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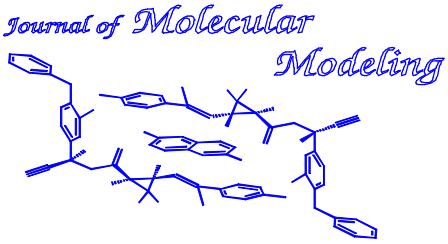

Proceedings of 9th Molecular Modelling Workshop Darmstadt, Germany, May 23 – 24, 1995

Preface

As editor of this journal and as secretary of the *Molecular Graphics and Modelling Society (Deutschsprachige Sektion)*, I have pleasure in presenting this volume: It contains a wealth of material including all aspects of molecular modeling, ranging from method development and application to multimedia data presentation.
With over 200 attendees the workshop attracted more people than ever before. As always, the meeting was devoted mainly to talks by graduate students and postdocs, so that the traditional workshop character was once again evident.
Thanks are due to all those who have submitted contributions and the keynote speakers Manfred Sippl (University of Vienna), Hugo Kubinyi (BASF Ludwigshafen) and Gerd Volkers (ETH Zürich). Special thanks go to Dr. Michael Krug (Merck, Darmstadt) who was in charge of the organization of the scientific program and to Prof. Jürgen Brickmann and his group for trouble-free course of the technical part of the program that also offered the chance to get insight into the possibilities of real multimedia application in the field of molecular modeling. The abstracts collected here give a flavour of the meeting.
We do hope that this collection of abstracts will encourage attendance of the 10th Molecular Modelling Workshop 1996 in Darmstadt. The *Molecular Modelling Workshops* are organized under the auspices of the *Molecular Graphics and Modelling Society - Deutschsprachige Sektion.*

Tim Clark, Erlangen 6th July 1995

keynote lecture

Progress in Fold Recognition

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The prediction experiment reveals that fold recognition has become a powerful tool in structural biology. We applied our fold recognition technique to 13 target sequences. In two cases, replication terminating protein and prosequence of subtilisin, the similarity between predicted structures and experimentally determined folds is close to atomic resolution. For the first time, in a public blind test, the unknown structures of proteins have been predicted ahead of experiment to an accuracy approaching molecular detail. In two other cases the approximate folds have been predicted correctly. According to the assessors there were 12 recognizable folds among the target–proteins. In our post-prediction analysis we find that in 7 cases our fold–recognition is successful. In several of the remaining cases the predicted folds have interesting features in common with the experimental results.

We present our procedure, discuss the results and comment on several fundamental and technical problems encountered in fold recognition.

Which Factors Determine the Strength of Protein-Ligand Interactions ?

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80 protein-ligand complexes with known 3D–structure and binding constant have been analysed to obtain some information about the factors that determine the strength of protein-ligand interactions. The following parameters have been investigated:

1) The number and geometry of hydrogen bonds and ionic interactions between the protein and the ligand.
2.) The size of the lipophilic contact surface.
3.) The flexibility of the ligand.
4.) The electrostatic potential in the binding site.
5.) The size of holes along the protein-ligand interface.
6.) Water molecules in the binding site.

Based on these investigations, a new simple empirical scoring function has been developed to estimate the binding constant of a protein–ligand complex of known 3D–structure. The function distinguishes between buried and solvent accessible hydrogen bonds. It contains 6 adjustable parameters and reproduces the binding constants of the calibration data set with a standard deviation of 7.5 $kJ \cdot mol^{-1}$. The scoring function can be used for the priorization of the hits obtained from de–novo ligand design programs (such as for example LUDI).

The Determination of Maximal Common Subtopologies in Protein Structures

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For many applications the determination of structural similarities is an essential part of analysing chemical compounds and biochemical structures. In contrast to small chemical compounds protein structures are more complex so that they are often described on different structural levels. The secondary and supersecondary structure level is of special interest, because structural motifs of spatially adjacent secondary structure elements are often responsible for the function of the protein without constituting already a domain structure itself.

We describe a method which enables us to search efficiently for maximal common substructures in a set of protein structures. In order to obtain a unique description of the secondary structure of a protein we model the protein topology as an undirected labelled graph so that the vertices represent helices or strands, respectively, and the edges describe spatial adjacencies between the vertices. Connected components in these graphs represent structural motifs and are called topology graphs. In order to find maximal common substructures in a set of topology graphs we reduce the maximum-common-subgraph problem in two graphs to the maximum-clique problem in one graph. For this purpose we define the product graph for two corresponding graphs. Each maximal complete subgraph (each maximal clique) in the product graph corresponds to a maximal subgraph in both participating topology graphs.

For solving the NP-hard maximum-clique problem we enumerate all maximal cliques in product graphs. Our method bases on the algorithm of Bron & Kerbosch . The efficiency of our method is founded on two optimizations. First, we recognize and eliminate equal search spaces. Second, we cut the search space and reduce the number of maximal cliques drastically by building up only those maximal cliques, which correspond exclusively to isomorphic connected subgraphs in the participating topology graphs. For the largest topology graphs we considered (with 32 and 55 vertices, respectively, and 36 and 74 edges, respectively), the product graph has 316 vertices and 40109 edges. We can enumerate the resulting 323 cliques for this example in a few minutes.

For searching for maximal connected subgraphs in more than two topology graphs we compute all maximal common subgraphs for all pairs of the given topologies and store the appropriate edge sets of both topology graphs. Using set operations such as intersection on these edge sets different analyses are possible. For instance we can quickly compute the maximal common substructure in a set containing more than two topology graphs.

In the talk we explain the function of our algorithm for computing of maximal common substructures in protein topologies on the basis of examples from the PDB.

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Development of a Receptor-Ligand Database

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New biomolecular and computational methods have led to an explosion in the available biomolecular data, e.g protein sequences and structures. Unfortunately, existing data is spread over different sites in different formats or is not available in electronic format at all. A common data model and flexible and efficient access mechanisms are missing. One goal of the RELIWE project, a collaboration between GMD, EMBL, BASF and E.Merck for the “Computation and Prediction of Receptor-Ligand Interactions”, is the development of a database which provides all available experimental information relevant for the modelling of receptor ligand complexes.

