A Theoretical Study on The Structures of Monosila[5.7]$_n$cyclacenes

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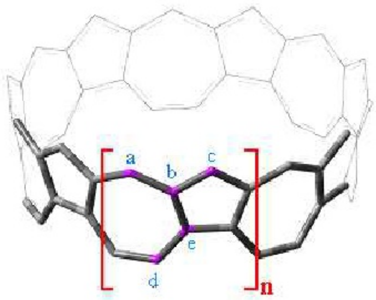
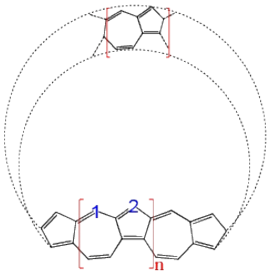
Cyclacenes are currently a major topic of interest because of their remarkable structural similarity to carbon nanotubes [1] and the possible utility of their cylindrical cavities cavities in host–guest chemistry [2]. Hence, many of the theoretical and experimental chemists have studied the cyclacenes and the silacyclacenes to gain an insight into the physical and chemical properties of these interesting molecular systems or to find out some synthetic routes to obtain hitherto unknown compounds [3-6].





Hence, we have been keen on investigating a novel family of [n]silacyclacene isomers; the [5.7]$_n$ silacyclacenes (Figure are depicted above). The nomenclature presented herein is as follows: “n” for [n]silacyclacenes refers to the number of fused benzene rings, whereas “n” for [5.7]$_n$ silacyclacenes refers to the number of fused azulene ring systems. In this work, we report several theoretically predicted properties of this new family of molecules using Density Functional Theory (DFT) with the B3LYP functional and the 6-31G(d) basis set.

As the [5.7]$_n$ silacyclacenes increase in size, the bond length alternation along the top edge decreases suggesting greater delocalization of the π-system with increasing size. The [5.7]$_n$ silacyclacene optimized geometries show C_{nV} symmetry. NICS may be considered as a useful indicator of the aromatic character of a system and usually correlates well with the other energetic, structural, and magnetic criteria for aromaticity [7]. For n=3, the NICS values are close to zero, indicating the molecule is nonaromatic, whereas for n>4, the NICS values become more negative with increasing size and the negative NICS values denote aromaticity.

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SAMs on α-Al_2O_3(0001): Chemical bonding of linker groups and thermodynamic stability of surface structures

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Al_2O_3 is used in materials science as substrate for self-assembled monolayers (SAM). SAMs play an important role in the construction of novel organic electronic components such as transistors (SAM-FETs) [1,2]. Despite this promising technological use the chemistry at the monolayer-substrate interface is not completely understood. This lack in understanding hinders the purposive design of optimal substrate properties and reaction parameters.

With phase diagrams based on total energy calculations we explain the linkage mechanisms of methyl phosphonic acid and methyl carboxylic acid to α-Al_2O_3(0001) surfaces. We show the dependence of chemical bonding on ambient conditions such as humidity and the dependence of SAM stability on surface structure. We comment on the possibility of α-Al_2O_3(0001) surface reconstruction from its UHV structure to the thermodynamically more stable pseudo gibbsite phase.

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β-Lactoglobulin at the Water-Air Interface: MD Simulations on Different Time and Length Scales

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Second order spectroscopic techniques allow to selectively probe properties of molecules adsorbed to surfaces or interfaces, rather than bulk properties. E.g., sum frequency generation (SFG) has been used to study the proteins that stabilize foams formed by milk or whey. Additionally, ellipsometry provides information on the layer thickness of the adsorbed species. These experimental methods provide information on the order and layer thickness of the molecules adsorbed to the interface, over a range of pH values. [1] However, many of the molecular details of the aggregation and surface adsorption process remain unclear. Here, we use atomistic and coarse grained molecular dynamics simulations to investigate the aggregation and surface adsorption of beta-lactoglobulin in aqueous solutions at different pH values. We also investigate the influence of the electrolyte used.

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Benchmarking TDDFT functionals in calculations of CD spectra of flexible peptides

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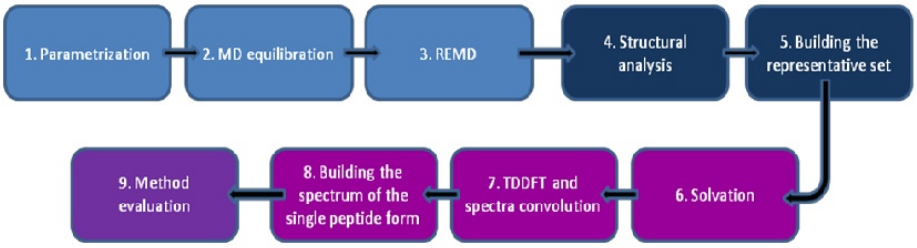
Circular dichroism (CD) spectroscopy is a standard experimental method for structural characterization of optically active chiral molecules, such as proteins and peptides. CD spectrum emerges as an ensemble average over the entire conformational phase space of the molecule. For highly flexible peptides with no dominant secondary structure, the interpretation of the experimental data becomes particularly challenging. Hence, theoretical modelling needs to be evoked to understand the measurements. Yet, until recently, no reliable method for calculating the CD spectrum was available. We combine a number of state-of-the-art theoretical approaches to provide a procedure for calculating CD spectra, as shown in the scheme below. [1] More specifically, conformational phase space is generated with replica exchange molecular dynamics. A set of representative structures is built by applying clustering methods. Finally, the CD spectrum of each representative structure is calculated using TDDFT. The final spectrum emerges as a weighted average of individual spectra.



Many studies in recent years pointed to a problem with modelling charge transfer excitations with TDDFT, which may affect the accuracy of calculated CD spectra. [2] Peptide systems prove to be especially interesting in this respect, as they were one of the first highlighted cases where conventional functionals exhibited relatively large charge transfer errors. [3] Motivated by these problems, we benchmarked the performances of B3LYP, CAM-B3LYP and M06-2X against high level ab-initio RI-CC2 calculations for selected peptide structures. Furthermore, we compared the performance of the functionals with the experimentally available data. Our results show that both CAM-B3LYP and M06-2X functionals correlate well with ab-initio calculations, while B3LYP exhibits aforementioned charge transfer errors. On the other hand B3LYP and M06-2X agree better with the experimental data compared to CAM-B3LYP. We clarify this apparent discrepancy by finding average excitation energies for charge transfers over many individual structures. In the case of B3LYP the surplus transitions, which are usually small in rotary strength, seem to become negligible upon finding a mean over many structures.

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Benchmark calculations of absorption spectra for fluorescein and related dyes in various environments

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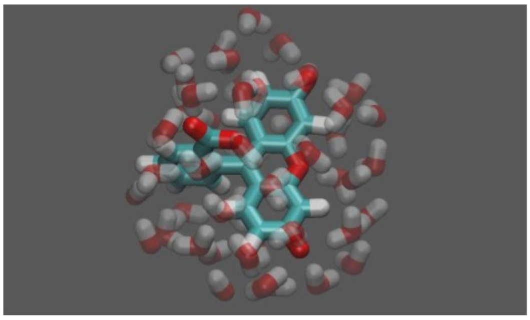
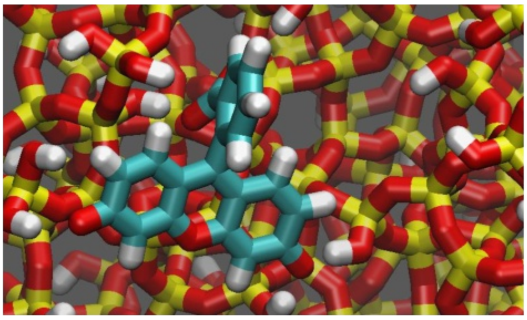
Fluorescein adsorbed on an amorphous silica substrate is widely used in materials for optical chemical sensors in biology. Fluorescein and its chemical derivatives normally exist and fluoresce in anionic or even dianionic forms. Therefore, numerous calculations by different quantum-chemical methods were performed for these compounds to determine a reliable and computationally feasible approach providing reasonable agreement with experimental spectral data.

First, we calculated the absorption spectra of ionic forms of fluorescein, rhodamine 123, Alexa Fluor 488, Oregon Green, and carboxyfluorescein dyes by TDDFT (PBE0/6-31G(d,p)). The calculated energies for the first electronic transition differ from the positions of the first peak in the experimental absorption spectra by approximately the same value of 0.5 eV for all the compounds. Then, we performed TDDFT calculations for the mono- and dianionic forms of fluorescein, considered as a representative example, using all different density functionals available in the GAMESS program and various basis sets ranging from double-zeta of triple-zeta augmented with polarization and diffuse functions. However, the results were, in general, unsatisfactory. In order to check the effects of real environment, we also performed TDDFT (PBE0/6-31G(d,p)) calculations for fluorescein surrounded by some water molecules, including H_3O+ and Li+ counterions, and by polarized continuum medium using the PCM model. In these calculations we did also not observe significant effects of the environment on the calculated spectral parameters of the dye. The results obtained using the CIS approximation were even worse.





