow user-friendly search and retrieval of molecular structures both from the web and via scripting. Search criteria will be based on structural features, property values and user-produced annotations. Standard data formats, such as CML[1], RDF, and Q5Cost[2] will be used for maximum interoperability.

[1] P. Murray-Rust, H. S. Rzepa, *J. Chem. Inf. Comp. Sci.*, **1999**, *39*, 928.
[2] S. Borini, A. Monari, E. Rossi, A. Tajti, C. Angeli, G.L. Bendazzoli, R. Cimiraglia, A. Emerson, S. Evangelisti, D. Maynau, J. Sanchez-Marin, P. G. Szalay, *J. Chem. Inf. Model.*, **2007**, *47(3)*, 1271-7.

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Kinetics of ligand docking sites in truncated hemoglobin: Combining atomistic simulations and transition network analysis

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The role of conformational transitions for the functions of proteins and nucleic acids are well known. In recent years, there have been many studies employing transition network analysis to study protein folding, protein-protein interactions, and protein-enzyme reactions. We, being inspired by such work, have applied transition network analysis to another challenging problem, i.e., ligand migration, and aim to extract kinetic informations of the ligand docking sites in the protein matrix.

We have recently reported atomistic simulations of nitric oxide (NO) dynamics and migration in group I truncated hemoglobin (trHbN) of Mycobacterium tuberculosis, the causative agent of human tuberculosis. Our simulations reveal, in addition to the crystallographically observed Xe pockets, several novel ligand docking sites and migration pathways [1]. By following the ligand inside the protein matrix, we have established a connectivity network between the ligand docking sites [1]. While such a network provides useful information regarding structural proximity of the docking sites, we have extended our analysis to obtain kinetics of ligand migration. To this end, we have distributed the ligand densities over several discrete clusters and calculated transition matrices for a range of lag time. These transition matrices render: a) time-resolved connectivity network in the protein matrix; b) half lives of the docking sites; c) transition time scale between two given docking sites; and d) extent of population transfer among different docking sites of the protein as a function of lag time.

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Novel Anticancer Drugs and their Interaction with Non-Classical Targets: Insights from Molecular Dynamics Simulations

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The field of anticancer metallodrugs has been traditionally dominated by the so-called classical drugs like cisplatin $[Pt(Cl)_2(NH_3)_2]$ and the "DNA paradigm", which presumes that the mode of action of these compounds relies on direct DNA damage. However, non-classical chemotherapeutic strategies based on DNA independent cytotoxicity are gaining significant prominence [1]. The main drawback of the classical chemotherapeutic strategies is that blocking the metabolism of the rapidly dividing cancer cells by means of drug-DNA binding inadvertently also inflicts damage on healthy cells that divide frequently as well, therefore causing undesirable side-effects. In contrast, non-classical drugs focus on specific cellular pathways by interacting with targets different from DNA and are therefore much more selective [2].
One of these targets is the Glutathione S-Transferase (GST) P1-1 enzyme. Its main function is the detoxification of toxic compounds, including anticancer drugs, in the cytoplasm. In addition, GST P1-1 regulates the mitogen-activated protein (MAP) pathway, involved in cellular survival and death signaling. Several organometallic GST inhibitors showing antitumoral properties have been recently synthesized and the corresponding GST-drug adducts have been also characterized.
The atomistic knowledge of the GST-drug binding modes and the possible chemical transformations that occur upon binding is important to guide further experimental investigations and assist the rational development of more effective and targeted anticancer drugs. This knowledge can be gained by combining classical and QM/MM MD simulations. In this contribution, we will discuss the main results obtained by applying this mixed approach.

[1] J. S. Sebolt-Leopold, J. M. English, *Nature* **2006**, *441*, 457.
[2] H. Varmus, *Science* **2006**, *312*, 1162.

