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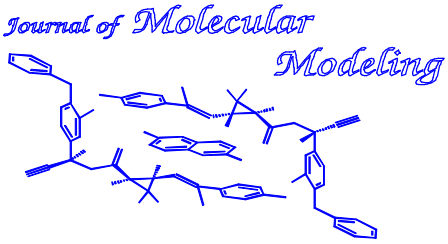

Proceedings of 10th Molecular Modelling Workshop Darmstadt, Germany May 14 - 15, 1996

Preface

As editor of this journal and secretary of the *Molecular Modeling and Graphics Society (Deutschsprachige Sektion)*, I have pleasure in presenting this collection of abstracts and full papers from the Workshop. It contains a wealth of material on aspects of molecular modeling ranging from method development and application to multimedia data presentation.

The abstracts and full papers collected here give a flavour of the meeting. The electronic mode of publication makes it possible to give a true image of the workshop presenting – for the first time – videos and VRML-scenes.

Thanks are due to all those who have submitted contributions and the keynote speakers Paul Madden and Soeren Toxvaerd. Special thanks go to Alfons Geiger (University Dortmund), who was in charge of the organization of the scientific program and to Jürgen Brickmann and his group for the immaculate organization of the technical part of the program.

We hope that you will enjoy this collection of abstracts and full papers and are looking forward to welcoming you at the 11th Molecular Modelling Workshop 1997 in Darmstadt. The Molecular Modelling Workshops are organized under the auspices of the *Molecular Graphics and Modelling Society – Deutschsprachige Sektion.*

Tim Clark, Erlangen, September 16th, 1996

keynote lecture

Molecular Dynamics without Effective Potentials via the Car-Parrinello Method

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Abstract

It is now possible to perform molecular dynamics without the a priori introduction of a potential, by calculating the energy and forces on the nuclei at each instantaneous nuclear configuration from a variational prescription for the electronic energy, following methods introduced by Car and Parrinello. The method thus opens the way to the simulation of systems in which the prescription of an internuclear potential is difficult [1]. Such difficulties may arise from a variety of causes:- because chemical bonds are being broken and formed, because of polarization and other many-body phenomena, in the description of 'screening' in metallic systems..... The C-P method promotes a general solution to such problems by introducing an ab-initio prescription for the electron energetics, which should be applicable to all electronic phenomena. A high computational price paid for this generality, although some very significant calculations have been undertaken.

In order to circumvent the computational cost of a full ab-initio description of the electronic structure in large-scale applications of Car-Parrinello MD, we have developed simplified representations of the electronic structure in the C-P scheme which are applicable to particular physical systems. By sacrificing generality, it becomes possible to incorporate the relevant aspects of the electron energetics, for these particular systems, in an energy functionals which may be evaluated at a small fraction of the computational cost of a full ab-initio description whilst retaining the essential physics and accuracy of a first principles approach.

For ionic systems, the many-body aspects of polarization and dispersion interactions are included by adding additional degrees of freedom, which represent distortions of the electronic structure of an ion due to interionic interactions, to the ionic coordinates and extending the equations of motion accordingly [2].

Short-range corrections to the asymptotic induction and dispersion terms are parameterized on the basis of ab-initio electronic structure calculations. The polarizable ion model reproduces distinctive features of short- and intermediate-range order in MCl_2 melts (where M is a group IIA or IIB metal) and gives global energy minimum structures in agreement with experiment for the MX_2 crystals.

For metals we use a density functional formalism which involves the use of the electron density as the basic variable and avoids the introduction of orbitals [3]. The form of the kinetic energy functional is chosen to incorporate several exact limits (uniform system, linear response and rapidly varying density) while the rest of the energy functional is exactly the same as in a Kohn-Sham calculation within the local density approximation. For metals the orbital-free scheme has particular advantages – the dynamics are stable and Brillouin-zone sampling is avoided. The electronic part of the algorithm scales linearly with system size and large simulation cells and long run times become possible. Good results for simple metals have been obtained.

In the talk, the general framework of the C-P method will be described and the process of 'tailoring' the electron energetics to the problem at hand will be illustrated with a number of applications.

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Dynamic AM1 Calculations of Polaron Migration in Polysilanes

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Abstract

Polysilanes are of interest because of their unusual electronic properties [1]. The conductivity of bulk polysilanes has been reported to occur via hole transport [2], which can be induced by doping with strong oxidizing agents [3], electro-oxidation [4], light [5] or heat [6]. Since there is considerable -delocalization along the backbone chain, a polysilane molecule may be considered as a one-dimensional molecular wire, the backbone being the wire, the alkyl side groups the insulator. We have demonstrated the ordering of polysilanes by self-assembly on graphite. This is an experimental prerequest for future conductance measurements on insulating substrates [7].

Here we focus on dynamic quantum mechanical calculations concerning the migration of an electron hole along a single polysilane backbone. The ease of migration relates to electrical conductivity.

The linear polymethylsilane radical cation $Si_{17}(CH_3)_{36}^{+\bullet}$ has been used in dynamic AM1 calculations to investigate the migration of a positive charge along the backbone chain. Both the bond length (Figure 1) and charge distributions (Figure 2) indicate polaron formation. The polarons were localized over about 6 Si-Si bonds with a significantly longer central bond. If an external field is applied to the molecule the polaron migrates several Angstrom along the backbone. The speed for polaron migration depend on the strength of the electrical field (Figure 3).

Calculations were performed using the standard AM1 (Austin model 1, Dewar, 1985) method. All calculations used the VAMP 5.6 program [8].

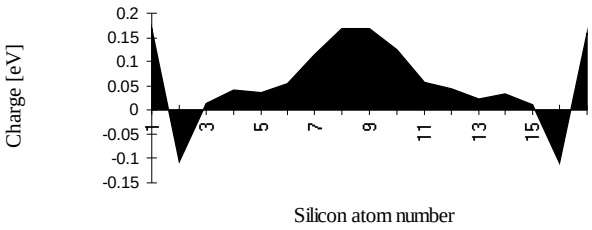

Figure 1.*Charge distribution per Si(Me)$_2$-group.*

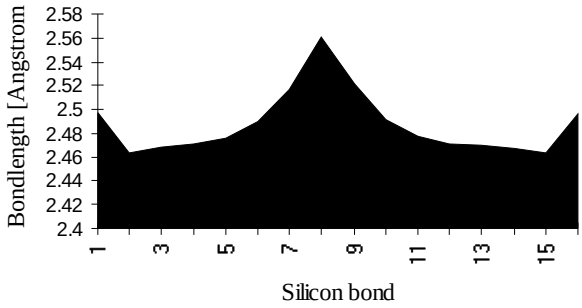

Figure 2. *Bond length distribution along the backbone chain.*

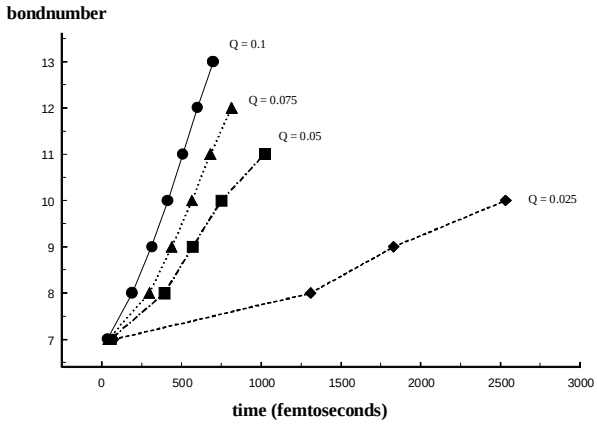

Figure 3. *Polaron-speed dependence on the electrical field-strength.*

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keynote lecture

Equilibrium and non-Equilibrium Molecular Dynamics of Complex Systems.

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Abstract

Large scale molecular dynamics simulations are performed on complex systems by parallel computers. The systems investigated include a biological system with enzyme activation, open systems with chemical reactions including oscillating reactions (Volterra- Lotka) and phase separation dynamics.

Some general and technical problems concerning large scale parallel computation as well as MD of chemical reactions in open systems will be discussed.

Temperature Dependence of Hydrogen Bonding in Liquid Amides

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Abstract

Temperature dependence of hydrogen bonding in neat, liquid amides is studied in a pure theoretical way. These calculations are based on standard ab initio self-consist field (SCF) methods for different molecular clusters and a quantum cluster equilibrium (QCE) model of liquids. The cluster sizes varied from one to six molecules and include linear and cyclic structures. The QCE method employs the optimized geometries, harmonic frequencies, and binding energies of each cluster to evaluate translational, rotational, vibrational and electronic partition functions by standard methods of quantum statistical thermodynamics. The condition of chemical equilibrium is used for solving the cluster populations in the canonical ensemble. The equilibrium cluster populations were determined for a large range of liquid phase temperatures. Macroscopic phase properties were then calculated by weighting the properties for each cluster by the appropriate cluster population at chosen temperatures. Quadrupole coupling constants, asymmetry parameters and geometries are sensitive probes of solution state hydrogen bonding. Therefore these properties were calculated for formamide, n-methylformamide and n-methylacetamide in the described fashion. Their temperature behaviour is in good agreement with results from NMR relaxation time and diffraction experiments.