At the next step, we studied the absorption spectra of the mono- and dianionic forms of fluorescein by the CASSCF and CASSCF/MCQDPT methods and obtained an excellent agreement with experiment. Again, taking into account the environment effects of water within the PCM model did not affect the calculated spectra.

Finally, we constructed models of fluorescein adsorbed on an amorphous silica substrate by molecular dynamics (MD) simulations. The broadening of the absorption bands were calculated using TDDFT calculations for 200 points in the calculated MD trajectories and compared the results with similar calculations for the isolated dye.

We conclude that the band positions and shapes for the absorption spectra of fluorescein and similar dyes adsorbed on an amorphous silica matrix are best described by a combination of CASSCF + MD/TDDFT methods.

Modeling of the structure and properties of amorphous layers for organic light-emitting diodes

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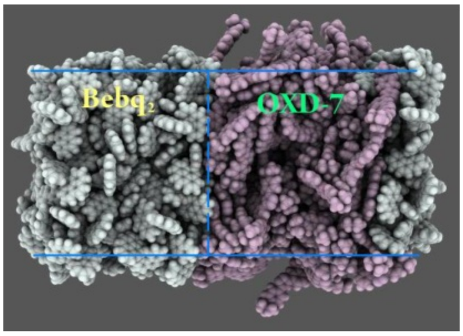
The geometrical structure and electronic properties of an 1,3-bis[2-(4-tert-butylphenyl)-1,3,4-oxadiazol-5-yl]benzene (OXD-7) electron-transporting layer, an emitting layer composed of beryllium complexes ($Bebq_2$, $Be[4\text{-}mpp]_2$, $Bepp_2$), and an interface between these two layers are studied by MD simulations combined with quantum-chemical DFT/TDDFT calculations for sample structures along MD trajectories. The AMBER force field has been used in MD simulations. Because some important force-field parameters are lacking in the AMBER force field, these parameters have been estimated by fitting AMBER potential energy scans to results of first-principles calculations.



The estimated force constants have been verified by available experimental data (densities and crystal structure). Amorphous layers composed of OXD-7, $Bebq_2$, $Be[4\text{-}mpp]_2$ and Bepp2 molecules and the interfaces between the OXD-7 layer and the $Bebq_2$, $Be[4\text{-}mpp]_2$ and Bepp2 layers have been built using the GROMACS software package. HOMO and LUMO energy level distributions and the band shape of the absorption spectra of molecules in the amorphous layers have been calculated by the DFT and TDDFT methods. The layer structures and calculated distributions can then be used for charge-transfer modeling.

Diatomic molecules encaged in fullerene C_{60}: a high-level exploration of their energetic, structural and vibrational properties

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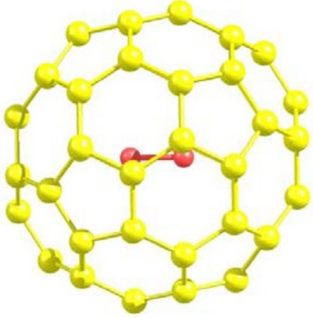

The possibility to encapsulate guest molecules into the cavity of a fullerene (such as C_{60}) is one of the most outstanding properties of this allotropic form of carbon. Many endohedral complexes involving H_2, N_2, H_2O and NH_3 guests with C_{60} have been successfully synthesized via so-called 'molecular surgery' approach (see, for instance, Table 1 of Ref. [1]). However, there is still a lack of accurate computational studies for such endohedral complexes as the large number of atoms to be considered precludes the usage of post-Hartree-Fock methods for these systems. As early as in 1991, Cioslowski predicted [2] stabilization effects of polar and nonpolar diatomic guests in C_{60} cage based on low-level Hartree-Fock calculations, some of which (i.e., harmonic frequency shifts) were not confirmed experimentally. We recently demonstrated [3] that the results of more advanced density-fitting local second-order Møller-Plesset (DF-LMP2) calculations with a triple-zeta basis set lead to an excellent agreement of equilibrium geometries, stabilization energies and harmonic frequencies of the $H_2@C_{60}$ complex with some other sophisticated theories and with experiment.

In the present study, we concentrate on the encapsulation effects associated with the formation of complexes consisting of C_{60} host and diatomic guest molecules by means of (DF-L)MP2 theory. The guest molecules studied include homonuclear (N_2, O_2) as well as heteronuclear (HF, CO, LiH, LiF) species. Stabilization energies, changes in equilibrium bond lengths and harmonic frequencies will be presented and discussed.

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Doped Polycyclic Hydrocarbons for Nanoelectronics and Energy Conversion

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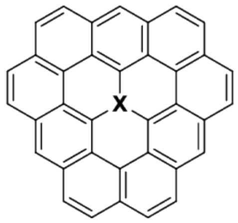
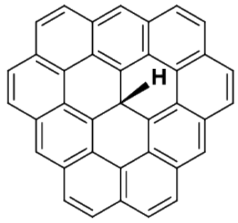
Polycyclic aromatic hydrocarbons (PAHs) are typical organic semiconductors with interesting properties for many (nano-) electronics applications and for photovoltaics. [1] On the other hand, PAHs in the infinite size limit represent the "miracle material" graphene. However, in contrast to the "finite-size" nanoscale PAHs, graphene has no band gap and opening a band gap in graphene is a challenging task that must be solved for semiconducting technologies including nanoelectronics based on graphene. [2] One way to open a band gap is internal doping of graphene. [2]

Thus, we have recently studied the effect of internal doping on the properties of PAHs by performing calculations with density functional theory (DFT) and semiempirical configuration interaction methods on a series of doped PAHs **1–5** with the dopants X = CH, SiH, B, N, and P (see Figure). [1] Such calculations also serve to model and understand the effects of internal doping in graphene.



X = CH, SiH, B, N, P



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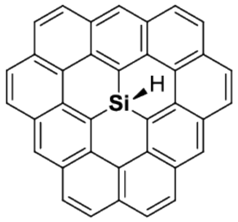

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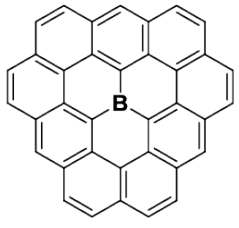

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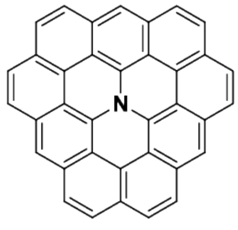

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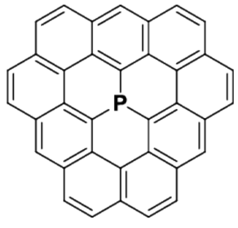

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Adiabatic and vertical electron affinities and ionization potentials, optical and transport band gaps and exciton binding energies were calculated for **1–5** based on the DFT, time-dependent (TD) DFT and semiempirical unrestricted natural orbital–configuration interaction singles (UNO–CIS) methods. [1] In addition, we have estimated the chemical reactivity of **1–5** by calculating their aromaticity and diradical characters. [1] Photoinduced electron transfer in complexes of **1–5** with fullerene C_{60} and porphin was also shown to be plausible with the above methods. [1] We have determined that dopants can be classified into three groups based on the results of our calculations: 1) CH- and P-dopants, which interact weakly with the π-system, 2) SiH-dopant, which interacts weakly with the π-system, but strongly deforms the planar PAH skeleton and therefore changes its electronic properties, and 3) B- and N-dopants, which interact strongly with the π-system, although they influence the electronic properties in opposite directions. [1]

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Structure and thermodynamics of nonaqueous solvation by integral equation theory

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Electronic structure theory under the influence of apolar solvents suffers from substantial methodical difficulties since in this case the solvent-induced solute polarization originates mainly from specific directional interactions and higher electric multipoles. Continuum solvation models based on the dielectric solvent response such as the PCM (polarizable continuum model) approach ignore such interactions and can therefore not adequately model solvation effects in nonaqueous environments. The embedded cluster reference interaction site model (EC-RISM [1]) retains the granularity of the solvent and represents a microscopically detailed and therefore improved approach towards solvation modeling. EC-RISM is based on a self-consistent solution of solvent distribution functions described by 3D-RISM integral equation theory and solute electronic structure by mapping the solvent charge distribution onto discrete, solute-embedding point charges. In aqueous solution EC-RISM theory is capable of calculating pK_a shifts[1] and tautomer ratios relatively fast and with high accuracy [2].

Here we outline the strength of the integral equation model by studying nondipolar benzene and hexafluorobenzene solutions. In particular, the thermodynamics of differential solvation is quantified for small molecules dissolved in these media. We show that EC-RISM is capable of predicting the correct tendency of transfer free energies, in contrast to PCM calculations which are not satisfactory for quadrupolar solvents. Moreover, we delineate the importance of intramolecular electronic polarization for explaining the data.

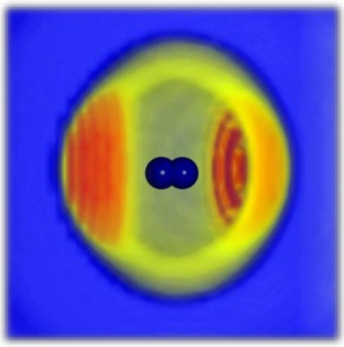

Fig. 1. Solvent distribution for benzene carbon atoms around nitrogen computed with exact electrostatic potential.