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Insights into structure and function of adrenergic receptors from all-atom molecular dynamics simulations

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G protein coupled receptors (GPCRs) are a large family of integral membrane proteins involved in signal transduction pathways, making them appealing drug targets for a wide spectrum of diseases. The recently crystallized structures of two engineered adrenergic receptors have opened new avenues for the understanding of the molecular mechanisms of action of GPCRs, but they also generated some controversy on the proposed mechanism of GPCR activation[1,2]. Taking the two crystal structures as a starting point, we carried out submicrosecond molecular dynamics simulations of wild type β_1 and β_2 adrenergic receptors in a lipid bilayer under physiological conditions. We identified highly conserved Asp(2.50) as a crucial residue in the activation mechanism and a direct correlation between its protonation state and the cytoplasmatic conformation of the receptors. In particular, protonation of Asp(2.50) leads to recovery of all the previously suggested features of inactive GPCRs including formation of a salt bridge between the cytoplasmatic moieties of helices III and VI ("ionic lock") that is absent in the crystal structures[3], while deprotonation of Asp(2.50) keeps the "ionic lock" open and drives the receptors in an active-like conformation. Evolutionary conserved differences between opsins and non-opsins GPCRs in the surrounding of Asp(2.50), that influence the acidity of this residue, can be rationalized with respect to the constitutive activity of many class A GPCRs.

[1] Cherezov, V. et al, *Science*. **2007**, *318*, 1258.
[2] Warne, T. et al, *Nature*. **2008**, 454, 486.
[3] Vanni, S. et al, *Biochemistry*. **2009**, in press.

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Efficient evaluation of accuracy of molecular quantum dynamics using dephasing representation

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Ab initio methods for electronic structure of molecules have reached a satisfactory accuracy for calculation of static properties, but remain too expensive for quantum dynamical calculations. We propose an efficient semiclassical method for evaluating the accuracy of a lower level quantum dynamics without having to perform a higher level quantum dynamics. The method is based on dephasing representation [1, 2] of quantum fidelity [3] and its feasibility is demonstrated on the photodissociation dynamics of CO_2. We suggest how to implement the method in existing molecular dynamics codes and describe a simple test of its applicability.

[1] J. Vaníček, Phys. Rev. E **70**, 055201(R) (2004).
[2] J. Vaníček, Phys. Rev. E **73**, 046204 (2006).
[3] T. Gorin, T. Prosen, T.H. Seligman, M. Žnidarič, Phys. Rep. **435**, 33 (2006).

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Calculation of chemical shift using LF-DFT

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Ligand field- density functional theory (LF-DFT) [1] is a tried and tested method for calculating ligand field parameters in a non-empirical approach and therewith obtain properties of transition-metal complexes. Its power has been showed for the calculations of e.g. zerofield splitting [2], g- and A-tensor [3].
In given framework of LF-DFT, ^{59}Co-NMR chemical shift σ of transition-metal complexes is calculated using perturbation theory.

[1] a) M.A. Atanasov, C.A. Daul, C. Rauzy, *Chem Phys Lett*, **2003**, *367* 737.
b) M.A. Atanasov, C.A. Daul, C. Rauzy, *Struct Bond*, **2004**, *106* 97.
[2] M.A. Atanasov, C. Rauzy, P. Baettig, C.A. Daul, *Int J Quant Chem*, **2005**, *102* 119.
[3] M.A. Atanasov et al, *Chem Phys Lett* **2004**, *399* 433.

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Density Functional Theory for the Study of the Multimode Jahn-Teller Effect

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Computation and analysis of the Jahn-Teller (JT) distortions in complex molecules presents a challenge due to the superposition of effects produced by different vibrational modes [1]. The treatment of this, multimode problem, recently proposed by us will be presented [2]. It is based on the analogy between the JT distortion and reaction coordinates [3]. In contrast to the usual treatment of the JT systems, the reference point is not the high symmetry configuration, but the low symmetry minimum energy conformation. Contribution of the normal modes to the distortion, their energy contribution to the JT stabilisation energy, the forces at high symmetry point and detailed distortion path can be estimated. This allows getting very detailed picture on the interaction between the deformation of the electron distribution and the displacements of the nuclei.

Examples of our work include studies of several organic radicals, JT active metallocenes, Cu(II) chelate complexes etc. Calculations are performed by the means of a multideterminental DFT procedure, developed by our group for the study of the JT systems [4].