Molecular Dynamics Simulation of the Proton Transport in Water

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Abstract

The results of molecular dynamics simulations of a rigid hydronium ion $(H_3O)^+$ in liquid water are reported. The water molecules are represented by the TIP3P-model, the ion has a pyramidal structure.

From NVE simulations the equilibrium spatial and temporal distributions of the first solvation shell water molecules to the hydronium ion were ascertained. It could be shown that a nearest neighbor water molecule is most probably found within a distance of 2.6 Å between the oxygen atom of the H_3O^+ -ion and the oxygen atom of the H_2O-molecule.

A two dimensional potential energy surface of the proton transfer within the $H_5O_2^+$-complex was calculated at the ab initio-level. The two coordinates of the surface were chosen to be the decisive degrees of freedom for proton transfer reactions, the oxygen-oxygen distance $R_{O\text{-}O}$ and the position of the transfering proton. Calculation of the energy levels, the position distribution and the temporal behaviour of the proton in the double minimum potential surface together with the results of the equilibrium distributions lead to the following conclusions:

i) The proton resides in a flat double minimum potential with low barrier inbetween the oxygen atoms. Consequently, the proton transfer in water is mainly an adiabatic process with no tunneling involved.

ii) The reaction coordinate is found in the solvens coordinates rather than in the quantum coordinate of the proton. This means that the rate limiting step of the proton mobility is the association to and dissociation of a $H_5O_2^+$-complex.

On account of these findings we propose a model for treating the proton transfer process by means of a mixed MD/MC algorithm. The hydrodynamic single particle diffusion is integrated within the framework of a classical molecular dynamics simulation, the quantum mechanical proton transfer along a O—H···O hydrogen bond is performed by a proton jump between the donating hydronium ion and an adjacent water molecule. After parametrization the model is able to correctly simulate the diffusion coefficient of the proton in water.

pH-Dependent Protein Stability Calculation of Absolute Free Energy Differences

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Abstract

A method for calculating the absolute electrostatic free energy of a titrating system as a function of pH is proposed. Based on the theory of linked functions, the free energy is calculated by integration of the titration curve of the system. The charge-state dependent electrostatic free energy of the system is calculated using the Finite-Difference Poisson-Boltzmann program UHBD [1]. For the calculation of the titration curve, a Monte Carlo program by Beroza et al. [2] is employed.

The new approach differs from the known methods of calculating the relative pH-stability of proteins by the use of pH= ∞ as the reference for the titration curve integration, where the energy is uniquely defined by the electrostatic free energy of the unprotonated state. It thus allows for the calculation of absolute free energy differences between two conformers as a function of pH, e.g., the native and denatured states of a protein or the bound and unbound states of a protein-ligand system.

The new method is applied to the protein hen egg-white lysozyme. To account implicitely for conformational flexibility, a dielectric constant of 20 is assigned to the protein interior. The relative pH-stability of lysozyme is calculated using an extended b-structure and the "Null" model of non-interacting sites as the unfolded reference state, finding good quantitative agreement with experiment. For the extended b-structure, a net free energy difference of -1.5 kcal/mol at pH=7 is found relative to the Null model, indicating that there are significant interactions between titrating sites in the unfolded state. Good agreement between theory and experiment is shown for the pH-stability of pepsin, the dimerization of HIV-protease, and the stability of foot-and-mouth disease virus capsid.

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Molecular Dynamics Simulations of Polypeptide Chains in Internal Coordinates

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Abstract

Using a new method for MD simulations of partially rigid macromolecules we study the influence of geometrical constraints on the dynamics of 16-polyalanin. In our approach a macromolecule is modelled as a chain of topologically linked rigid bodies where two rigid bodies can be connected in a common point or a common axis. A rigid body can have three moments of inertia or two, in case of a linear rigid body. The orientations of the rigid units are described by quaternions. This approach is well established in robot mechanics and has also been applied in MD simulations of molecular liquids consisting of completely rigid molecules. The main result of our study is that angle constraints may be imposed as long as the binding geometry of the C_{alpha} carbons is left flexible. Keeping e.g. the peptide planes rigid does not alter the essential dynamics of our model system. However, simulations in torsional angle space ('Phi-Psi-angles') lead to an unacceptable rigidification of the polypeptide backbone.

Stokesian Dynamics Simulations of Sedimenting Spheres

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Abstract

The dynamics of particles which move in a highly viscous liquid such that all motions are overdamped and random forces can be neglected is called Stokesian Dynamics. The simplest example is a macroscopic sphere which is pushed by a constant force through a viscous medium. According to the famous Stokes law the resulting velocity is proportional to the driving force. To describe the dynamics of many-particle systems one needs to take into account hydrodynamic interactions (HI) which are mediated by the liquid. Mathematically they are described by the friction matrix which replaces the friction constant appearing in the Stokes law for a single sphere. HI are long-ranged many-body interactions. Here we present Stokesian Dynamics (SD) simulations of clusters of spheres which sediment in a viscous liquid. The friction matrix is computed by using a force multipole approach developed recently. Since the friction matrix becomes singular for particles at contact the integration of the equations of motion requires a careful handling of close contacts. To be able to describe geometrically constrained assemblies, like e.g. large multidomain proteins, we develop schemes to compute friction and mobility matrices of such constrained systems. Depending on the applied forces these matrices can be used as well for Brownian Dynamics as for Stokesian dynamics simulations.

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Best Paper Award

Modelling of tripod Metal Compounds $RCH_2C(CH_2PR´R´´)_3ML_n$: Optimisation of Force Field Parameters by Genetic Algorithms

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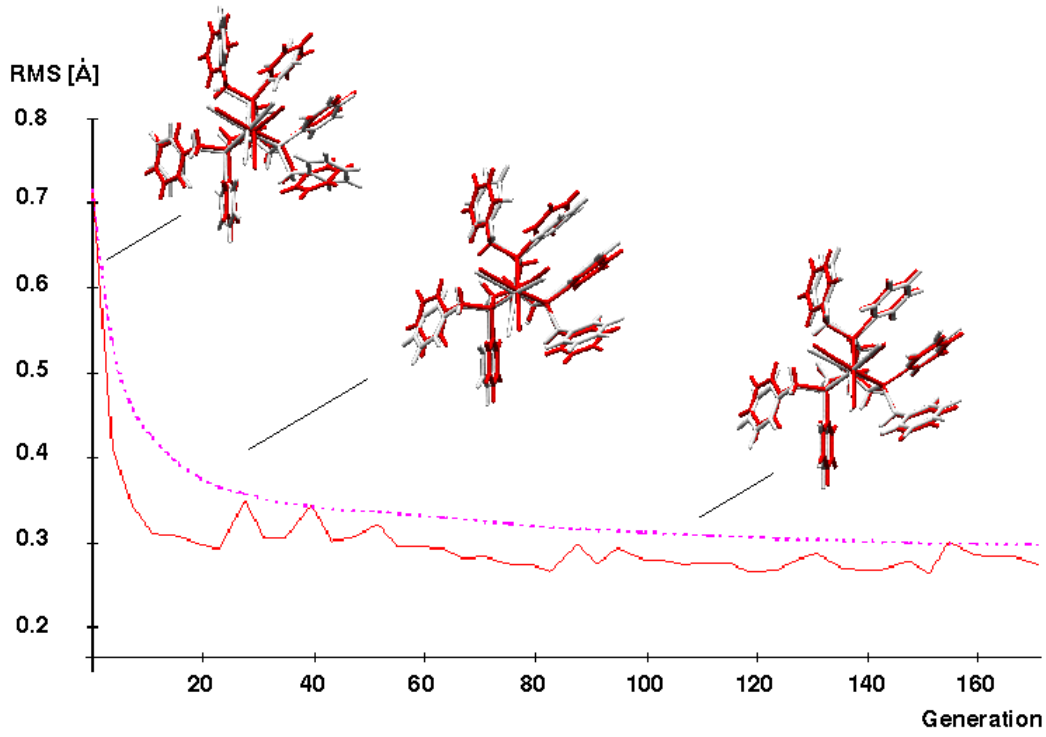
Abstract

The method of force field calculations has been established nearly exclusively on the basis of experimental data derived from organic compounds. In the last decade its application has been expanded to the modelling of inorganic compounds. This lead to the problem of lacking parameters, which describe the interactions of the metal center. Apart from the possibility of a more or less trial and error guess, no real method for the empirical developement of those parameters exists. Genetic algorithms [1] were found to be an efficient tool to develop missing parameters in a way highly superior to manual fitting. Often applied in Molecular Modelling for conformational search[2] they are, as far as we can see, the first time used to find local minima on the parameter hyper surface. This surface describes the caclulated potential energy of one and the same conformation varying the force field parameters. Applying an evolutionary algorithm in this way it is possible to generate a subset of selected parameters on the basis of a given set of solid state structures (Figure 1).