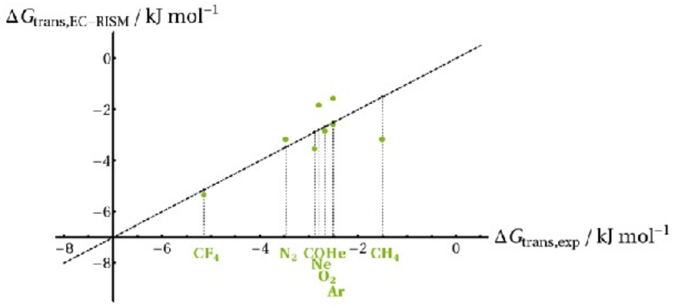

Fig. 2. Calculated vs. experimental transfer Gibbs free energies for several simple gases from B3LYP/6-311G(d,p)/PCM// B3LYP/6-311G(d,p)/EC-RISM/PSE-1 calculations.

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Local Dynamics in Protease Recognition

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Proteases catalyze cleavage of peptide bonds and are vitally important in a wide range of fundamental cellular processes. Far more than 500 proteases have been identified in the human genome, each individually tied to a unique cleavage pattern [1]. These patterns reach from specificity for a single peptide in case of proteases involved in signaling cascades to broad spectra of cleaved peptides for digestive enzymes.

To analyze the impact of local dynamics on protease specificity, a series of homologous proteases including highly specific as well as unspecific proteases was selected. Inspired by information theory, subpocket-wise substrate cleavage entropy values are presented based on cleavage data from the MEROPS database [2]. Calculated entropy scores, ranging from 0 for a conserved substrate to 1 for a random distribution of substrates [3], appear to be qualitatively linked to local flexibility of the binding site region. Consequently, temperature factors from X-ray structures as well as all-atom 100ns molecular dynamics trajectories using the AMBER package [4] are compared in respect to subpocket specificity.

Analysis of specificity and flexibility patterns reveal a consistent correlation of binding site rigidity and specificity. As conformational plasticity is paralleled by a broader conformational space, a mechanism of conformational selection [5] in the binding process of proteases is proposed. According to this model, the whole conformational ensemble contributes to the substrate specificity of proteases rather than single interactions derived from a static point of view. This finding implies the need for refined rules for substrate cleavage considering binding site flexibility in agreement with earlier findings for snake venom metallo proteases [6].

Acknowledgement:
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3D-QSAR based on Quantum-Chemical Molecular Fields: Towards an Improved Description of Halogen Interactions

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Current force field-based methods have limitations in the description of molecules. This is especially true for halogens and hypervalent elements such as sulphur. Here, the anisotropy of the electron density distribution ('σ-hole') is ignored. As a consequence, some important non-covalent interactions such as halogen-bonds or halogen-pi interactions, which are of high relevance in lead optimization [1,2], can not be accounted for.

Using tailored scoring functions or 3D-QSAR techniques employing molecular fields it is possible to compensate in part for such limitations. It is interesting to note that QM-based methods, which do not suffer from those limitations, have not been used widely in the context of 3D-QSAR in the past. Recently, the concept of calculating QM properties such as ionization potential, electron affinity or polarizability in a local context was introduced [3].

We have demonstrated the usefulness such local properties in molecular-field-based 3D-QSAR with a public data set of $GABA_A$/Benzodiazapine receptor ligands and an internal data set for factorXa (fXa) inhibitors.

A ligand-based alignment of a set of 1,4-diazepine inhibitors [5] formed the starting point for 3D-QSAR models predicting the affinity against two receptor subtypes, $GABA_A$ and Benzodiazapine receptor. Here, models of higher predictive power were obtained for the QM-based properties based molecular fields than for those derived with the standard CoMFA method.

Furthermore, a structure-based alignment was created for a set of fXa inhibitors by docking into a representative crystal structure. This alignment was previously used to deduce 3D-QSAR models based on CoMFA and CoMSIA methods [4]. While predictive models have been obtained, important SAR-features have not been picked up, such as the interaction of chlorine and bromine atoms with a tyrosine side-chain that ultimately led to the development of orally active fXa drugs. Using QM-based molecular fields models of equal predictive power were obtained that were able to provide additional insights into the SAR.

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Molecular Dynamics and Umbrella Sampling Simulations of 8-Arg-Vasopressin

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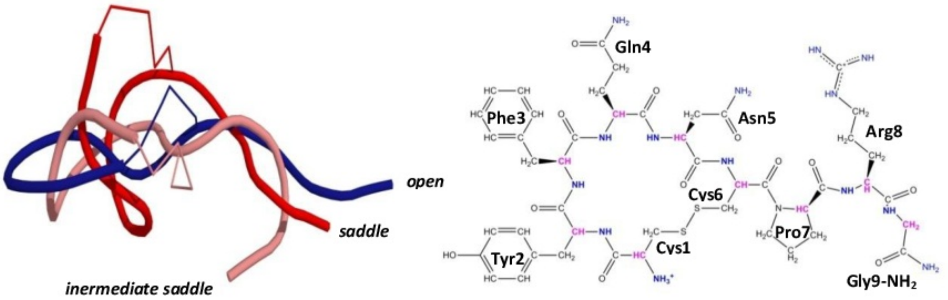
A long-term (5 µs) molecular-dynamics simulation of 8-Arg-Vasopressin was performed in aqueous solution at 300 K. Two main conformational ring states were identified via DASH [1] analysis: **DRS$_{\mathbf{open}}$**, a stretched, open conformation with no intramolecular hydrogen bonds in the ring; and **DRS$_{\mathbf{saddle}}$**, a folded, saddle-like conformation with strong hydrogen bonding interactions between the carbonyl oxygen of the ring residue Tyr^2 and the amide protons of the ring residues Asn^5 and Cys^6. Only one transition between both main states was observed during the 5µs simulation run. In addition to these two main states, a sparsely populated DASH state, **DRS$_{\mathbf{intermediate}}$**, was found with mixed conformational characteristics of the two main states. Umbrella Sampling [2, 3], post-processed with WHAM [4-6], was used to estimate the free energy profile for the conformational change from open to saddle and led to a reaction path via **DRS$_{\mathbf{intermediate}}$** (see video clip [7]), with barrier heights of 7.7 kcal mol^{-1} and 14.2 kcal mol^{-1} and a free energy difference between the open and saddle states of 4.0 kcal mol^{-1}.



8-Arg-Vasopressin

8-Arg-Vasopressin (AVP) is a neurohypophyseal hormone with a wide range of endocrinological and neurological functions, e.g. water homeostasis, blood pressure regulation and mediation of social and sexual behavior. Main structural characteristics are a 6-residue ring closed *via* disulphide bridging, and a α-amidated 3-residue tail. Figure: Structure and backbone conformations (blue: *open*; red: *saddle*; rose: *intermediate*; cartoon: backbones; sticks: disulphide bridges; not shown: sidechains)

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pK_a prediction for small organic molecules in dimethyl sulfoxide (DMSO)

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The embedded cluster reference interaction site model (EC-RISM) approach combines statistical-mechanical integral equation theory and quantum-chemical calculations in order to predict thermodynamic data for chemical reactions in solution [1]. The electronic structure of the solute is determined self-consistently with the structure of the solvent which is described by 3D-RISM integral equation theory. Recent progress in the understanding of conceptual and numerical features of the integral equation approximations [2] allows computations on hundreds of compounds in a reasonable time with good accuracy. The EC-RISM method proved for instance useful for determining the tautomer state of small molecules in the context of the SAMPL2 challenge [3]. In comparison with typically employed dielectric continuum models the 3D-RISM methodology properly accounts for the molecular details of the solvent species.

Here we use EC-RISM to predict the acidity of small organic molecules in pure dimethyl sulfoxide (DMSO) solution. We critically discuss the influence of different solvent force field models and compare the performance of the EC-RISM method with results computed using the established polarizable continuum model (PCM). The results reveal significant improvements for various classes of compounds.

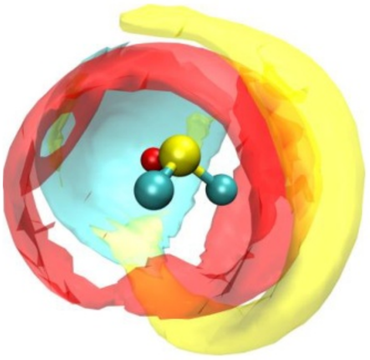

Fig. 1. Isosurfaces of distribution functions from calculations with 3D-RISM/HNC with the Liu model for DMSO solvent and solute [4], yellow/light: sulphur, red/dark: oxygen, blue/middle: methyl groups.