[1] I. B. Bersuker, *The Jahn-Teller Effect*, **2006**, Cambridge University Press.
[2] M. Zlatar, C. -W. Schläpfer, C. Daul, in *Springer Series in Chemical Physics, The Jahn-Teller Effect–Advances and Perspectives*, **2009**, accepted.
[3] R. G. Pearson, *Symmetry Rules for Chemical Reactions*, **1976**, A Willey Interscience Publication.
[4] R. Bruyndockx, C. Daul, P. T. Manoharan, E. Deiss, *Inorg.*

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Modeling chirally modified metal surfaces using the Gaussian and Plane Wave DFT formalism

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Desirable features for the computational investigation of catalytic surfaces and chemisorption phenomena are: i) large surface areas, in order to accommodate reactants, products, and possible surface functionalities, ii) the inclusion of finite temperature effects through the generation of molecular dynamics trajectories and, iii) basis sets constituted of localized orbitals. The application of the Gaussian and Plane Waves (GPW) formalism [1] in the description of the metallicity of Pt bulk, Pt(111) and Pt(100) surfaces is shown to yield excellent agreement with standard Plane Waves (PW) calculations in the evaluation of structural, electronic and dynamic properties for either bulk and surface systems [2]. The GPW formalism, with simulation cells of 400-800 atoms, can be safely used in the study of chemistry related problems involving transition metal surfaces. The methodology is applied to the study of chirally modified surfaces [3].

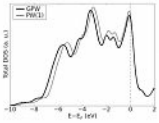

fig. 1: DOS of Pt(111) with GPW and PW formalisms.

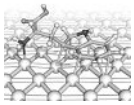

fig. 2: Adsorption of Trp to Pt(111) surface.

[1] G. Lippert, J. Hutter, and M. Parrinello, *Theor. Chem. Acc.*, **1999**, *103*, 124.
[2] G. Santarossa, A. Vargas, M. Iannuzzi, C.A. Pignedoli, D. Passerone and A. Baiker, *J. Chem. Phys.*, **2008**, *129*, 234703.
[3] C. Mondelli, A. Vargas, G. Santarossa, and A. Baiker, submitted to *J. Phys. Chem. C*

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Ab-initio assignments of IR and Raman bands of bulk Ba species relevant in the NO_x storage and reduction

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NO_x storage and reduction (NSR) process is one of the most important technologies for the reduction of NO_x components in automotive exhaust. There are numerous vibrational spectroscopic studies aimed at elucidating the NSR mechanism; however long-standing controversy exists in the band assignment of Ba species (NO_x storage component) present in the catalyst, existing as nitrates, carbonates, and possibly oxides.[1]
Based on DFT framework, the fundamental modes of bulk $Ba(NO_3)_2$ and $BaCO_3$ are calculated using the PBE functional by Quantum Espresso[2] and compared to experimentally obtained mid-/far-IR and Raman spectra.[3] Crystal symmetry has been taken into account to achieve accurate calculation of lattice modes and to explain the spectral features observed in far-IR spectra. A clear and firm assignment of IR- and Raman bands of $Ba(NO_3)_2$ and $BaCO_3$ could be given, evidently showing incorrect, but widely accepted band assignments, highlighting the importance of reevaluation of band assignments by *ab initio* methods. This study serves as a reference for IR and Raman spectra of bulk barium species relevant in NSR.

[1] E. Roedel, A. Urakawa, S. Kureti, A. Baiker, *Phys. Chem. Chem. Phys.* **2008**, 10, 6190 – 6198.
[2] P. Giannozzi et al., http://www.quantum-espresso.org
[3] Hesske, H.; Urakawa, A.; Baiker, A. *J. Phys. Chem.* **2009**, *submitted for publication*.

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Ab initio dynamics of metal nanoparticles: structure and properties

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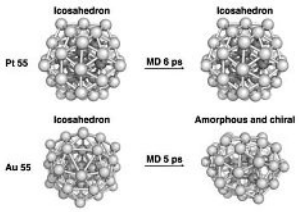
The study of the electronic properties of metal nanoparticles is of great relevance for the tailoring of new materials in general, and in particular for catalysis. It is well known that in the nano-size range metal particles have distinct features from bulk properties. Improved computational techniques and highly parallel computational resources allow performing ab initio molecular dynamics of metal nanoparticles, and the theoretical study of their chemical behavior [1][2]. In particular the structure and electronic properties of gold nanoparticles is investigated in order to uncover the marked change of reactivity between the unreactive bulk and the catalytically active gold nanoparticles [3].