This is illustrated by the example of a subclass of metal complexes formed by *tripod* ligands of the type $RCH_2C(CH_2PR´R´´)_3$. A statistical analysis of the solid state conformations of *tripod* metal compounds $CH_3C(CH_2PPh_2)_3ML_n$(n=2,3) demonstrates that the conformations observed for these templates are dominated by the inner forces while the influence of packing forces is not determining [3]. A basic condition to model compounds of the type *tripod* ML_n (n=2,3) with Molecular Mechanics on the basis of solid state structures is thus given.

One way to reduce the multiplicity of possible solutions, given by the mathematical nature of the optimisation problem, is to expand the number of underlying solid state structures. In addition this can be achieved by reference to NOE-Data.



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GROMOS 96

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Abstract

The program package GROMOS has been used for many years as a versatile tool to perform energy minimization, molecular and stochastic dynamics simulations including free energy calculations, distance and position restraint simulations (e.g. for NMR refinement, model-building). Most applications were in the field of biomolecular systems, but also simulations of crystals, of small molecules or of pure solvent were performed. The new version of GROMOS, called GROMOS 96, is an essentially rewritten version of GROMOS 87. It uses standard FORTRAN 77 and is therefore easy to install on machines, ranging from a PC to a supercomputer. Concerning the handling of the program a number of improvements have been made, as for instance the input/output files being now more flexible and therefore easier to read, to commentor to change. Besides an improved force field, a number of new functions were added. The main aspects are:

- Soft core potential for the non-bonded interactions
- Molecular dynamics in 4 dimensions (extended conformational search, e.g. NMR refinement, loop search etc.)
- Free energy calculation of a system simulated in 4 dimensions
- Path integral calculations
- Inclusion of a reaction field
- Time-averaged atom-atom distance and J-value restraining
- Local elevation search
- Position constraining
- Separate temperature coupling to different parts of a solute molecule
- SHAKE free energy contributions

A number of new buildings blocks (defining the topology of molecular segments) have been added and the aromatic rings of amino acid residues contain hydrogen atoms. The following solvents are available, i.e. defined in the topology and interaction function parameters set: H_2O, CH_3OH, $CHCl_3$, DMSO, CCl_4. As its previous version, GROMOS 96 will be available to academic users for a price mainly covering the processing costs. This version will be delivered with a manual, not only describing the details how to handle the input, file formats etc., but also explaining the theoretical background of the simulation technique itself and the GROMOS specific extensions.

The Puzzling Forces and Energies Occuring at Simulated Conformational Transitions

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Abstract

The simulation of conformational transitions in macromolecules ranging from local events to large scale changes like refolding or unfolding is a rather new field of growing interest. The common goal of all techniques applied is the search for realistic pathways including barriers and intermediates and their energetic characterization. The quantative comparison with experimental equilibrium constants and rates re-

quires determination of free energy profiles. With a new technique also force profiles can be measured.

Like for small molecules, approximative minimum energy pathways (MEP) are sometimes determined by energy minimization (EM) to give a first idea of the actual pathway. They are characterized by the profile of minimum potential energy E_{pot}, U_o. For several reasons molecular dynamics (MD) simulations [1,2] are superior to energy minimization or even essential [3,4]. They yield broad pathways with large fluctuating energies E_{tot}, and show that the underlying true MEP has only little meaning. We shall show, however, that its energy profile U_o can be determined in a simple way by means of the Lagrangian L as $U_o \sim \langle -L \rangle = \langle E_{pot} \rangle - \langle E_{kin} \rangle$. The expression has proved to be a good estimate which never underestimates the true value U_o [5]. By comparison of U_o as obtained by EM and MD, it is shown that the latter method caused an enormous progress in the search for favourable pathways.

The free energy profile is identical with the potential of mean force. It is therefore obtained by thermodynamical integration of a mean force <F> over the reaction coordinate, which usually is a geometric variable like, for instance, the euclidian distance from the target configuration [5]. We have proved that this force is identical **in the mean** with the negative constraint force, $\langle F \rangle = - \langle F_{constraint} \rangle$, that must be applied in order to keep a given value of the reaction coordinate. This finding opens a practicable way for the numerical evaluation. Moreover, the fluctuations of the force can be minimized by using mass-weighted coordinates in a suitable way [6].

Recently MD simulations were successfully applied to determine force profiles and rupture forces which had been measured before by single molecule atomic force microscope experiments [7]. It is discussed why these forces are different from those mentioned above and are not related to free energy.

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A Hybrid-Approach for Flexible 3D-Database Searching

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Abstract

A combined method for flexible 3D-database searching is presented which addresses the problem of ring flexibility. The proposed hybrid-approach combines the explicit storage of ring conformations generated by the 3D-structure generator CORINA [1] with the strength of a flexible search technique which is implemented in the 3D-database system UNITY [2]. A comparison of the hybrid approach with the original UNITY-approach was performed by using a public domain database of about 130,000 molecular structures [3].

Five pharmacophor queries taken from the literature were searched following the hybrid-approach and the original method. The hybrid approach gained on average 10-20% more hits than the original UNITY-method.

In addition, specific problems with unrealistic hit geometries produced by the original approach could be excluded.

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Free Energies for Active Site Hydration and Substrate Binding to Cytochrome P450cam Computed by Molecular Dynamics Simulation

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Abstract

Solvent makes an important contribution to the thermodynamics of protein- ligand interactions. The active sites of proteins usually contain water molecules which are displaced into bulk solution when ligands bind and make a favourable entropic contribution to ligand binding. In order to calculate substrate binding free energies by computer simulation it is essential to account for the solvent. Yet, when a ligand binds on the surface of a protein, it is often difficult to identify the solvent molecules involved in the binding process. Cytochrome P450cam is therefore an ideal model system because the natural substrate, camphor, binds in a buried active site and the protein is experimentally well-characterized. Six water molecules were assigned to the electron density in the crystal structure of the ligand-free form [1]. Five of these cluster in one electron density blob and their actual number is not well defined. No water molecules were detected in the active site of the complex with camphor [2]. In order to calculate the absolute binding free energy of camphor, it is necessary to know the exact number of water molecules in the unbound state. We calculated the free energy differences for having six, seven, or eight water molecules in the active site from molecular dynamics simulations by thermodynamic integration employing a 3-step perturbation scheme. The energetic differences between the different degrees of hydration were relatively small (within 10 kJ/mol). In agreement with the crystallographic determination, we calculated that six water molecules is the most favourable arrangement. In further simulations, the six water molecules were exchanged with camphor, resulting in a computed absolute binding free energy of camphor within 5 kJ/mol of the experimental value.

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Correct Ranking of the Carboxypeptidase A Inhibition Strength using mixed QM/MM calculations

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Abstract

A combined QM/MM approach has been used to dock a series of seven flexible molecules into the active site of Carboxypeptidase A (CPA). In order to estimate the ranking of their inhibitor strengths (K_i), the difference between the heats of formation within the protein environment and a water cage was used. The starting structures for this investigation are the X-ray geometries of the corresponding protein/inhibitor complexes. The ligands were fully optimized within the fixed environment using our point charge model (PCM) including electrostatic polarisation and van der Waals interactions.

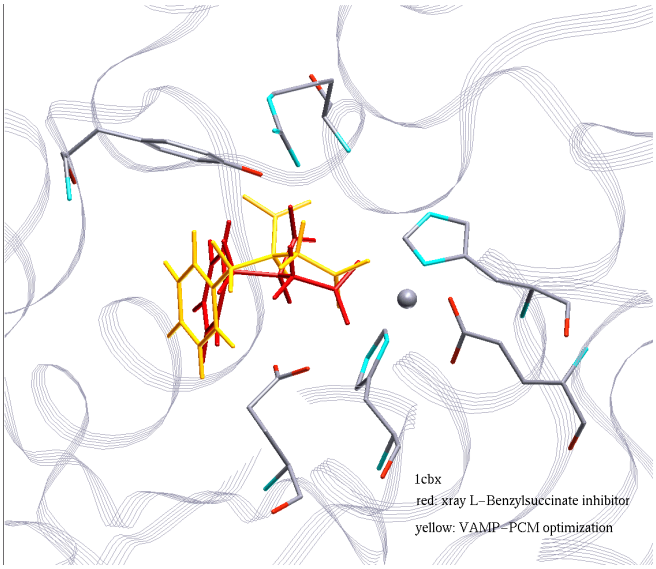

Figure 1. *X-ray structure of the active site of Carboxypeptidase A in complex with L-Benzylsuccinate inhibitor (red); VAMP-PCM optimized inhibitor (yellow).*

The figure shows an overlay of the X-ray structure of L-Benzylsuccinate (red) with the ligand calculated by VAMP-PCM (yellow).