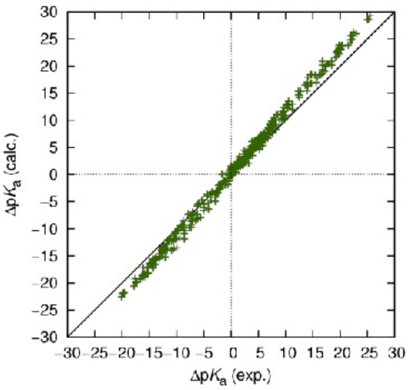

Fig. 2. Calculated vs. experimental pK_a shifts for phenole, aniline and thiophenole derivatives from B3LYP/6-311+G(d,p)/PCM//MP2/6-311+G(d,p)/EC-RISM/PSE-2(Liu) calculations.

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Predicting ion selectivity of biological and synthetic nanopores by MD simulations and 3D integral equation theory

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Several membrane proteins form nanometer-sized pores that act as ion channels in living systems, representing key regulators of essential cellular processes such as homeostasis. Their principle function is to establish a controllable electrostatic potential across the cell membrane by exhibiting highly selective ion conductance. Constructing synthetic analogues of biological pores with designed properties is an important goal in nanotechnology which requires to understand and to control the relevant parameters facilitating selective conductance. As a result, much experimental and theoretical effort is currently spent in attempts to understand design principles.

A computational approach to the design problem has the advantage that control parameters can be systematically varied in a broad range of models, from artificially reduced toy systems up to molecular-scale representations. Here we show that the combination of nonequilibrium molecular dynamics simulations under the influence of an external field in conjunction with the 3D RISM (reference interaction site model) integral equation theory provides consistent data in order to characterize conductance properties and relevant chemical features that control selectivity [1]. We demonstrate results of the integrated approach for a recently described synthetic nanopore that should mimic biological K^+ selective ion channels [2].To some extent, the data challenge the experimental interpretation and show that theory can make important contributions to understand nanopore design.

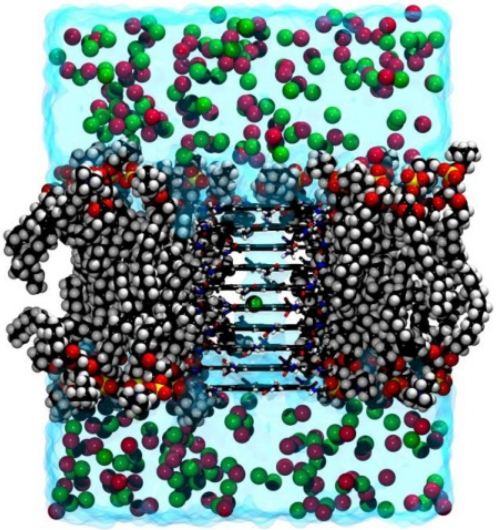

Fig. 1. Simulation snapshot of the synthetic nanopore [2] embedded in a lipid bilayer, solvated by 4 M aqueous KCl solution (green/middle balls: chloride, magenta/dark balls: potassium).

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In silico Identification of Precursors for CYP Profiling Breath Tests

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The family of cytochrome P450 (CYPs) plays a key role in the metabolism of xenobiotics. The high degree of polymorphisms and possible transcriptional regulation make it impossible to predict the individual patient response based on genomic information. [1] Hence, personalized medicine requires high-throughput measurement of the CYP phenotype. Breath tests are established for individual CYP isoforms and proven as diagnostic tools. [2] Breath tests detect volatile organic compounds (VOCs) in the patients' exhaled air, allowing for CYP tests by detection of $^{13}CO_2$ originating from CYP-catalyzed oxidative degradation reactions of an administered precursor. These small metabolites of CYP-catalyzed degradation of xenobiotics are generally considered unimportant for further drug metabolism and thus not listed in established CYP databases.

The presented work focuses on the establishment of an *in silico* workflow aiming at the identification of novel precursor molecules, likely to result in VOCs other than CO_2 upon oxidative degradation by CYPs. The proposed workflow comprises three parts: CYP profiling to identify most-likely CYP isoforms for given substrates, reaction encoding to predict metabolites from CYP-catalyzed reactions and subsequent volatility prediction.

CYP profiling was encoded as a ligand-based decision tree based on 2D descriptors derived from established models in the literature [3] and validated against publicly available data sets extracted from the DrugBank. [4] Oxidative degradation reactions (O- and N-dealkylations) were found to be most promising in the release of VOCs. Thus, the CYP-catalyzed oxidative degradation reaction was encoded as SMIRKS to enumerate all possible reaction products. A QSPR model aiming to predict the Henry constant k_H was derived from a data set of 488 small organic compounds. [5] This QSPR equation is finally applied to identify potentially volatile compounds amongst CYP reaction products.

A list of potential novel breath test precursors was identified based on the presented three stage workflow and subsequent comparison to metabolism data from literature. These candidate precursors are currently undergoing *in vitro* testing for their release of VOCs and hence applicability as precursors for CYP profiling breath tests.

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Modeling Charge Transport in “Soft” Organic electronic Devices

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Organic electronic devices such as thin film transistors (TFTs) or organic field-effect transistors (OFETs) play a key role in the development of electronics independent from silicon. Their potential use in flexible electronic devices has led to much development effort. Self assembled monolayers (SAMs) of organic molecules are often incorporated in such devices either as an additional dielectric component underneath the organic semiconductor or directly functionalized with a semiconducting moiety (see Figure 1). [1]

Modeling charge transport in such flexible and “soft” devices raises two major concerns: A proper electronic description of the system along with a satisfying picture of the essential molecular motions. We present a multistep hierarchical modeling approach for modeling charge transport in these amorphous systems.

Extensive conformational sampling by classical atomistic molecular-dynamics (MD) simulations provides us the major structural and dynamic information of the two-component monolayers. Subsequent large scale semiempirical quantum mechanical (QM) calculations on hundreds of snapshots are the basis for the electronic characterization of the systems.

As a central point we use local molecular properties e.g. the local electron affinity (EA_L) derived from the semiempirical wavefunction within our framework of the electronic characterization. [2] Using these properties allows us, unlike many other methods, not to be limited to a pure intermolecular hopping or classical band transport description.

We will describe Monte Carlo (MC) based path searches, [3] to visualize and rationalize possible conducting paths, introduce agent-based MC simulations to account for charge carrier interactions, and will give an outlook of possible applications of Diffusion Quantum Monte Carlo (DQMC) related techniques.

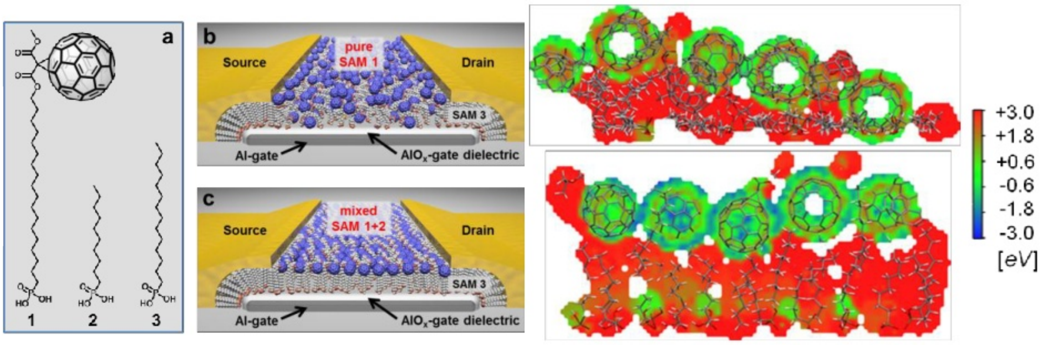

Figure 1: (left) Schematic composition of SAM-FET devices. (right) Slices through $-EA_L$ for a SAM of pure **1** (top) and a mixed SAM (molecules **1** and **3**). [3]

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An information-theoretic classification of amino acids for the optimization of interfaces descriptions in protein-protein docking

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One major challenge in protein-protein docking is the definition of suitable criteria for a scoring function that allows the identification of a good docking solution among many false arrangements.

In a previous work we demonstrated that the concept of mutual information (MI) from information theory can be used to investigate structural features of protein-protein interfaces and to assess their information content in protein docking. These MI-values can be converted into a scoring function [1]. However, this first "proof-of-concept" also revealed aspects that had to be improved to result in a robust and widely applicable approach.

Originally, structural features were derived after the grouping of the 20 aminoacids into a four-letter alphabet [1]. The use of such reduced alphabets has the advantage of an improved statistics; however, a four-letter alphabet might be too small to adequately represent the properties of individual amino acids.

Therefore, the main goal pursued in the present work was the generation of more sophisticated aminoacid alphabets (or structural descriptors) that allow a more accurate description of the biological features that govern protein-protein recognition.

Optimized aminoacid alphabets were generated starting from known ones using a clustering approach and a MI-based assessment of their information content. The alphabets resulting from this approach were tested for their performance in scoring docking solutions in a five-fold cross-validation and demonstrated a significantly improved performance. Furthermore, a web service for scoring protein-protein docking solutions based on our approach has been developed and will be soon made available to the scientific community.