[1] J. VandeVondele, M. Krack, F. Mohamed, M. Parrinello, T. Chassaing and J. Hutter, *Comp. Phys. Comm.*, **2005**, *167*, 103.
[2] G. Lippert, J. Hutter, and M. Parrinello, *Theor. Chem. Acc.*, **1999**, *103*, 124.
[3] P.P.Edwards, J.M. Thomas, *Angew. Chem. Int. Ed.*, **2007**, *46*, 5480.

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The failure of the time-dependent DFT and CC2 methods to predict the absorption spectrum of a donor-acceptor dyad

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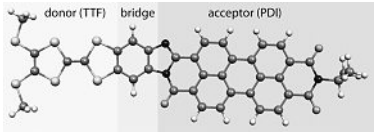
Electron donor-acceptor (D-A) molecules are of prime interest on account of their potential applications in molecular electronic devices. The tetrathiafulvalene donor (TTF) was fused to the acceptor perylene-tetracarboxydiimide (PDI) via a π-bridge [1]. The TTF-PDI dyad shows several charge transfer (CT) transitions as well as a PDI localized $\pi\pi^*$-excitation in the UV/vis spectrum.



Time-dependent DFT (TD-DFT) gives accurate predictions for valence excited states at low computational cost. However, it has been reported that TD-DFT shows serious problems with CT transitions of extended π-systems [2]. As an alternative, we have employed the second-order approximate coupled cluster singles and doubles method (CC2), which gives very accurate electronic excitation energies, albeit with much higher computational cost. CC2 correctly reproduces the CT transitions, but fails for the PDI-localized $\pi\pi^*$-excitation. The long-range corrected density functional method [3] (LC-BLYP) is the only approach to correctly predict both CT and $\pi\pi^*$ transitions of TTF-PDI.

[1] M. Jaggi, C. Blum, S.-X. Liu and S. Decurtins, *Poster contribution*, **2009**
[2] Z.-L. Cai, K. Sendt and J.R. Reimers, *J. Chem. Phys.*, **2002**, *117*, 5543. M.E. Casida, K.C. Casida, D.R. Salahub, *Int. J. Quantum Chem.*, **1998**, *70*, 933.
[3] H. Iikura, T. Tsuneda, T. Yanai and K. Hirao, *J. Chem. Phys.*, **2001**, *115*, 3540.

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Path integral evaluation of equilibrium isotope effects

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A general and rigorous methodology to compute the quantum equilibrium isotope effect is described. Unlike standard approaches, ours does not assume separability of rotational and vibrational motions and does not make the harmonic approximation for vibrations or rigid rotor approximation for the rotations. In particular, zero point energy and anharmonicity effects are described correctly quantum mechanically. The approach is based on the thermodynamic integration with respect to the mass of the isotopes and on the Feynman path integral representation of the partition function. An efficient estimator for the derivative of free energy is used whose statistical error is independent of the number of imaginary time slices in the path integral [1], speeding up calculations by a factor of ~ 100 at 500 K and more at room temperature. We describe the implementation of the methodology in the molecular dynamics package AMBER 10. The method is tested on three [1,5] sigmatropic hydrogen shift reactions. Because of the computational expense, we use *ab initio* potentials to evaluate the equilibrium isotope effects within the harmonic approximation, and then the path integral method together with semiempirical potentials to evaluate the anharmonicity corrections. Our calculations show that the anharmonicity effects amount up to 30% of the symmetry reduced reaction free energy. Numerical results are compared with recent experiments of Doering and coworkers [2,3].

[1] J. Vaníček and W. H. Miller, *The Journal of Chemical Physics*, **2007**, *127*, 114309.
[2] W. V. Doering and X. Zhao, *Journal of the American Chemical Society*, **2006**, *128*, 9080.
[3] W. V. Doering and E. J. Keliher, *Journal of the American Chemical Society*, **2007**, *129*, 2488.