As a technical platform we use the object-oriented database management system VODAK, developed at the GMD-IPSI, which offers a structured data model, flexible retrieval mechanisms, support of persistent storage and sharing of data in a multi-user environment. In order to populate the database we have developed a parser for the automatic identification of receptor ligand complexes in the Brookhaven Protein Data-

base [1]. Complexes are identified using a flexible set of criteria which treats metals, small molecule ligands, nucleic acid ligands and peptide ligands adequately. Solvent molecules and molecules covalently connected to the receptor are ignored at present.

In order to allow a detailed chemical analysis of receptor ligand interactions the extracted ligand information is enriched with information unavailable in protein structure files, i.e. bond types and hybridisation states by analysing bonding distances and bond angles. Solvent accessibility and secondary structure of the receptor chains are calculated by executing the DSSP program [2].

The parser also produces cross-references for each chain of the receptor to the following databases: the sequence databases SWISSPORT [3], PIR [4] and EMBL [5], the dictionary of Protein Sites and Patterns PROSITE [6] and the protein mutant database PMD [7]. These cross-references are used to scan the SWISSPORT and PMD databases for sequence conflicts, such as insertions and deletions, residues missing due to disorders, conflicting and ambiguous experimental results (e.g. amino acids typed as ASX, GLX or UNK). The parser also extracts information about mutations and modifications, e.g. acylations, glycosylations or phosphorylations. Sequence positions of mutations and modifications from the SWISSPROT and PMD databases are automatically converted to the PDB sequence numbering system.

To enable an easy and selective retrieval of data, algorithms for substructure searching, similarity searching and sequence comparison have been implemented and integrated into the database system.

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FlexX: Time-efficient Docking under Consideration of Molecular Flexibility

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We present a program, called FlexX, for placing flexible molecules into the active site of a protein. The two major goals in the development of our docking program are the development of molecular flexibility of the ligand and the development of a model of the docking process that includes explicitly the physico-chemical properties of the molecules. Therefore we build up the receptor-ligand interaction by a few special types of interactions. These are hydrogen bonds, metal- acceptor bonds and some specific hydrophobic contacts. An interaction is modelled by an interaction center and an interaction surface located on a sphere around the center. Two groups A and B are able to interact, if the interaction center of group B lies on the interaction surface of group A and vice versa. In FlexX the interaction surfaces in the receptor are modelled by sets of discrete interaction points. Basically the implemented docking algorithm consists of three phases: The selection of a base fragment, the placement of the base fragment into the active site and the incremental construction of the ligand. Except for the selection of the base fragment, the algorithm runs without manual intervention.

The basic idea of the algorithm for placing the base fragment is to search for triples of interaction points in the active site which correspond in distance and type to a triple of interaction centres of the ligand. Once the base fragment is placed into the active site, we can start an incremental construction process, beginning at the base fragment. In each iteration, a new fragment is joined to all placements found so far in all conformations of a finite set of energetically favourable conformations (discrete conformational model [1]). Placements having overlap with the receptor are eliminated. In both phases the geometries of the ligand placements are calculated by superimposing interaction centres of the ligand onto corresponding interaction points of the receptor. For the new placements obtained, the binding energy is estimated by an empirical energy function [2] and

the best k placements are passed on to the next iteration. Optionally these placements can be optimized w.r.t. the energy function by a quasi-Newton method. This optimization leads to a decrease of the calculated binding energy by a few kJ/mol and to some differences in the ranking of the solutions, because the docking algorithm based on discrete methods produces complexes which normally are not local minima. Although the influence on the resulting rms deviations from the crystal structure is rather arbitrary, this procedure should be chosen if the estimation of binding energies is the main reason for the calculations.

Also for further studies and improvements of the energy function the local optimization is a necessary task. The program is tested by reproducing about a dozen receptor-ligand complexes with known X- ray structure. For an example of typical complexity like Thrombin {Napap (about 10 rotatable bonds and a flexible ring) the complete docking run needs about two minutes on a SUN SPARC station 20. In most cases, the algorithm predicts a placement of the ligand which is similar to the crystal structure (about 1.5 Å rms deviation or less) as the highest ranking solution. A placement with rms deviation of about 1.0 Å is normally found among the 10 highest ranking solutions.

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Transferred NOE-Experiments for the Determination of the Antibody-bound Conformation of a *Streptococcus* Antigen

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The replicating unit of the *Streptococcus* Group A cell-wall polysaccharide antigen consist of a trisaccharide shown in figure 1.

Immunological studies have shown, that size and the branch point of different fragments of the antigen are crucial elements for antibody recognition [1].

The branched trisaccharide α-L-Rha-(1→2)-[β–D–GlcNAc–(1→3)]–α–L–Rha–(1→0)–Pr[A'(C)B] is one of the fragments which are bound by the monoclonal anti–*Streptococcus* antibody **Strep 9** (mouse, IgG_3). The kinetics of the binding process allow the observation of TRNOEs (Transferred NOEs) and therefore the determination of the bound conformation of this antigen.

It was shown with the aid of TRROE (Transferred ROE) experiments [2], that lots of the observed TRNOEs arose through spin diffusion. Simulated annealing– and energy minimization calculations were performed with four remaining TRNOE– and TRROE effects. It turned out, that constraints derived from the absence or TRN(R)OE effects were important as constraints derived from TRN(R)OE effects in defining the bound conformation of the trisaccharide antigen.