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Local Tuning of the Conformational Flexibility of RfaH

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Bacterial gene transcription is regulated by various factors that initiate, elongate, and terminate the transcription process. Elongation factors, such as NusG, interact with the RNA polymerase (RNAP) and prevent the formation of a termination complex at termination sites. NusG is an essential elongation factor in Escherichia coli and is active for almost all genes. The NusG-homologue RfaH, on the other hand, antiterminates transcription via recognition of the *ops* (operon polarity suppressor) element, and therefore elongates the transcript ignoring emerging termination signals. In contrast to NusG, RfaH regulates the transcription of non-essential genes which contain information for different virulence factors, such as haemolysin or lipopolysaccharides.[1]

In the two transcription factors NusG and RfaH the N-terminal domain (NTD) is largely similar and sufficient for full transcription regulation, the different recruitment and activity patterns are caused by distinct structures of the C-terminal domains (CTD): a beta-barrel conformation linked to the NTD in NusG, an alpha-hairpin with hydrophobic contacts to the NTD in RfaH. Dissociation of the two domains in RfaH is thought to be triggered by *ops*-binding and uncovers the RNAP-binding residues on the NTD-surface. Refolding of the alpha-helical CTD into a beta-barrel might lead to interactions of RfaH with translation and secretion machineries.[2]

To gain further insight into domain interactions and stability of the CTD, we performed all-atom molecular dynamics simulations of the crystal structure at different temperatures and salt concentrations and for three double mutants in explicit solvent using the ff99SB force field implemented in AMBER.

Our simulations show that the alpha-helical conformation of the CTD largely fluctuates at 310 K resulting from intrinsic instabilities in the protein sequence. These motions in the CTD – the NTD behaves as a globular protein – can be reduced by lowering the temperature or by increasing the ionic strength. The simulations also revealed that breaking of the helices preferentially occurs at G121 and G125. In silico mutation of these two residues resulted in stabilized CTD-helices suggesting that the flexibility of the two glycines is crucial for the conversion of the alpha-helical CTD into a beta-barrel.

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In silico SAR rationalization and evaluation of pharmacokinetic properties of σ_1 receptor ligands

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The σ_1 receptor is implicated in numerous studies, concerning both its function and mechanism of action and possible ligands. This receptor is very interesting from the pharmacological point of view, as it is involved in several diseases, e.g. Alzheimer's and addiction to drugs and alcohol. Since a crystal structure of the σ_1 receptor is not available, we conducted ligand-based studies.

We analyzed 72 congeneric compounds with a propyl-aminic sub-structure, but having different K_is in the range from nanomolar to millimolar, partially published [1]. In order to assess the potential of novel ligands, we divided this work in two parts: affinity rationalization and evaluation of pharmacokinetic properties. First, we generated a shape-based alignment with ROCS [2,3], using only 45 compounds, with a K_i<100 nM, excluding the other 27 less affine compounds. We refined the alignment of the compounds giving more importance to the positive charge on the residual nitrogen. Based on this alignment [4] we generated a 3D-pharmacophore model with LigandScout [5]. A shared-feature model finally had 3 important features: 2 hydrophobic regions, one of them containing an aromatic ring, and a H-bond donor, that usually is a protonated nitrogen. The pharmacophore model was used to compare the ligands with active ligands from literature and the similarity suggests similar binding modes. We complementary created a QSAR model using 2D and 3D descriptors [6], to quantitatively rationalize activity. Our model shows the activity to be linearly correlated with logS, logP, molecular refractivity and related descriptors, as evaluated with Pearson's correlation coefficient.

In the second part of this work, we evaluated aspects of ADME and pharmacokinetic properties for our set. We verified that the compounds obey the 'rule of 5' of Lipinski [7], suggesting potential oral bioavailability. Then we analyzed which cytochrome P450 enzymes (CYPs) are potentially involved in the metabolism, using a 2D-descriptor based decision tree model [8]. With this in-house CYP isoform assignment tool, all compounds are predicted to be metabolized by the isoforms CYP 3A4 or 2D6, which have respectively a large and basic binding pocket. These characteristics fit perfectly with the characteristics of our compounds, that have a molecular weight in the range 216 Da through 403 Da and have at least one basic nitrogen. With this study we are able to explain how the features of our σ_1 ligands are directly related to the activity, and our insights will further be exploited in lead optimization of this set of σ_1 receptor ligands.

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Application of QM/MM Methods to probe reaction mechanisms

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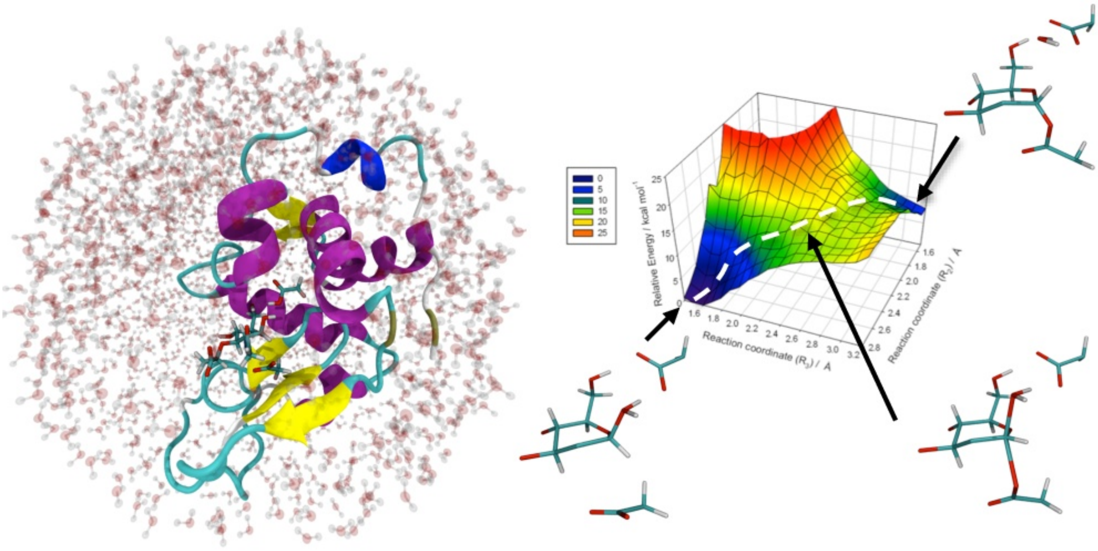
QM/MM (Quantum Mechanics/ Molecular Mechanics) methods are increasingly important in analyzing and predicting enzyme activity. QM/MM methods allow a detailed atomic level investigation of reactions in enzymes by coupling quantum chemical calculations on the active site with a simpler, empirical 'molecular mechanics' treatment of the rest of the protein. This has the significant advantage of probing possible reaction mechanisms in enzymes with quantum methods of potentially high accuracy, while retaining the ability to produce results for large, solvated enzymes, on reasonable time scales and at relatively small computational expense [1].

An example of QM/MM analysis of the effects of mutations, and investigations of alternative substrates, is provided by HEWL (Hen Egg White Lysozyme). GPU (Graphics Processing Unit) aided, long timescale MD (Molecular Dynamics) simulations were performed on the enzyme system allowing suitable 'reactive frames' to be generated for the reaction. QM/MM calculations where then used to determine the nature of the catalytic intermediate formed during the enzyme-catalyzed reaction [2]. Reactions of mutant enzymes and alternative (fluorinated) substrates were then modeled, for comparisons with experimental studies: such modifications were necessary for the experimental trapping of a reaction intermediate [3]. QM/MM calculations compared the reactions with the wild-type and native substrate, and analyzed the changes caused by these modifications, testing the conclusions drawn from mutant enzymes and non-natural substrates.



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Quantum Dots for Solar Energy Conversion

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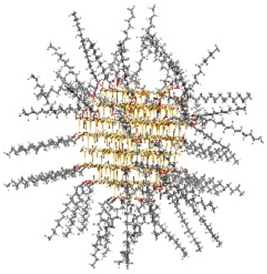
Semiconductor nanoparticles (quantum dots, QDs) have high potential for low cost solar cells. This is because their optical and electronic properties are size dependent and thus tunable. Furthermore, their particulate nature allows simple processing. [1] While the properties of individual particles are well understood, the behavior of QD films and interfaces between QDs and other materials is not. We aim to improve QD-based materials and devices by studying the charge transfer and excited-state properties of large systems.

Theoretical and experimental studies have allowed us to determine the role of organic linker molecules in QD solar cells. [2] Since the cost of conventional theoretical methods prohibits the quantum mechanical description of QD photoelectrodes, we are currently implementing a semi-empirical approach to this problem. Calculations of such systems will also allow us to address issues such as charge trapping or energy transfer between particles.



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Molecular Modeling of Silver Nanoparticle Nucleation & Growth

Theodor Milek and Dirk Zahn

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We demonstrate the molecular modeling of the association of silver ions and the nucleation of small silver nanoparticles from ethylene glycol solution.

$$x\mathrm{Ag}^{+} + y\mathrm{Red} \xrightarrow{(CH_2OH)_2} \mathrm{Ag}^{x-y}\downarrow + y\mathrm{Ox}^{+}$$

By using sophisticated many-body potentials and our Kawska-Zahn-Method [1,2] we are able to explore atom-by-atom aggregation, redox reactions and structural reorganization as functions of aggregate size. Our simulation scheme is combining several simulation techniques like Molecular Dynamics, Monte-Carlo simulations and QM/MM modeling to overcome the time/length scale restrictions inherent to diffusion controlled crystallization from solution [3].