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Computing Magnetic Properties of Resonance Structures

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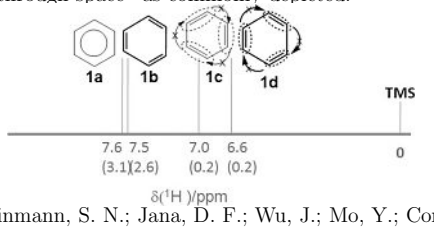
The computational design of molecules with specific tailored properties is a central goal of chemical research. To date, most organic-based molecular devices are π-conjugated. Therefore, the direct probing and tuning of the effect of π-electron delocalization on (bio)molecules properties is appealing. We here introduce a computational strategy that combines the Block-Localized Wavefunction formulation with Individual Gauge for Localized Orbitals, called BLW-IGLO. This computational strategy is designed to analyze the magnetic properties of structures with non-interacting (isolated) double bonds (i.e. non-resonanting structures).
The scope of the methodology is illustrated through the 3D visualization of the chemical shielding function of both the localized and delocalized electronic structures of a series of prototypical systems. The effect of conjugation, hyperconjugation, ring current and transannular delocalization on the magnetic responses is identified unequivocally. The results indicate that the effect of delocalization on the magnetic shielding of simple conjugated compounds is more tunable than that of benzene and its derivatives. It is also demonstrated that transannular delocalization is not only "through-space" as commonly depicted.



[1] Steinmann, S. N.; Jana, D. F.; Wu, J.; Mo, Y.; Corminboeuf, C.; Submitted.
[2] Mo, Y.; Song L.; Lin, Y.; *J. Phys. Chem. A*, **2007**, *111*, 8291.

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Modeling of Naphthalenediimide π-π Complexes as Building Blocks for Supramolecular Assemblies

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Supramolecular assemblies of *p*-oligophenyl/2,6-dialkoxy-naphthalenediimide diads are proposed to give access to the unique zipper architecture [1] with long lived photoinduced charge separation and an efficient photocurrent generation. In the present contribution we report quantum chemical investigations of substituted naphthalenediimides (NDI) and their π-π dimeric complexes as the essential building blocks for this architecture. Computed electronic properties suggest that among the series of substituted NDIs, the 2,6-dimethoxy-NDI is a good candidate to form the π-stacks with high conductivity [2].
The capacity to form the π-stacks from the substituted NDI monomers is evaluated by modeling of π-π dimer complexes. They are optimized with several DFT methods and namely the Truhlar's M06-class functionals [3], which was reported to give good results for π-π interactions. Comparison of results obtained with several DFT and *ab initio* methods will be discussed.
For the 2,6-dimethoxy-NDI, the computed properties of the dimeric complexes indicate particularly strong π-π interaction, which is reflected in the fairly strong binding interaction energy. The QM results for NDI monomers and π-π complexes were also correlated with molecular dynamic simulations of the supramolecular zipper assemblies.

[1] A.L. Sisson, N. Sakai, N. Banerji, A. Fürstenberg, E. Vauthey, S. Matile, *Angew. Chem. Int. Ed.* **2008**, *47*, 3727.
[2] R. S. K. Kishore, O. Kel, N. Banerji, D. Emery, G. Bollot, J. Mareda, A. Gomez-Casado, P. Jonkheijm, J. Huskens, P. Maroni, M. Borkovec, E. Vauthey, N. Sakai, S. Matile, *J. Am. Chem. Soc.*, submitted
[3] Y. Zhao, D.G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.

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Theoretical Study of Dioxygen Induced Inhibition of [FeFe]-Hydrogenase

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Hydrogenases comprise a variety of enzymes that catalyze the reversible oxidation of molecular hydrogen. Out of this group [FeFe]-hydrogenase shows the highest activity for hydrogen production and is therefore of great interest in the field of renewable energies. Unfortunately, this comes with the flaw of a generally very high sensitivity against molecular oxygen that irreversibly inhibits this enzyme [1, 2]. While many studies have already addressed the mechanism of hydrogen formation by [FeFe]-hydrogenase little is kown about the molecular and mechanistic details leading to enzyme inactivation by O_2. In order to elucidate this process we performed density functional theory calculations on several possible O_2-adducts of the catalytic center – the so called H-cluster – and show that the direct interaction of the $[2Fe]_H$ subsite is an exothermic and specific reaction in which O_2 most favorably binds in an end-on manner to the distal Fe_d. Based on the results we propose a protonation mechanism that can explain the irreversibility of dioxygen-induced enzyme inactivation by water release and degradation of the ligand environment of the H-cluster [3].

[1] K.A. Vincent *et al.*, *Chem. Rev.*, **2007**, *107*, 4366.
[2] C. Baffert *et al.*, *Angew. Chem. Int. Ed.*, **2008**, *47*, 2052.
[3] M.T. Stiebritz and M. Reiher, submitted to *Inorg. Chem.*.