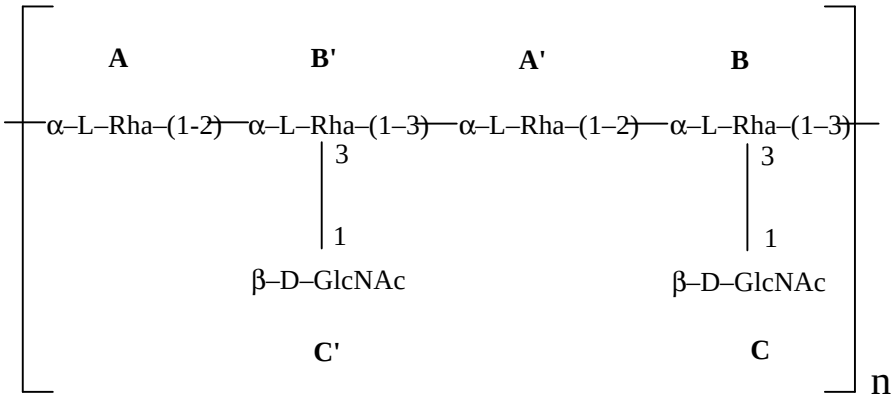

Fig. 1: *Replicating unit of the Streptococcus Group A cell-wall polysaccharide antigen.*

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Virtual Reality Modeling Language: A New Tool For Molecular Modeling On The World Wide Web ?

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A new technique to provide chemistry related information is presented. The approach is based on the Virtual Reality Modeling Language (VRML) which extends the World Wide Web (WWW) interface with the additional ability to visualize three dimensional (3D) object oriented scenarios and interact with the basic elements. Since most of the models in molecular science need 3D representations the new technique can be applied very effectively in chemical information networks.

This is demonstrated in a distributed environment with an example from molecular recognition: The active site of the enzyme Cytochrome P450 is systematically explored. This enzyme plays a key role in cancer research.

BPT Molecular Mechanics : A New Approach to Force Fields With Fluctuating Atomic Charges

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The bond polarization theory (BPT) as described in [1] is a general semiempirical scheme to calculate diverse molecular properties if they depend primarily on the local electron distribution around a nucleus. Its quantum chemical starting points resemble the PCILO–method.

The virtue of this theory is that we get bond-additive linear equations for description of the change of molecular properties with bond polarization. The parameters within these equations can be calibrated directly to experiments or more sophisticated calculations. In the case of atomic charges the parametrization was performed for C, H, N, O using the results of ab initio STO-3G calculations. Once the set of parameters is determined the charge calculation requires only the solution of a set of linear equations with the dimension of the number of atoms.

This method is suited for the application in molecular mechanics and dynamics simulations to overcome the limitations of most force fields used up to now. One of the weakest points in these simulations is the use of fixed or topological charges to define the electrostatic potential. The BPT method is integrated in the molecular modelling program COSMOS 4.0, which was awarded with the “European Academic SoftwareAward 1994”. The BPT charge calculation method as well as the molecular mechanics and dynamics program are available in ANSI-C language for implementation on workstations and other programs.

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Conformational Dependence of Molecular Charge Distributions

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Conformational changes are often accompanied by significant changes in the molecular charge distribution [1]. This effect can have important consequences for the intermolecular interaction potential of molecules as well as for their conformational potential surface. For example it has been shown that the neglect of the difference between the charge distributions of the cis- and trans forms of N-methylacetamide yields wrong relative hydration energies [2].

We will discuss the influence of conformational changes on the molecular charge distribution for three model compounds. In order to improve the description of the charge distribution of flexible molecules we will start from the assumption that there are two contributions. The first is the polarization of parts of the molecule in the electric field of other parts. The second is a local effect, for which there is no analogue in intermolecular perturbation theory and which seems to be more important. We will present a method for describing the second effect in terms of a simple Fourier series in the torsional angle. We will compare the electrostatic potentials obtained from torsion-dependent and torsion-invariant atomic multipole moments and atomic point charges and use the potential from ab initio densities as a benchmark [3].

Finally, we will address the question to what extent the torsion dependence of the charge distributions alters the torsional potential if the molecule is exposed to an external electric field, for example, the field might be caused by another molecule acting as a hydrogen bond donor. The interaction energy will become more favourable if the electron density on the acceptor atom is increased. If this becomes possible by a change of a dihedral angle, we obtain a new field induced torsional potential.

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GRASP: Minimization of Arbitrary Target Functions of Internal Coordinates of Solvated (Bio-)Polymer Systems

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GRASP (Gradient in Angular SPace) can be used for minimizing any cost-function of a system of (bio-)polymers with solvent. There is no inherent constraint w.r.t. the number of molecules, apart from hardware restrictions. GRASP may also be usefully applied to smaller molecules.

Some simple but instructive sample calculations will be presented for illustrating and analysing the performance of GRASP. GRASP uses the relevant internal coordinates, i.e. torsional angles and relative translations and rotations of non-covalently bonded molecules. The constraints of constant bond lengths and valence angles are respected exactly. The cost-function can be given as some function of the cartesian coordinates of the atoms and molecules. GRASP frees the user from caring about the relative degrees of freedom, i.e. he merely provides a separate file for each molecule of the system. The simple fact that for (bio-)polymers the number of internal degrees of freedom (d.o.f.) is considerably lower than the number of cartesian d.o.f. yields the important speed-up factor. Being based on an analytical formula, which markedly generalizes the one of Go et al., GRASP does not waste time for the calculation of the gradient in internal d.o.f.; GRASP rather shows a significant net gain in speed, which amounts to at least a factor of five.

So far GRASP is not parallelized, which is possible, since our algorithm is highly parallelizable.We emphasize that GRASP can be applied to almost any cost-function, e.g. potential energy. In particular, the cost-function may merely be given on a grid. Therefore, GRASP can be useful in a very large range of problems concerning the conformation of (bio-)polymers, including most important areas like protein crystallography and docking calculations based on discrete molecular affinity potentials.

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keynote lecture

Molecular Modeling and Drug Design – Dream and Reality

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Specifically acting drugs bind to receptors, enzymes, ion channels, signal– or carrier–proteins, DNA or other biological macromolecules.