The solvent calculations used a supermolecule approach including 28 water molecules around the inhibitor to obtain the heat of formation within the solvent. Using this approach we can reproduce the experimental inhibition strength ranking of the set of CPA ligands correctly. The following table shows the relative binding energies [kcal/mol] compared to experimental K_i values. To compare the orientation/conformation of the ligands after geometry optimisation with experimental data, the RMS deviation of the coordinates in relation to the corresponding X-ray structures is given (only heavy atoms are included).

system	binding energy [kcal/mol]	K_i [M]	RMS [Å]	Ref.
7cpa-fvf	-176.89	1.1E-14	1.65	1
6cpa-zaf	-171.88	3.0E-12	2.34	1
8cpa-agf	-144.85	7.1E-10	3.79	1
1cpa-cpm	-123.12	2.2E-7	1.29	2
1cbx-bzs	-107.15	4.5E-7	1.16	3
2ctc-lof	1.43	–	1.27	–
3cpa-gy	191.91	1.0E-4	1.58	4

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Stabilities of and Hydrogen Shifts in Oxidized DNA Base-Pairs: *ab initio* and DFT Calculations

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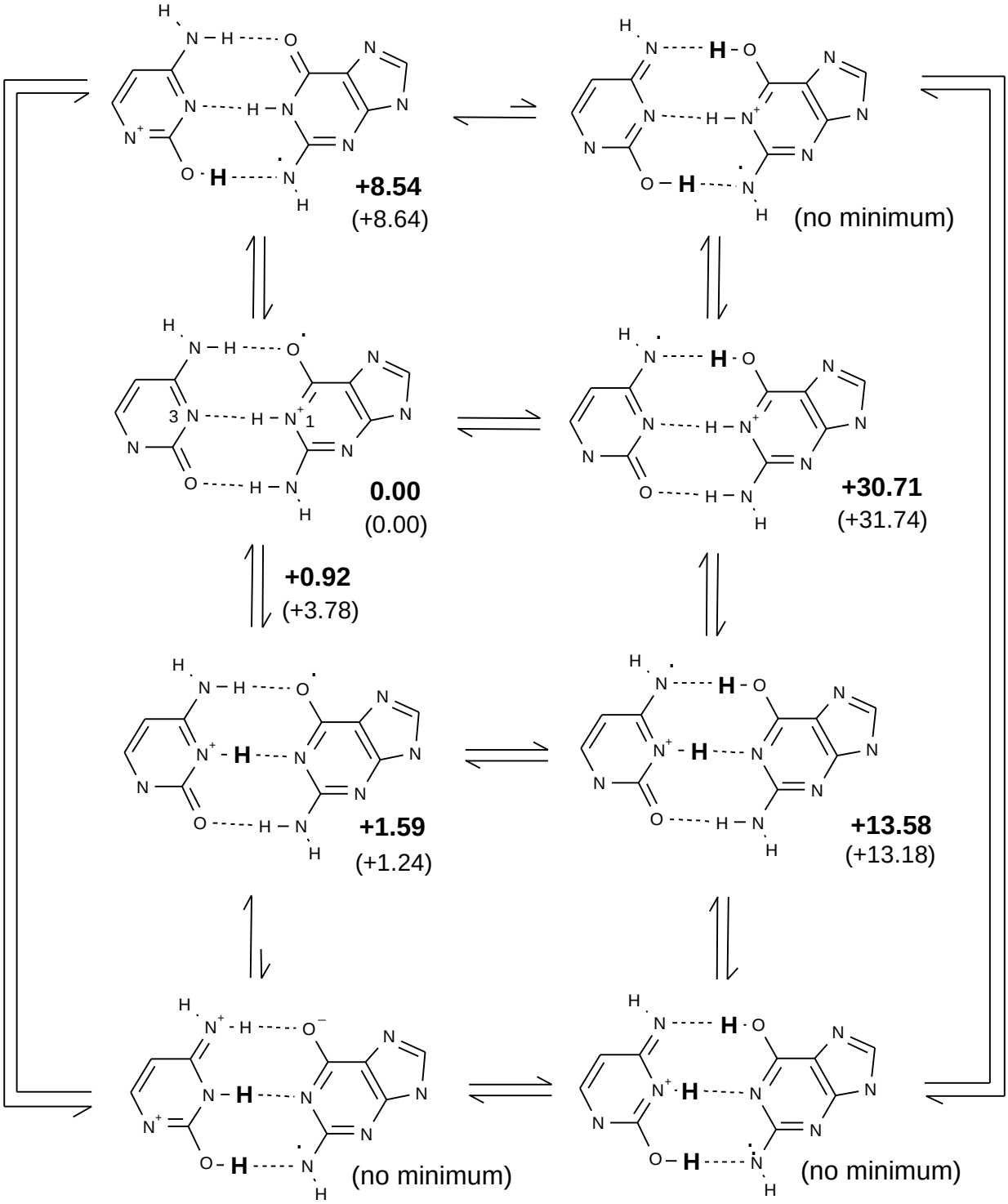
Abstract

Ab initio (UHF/6-31G*) and density functional (Becke3LYP/D95*) calculations have been used to investigate the structures and stabilities of radical cations of the DNA base-pairs as well as possible hydrogen shifts. The calculated structures of the corresponding neutral base-pairs show excellent agreement with crystallographic data. A particularly stable radical cation is formed by guanine (which has been shown to be the most easily oxidizable base) together with cytosine, so that the calculated adiabatic ionization potential for the guanine-cytosine hydrogen-bonded complex is about 0.75 eV lower than that of guanine itself. Isodesmic reactions show that the extra stabilization enjoyed by the base-pair radical cation relative to the uncomplexed base radical cation is about 7 kcal·mol^{-1} compared to AT$^{+\cdot}$. Calculations at UBecke3LYP/D95*//UHF/6-31G* show that shift of the central hydrogen-bonded proton at N1 of guanine to N3 of cytosine is only slightly endothermic (+1.6 kcal·mol^{-1}), while the product of the corresponding proton shift in the adenine-thymine system is unfavorable by +14.1 kcal·mol^{-1} . The two other proton exchanges in the guanine-cytosine system also result in higher energies (+8.5 and +30.7 kcal·mol^{-1}). Thus GC$^{+\cdot}$ can be considered as a resonance structure of two tautomers with rapid proton exchange along the central low-barrier hydrogen bond. These results suggest that the guanine-cytosine radical cation represents even more of a thermodynamic sink in oxidized DNA than might be concluded from the ionization potentials of the individual bases.



Scheme 1. *Energies of the guanine-cytosine radical cation tautomers in kcal/mol. Shifted protons are marked* ***bold****. values in brackets: UBecke3LYP/D95*//UHF/6-31G* values in* ***bold****: UHF/6-31G* (incl. zero point energies)*

Comparison of Molecular Dynamics and Energy Minimization Techniques for Pathway Determination

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Abstract

The determination of realistic pathways for conformational transitions in proteins ranging from local changes to complete unfolding is a rather new challenging task in the field of molecular simulations. As such transitions are rare events hindered by considerable barriers they are hardly seen in MD simulations except at extremly high temperature. Recently several techniques have been developped which are based either on energy minimization or modified MD simulation. Here we report studies of the extended T-R transition in the insulin hexamer and a conformational transition in alpha-chymotrypsin with both kinds of techniques. Insulin [1] was investigated using the targeted energy minimization (TEM) method [2], chymotrypsin [3] using the self penalty walk (SPW) method [4]. These techniques are based on energy minimization with different protocols for generating a pathway from a given starting structure to an given target structure. The same transitions were also investigated using targeted molecular dynamics simulation (TMD) [5,6] which differs from usual MD in that the distance from the target structure is a constraint variable which is continuously diminished during the simulation. The main features of TMD pathways are as follows:

(i) The deviation from the ficticious linear pathway is larger than with SPW. Similarity with the SPW path occurs near both ends.
(ii) They exhibt a less smooth course although they are quasi continuous with a large number of calculated points (some 10^5)
(iii) In contrast to TEM, symmetry is not maintainted on the way between the symmetric end states in the case of insulin.
(iv) Nonproductive pathways can be identified.
(v) The energies lie about 1 Megajoule/Mole below those found for energy minimization pathways.
(vi) The mean energy decreases with increasing simulation temperature.

The favourable energy behaviour has to be attributed to the fact that MD at room temperature can cross many of the numerous small barriers between conformational substates which are known to exist in proteins [7]. TMD pathways should not be interpreted as representative trajectories since they exhibit oscillations in a rather broad groove connecting the end states with intermediates. Therefore a thermostatistical evaluation, in particular a determination of free energy seems to be more appropriate, which is now in progress.

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Development of a Force Field for N-Oxides

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Abstract

For the development of a new set of force field parameters based on the CHARMM22 force field, *ab initio* Hartree-Fock and post-Hartree-Fock calculations at the MP2 level were carried out for pure compounds, mono- and dihydrates of aliphatic N-oxides. Structural information of the N-oxides and the position of the water molecules in the hydrates was obtained using the SCF/6-31G** basis set. Charges and dipole moments were calculated on the same level of theory.[1]

Coulomb interactions are described using "potential derived" (pd) charges, which represent the high dipole moment resulting from the wavefunction better then the charges derived from Mulliken population analysis. The Lennard-Jones parameters describing the non-bonded interactions were obtained by a simulated annealing fit [2] to the optimized structures of two N-oxide dihydrates.

Due to the high dipole moments of the N-O bonds, large H-bond energies were determined by single point *ab initio* calculations at MP2/6-311+G(2d,2p) level.1 The achieved parameters were able to reproduce the H-bond energies and geometries of optimized gas phase structures. Crystal parameters using rigid molecules are also in good agreement with experimental data.