Atomistic level insights include the complex reaction networks leading to charged metal clusters and the interplay of the solutions redox potential and the size, shape and internal structure of forming silver aggregates. In uncharged metal clusters the evolution of structural motifs and aggregate shape is closely connected to multi-twinned or close-packed packings [2]. By tuning the redox potential we investigate the influence of the net charge on the surface/volume ratio. Indeed, charge may alter this balance and thus lead to novel particle shapes.

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Determining the shear viscosity of a solvent in the presence of electric fields

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The shear viscosity is a very important kinetic property characterizing the macroscopic properties of molecular systems and is hence useful for the parametrization of reliable force fields. However, calculating the shear and bulk viscosities from molecular dynamics simulations is still a challenging task.

Here we study the shear viscosity of water by performing extensive MD simulations using the GROMACS software package and different models of water (e.g., SPC/E and TIP4P) as a function of the electric field strength. The latter breaks the otherwise isotropic nature of the solvent. The shear viscosity is related to the autocorrelation function of the off-diagonal elements of the pressure tensor by the Green-Kubo relation, which is used to analyze pure water simulations. Alternatively, the viscosity is calculated from the mobility of a spherical particle, the latter arising from the diffusion constant evaluated in independent simulations. Apart from the fact that different treatments show excellent agreement, we find that the field decreases the component of the shear viscosity perpendicular to the field and increases the components parallel to the field.

Recent developments in the prediction of drug-induced phospholipidosis

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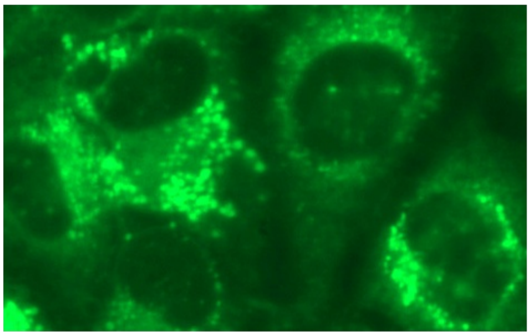
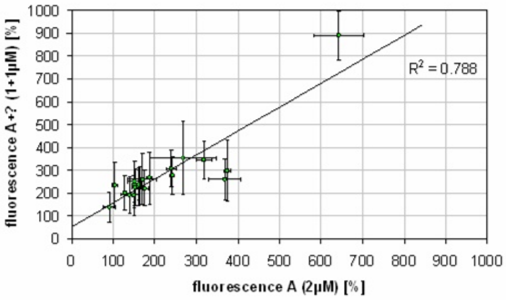
Drug induced phospholipidosis (PLD) is characterized by an excessive accumulation of phospholipids within cells, mainly lysosomes. Although it is not clearly known which enzymatic pathway is responsible to reduce the phospholipids degradation, several well-known drugs induce PLD. This effect can be monitored *in vitro* using a fluorescence-labeled phospholipid assay [1], where a green fluorescent phospholipids mix accumulates for PLD inducing drugs. We tested approximately 300 drugs for their effect on the cellular phospholipids level and identified 55 drugs that resulted in a significant increase of the phospholipid fluorescence at a concentration of 10µM [2].

Based on these experimental results we established an *in silico* prediction system. One of the major objectives for the prediction systems was to keep the number of descriptors low and subsequently the models interpretable and intuitive. A random forest algorithm (N=5) resulted in a validated accuracy of 84.7% using 3 descriptors and 86.3% using 4 descriptors.





In an additional study we examined PLD induced by combinations of two drugs. The main goal of this study was to find out if the total drug concentration is decisive for PLD beyond individual drug effects, which would implicate that drug-induced PLD can be considered as an additive effect. To test this hypothesis we used binary combinations of 21 drugs. For an additive mechanism the PLD induced by combinations should be available via linear combinations of the individual results.

$$fluorescence(A) + fluorescence(B) - 100\% = fluorescence(A+B)$$

Remarkably, this equation is able to generate reasonable estimates for drug-induced PLD of binary combinations. Altogether, an additive mechanism can be assumed for drug-induced PLD. PLD caused by combinations can be estimated using PLD induced by the individual drugs.

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Molecular modeling of small molecules thin film on the surface

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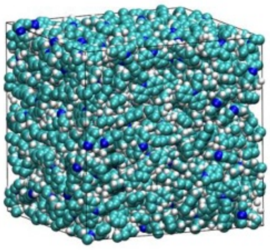
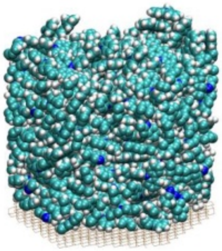
The electronic properties of amorphous organic thin films are of great interest, because they can be used in organic light-emitting diodes (OLED) displays and other devices. Compared to conventional inorganic semiconductors, amorphous organic thin films have the potential to cover larger areas and create some devices on flexible substrates.

In this study, two methods of modeling amorphous organic thin films, consisted of 4-4'-N,N'-Dicarbazolylbiphenyl (CBP) molecules, have been implemented. The first method is based on the molecular dynamics compression of the unit cell with molecules located randomly inside it with low initial density. As a result, we obtained an amorphous isotropic material structure. Then it becomes possible to further simulate generated material by molecular dynamics. The second algorithm imitates the process of vacuum deposition. The main goal of such method is getting anisotropic packing near a flat surface, because the detailed investigation of molecular orientation and ordering in such materials is very important for explaining the relationship between the chemical characteristics of single molecules and physical properties of the films. All molecular dynamics calculations were performed with the aid of GROMACS [1] package.





The molecular orientation of OLED materials in vacuum-deposited amorphous films has been investigated. Also the time dependence of the molecular orientation and mean square displacement of the molecules were calculated at different temperatures. These data can serve as a measure of the molecular mobility in the material.

The results indicate that CBP molecules perfectly oriented horizontally to the substrate surface at the room temperature. Also these molecules have low diffusion rate. It means that for determining of values of different physical parameters we have to average over several cells generated independently, not only over one trajectory.

Recently experiments show that the horizonlal orientation of the transition dipole moment of emitting molecules positively affects on charge transport and light outcoupling [2], because the light is emitting mainly in the direction orthogonal to the transition dipole moment.

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Sensing Molecules by Charge Transfer through Aptamer-Target-Complexes

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Aptamers, i.e. short sequences of RNA and single-stranded DNA, are capable of specifically binding objects ranging from small molecules over proteins to entire cells. Here, we focus on the structure, stability, dynamics and electronic properties of oligonucleotides that interact with aromatic or heterocyclic targets. Large-scale molecular dynamics simulations indicate that aromatic rings such as dyes, metabolites or alkaloides form stable adducts with their oligonucleotide host molecules at least on the 20 ns time scale. From molecular dynamics snapshots, the energy parameters relevant to Marcus' theory [1] of charge transfer are computed using a modified Su-Schrieffer-Heeger Hamiltonian [2], permitting an estimate of the charge transfer rate, k_S, through the whole system. In many cases, aptamer binding seriously influences the charge transfer kinetics and the charge carrier mobility within the complex, with conductivities up to the nanoampere range. As a consequence, these adducts constitute a new class of model systems that enable the investigation of macromolecular charge transfer with potential applications as nanoscopic single-molecule sensors [3].

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Fast 3DRISM algorithms for biochemical applications

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Integral equation theory of liquids (IETL) gives a possibility to describe structural and thermodynamical parameters of liquids. One of the key equations in this theory is the Ornstein-Zernike (OZ) equation. For molecular systems OZ is a six dimensional integral equation and it is still a challenging task to solve it numerically. There is a possibility to decrease the dimensionality of the problem by averaging the angular degrees of freedom. Such kind of models are Reference Interaction Sites Model (RISM) or 3D-RISM model. To apply methods of the IETL for screening of large sets of bioactive compounds one requires fast RISM and 3D-RISM implementations.

Recently it was shown that after proper parameterization, both: RISM and 3DRISM equations can be used for accurate prediction of the Hydration Free Energies (HFE) of bioactive compounds [1,2]. The structural descriptors correction (SDC) model, which is based on a combination of the RISM with several empirical corrections, substantially increases the accuracy of calculated HFEs by RISM giving the standard deviation of the error for a test set of 120 organic molecules around 1.2 kcal/mol [1]. As well, for 3D-RISM by using only the partial molar volume as a linear empirical correction (universal correction, UC) to the calculated hydration free energy, one obtain predictions of hydration free energies in excellent agreement with experiment ($R = 0.94$, $\sigma = 0.99$ kcal/mol) [2].