The indispensable prerequisite for this bonding is the complementarity of the surface properties of both partners.

Following advance in the structure elucidation of proteins rational drug design shows increasing importance. However, every structure or computer based drug design depends on several essential requirements:

- all analogs show the same mechanism of physiological activity.
- the biologically active conformations of the drugs can be predicted.
- all analogs bind in a similar manner.
- the influence of isosteric structural modifications can be estimated.
- the bonding is closely correlated to the energy of interaction.
- the physiological activity shows a close correlation to the bonding.
- animal assays can be substituted by simple *in vitro* assays.
- drug design is a rational deterministic method.

Unfortunately not all these requirements are met in the majority of practical cases. The preferred conformation of a ligand depends on its surroundings, it can show considerable differences *in vacuo*, in solution, in the crystal state and especially at the binding site. Structurally closely related molecules often bind in a different fashion. Even in the case of identical binding modes the biological activities can differ considerably. Minor structural modifications of a protein (e.g. enzymes or receptors of different species) may cause drastic differences in the affinities and hence in the physiological activities.

Additionally, structure or computer based drug design can take into account only the affinity to a single binding site, mainly from an enthalpic point of view. For a ligand to qualify as a drug further requirements have to be met. Resorption, transport– and distribution properties, metabolic and catabolic reactions, together with a high selectivity and the absence of severe side reactions play an important role.

Present theories and methods are far from giving reliable predictions in every case. In spite of indispensable advances in QSAR, 3D QSAR and rational drug design the search for new drugs is often based on arbitrary assumptions.

Only from 3-dimensional structures of ligand–protein–complexes we can obtain the sound knowledge we need to broaden our arsenal of methods for the specific design of new drugs

Then maybe we can turn the vision of a rational drug design into reality.

Suggestion of a New Catalysis Mechanism in Serine Proteases Exhibited by Dipeptidyl Peptidase IV. Unusual Stabilization of the Oxyanion Tetrahedral Intermediate may cause a *trans-cis*Pro Isomerisation of the Substrates.

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A molecular model of the active site of the serine protease dipeptidyl peptidase IV (DPP IV or CD26) has been developed on the basis of a Comparative Molecular Field Analysis (CoMFA) of competitive inhibitors and by force field calculations. The model helps to understand a multitude of experimental findings concerning the substrate specificity of this enzyme as well as results obtained by gentechnique experiments [1].

Semiempirical PM3 reaction coordinate calculations were performed to study the catalysis mechanism. Surprisingly, the first tetrahedral intermediate (oxyanion) in the acylation step may be stabilized by formation of a chemical bond of the oxygen atom of the oxyanion to the carbonyl carbon atom of the Xaa-Pro(Ala) peptide bond of the substrates. The calculations indicate that in this way the negative charge of the oxyanion is transferred to the oxygen atom of the peptide bond preceding the proline residue. This negative charge may

be compensated by a transfer of a proton of the positively charged N-terminus of the dipeptide to this oxygen atom that additionally (by about 8 kcal/mol) support the complete mechanism. This mechanism leads to a loss of the mesomeric stabilization of the X-Pro(Ala) peptide bond indicated by a pyramidal nitrogen atom, the tetragonal bound carbon atom and a resulting dihedral angle C_{δ}-N-C´-O(H) of about 70°. These results are supported by an observed secondary hydrogen isotope effect for k H cat /k D cat = 0.85 ± 0.09 for the H-D exchange of the proton of the C_{α}-atom in P 2 -position during the substrate hydrolysis of Ala-Ala-pNA.[2] That could not be explained for a long time since this position is relatively far from the cleavage position of the peptide bond. The proposed model may explain for the first time this observed secondary hydrogen isotope effect on the basis of quantum chemical calculations.

As a next step we performed PM3 reaction coordinate calculations of the decomposition of the tetrahedral intermediate. The finally formed acylenzyme may be stabilized more by interaction of the N-terminus with the carbonyl oxygen atom of the ester group with a *cis*Pro than with a *trans*Pro conformation.

This may be an indication for a new mechanism of a *trans-cis*Pro isomerization of the substrates of DPP IV substrates but that may be also of importance for other enzymes.

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Ionized DNA-Base-pairs: Ab initio Calculations

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Ab initio (UHF/6-31G*) and density functional calculations (UBecke3LYP/D95*) have been used to investigate the structures and stabilities of the radical cations of the DNA bases and base-pairs. All geometries were fully optimized at HF/6-31G*. Corresponding single point energies were performed at Becke's 3 parameter functional with the non-local correlation provided by the Lee-Yang-Parr functional. For the DFT Calculations the basis set D95 of Dunning and Huzinaga was applied with an additional polarization function.

The calculations of both vertical and adiabatic ionization potentials show a constant deviation of 0.3 eV compared to experimental data. The most easily oxidizable base, guanine, forms a particularly stable cation base-pair with cytosine, so that the calculated adiabatic ionization potential for the guanine-cytosine hydrogen-bonded complex is 0.78 eV lower than that of guanine itself. These results suggest that the guanine-cytosine radical cation represents even more of a thermodynamic well in oxidized DNA than might be concluded from the ionization potentials of the individual bases. Isodesmic reactions at UBecke3LYP/D95*//UHF/6-31G* show that the stabilization of the guanine radical cation during base-pair formation is about 7.2 kcal/mol better than the corresponding adenine radical cation.

The proton shift in the guanine-cytosine radical cation from N1 of guanine to N3 of cytosine is with 1.2 kcal/mol only slightly endothermic and has an activation barrier of 3.8 kcal/mol, although unrestricted CI calculations at 6-31G* level have shown that more than 90% of the positive charge is located on guanine. These results show that guanine is especially exposed to subsequent ionic reactions leading to mutations of DNA.