The intramolecular force parameters were fitted to vibrational and structural data obtained from *ab initio* calculations by again using the simulated annealing approach.[3]

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Simulation of Small Polar Molecules on Oxide Surfaces

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Abstract

A realistic model of molecularly absorbed ammonia on the (110) surface of TiO_2 (rutile) has been studied by means of Molecular Dynamics. The simulations were carried out within a temperature range between 100 K and 450 K. The complex behaviour of the translational dynamics was attributed to the specific structure of the substrate and has been characterized as an "exchange reaction" between two distinct adsorbed states on the surface. The high lateral mobility of weakly bound 2nd layer molecules leads to rapid isotropic diffusion on the surface of micro-crystalline powders and thus serves as an explanation for the experimentally obtained singulett peak in ^{1}H-NMR spectra.

Unique Optimum Superposition of Molecules

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Abstract

A physically unique optimum superposition of equally large clusters of atoms or, more generally, of any data points in some d-dimensional real space can be obtained naturally in the set of inhomogeneous linear mappings. We define a quantitative measure for the similarity of (shapes of) clusters modulo linear distortions.

A Systematic Study on the Effect of Different Quantum Mechanical Methods in Combined QM/MM Potentials

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Abstract

A program has recently been developed in our group which allows us to do combined QM/MM studies using semi-empirical, *ab initio* and DFT methods for the quantum mechanical part. It has a modular structure and includes an interface between the quantum mechanical programs MNDO (semiempirical methods) and CADPAC (*ab initio* and DFT methods) and the molecular simulation program AMBER. In addition to the standard electrostatic coupling model widely used [1], a classical treatment of the polarization of the molecular mechanics region by the electric field of the quantum mechanical subunit has been implemented [2-4]. To partition a molecule into a small region which can be studied quantum mechanically and a larger part which is treated in a classical way we use the concept of link atoms [1].

Calculations have been done on small organic test molecules, using the different quantum mechanical methods available in the program. We compare the effects of these methods on the combined QM/MM potential and discuss the influence of the different coupling models, the link atom treatment, and the MM charges.

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Ab Initio Calculations on Propanediol Systems

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Abstract

The structural and energetic properties of monomers, dimers and monohydrates of 1,2-propanediols (PDL1,2) and 1,3-propanediols (PDL1,3) were investigated in a comparative way within the program package TURBOMOLE [1]. Moreover, conformational studies on perfluoric PDL1,2 and PDL1,3 molecules were taken into account.

The *ab initio* calculations were performed on the 6-31G level. The aim of these investigations was to study the influence of intramolecular and intermolecular hydrogen bonding on the structure and stability of such diols in a systematic way. By calculations on the dimers of the chiral PDL1,2 it was tested if there is a distinct stabilization of $(PDL1,2)_2$ formed by the same (R-R) and different (R-S) enantiomers, respectively.

In the case of the perfluoric diols the influence of alternative hydrogen bonds under participation of fluorine atoms on the conformational behavior was investigated in more detail.

Finally, the *ab initio* results on the perfluoric diols were used as reference data in order to adjust fluorine parameters in force field methods.

Up to now *ab initio* calculations [2,3] and experimental studies [4] on such diols were mainly performed to investigate the hydrogen bonding of the isolated molecules. Our results on PDL1,2 and PDL1,3 monomers are compared with theoretical data and IR spectroscopic findings of other authors.

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Molecular Dynamics Simulations on Chiral Biamphiphilic Tetraol Clusters

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Abstract

Investigations on the structure, stability and dynamics of biamphiphilic 1,2,7,8-octanetetraol (OTL) as well as 1,2,15,16-hexadecanetetraol (HDTL) were performed within MD simulations using the program package GROMOS87 [1].

These bolaamphiphilic molecules represent a new class of recently discovered amphotropic liquid crystals [2,3] which are also interesting as model systems for the study of molecular self-organization in bilayers. First results of MD simulations on clusters up to 64 tetraol molecules in the gas phase are presented. Especially, the role of intramolecular and intermolecular hydrogen bonding as well as the function of the bolaamphiphilic head groups on the process of association were studied in more detail.

Moreover, by structural modifications in the hydrophobic part of the monomers, e. g. regarding phenyl and cyclohexyl rings as well as olefinic bonds, the formation of the energetically preferred arrangements of the cluster were investigated in a systematic way. Clusters with HDTL molecules as monomers were taken into account in order to study the hydrophobic-hydrophilic balance on the molecular self-organization.

Comparing MD simulations on (OTL)16 and (HDTL)16 clusters in aqueous solution are presented. For the visualization of the molecular dynamics results a graphics tool was created on workstations. By this tool the results of the MD runs are illustrated and analyzed in a useful way. Especially, from trajectories of the distances of the chiral carbon atoms hints on the flexibility of the hydrophobic chain were obtained.

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A Simple Technique for the 3-D Projection of Moved Stereoscopic Images

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Abstract

A hard- and software development for the 3-D projection of moved stereoscopic images is presented. By an optical equipment the light from a video projector is orientated through a mirror construction as well as two polarization filters and projected on a screen. Using simple polarization glasses the 3-D projections can be viewed. In principle, the new optical equipment can be attached to any commercial video projector.

The stereoscopic image-pairs, generated by a corresponding graphics tool, can be projected both on-line from a graphics workstation and a video cartridge via the video projector. The hard- and software development enables a facil access for the projection of stereoscopic images and the 3-D viewing of moved pictures as e.g. the dynamics of molecular systems. This is of interest especially for the simulation and visualization of molecular processes in chemistry and biochemistry.

Moreover, by extentions of the graphics software any objects also under simulation of a changed viewer position can be generated as 3-D projections.

Calculation of ^{13}C NMR Shifts for the Analysis of Relative Configuration in Polyketide Natural Products

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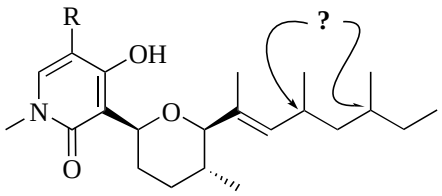
Abstract

^{13}C NMR shifts can vary strongly for different low-energy conformations as well as for different diastereomers of flexible hydrocarbon compounds [1]. The accurate calculation of ^{13}C shifts can therefore be a valuable tool to analyze relative configuration, if the conformational behaviour can be modeled reliably. However, in order to be applied routinely in organic chemistry, the computational methods involved must be quite efficient.

This goal is met in a three-step procedure: Molecular mechanics calculations are used for conformational analyses (MACROMODEL 4.5[2], MM3(94)[3]) and relative energies of the conformers, chemical shifts are calculated by a density functional method on the force field geometries (SOS-DFTP/IGLO in deMon/Master[4,5]) and the shifts are then weighted according to a Boltzmann distribution. This computational procedure is tested with a series of 1,3-dimethylated hydrocarbon compounds, which occurs often as segments in polyketide natural products. This yields an excellent agreement between calculated and experimental shifts. The method is then applied to elucidate the relative stereochemistry in the side chain of sambutoxine **1** and the bradykinin inhibitor **2**. It is shown that the methyl groups have relative *anti* configuration in compound **1** and *syn* configuration in **2**.



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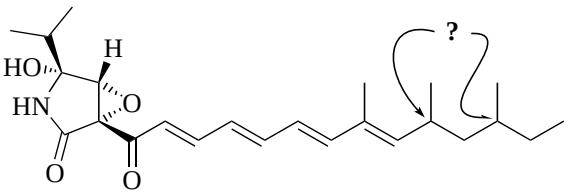

2

Figure 1. *Target molecules*

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Binding of LMW Inhibitors to Thrombin and Trypsin Studied by Electrostatics Calculations

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Abstract

The electrostatic free energy of binding has been calculated for a series of thrombin and trypsin X-ray structures in complex with LMW inhibitors. The calculations have been performed either with the UHBD or the MEAD program. Both programs use the finite difference solution to the Poisson-Boltzmann equation for determing electrostatic interactions. A modeling protocol has been optimized which also takes into account solvation entropy changes during the binding process. We demonstrate that the electrostatic energy and the empirically derived solvation entropy can reproduce the experimental binding energies almost quantitatively.

Rotational Barriers of Various Ureas - a New Force Field Parametrization

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Abstract

To build a parameter set for force field calculations of ureas the accuracy of semiempirical calculations was not sufficient. Exact ab initio data concerning the rotational barriers of different substituted and unsubstituted ureas were necessary. The presented material also gives insight into the rotational barriers of different ureas.

High-level ab initio calculations have been performed on urea, methylurea, tetramethylurea and three isomers of dimethylurea to obtain accurate rotational barriers. Results of MP2(fc)/6-31G(d) calculations are compared to those with lower basis sets and semiempirical calculations.

The MM2(87) force field was reparametrized [1] for the R_2N-CO-NR_2-unit through fitting of ab initio and Xray data. Molecular geometries and rotational barriers were calculated on different levels of theory. With the new parameter set MM2 was able to reproduce the results of ab initio calculations als well as the Xray data of several compound classes. Ab initio calculations of the rotational barriers of urea, methylurea, different dimethylureas and tetramethylurea allow a comparism of the influence of the basis set on the rotational barrier.