Recently we proposed the multigrid algorithm for solving RISM equations and showed that the proposed method is over 30 times faster than the standard one [3]. In out last paper we report the multi-grid based algorithm for the 3D-RISM equations [4]. We performed the benchmarking of the algorithm and compare its performance with the standard Picard and DIIS one-level iterative schemes. We showed that the algorithm is 24 times faster than the Picard and 3.5 times faster than the DIIS algorithms. We also benchmarked the algorithm on a set of 99 organic compounds and showed that average computation time on a standard PC is only few minutes per molecule (10-20 atoms). On the base of the Multi-grid 3DRISM algorithm the program package for 3DRISM calculations and visualizing results was developed. We will describe the main features of the programming package and algorithms which were used in it.

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Fullerene Dimers and their Anions

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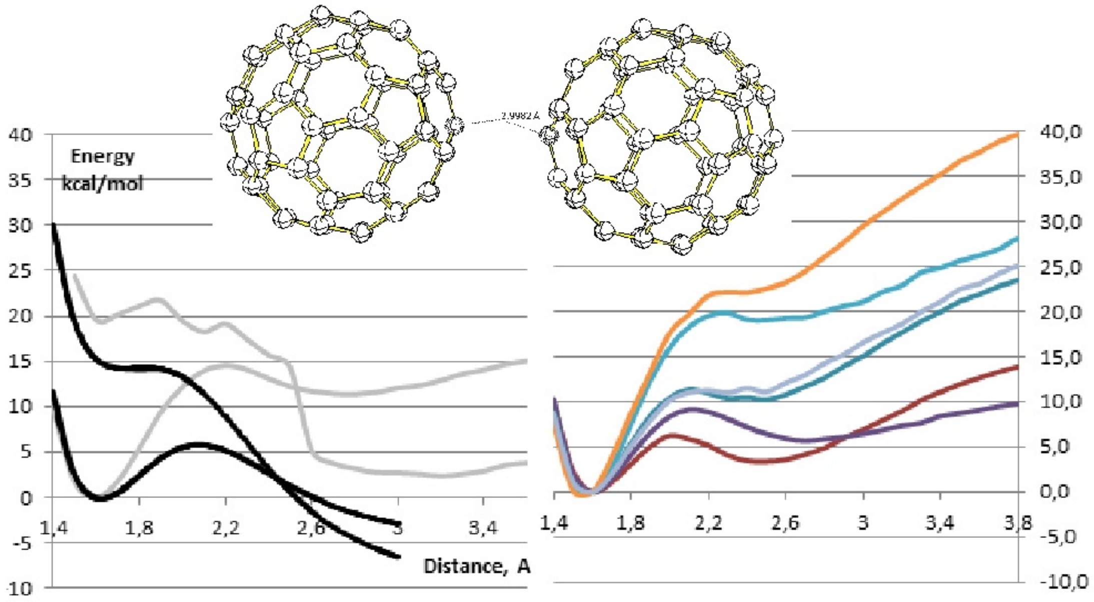

The interaction between two fullerenes is important for understanding the principles of electron transfer in fullerene-containing devices. Up to now, only two types of fullerene dimers were considered: the double-bonded neutral dimer [1] and the single-bonded dianion dimer [2].

We observed that there is one more minimum on potential energy surface of the system containing two fullerenes. This minimum corresponded to a Van-der-Waals bonded (non-bonded) dimer with distance between the surfaces of the fullerenes of 0.27-0.28 nm (≈ 1 nm between centers of buckyballs). That is the normal distance between fullerenes in crystal fullerite. The results of the calculations strongly depend on Hartree-Fock exchange and dispersion correction. Also for the dianion dimer crossing of spin-states between single-bonded and non-bonded dimer was observed. The stability of the ground state of the single-bonded dimer is comparable to that of the excited state of the van-der-Waals dimer.

Investigations of new dimer, spin-states crossing and electron transfer are in process.

DFT-calculations (PPE-scans) were performed using Becke 88 functionals with different HF exchange, BHHLYP and CAM-B3LYP functionals in ADF, NWChem and Gaussian.

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Amyloid-β Tetramer: Structural Stability of a New Fold

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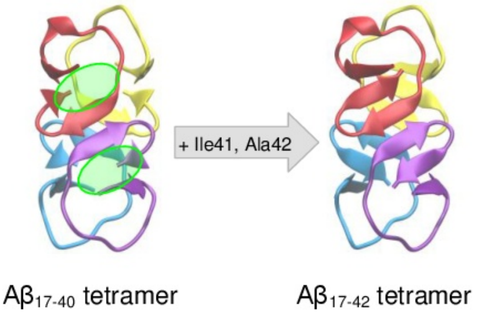
Worldwide, more than 35 million people are living with dementia.[1] The most common type of dementia is Alzheimer's disease (AD),[1] which is also the most common neurodegenerative disorder.[2] One of the key molecules in the pathogenesis of AD is the amyloid-β peptide (Aβ), which occurs in two major forms: 40 ($A\beta_{40}$) or 42 ($A\beta_{42}$) residues long. Thereby, $A\beta_{40}$ is produced at higher levels, whereas the more hydrophobic $A\beta_{42}$ is more neurotoxic.

The neuritic plaques, which are a major pathological hallmark in the brain of AD patients, are mainly composed of Aβ fibrils.[3] However, recent studies showed that not the insoluble Aβ fibrils seem to be the neurotoxic agents: the small Aβ oligomers, as a preliminary stage of the fibrils, exhibited much higher cytotoxicity.[4] Despite the fact that newer studies on AD have focused on the small Aβ oligomers, the structural information on the Aβ oligomers is restricted, because of their noncrystalline and unstable nature.

Lately, Streltsov et al. have described a crystal structure of the amyloidogenic residues 18-41 of the Aβ peptide genetically engineered into the CDR3 loop region of a shark Ig new antigen receptor (IgNAR) single variable domain.[5] They suggested this structure as a potential model system for nonfibrillar oligomer formation in AD, because the Aβ-IgNARs formed a tight homo-tetramer as a dimer of dimers through interactions mediated by the Aβ-peptide component. In our study, we extracted the Aβ-peptide component from the crystal structure and investigated it in two lengths ($A\beta_{17\text{-}40}$ and $A\beta_{17\text{-}42}$) to study the structural stability in explicit solvent by means of all-atom molecular dynamics simulations. In addition to the simulations of the tetramers, we examined the derived dimer and monomer structures.

In summary, the results suggest that the novel tetramer topology is a stable conformation for $A\beta_{17\text{-}42}$, but not for the $A\beta_{17\text{-}40}$ variant. Generally, the dimer and monomer simulations revealed the same trend: the structures of the $A\beta_{17\text{-}42}$ variant were more stable than the $A\beta_{17\text{-}40}$ variants. The increased stability of the $A\beta_{17\text{-}42}$ variants can be explained by the C-terminal extension of the middle strand in a 3-stranded antiparallel β-sheet.



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CELLmicrocosmos 2.2 MembraneEditor – Modeling Membranes for MD Simulations

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The CELLmicrocosmos 2.2 MembraneEditor (CmME) is a freely available software tool which enables the fast and easy modeling of heterogeneous biological membranes. It is based on the PDB format and uses a shape-based approach to distribute lipids along a two-dimensional plane. The theoretical description was presented as the 2.5-D Knapsack Packing Problem [1]. The membrane generation is supported by different lipid packing algorithms optimized for special application cases. CmME supports the semi-automatic placement of proteins based on PDBTM and OPM [2,3] as well as the use of custom PDB files. The generation of stacked membrane bi-layers or mono-layers is possible as well as the definition of microdomains.

Currently we are developing a plugin providing an interface between the MembraneEditor and GROMACS [4]. This interface should simplify the first steps into the field of molecular dynamic simulations (MD). The GMX-Plugin is able to connect CmME via ssh to a computer cluster and run the MD simulation with GROMACS, using the starting structure from CmME [5]. Different all atom and coarse-grained membrane simulations are currently being analyzed.

In addition, we are currently working on a plugin solving three-dimensional packing problems, which enables the generation of ellipsoid vesicles.

The alpha version of the Vesicle Builder, the source code of the MembraneEditor as well as its Java WebStart application are located at:

http://Cm2.CELLmicrocosmos.org

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On- and Off-Target Prediction using 2D and 3D Molecular Similarity

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Drug structures may be quantitatively compared based on 2D topological structural considerations and based on 3D characteristics directly related to binding. The present study establishes a framework in which 2D and 3D similarity computations can be directly compared and also combined. Given this framework, we studied the similarity patterns exhibited by 358 marketed small molecule drugs linked through partially shared molecular pharmacology and addressed two broad questions. The degree to which primary and secondary targets could be predicted was quantified using 2D similarity, 3D similarity, or a combination of both by making use of sets of drugs whose targets were known. The specific methods used were Surflex-Sim, and the 2D GSIM computation implemented within the Surflex platform.

The results were expected, but striking as to degree. The performance of the methods for predicting target annotations was 2D < 3D < 2D + 3D. Consistent with prior observations, 3D similarity did not yield a dramatic gain over 2D for primary targets due to the historical design bias problem: molecules designed to hit target X are often made specifically to look (in 2D) very much like molecules that are already marketed to modulate X. However, for off-targets, a dramatic improvement over 2D in the ability of 3D molecular similarity to identify relevant pharmacological effects was observed.