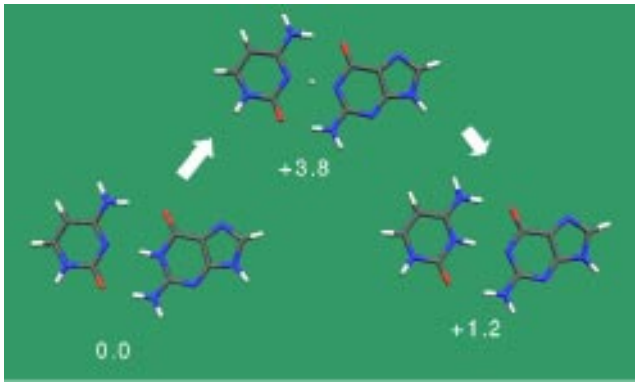

Figure 1: *Reaction profile for the proton shift in the GC radical cation base-pair at UBecke3LYP/D95*//UHF/6-31G* (energies in kcal·mol^{-1})*

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The Influence of Lewis Acids on Structure and Dynamics of Lactone–Bridged Biaryls: Quantum Chemical Studies

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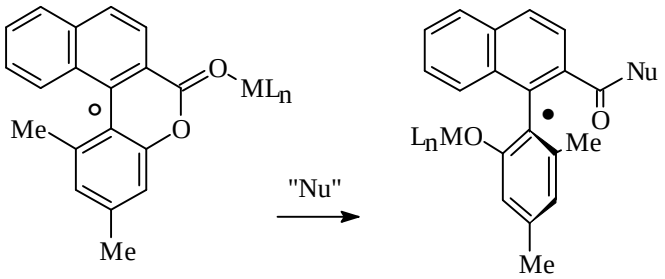
Lactone–bridged biaryls like **1a** (Scheme 1) play an important role in a novel concept for the stereoselective synthesis of axially chiral biaryl compounds: Triggered by a nucleophilic attack to the carbonyl function, these configuratively unstable lactones can be opened so that only one of the two axially chiral, since configuratively stable atropisomeric products **2**, *e.g. (M)*–**2**, results.[1]



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

ML$_n$	-	H^+	Li^+	BF_3	$AlCl_3$
1	**a**	**b**	**c**	**d**	**e**

Scheme 1: *Atrop–selective ring opening of lactone– bridged biaryls **1**;(°): stereochemically unstable; (•):stereochemically stable*

This interesting reaction can be assisted by various types of Lewis acids.[2] In order to provide information about principal effects of Lewis acid coordination on structure and helimerization behaviour of these lactones, semiempirical (MNDO, PM3) and *ab initio* (MP2/6–31G ˜//RHF/3–21G) calculations were applied to the model compounds **1a**–**e**. Structurally, these calculations show an increase of the exocyclic C=O bond length accompanied by a contraction of the endocyclic C–O bond and a significant planarization of the central lactone ring which unexpectedly does not lead to a lower overall distortion of the molecule. In addition, we had previously performed semiempirical force calculations for the prediction of vibrational frequencies of the free lactone **1a** and the complex **1e**.[3] In that study, an excellent agreement of the experimental und the calculated shifts of frequencies was observed, demonstrating the good reliability of the calculations. The helimerization barriers of the free lactone compound and the corresponding complexes, as defined by the zero point energy corrected differences of the enthalpies of the ground and transition structures, were determined performing *ab initio* calculations (MP2/6-31G ˜// RHF/3–21G) for each of these stationary points. Depending on the strength of the Lewis acid, the calculations predict a more or less distinct decrease of the helimerization barrier for all the complexes **1b**–**e**. An unexpectedly strong effect was observed for the $AlCl_3$ complex **1e**: while the helimerization of **1a**–**d** passes two enantiomeric non–planar transition states, 4 the complex **1e** helimerizes *via* only one planar and thus achiral transition state (Scheme 2).

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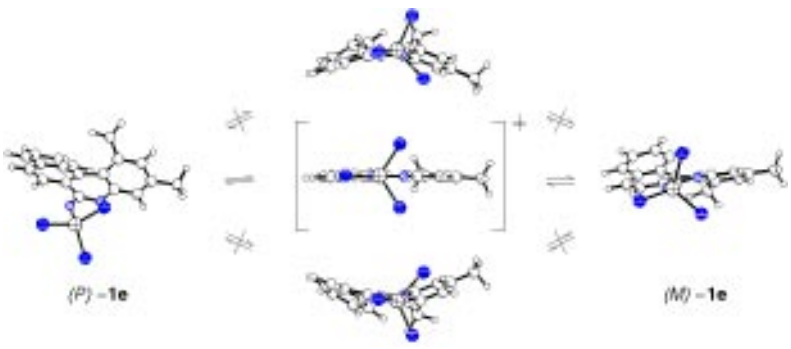

Scheme 2: *Helimerization process of **1e*** via *a planar transition structure*

Orthogonalization Corrections for Semiempirical Wavefunctions

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A new quantum chemical method is introduced which is based on the semi-empirical NDDO approximation. It is suggested to improve the established semiempirical models such as MNDO, AM1 and PM3 by the explicit inclusion of valence-core and valence-valence orthogonalization corrections and penetration integrals in the core Hamilton matrix. The core repulsion function is based on a simple point-charge model. There is no longer need for special parametrized exponential correction terms to account for the neglect of repulsive orthogonalization terms in the Hamiltonian. The mentioned corrections in the one-center part of the core Hamiltonian were implemented at the NDDO level only recently [1].

Improvements were especially found for ionization potentials and excitation energies. However, conformational properties such as rotational barriers and conformational preferences still are reproduced only poorly. Guided by basic considerations on the origin of those barriers it seemed necessary to include valence-valence orthogonalization corrections also in the two-center part of the core Hamiltonian, i. e. in the resonance integrals. Those pseudo-potentials were derived from a second-order expansion of the S-1/2 matrix as suggested already before [2]. To our knowledge, however, they have never been implemented and tested in actual calculations.