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Structures, Energetics, and Dynamics of Transition Metal-Activated Lactone-Bridged Biaryl Complexes: a Density-Functional Study

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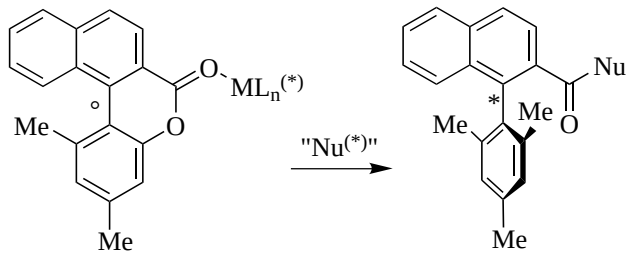
Abstract

Axially chiral biaryls can be stereoselectively synthesized by metal-assisted cleavage of lactone-bridged helically twisted biaryl systems [1]. The stereoselective ring opening (s. Scheme 1) of the helimerizing lactone-bridged biaryls to give configuratively stable products can be achieved either by chiral metal-activated nucleophiles or by achiral nucleophiles and activated benzonaphthopyranones *e.g.* by coordination of a chiral Lewis acid to the carbonyl group.

A most promising modification of this concept is the use of planar-chiral η^6-coordinated transition metal fragments **3** [2]. Hereby three crucial questions are of interest:



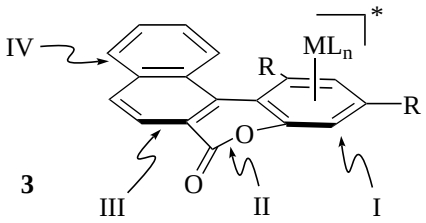
1 *(M)*-**2**

Scheme 1. °: *stereochemically unstable*
**: stereochemically stable*

1.) Which regioisomer (**I**, **III**,or**IV**) will be formed by variation of the substituents R and the metal fragment ML_n?
2.) How is the influence of transition metal fragments on the structure and the barriers for the interconversion of the two helimers?
3.) What kind of mechanism is involved in the ring opening reaction of **3**?

In previous work we performed *ab initio* calculations [3,4] on structure and dynamics of free and main group Lewis acid activated biaryl lactones.

Here we present first results on *ab initio* DF-calculations of the transition metal-activated biaryl lactone complexes **3**. Ground state structures and relative energies of the regioisomers of **3a** and **3b** were calculated by means of the LDA-VWN method [5]. The thermodynamically most stable regioisomers calculated agree with those found experimentally. The calculated global minimum structure parameters of the helically twisted complex **3a** match very well with those previously obtained through X-ray structure analysis [6]. Additionally, two atropisomeric minimum structures with different rotating positions of the $Cr(CO)_3$ rotor were found per regioisomer. Therefore and due to the periodically increasing steric interaction during the helimerization process, we assume a correlation of the dynamic of the $Cr(CO)_3$-group with that of the biaryl axis.



3

	ML_n	R
3a	$Cr(CO)_3$	Me
3b	$Cr(CO)_3$	*t*Bu

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Visualization of Local Physical Properties on Molecular Surfaces: The Mapping Function

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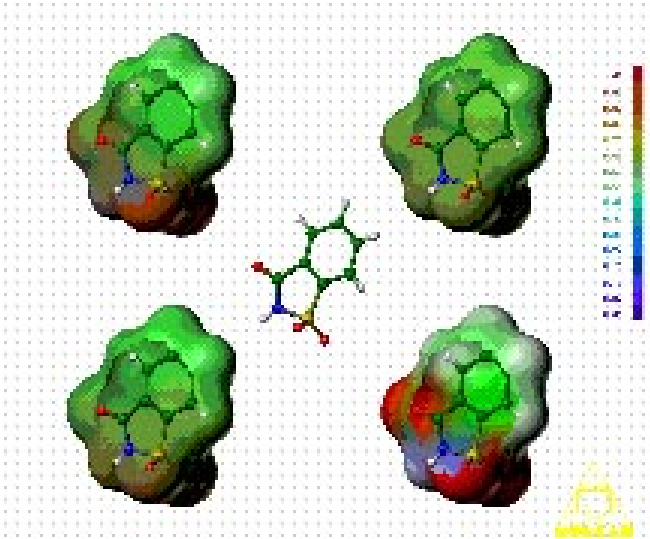
Abstract

The display of local lipophilicity/hydrophobicity mapped on a molecular surface is a well established example of visualization of an intrinsic physical quality [1]. This implies that the overall hydrophobicity of a molecule can be obtained by the superposition of any defined set of atomic/fragmental contributions. However, the mapping procedure is based on the concept of molecular lipophilicity potentials (MLP) first introduced by Audry [2] in order to describe a 3D lipophilicity potential profile in the molecular environment. Crucial to the physical relevance of the lipophilicity potential is the choice of a function which governs the behavior of a physical quality with distance. While Audry chose a simple $(1+d_i)^{-1}$ term, d_i being the distance of a molecular/atomic fragment i from any point in 3D-space, several other authors proposed different functions, e.g. an exponential distance dependence



or the concept of a 'hydrophobic dipole moment' by Fauchère [3] and Eisenberg [4], respectively. The function under investigation is that developed by Brickmann and coworkers [1]. This particular function was successfully applied for predicting logP (Octanol/Water) values [6] as well as to an qualitative assessment of receptor sites by Lichenthaler et al. [7].

In this presentation the quality mapped on Connolly's *solvent accessible surface* [5] does not have any physical meaning, it merely represents the portion of an atom to the surface indicated by a predefined color code for each atom. Depending on the choice of function parameters this will result in a colored surface with areas of great atomic overlap (mixed colors) or rather single colored regions where only one atom dominately contributes to that particular surface increment. Therefore the function devises a 'contribution range' to the generated surface allowing both localization and quantification of surface dependent qualities as it has been demonstrated for *free energy surface density* (FESD) by Pixner et al. [6] The parameter dependency of the function and the consequences for the visualization is presented and illustrated.

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Density Effects on the Structure of Liquid Silicon A Molecular Dynamics Study

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Abstract

The effect of a global and local density decrease on the structure of the tetrahedral bond network of liquid silicon is studied via molecular-dynamics simulations. It is found that the structural changes resemble those already obtained in molecular-dynamics models of water. Decreasing the global density leads for example to more pronounced peaks in the radial distribution function and to a smaller number of nearest neighbours up to the point where the network disrupts. In this case very large holes occur, indicated by the distribution of the volumes of the Voronoi polyhedra.

The local density decrease produced by a dissolved Lennard-Jones particle causes a similar structural enhancement in its nearest surrounding. This is indicated by more pronounced peaks in the radial distribution function of the atoms in the "solvation shell" compared to the bulk atoms. An analysis of the orientation of the Si-Si-bonds around the solute reveals that the structure of the shell can be compared to that one found in molecular-dynamics models of the hydrophobic hydration shell in water/Lennard-Jones systems.

Solvation Effects in PIMM

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Abstract

The force field used in PIMM [1-3] is parametriced for vacuum calculations. To consider solvation effects we applied and tested several continuum models.

The most suitable method is based on the algorithm of W.C. Still et al [4] by using the generalized Born equation and calculating effective born radii for all atoms.

By using optimized contact radii for the different atom types it is possible to calculate heats of solvation in good agreement with experimental data. The continuum model we use works without any problem with our MD.

Correct trends are calculated for solvent effects such as keto enol tautomerization of acetylacetone and cyclohexandione and the rotational barriers in amides.

We are currently starting to use this approach with our MD to study small peptides in solution and the effects of solvation on the Ramachandran plots.

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A Combined Semiempirical MO/ Neural Net Technique for Estimating vicinal H,H-Coupling Constants $J(H,H)_{vic}$

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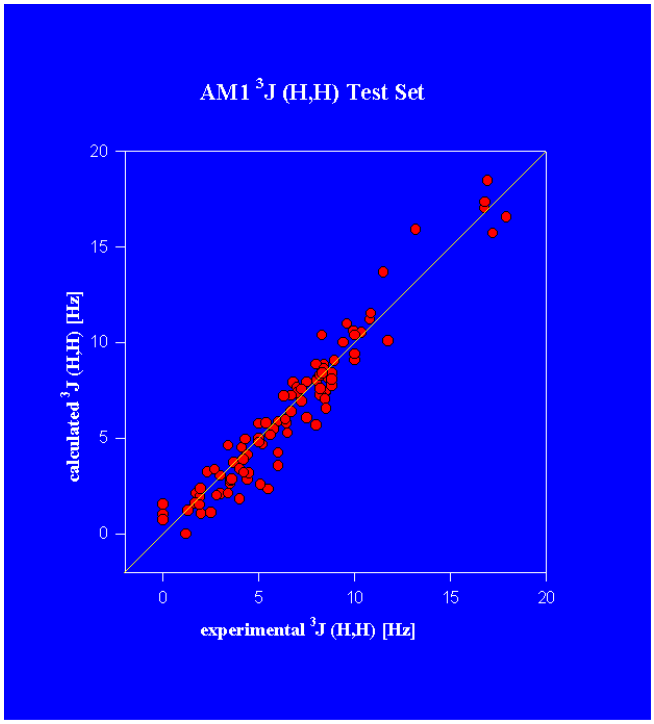
Abstract

A back-propagation neural net has been trained to estimate J (H,H) from the vic results of AM1 semiempirical MO calculations. The input descriptors include the complete electronic environment (bond orders and atomic charges) and all geometrical factors as dihedral angle, valence angles and distances for an individual H-C-C-H moiety. Our net can mainly handle rigid organic compounds, because we are not able to consider conformational effects.The resulting net estimates the vicinal H,H-coupling constants of a test set of 95 different coupling constants with a standard deviation of 0.98 Hz from the experimental values for AM1 with a maximum error of 2 Hz.