A broad observation is that a drug that shares high 2D and 3D structural similarity with another drug is likely to have indistinguishable pharmacological effects at the level of biochemically characterized modulation of protein targets. If, on the other hand, a drug shares little 2D similarity to existing drugs for the same cognate target but has high 3D similarity, there is greater likelihood to obtain a novel pharmacological effect. Specifically, drug pairs with high 3D and high 2D similarity showed identical biochemical targets four times more frequently than did pairs with high 3D similarity but low 2D similarity.

The work reported here introduces a new methodological approach for data fusion, demonstrated with 2D and 3D molecular similarity. Given other recent reports of methods for data fusion and off-target prediction, the differentiating features of what can be concluded based upon 2D and 3D molecular similarity is important to understand.

Molecular Dynamics of the Viral IE1 Protein That Represents a Novel Protein Fold

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Recent studies have identified an intrinsic defense mechanism located in the nucleus of the cell that counteracts infection by cytomegalovirus. [1] One viral protein that targets this cellular immune response is immediate early 1 (IE1). The crystal structure of rhesus cytomegalovirus IE1 (rhIE1), which was recently determined by the group of Yves Muller, revealed a predominantly helical fold that exhibits no significant structural homology to any known structure. Interestingly, IE1 crystallizes in two slightly different dimeric forms, which exhibit small deviations of their monomer conformations and dimer interfaces. This indicates a certain degree of conformational plasticity of IE1, which was further investigated by molecular dynamics (MD) simulations.

All MD simulations were performed with AMBER/parm99SB force field in an octahedral box of explicit solvent. We simulated two dimer structures for 50 ns and three of the different monomers for 100 ns.

Furthermore we used MODELER 9.9 to create a homology model of HCMV IE1 (hIE1) with rhIE1 as a template. The modeled structure was then analyzed by MD in a similar fashion as rhIE1.

The monomers generally behaved much more flexible than the dimers. Interestingly, we detected a pronounced flexibility in adjacent parts of the helix-bundle resulting in a hinge like movement. Despite the low sequence identity of 24% between rhIE1 and hIE1, the same motions could also be detected in the simulations of modeled hIE1. We therefore assume that these hinge motions might be of biological relevance, e.g. for giving sufficient conformational plasticity for the interaction with different host proteins. In summary, we provide a first comprehensive insight into the dynamics and behavior of a novel protein fold.

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Towards a thermodynamically consistent, quantitatively accurate integral equation theory

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The integral equation (IE) formalism of theories of the liquid and solution state is based on a set of nonlinear equations that connect the total and the direct correlation functions by a convolution product and by a so-called closure relation which also contains the interaction potential. In contrast to explicit molecular simulations the solution to an IE theory allows for fast, noise-free calculations of structural properties such as the pair distribution functions as well as of thermodynamic quantities like the free energy or the chemical potential. The quality of an IE calculation relies on the accuracy of the so-called bridge function that is in principle, though not easily, obtained from simulations, but for which several approximations have been described.

Here we follow-up on our earlier formally exact result concerning conditions on the bridge function leading to thermodynamic consistency in the sense that the free energy is required to be a path-independent state function [1]. We demonstrate for the Lennard-Jones fluid that bridge data taken directly from a simulation can be used in an analytical expression [2] for the free energy which matches reference data from molecular dynamics simulations very accurately. Moreover, a novel exact result is presented by deriving an inequality between the renormalized direct correlation function and the bridge function which is useful for the development of bridge approximations and for controlling the numerical stability of IE solutions [3].

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Parameterization of a Coarse-Grained Model for Ceramides

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The stratum corneum is the main barrier to prevent drugs from penetrating the skin. It's the outermost layer of the epidermis consisting of corneocytes embedded in a lipid membrane region which contains ceramides, cholesterol and free fatty acids [1]. The lipid region which is the only continuous structure in the stratum corneum plays an important role in the barrier function. We use molecular dynamics simulations to investigate this barrier function on an atomic scale. Due to the large amount of degrees of freedom in the membrane, coarse-grained models were used to enlarge the time scale and the accessible system size in the simulation.

Our work is based on the forcefield called MARTINI developed by Marrink and co-workers [2, 3]. This coarse-grained model is simple and has only a small number of coarse-grained atom types and can reproduce a lot of properties of amino acids, lipids, polymers, etc. For example the model can correctly reproduce the lipid bilayer self-assembly process.

However, the forcefield parameters of the ceramides which are the most abundant lipid class in the stratum corneum [1] is not available in MARTINI. So parameterizing the ceramides becomes one of the most important tasks for the stratum corneum simulations. In general there are two ways to parameterize a coarse-grained forcefield. First, we can compare the results with more accurate simulations such as all-atom simulations. Second, comparing the results with available experimental results is more preferred. The suggested ceramide parameters were derived from all atom simulations using GAFF [4] and complement preexisting MARTINI lipid parameters. The preliminary results show that with our parameters, the main phase-transition temperature of ceramide (~90.0 °C [5]) and the area per lipid (55.1 ± 0.7 Å^2 [5]) can be reproduced.

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Substituent Effects on The Ring-Opening Mechanism of 1-Bromo-1-Lithiosilirane to Silaallenes: DFT Study

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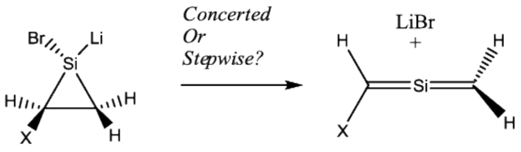
The chemistry of silaallenes has been attracting more interest in past few decades due to their unique structural properties compared to carbon analogs [1]. Recently, our group has proposed the concerted and stepwise mechanism about the ring-opening mechanism of lithium bromocyclopropylidenoids, 1-bromo-1lithiosilirane, and 2-bromo-2-lithiosilirane to allenes and silaallenes with the help of DFT calculations, respectively. The effects of substituents were reported for carbon analogs. Briefly, the stability of the reactive intermediate, i.e., the carbene, is dependent on the substituent. Cyclopropylidenes bearing an electron-donating group are extremely unstable and ring-open readily to the allene [2]. In addition to that, it is proposed in another study that the ring opening mechanism of 1-bromo-1-lithiosilirane to 2-silaallene can proceed in a stepwise fashion. On the contrary, the ring opening mechanism of 2-bromo-2-lithiosilirane to 1-silaallene can proceed in a stepwise fashion [3].



In this study, the ring-opening reactions of lithium bromosilaranes to silaallenes have been investigated computationally at B3LYP/6-31G(d) level of theory. Formally, two pathways can be considered: the reaction can be concerted or stepwise with intermediacy of a free carbene. In both case, loss of bromine ion determines the kinetic of the reaction. To analyze the possibility of the reactions, we worked on the potential energy surfaces for the elimination of LiBr from substituted 1-bromo-1-lithiosiliranes (X= -H, -Br, -SiH_3, -CH_3, -CF_3, -Cl, -F, -CN) at the B3LYP/6-31G(d) level of theory. With using DFT molecular orbital calculation, we estimate that the energy barrier for conversion from –CN substituted siliranes to TS1 has 18.1 kcal/mol which is the highest activation energy and –Br substitued siliranes has lowest energy barrier by 10.4 kcal/mol. The reaction of –SiH_3 and –CN substituted siliranes can be proceed concerted and stepwise fashion, whereas X= -H, -Br, -CH_3, -CF_3, -Cl, -F are only stepwise reaction type. Finally, we discussed required energies and reaction process from 1-Bromo-1-lithiosiliranes to silaallenes in accordance with Doering-Moore-Skattebol method.

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A DFT STUDY OF MODELLING CELLULOSE RADICALS

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Cellulose is one of the most abundant renewable biopolymers, which consists of linear chains of D-glucose units linked β(1-4) glycosidic bonds. Different basic crystalline forms of cellulose have been studied so far. Native cellulose I, occuring in wood cell walls, is found in two different forms, Iα and Iβ. Nishiyama et al. have been identified the crystal structure of cellulose Iα and Iβ by means of X-ray and neutron fiber diffraction.

Although the structure of cellulose has been studied for years, mechanism of cellulose reactions for example radicals occuring during graft copolymerization with vinyl monomers have not been identified fully. In order to provide insight into these mechanisms theoretically, this preliminary study has focused on investigation of the electronic structure of glucose free radicals. Conformational analysis of the unit structure of cellulose has been performed by SPARTAN using semi-empirical PM3 method. The most stable conformer has been optimized by UB3LYP/6-31G** method. The calculated spin densites and charges were interpreted in terms ofthe proposed radical mechanism. The effect of additional units on the spin density has been investigated by increasing the number of unit structure.

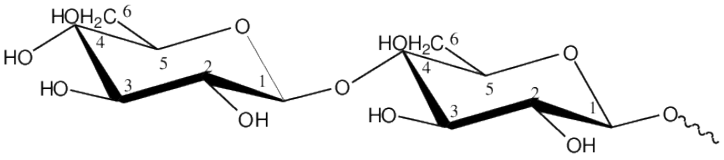

Figure I. The structure of cellulose unit.

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