We added these corrections with three-center contributions to the mentioned NDDO implementation and parametrized the new model preliminarily for the elements H, C and O. The statistical evaluation of ground-state properties shows the same improvements over MNDO, AM1 and PM3 as the 1993 model and results in a mean absolute error in the computed heats of formation of 3.5 kcal/mol. Improvements over the 1993 model are indeed found for conformational properties.

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The Morphon Concept - a Way to Molecular Morphogenesis

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An algorithm is presented for a “self assembling”-program. It uses abstract objects - so called morphons - to calculate 3D models of multimolecular complexes in an acceptable time. Morphons are wireframe models of real proteins or their 3D atomic models that can represent the attributes of real molecules with any given accuracy. Therefore, they present an ideal interface permitting different formats for the atomic models of the single proteins for the “self assembling”-program.

The introduction of formal parameters for binding site, code sides and positional information makes it possible to formulate unique conditions for docking and fixing of the modelled objects. The examination of all geometrically possible orientations of the individual morphons relative to each other or to the final objects of morphogenesis makes it possible to find all complementary and affinity positions of each component. Therefore, formal conditions are described to define the genesis of a form. The subsequent permutation and comparison of the final objects permits identification of the final objects. Application of the program results in identical objects or a set of isomers or homologous objects.

The formation of the final objects from the morphons used is obligatory and reproducible. Finally, the original atomic models of the proteins can be substituted for the morphons.

Assessing Combinatorial Libraries by Spatial Autocorrelation Functions and Neural Networks

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Different approaches to the combinatorial synthesis of large libraries are being developed in many research groups all over the world. They provide the chemist with an abundant number of libraries he has to chose from in the search for new potential drugs. We present here a means to compare combinatorial libraries and to assess their diversity and the degree of difference between them.

Spatial autocorrelation functions are used to describe the three-dimensional structure of the library compounds [1]. A subsequent analysis of these autocorrelation functions with a Kohonen neural network allows to map the high-dimensional chemical space described by a combinatorial library into two dimensions. Then it is possible to estimate three criteria for the position of several libraries in chemical space:

- the overlap of two or more libraries
- the degree of sampling of chemical space
- the partition of chemical space into subspaces of comparable size

An example from the literature [2] was analysed using these methods. Several different partitions of a given chemical library into sublibraries were visualised and evaluated.

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A Neural Network based Method of Topology Preserving Mapping of Molecules in Drug Design

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We present a neural network based method of topology preserving mapping of molecules for similarity analysis of biologically active molecules in drug design. The method is based on an extension of the self-organizing map (SOM) [1], called self-organizing surface (SOS) [2] [3], which has been developed for topology preserving mappings of 3D molecular surfaces onto reference surfaces [4]. The SOS replaces the local grid of the well-known SOM neural network with a parallel distance calculation on arbitrary topologies.

The algorithm is used and demonstrated in two mapping problems which appear in the similarity analysis of molecular surfaces: first, mapping van der Waals surfaces to a sphere, and second, mapping the surfaces of molecules to other molecules.

In the first application we placed the neurons on the surface of a sphere. The electrostatic potential is used to colour the neurons. The self-organizing surface has been trained with KNet [5], a parallel simulator on the MasPar MP-1 parallel computer with 16384 processors. The final stage of the comparison involves finding matching regions and rotating the sphere to test for similarity.

In the second application we use the same technique of the SOM to map the surface of a reference molecule to the surfaces of other molecules, instead of a sphere, by generating the neuron positions on the surfaces of the target molecules. It is equally possible to map all surfaces of a database of molecules to one reference molecule.

The method is independent on the local surface para–meters used to compare the mapped surfaces with the target surface.

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Integrated Ansatz for the Modeling of Protein-Ligand Complexes

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The molecular basis of drug activity is the information transfer by ligand-biopolymer interaction. This hypothesis holds for nearly all of the drugs whose molecular mechanism is known up to now. Formation of ligand-biopolymer complexes occurs for nearly every step in the fate of the drug, including the pharmacodynamic phase, metabolic reactions and transport.

Therefore, knowledge of the structure of the ligand-biopolymer complex would provide an excellent starting position for optimization of ligand–properties.

However, in spite of spectacular success of modern structure elucidation methods, knowledge of ligand interaction complexes is still the exception rather than the rule.

Integrated structure prediction might be an alternative way in order to get knowledge about the binding sites of the interaction complex. Computer aided molecular design in close relationship with CD-spectroscopy, site-directed mutagenesis, peptide synthesis and protein chemistry has in our lab resulted in a 70% prediction of the thymidine kinase from herpes virus, including nearly all structural features of the active site.

Poster-Abstracts

Developing Criteria for Prediction of β-strand Rich Proteins with a Genetic Algorithm

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Protein structures are predicted using a genetic algorithm, selecting optimal structures according to basic protein building principles. This approach has general utility in protein structure analysis [1]. Furthermore, the approach has already been successfully used by us for *ab initio* prediction of proteins with helical topology [2].

Current efforts investigate folding of beta-strand containing proteins:

(1) Simulations on such proteins using only the basic fitness function criteria were investigated first.
(2) Next the effect of different criteria for hydrogen bonds and packing of beta-strands was investigated.
(3) After these experiments, a detailed representation of hydrogen bonds in beta-sheets is studied now in detail.

Representative results for these steps are shown. Proteins investigated include lambda-repressor, anemona toxin and scorpion toxin as well as the domain B1 of protein G. The latter was chosen as a standard test fold in (3): Starting from sequence and a good secondary structure prediction, the topology of the main chain fold is derived in successful trials and achieves root-mean-square deviations of less than 5.0 Å. Many of the failed trials still allow recognition of the basic topology. The results suggest that also for small beta-strand containing proteins the genetic algorithm is a useful tool to derive a prediction of the three-dimensional structure. For more complex topologies or larger proteins further fitness criteria will have to be developed and are currently investigated.