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Dynamics of polypeptides 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 polypeptides 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. In order to improve the statistical sampling, the quantum mechanical NMR calculations are performed along MD trajectories, generated by using established empirical potentials. The analysis of conformation dependent signal patterns leads to the interpretation of the transitions in terms of secondary structures and dynamical reorientation of hydrogen bonds between donor–acceptor partners. Such reorientation processes involve both intra– and intermolecular interactions, in particular with the surrounding waters. This technique opens new perspectives towards the characterization of the solvation, and possibly clarifying how the conformational motion affects the spectra.

[1] A. Putrino, D. Sebastiani, M. Parrinello, *J. Chem. Phys*, **2000**, *113*, 7102.
[2] V. Weber et. al. *submitted to J. Chem. Phys.*

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Gaussian Delocalized Charge Approximation for the Computation of NMR Properties

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NMR is an essential tool in modern science and the computation of NMR parameters can help in understanding experimental data as well as be used to make predictions.
To compute NMR properties of large systems (e.g. proteins) approximations have to be used due to the atom size limits 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 introduce 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.
The molecule of ATP is used as a benchmark. Our approximation, as well as standard QM/MM methodology using point charges, are compared to full QM computations. Significant emphasis is put on the shielding tensor components, important in solid state NMR experiments, which are innacurately described by single point charges.
Our approximation offers a cheap, accurate and efficient alternative to the full QM computations, too expensive for extended systems.

[1] Das, D.; Eurenius, K. P.; Billings, E. M.; Sherwood, P.; Chatfield, D. C.; Hodoscek, M.; Brooks, B. R.; *J. Chem. Phys.*, **2002**, *117*, 10534.

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microRNA target prediction improved by RNA secondary structure calculations

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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 of ∼22 nt length, and this fact makes it difficult to predict the targets by standard bioinformatic tools. Recently Murphy et al. proposed a new algorithm to predict miRNA targets, in which conservation information of the binding sites can be included to improve predictions [1]. However, it is well known that in addition to conservation, accessibility of the target also plays a key role in the biological function of miRNAs, and therefore more reliable predictions might be obtained if accessibility of the binding site were included in the algorithm. Here we introduce an extension of the algorithm from Ref. [1], in which the accessibility of a given binding site is obtained by considering the canonical ensemble of all possible secondary structures for that gene, computed by RNAup [2]. We show how the previous predictions for human cytomegalovirus are improved with the new algorithm. In addition, we show a new set of predictions which support the idea that human miRNAs target important viral genes.

[1] E. Murphy, J. Vanicek, H. Robins, T. Shenk, A. J. Levine, *Proc. Nat. Acad. Sci. USA*, **2008**, *105*, 5453.
[2] U. Muckstein, H. Tafer, J. Hackermuller, S. H. Bernhart, P. F. Stadler, I. L. Hofacker, *Bioinformatics*, **2006**, *22*, 1177.

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Homology modeling of human tyrosinase active site, dicopper center optimisation and docking studies

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Tyrosinases (EC 1.14.18.1) are involved in the melanin biosynthesis process which is responsible for skin or hair color in mammals. Tyrosinase inhibitors are used to treat human hyperpigmentation and are interesting for cosmetic and food industries[1]. In order to steer inhibitor discovery, biostructural information about human tyrosinase would be of great interest but this protein has not been crystallized so far. Consequently, the active site of a human tyrosinase (SwissProt accession number P14679) model was built using the SWISS-MODEL/DeepView workspace[2]. An optimization protocol for the tyrosinase dicopper center was elaborated using the template structure (pdb ID: 2ahk) [3] and applied to the model. For the sake of indirect validation of the model, docking simulations were performed using Gold 4.0. The same ligand was first docked into the tyrosinase chain of the 2ahk complex including copper ions and explicit solvent. The same computation was performed into the model active site containing relevant water molecules. In both cases, an identical binding mode, consistent with the crystallographic information was returned.
This is a decisive step forward towards validation and then use of this homology model as a trustful structural target to design tyrosinase inhibitors.

[1] Parvez, S. et al., *Phytother. Res.* **2007**, 21, 805-816.
[2] Arnold, K. et al,. *Bioinformatics*. **2006**, 22, 195-201.
[3] Matoba, Y. *et al.*, *J. Biol. Chem.* **2006** *281*, 8981-8990.