Homology Modeling of the Small Sialidase from *Clostridium perfringens*: Use of Laser Photo CIDNP(Chemically Induced Dynamic Nuclear Polarization) Techniques and Site-directed Mutagenesis to Ascertain the Reliability of the Modeled Structures

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Abstract

Sialidases (N-acylneuraminosyl-glycohydrolases, EC 3.2.1.18) hydrolytically cleave alpha-glycosidically bound sialic acids, derivatives of the amino sugar neuraminic acid. Sialic acids are mostly found as terminal constituents of oligosaccharides, glycoproteins and glycolipids in higher animals. The sialidases, however, are widely distributed not only throughout the metazoan animals of the deuterostomate lineage, but also among protozoa, viruses, fungi and bacteria, most of which are unable to produce sialic acid by themselves. Remarkably, the enzyme is often produced by microorganisms, which live in close contact with an animal host, whereby the enzyme may serve as a pathogenicity factor, or as an important tool for nutrition [1].

X-ray structure of sialidase of *Salmonella typhimurium* was used as the template for homology modeling of *Clostridium perfringens* sialidase (CPS). Both FastA and BLAST algorithms indicate high similarity between these two enzymes. The amino acids located in the four 'Asp boxes' and those of the active site of the enzyme are highly conserved. Construction of the starting framework, fitting of the CPS backbone, addition of loop regions and missing side chains, and preliminary refinement of model were carried out using the Swiss-Model Automated Protein Modelling service [2]. The generation of hydrogen atoms and automatic assignment of partial charges of each atom were accomplished using the INSIGHTII. The structures were then submitted to an MD simulation using the CVFF force field at a temperature of 300 K with an equilibration time of 20 ps and production period of 100 ps. The ten lowest potential energy conformers were selected for further minimization and surface accessibility calculation of aromatic residues.

The function of sialidases can be studied with help of mutants constructed by site-directed mutagenesis [3]. Based on the known three-dimensional structure of the *Salmonella typhimurium* sialidase, amino acids analogous to those that seem to be important for substrate binding or catalysis, were selected for mutation in CPS. The activity of some of the mutant sialidases was strongly decreased but the Km-values were hardly changed.

The side chains of tyrosine, tryptophan and histidine are able to produce CIDNP (Chemically Induced Dynamic Nuclear Polarization) signals after laser irradiation in the presence of a suitable radical pair-generating dye [4]. The CIDNP technique has previously been used for comparative studies of non-specific and specific interaction between the lac-repressor headpiece and DNA denatured states of lysozyme as well as of glycoproteins in glycosylated and deglycosylated form or in sialylated and desialylated form in solution.

The results from CIDNP experiments with CPS and its mutant forms indicated significant changes in the pattern of surface accessibility of aromatic residues of CPS in all of the mutants, which is in complete agreement with the measured Connolly surfaces of amino acids in the modeled structures.

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The Conformation of *tripod* Metal Templates in $CH_3C(CH_2PPh_2)_3ML_n$: Statistical Methods, Neural Networks and Molecular Mechanics

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Abstract

In most cases specificity in coordination chemistry is dominated by a specific choice of the ligands surrounding the metal. Homogenous catalysis and, even more so, the subset of enantioselective catalysis are clear illustrations of this statement.

Part of this specificity will arise from steric interactions. In order to be able to predict specificity a thorough knowledge of these steric interactions is therefore needed. One basis for acquiring such a knowledge is currently available in many cases: A considerable amount of information exists on solid state structures (determined by X-ray analysis), most of it deposited in an orderly and easily retrievable way in internationally available databases. The wealth of information contained in these data files is, as yet, far from having been systematically exploited.

The systematic analysis of all such structural data describing the solid state conformation of *tripod*Co templates (*tripod* = $CH_3C(CH_2PPh_2)_3$) for compounds *tripod*CoL_2 and *tripod*CoL_3 is presented (Figure1). The interest in this analysis stems from a research programme aiming at an understanding of the chemical reactivity of a subset of ligand metal templates in which the ligand is a neopentane based tripodal entity. The programme involves the three following steps: 1) synthesis of a library of neopentane based *tripod* ligands $RCH_2C(CH_2X)(CH_2Y)(CH_2Z)$ (X, Y, Z = donor groups), 2) understanding and modelling the shape of *tripod* metal templates *tripod*M, 3) correlating the results of a catalysis mediated by *tripod*M with the shape of *tripod*M.

The synthesis of *tripod* ligands $RCH_2C(CH2X)(CH2Y)(CH2Z)$ with three different donor groups X, Y, Z is well established including the enantioselective synthesis of ligands containing three different phosphorus donor groups. Catalysis mediated by tripod metal templates has been observed and it is thus time to approach the understanding of the shape of tripod metal templates.

An experimental basis for the development of such an understanding may be found in the X-ray data pertaining to a

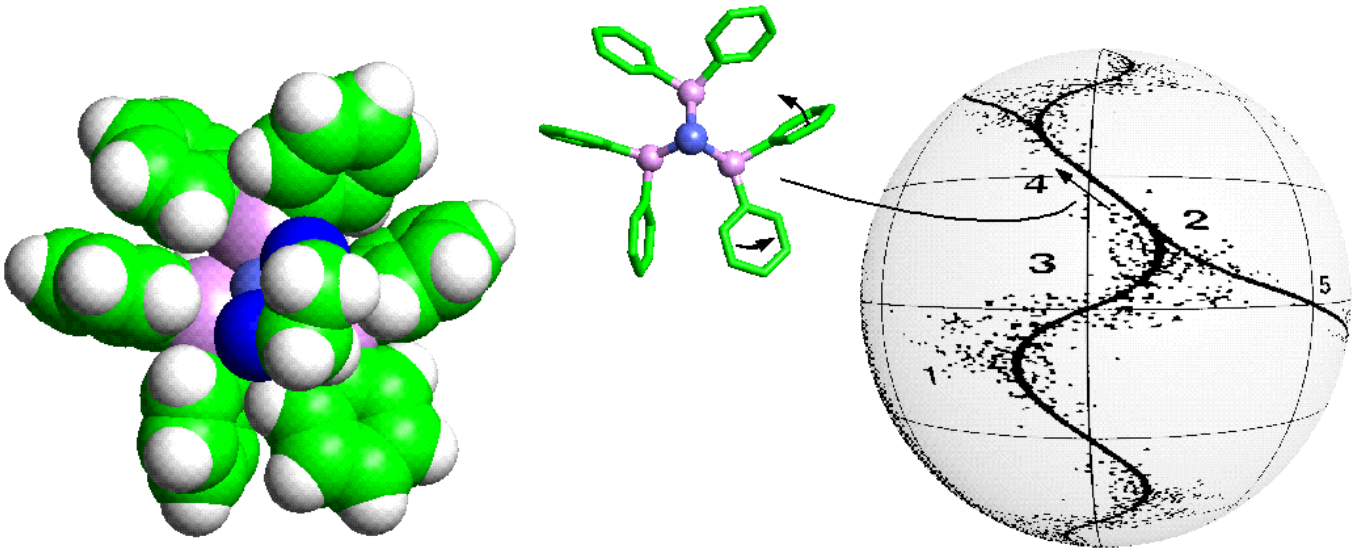

Figure 1. *Solid state structure of* $[CH_3C(CH_2PPh_2)_3Co(en)]^{2+}$ *(en = 1,2-Diaminoethane), the schematic* tripod*Co template of this compound, its symbolic mapping according to the torsional positions of the phenyl groups and indicated pathways for conformational change.*

specific tripod ligand CH3C(CH2PPh2)3. Since most of the data referring to this ligand are available for tripodCo templates the systematic analysis has been restricted to cover tripodCoL2 and tripodCoL3, thus resulting in a data basis of 82 tripodCo templates [1,2].

The traditional tools for this type of analysis [3,4], such as conformational space group scatter graphs (Figure1), principal component analysis (PCA), partial least squares (PLS) and hierarchical clustering, have been applied to the data [5]. They allow for the classification of conformations and the elucidation of pathways in conformational space. This type of information in itself forms a basis on which the construction of force field models may be built.

As a method that is not yet traditional in conformational analysis the methodology of neural networks has also been applied to the data [6,7]. It is shown that this technique reproduces the results from the traditional methods but also has merits of its own that recommend its further application in conformational analysis.