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De Novo Design of Ligands to Block Substrate Access to Cytochrome P450cam

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Cytochrome P450cam is a monooxygenase from Pseudomonas putida that catalyses the stereospecific hydroxylation of camphor. The active site is buried in the protein and there is no direct access to it from the protein surface. Although the crystal structures of the substrate-free and substrate-bound proteins do not show any significant structural–differences [1,2], the protein must undergo a conformational change in order for camphor to reach the active site.

Differences in the mobility of certain side-chains in the substrate-freeand the substrate-bound proteins suggest the location of a possible hydrophobic substrate access channel [3], and spectroscopic studies of camphor access to the active site suggest that the Asp251-Arg186 salt-link may be important in controlling substrate–access [4]. There is a depression on the surface of the protein at the entrance to the proposed substrate access channel; close to this is a second depression lined by the Asp251-Arg186 salt-link.

We have used de novo structure-based design techniques to model compounds to bind in these two depressions, and thus inhibit substrate access to the active site. Energetically favourable binding sites for different ligand moieties were located with the GRID program [5–8]. Then the LUDI program [9] was used to search databases for ligands that could bind in these sites. Additional moieties were modelled into the ligands to obtain compounds specific for the target binding sites and these will be used to investigate the substrate access mechanism.

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Simulation of the T <-> R Structural Transition in the Insulin Hexamer

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The T -> R transition in insulin, in which eight residues of the N-terminal B chain are transformed from an extended into a helical conformation can be seen as an element of a folding process. Although of limited extent in comparison with global unfolding / refolding processes, this transition has the advantage that the final structures are known and the pathways between them can be investigated by both experimental and theoretical methods. Either aspect of the studies still represents a major challenge: Experimental methods suffer from the lack of stable intermediates and theoretical methods to predict pathways depend on certain constraints to promote the transition. The combination of both approaches however offers new possibilities: Simulated transition pathways can suggest modifications of the protein with presumptive effects on the transition kinetics, which can be verified experimentally.

This poster reports on the prerequisites of such an investigation:

- first part: results of the kinetic experiments on native insulin.
- second part: analysis of the simulations of the transitions in both, the T -> R and R -> T direction.

The methods applied, "Targeted Energy Minimisation" (TEM) and "Targeted Molecular Dynamics" (TMD), have been successful in simulating the transition in the insulin monomer. The extension to the hexamer reported here is indicated because this is the molecular scenario where the transition actually occurs. The obtained pathways are analysed with respect to potential energies, steric interaction, dihedral angles and the conformational space explored. The potential energy of the transition in both directions does not show unrealistic barriers. The energy fluctuations are approximately within the range of normal MD and EM simulations. An analysis of the explored conformational space exhibits two roughly distinct pathways from T6 to T3R3 and from T3R3 to T6. They overlap in some parts, especially in regions close to the limiting structures. A comparison of the monomer pathways with those of the subunits in the hexamer clearly demonstrates the influence of the quaternary structure. In the T6 -> T3R3 direction the helix, as assessed from the main chain dihedral angles, essentially forms in the last third of the transformation, whereas it persists during almost half of the backward transformation.

Semiempirical Calculations on Large Peptidic β-sheets

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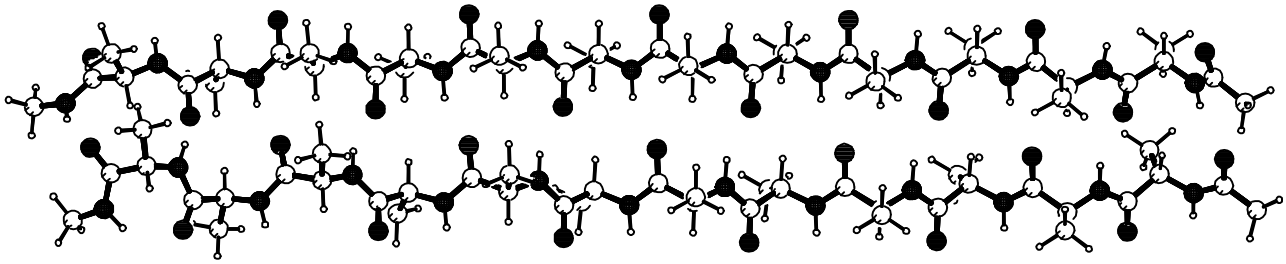
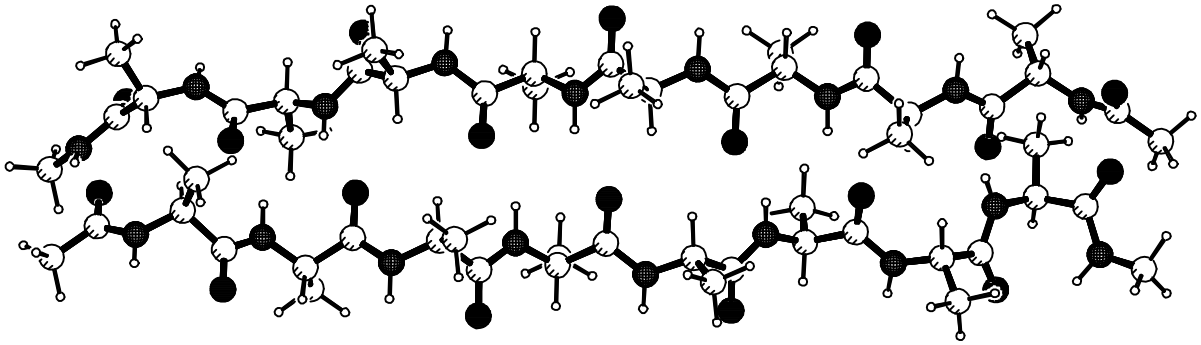
Proteins containing large regions of ß-sheets play an important functional role in various controlling and regulation processes of living organisms. Examples are electron transport processes, transport of vitamins and hormones in the serum or transcription of the DNA [1]. Depending on the orientation of neighbouring strands, ß-sheets are found either parallel or antiparallel.