The Molecular Mechanics approach proved its ability to reconstruct the patterns obeserved in conformational space of the tripod metal templates [8].

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Structure-Reactivity Correlations by a Modified PIMM Force Field

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Abstract

In our group a force field for carbocations and anions was developed which differs from other versions of PIMM [1,2] in its special parameters for charged carbon atoms. It is appropriate to all kinds of hydrocarbons like unsubstituted and substituted aromatic cations or aliphatic carbocations. Furthermore the program has been successfully tested for aromatic carbanions.

Carbocations

The heats of formation, proton affinities, and hydrid affinities of aromatic compounds with delocalized charge (e.g. allyl-, tropyliumions) calculated with PIMM agreed well with experimental values. Applied to σ-complexes of benzoid systems or substituted allyl cations we obtained relative stabilities of these systems that are in good agreement with experimental data.

Carbanions

Proton affinities and heats of formation in a series of about 20 aromatic systems were calculated with PIMM. The results reproduced well experimental values.

Strain-reactivity correlations for the solvolysis of tertiary alkylbromides

It is well known that the solvolysis rate of a tertiary hydrocarbon is dominated by the difference of steric strain between alkylbromide and cation. It is caused by the tertiary carbon atom holding the leaving-group which changes from a tetrahedral to a planar geometry. The first force field calculations were applied to these systems by Schleyer [3]. A good strain-reactivity correlation was obtained for the solvolysis of caged hydrocarbons. Miller et al. [4,5] included also acyclic and monocyclic tertiary halides in their calculation with a modified MM2-program. Our calculations for the molecules treated by Miller with PIMM resulted in a strain-reactivity plot with a comparable scattering.

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Temperature Dependence of the Properties of Liquid Crystalline PCH5 – A molecular dynamics simulation study –

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Abstract

A system containing 200 molecules of the liquid crystalline substance PCH5 is studied at temperatures between 310 K and 450 K by means of molecular dynamics simulations. These investigations are aimed to study the temperature dependence of the static and dynamic properties such as order parameters, translational and orientational diffusion and pair correlation functions of a realistic model of a mesogen. Special effort was made on the electrostatic part of the interaction potential. It is found that in many cases e.g. when dealing with macroscopic parameters, the influences of the system size and simulation time limitations are seen very clearly. On the other hand single particle dynamic properties and local processes such as pair formation can be successfully studied by computer simulations.

Computer Aided Modelling of *Rhizopus Oryzae* Lipase Catalyzed Stereoselective Hydrolysis of Triglycerides

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Abstract

Lipase from *Rhizopus oryzae* catalyzes the stereoselective hydrolysis of triacylglycerols and analogues. Enantio-preference and degree of enantiomeric excess of the product varies with the structure of the substrate: 2-O-octyl, 2-hexyl, and 2-octanoyl substituted triacylglycerols are preferentially hydrolyzed at pro-*sn*-1 with decreasing enantiomeric excess, substitution by 2-phenyl reverses the enantiopreference to pro-*sn*-3.

We have modelled the stereoselectivity of *Rhizopus oryzae* lipase by docking the tetrahedral intermediates of these substrates in both the pro-*sn*-1 and pro-*sn*-3 orientations.

The initial complexes were further relaxed by molecular dynamics simulations. In their preferred orientation the tetrahedral intermediates fit well into the binding site. In the unfavourable orientation the complex is destabilized by three effects: (1) Repulsive interaction of the *sn*-2 group with the side chain of Leu 258 and - to a minor degree - with other residues, which leads to (2) deformation of the substrate conformation and (3) destabilization of the oxyanion hole.

Our model is consistent with experimental data and explains the ranking of four different substrates. It can be used to design lipase mutants with modified enantioselectivity.

K411B, A Triazine-Binding Single-Chain Antibody: Structure Modelling and Hapten Docking

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Abstract

The single-chain antibody fragment (scFv) K411B, which binds to various triazine herbicides, was cloned, sequenced and tested for relative affinities in the group of Prof. B. Hock, Freising, Germany [1,2]. As there is no experimental structure available, we have modelled the structure by homology: for both light and heavy chain, antibodies with a known structure and a high degree of sequence homology in the framework regions were found. The complementarity determining regions (CDRs) were identified, and for three of the six CDRs, canonical structure classes according to the concept of Chothia and Lesk [3] were assigned using the Kabat database [4]. The remaining CDRs were modelled by loop searching or conformational search algorithms.

Hapten docking was performed while carefully examining the cross-reactivity pattern of the scFv. Thus, the number of possible orientations of the hapten within the binding site was significantly reduced by exclusion of orientations which are not consistent with the cross-reactivity data.

This model can be used to understand the molecular basis for the specificity pattern of K411B and to predict mutants with designed specificity for biosensor applications.

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Cyclofructins: Geometries, Electrostatics and Lipophilicity Patterns, and Inclusion Complexes

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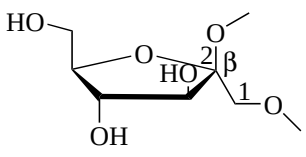
Abstract

Cyclofructins composed of six (α-CF, **1**) to ten (ε-CF, **5**) β(1→2)-linked fructofuranose units (i.e. *cyclo*[D-Fru*f*β(1→2)]n with n = 6 - 10) were subjected to conformational analysis using "Monte-Carlo" simulations based on the PIMM91 [1] force field [2,3]. Far reaching similarities and identical over all conformations of the solid state geometry [4] of a cyclofructin (**1**) and its computer generated form provide information about the reliability of the computational analysis.



1 *cyclo*[D-Fru*f*β(1→2)]$_6$
2 *cyclo*[D-Fru*f*β(1→2)]$_7$
3 *cyclo*[D-Fru*f*β(1→2)]$_8$
4 *cyclo*[D-Fru*f*β(1→2)]$_9$
5 *cyclo*[D-Fru*f*β(1→2)]$_{10}$

Calculation of the molecular surfaces for the energy minimum structures establishes a disk type shape of the cyclofructins with six to eight residues, ring enlargement to nine and ten residues leads to torus shaped molecules with central cavities that conceivably allow for the formation of inclusion complexes. The color coded projection of molecular lipophilicity patterns (MLPs) [5] and electrostatic potential profiles (MEPs) onto these surfaces displays the crown ether-

like properties of the disk shaped cyclofructins. The central cavities of **4** and **5** should be amenable to the formation of inclusion complexes similar to those formed by cyclodextrins.

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Molecular Similarities in Estrogenic Chemicals: Evaluation by Genetic Algorithms and Neural Networks

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Abstract

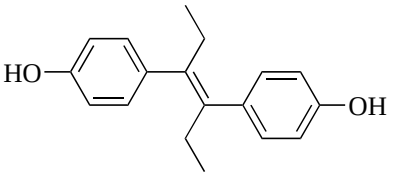
Applications of *Genetic Algorithms* and *Neural Networks* give rise to increased efficiency in toxicological and pharmaceutical research. In addition, new comprehensive analyses of specific receptor-substrate interactions are possible.

Natural or environmental estrogenic chemicals, such as insecticides and pesticides like p,p'-DDT, coumestrol or diethyl-4,4'-stilberol (**1**), displace the sexual hormone testosteron in male organism and prevent its binding to the androgen receptor. Blocking the natural action of testosteron causes abnormalities in male reproductive tracts. [1] The female sexual hormone estradiol (**2**) is also a well known testosteron antagonist. Thus, similarities between estradiol and thirteen environmental estrogenic chemicals have been investigated by Genetic Algorithms and Neural Networks.

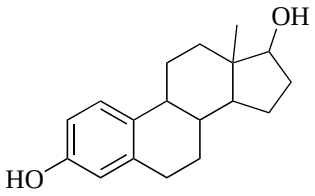
Superimposing the three-dimensional structures of **2** and the estrogen-mimetics (e.g. **1**) by a Genetic Algorithm [2] reveals the parasubstituted aromatic system **3** as *MCSS (maximal common substructure)*. The MCSS of the different ligands, which bind to the androgen receptor reveals the *pharmacophore.* The latter is a prerequisite for high affinity receptor binding.

Self organizing Kohonen-networks [3] generate two-dimensional maps, which allow the comparison of molecular shapes and physicochemical surface properties, such as van-der-Waals surfaces, electrostatic and hydrogen binding potentials. These qualities are of pre-eminant importance for the evaluation of similarities between **2** and the thirteen estrogenic chemicals. The similarities are less evident for the electrostatic potentials, but much more significant for the van-der-Waals surfaces. Excellent agreement is apparent from comparisons of the hydrogen bindingpotentials of **2** and the estrogen-mimetics.

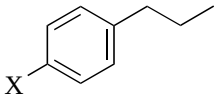
As is revealed by both, the MCSS **3** and the analysis of the molecular surfaces, the affinity to the androgen receptor is significantly determined by hydrogen bond acceptor functions (e.g. oxygen atoms) attached to the six-membered ring systems.



1 diethyl-4,4'-stilberol



2 estradiol



3 MCSS
X = O, Cl

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