Force field energy minimization studies suggest that parallel ß-sheets are slightly (1 kcal·mol^{-1}) less stable than the antiparallel counterpart [2]. This work reports the semiempirical approach to the problem using the quantum mechanical methods AM1 and PM3. Is there any energetic difference between antiparallel and parallel ß-sheets?

The model systems used are shown in figure 1.



parallel β-sheet: $CH_3(Ala)_{12}COCH_3$ AM1 minimum



antiparallel β-sheet $CH_3(Ala)_8COCH_3$ AM1 minimum

Fig. 1a: *Isolated β-sheets*

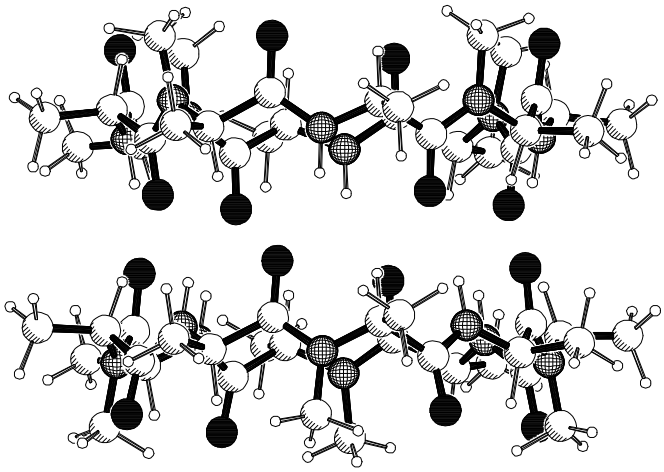


Fig. 1b: *Parallel cyclic b-sheet (8 Ala), AM1 minimum [3].*

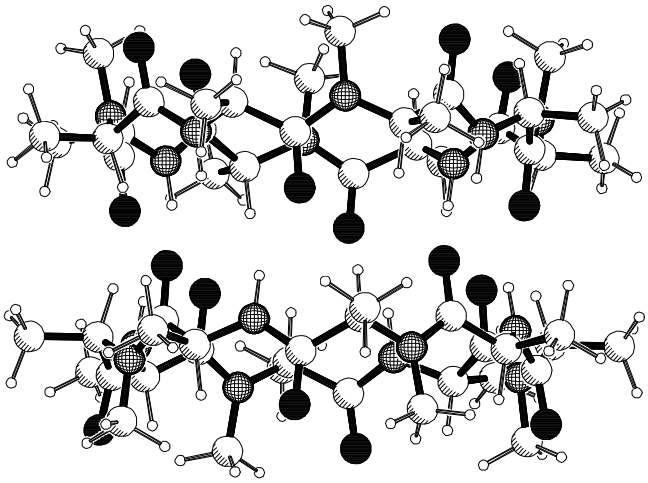


Fig. 1c: *Antiparallel cyclic β-sheet (8 Ala), AM1 minimum [3]*

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Relationships between Substrate Reactivity and Catalytic Effects in Enzymatic Reactions – A Case Study on the Deacylation of Acylated Chymotrypsins

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By studies on enzyme-ligand interactions it is assumed, that different substrate reactivities depend on different interactions between the receptor and a ligand. Enzymes accelerate reaction rates by interactions between the enzymatic active centre and states reached during the reaction [1], and by the usage of free energy produced during substrate immobilization to strain substrate and enzyme structures in order to reach the transition state [2]. Influences of enzyme-ligand-interactions on substrate and enzyme structure in the context of the reaction can be calculated by quantum and classical mechanics.

We performed such calculations on the deacylation of the serine protease chymotrypsin acylated with various substrates. The deacylation of acetylated chymotrypsin was modelled with MNDO/PM3 [3] with a reduced active site model. The ability of this method to handle hydrogen bonds and proton transfer reactions was tested by comparison with results from ab-initio calculations at the MP2/6-31+G*-level [4]. The rate limiting step of the deacylation reaction is the transfer of a proton from a water molecule to His57, which acts as a general base catalyst in serine proteases.

1.) At the transition state, a change of the position of the acyl portion of the substrate was observed.
2.) One hydrogen bond between the carbonyl oxygen of the ester bond to cleave and enzymatic residues was lost.
3.) The distance between the acylated Oγ(Ser195) and the protonated Nε (His57) is critical for the formation of a hydrogen bond prior to completion of deacylation.

All these observations are related to different substrate reactivity, caused by different binding of the acyl portion of the substrate in the recognition site of the enzyme. In order to estimate effects of different substrate binding on substrate and enzyme structure, we constructed structures of chymotrypsin acylated with various L-amino acid substrates. Therefore, an X-ray structure [5] was modified and optimized, using the AMBER-forcefield [6]. From the resulting reactant states of deacylation, several internal coordinates were measured and classified by hierarchical cluster analysis. The chosen variables describe structural variations in the binding region after substrate immobilization, substrate-induced differences of interactions between catalytic groups and substrate-dependent changes of interactions between the substrate and the enzymatic reaction centre. The obtained clusters of acylenzymes are in agreement with different deacylation rates, taken from the literature [7].

From our analyses, acylenzymes with low deacylation rates like Ac-Val, Ac-Ile and Ac-Leu tend to widen the binding region of the active site, if all possible conformations of the acyl group in the active site are included. This result can be interpreted in terms of Fischer's key-and-lock principle. Geometries of acylenzymes built from highly specific substrates like Ac-Tyr, Ac-Phe, Ac-Trp or Ac-Asn are related to necessary changes during the reaction. The hydrogen bond, which was broken at the transition state during our quantum mechanical simulation, is significantly lengthened in acylenzymes with high reactivity. They also show a shorter distance between Oγ(Ser195) and Nε (His57). These results can be interpreted by an induced strain and entropic effects, compared with less reactive acylenzymes built from short substrates like Ace, Ac-Gly or Ac-Ala. We find evidence for the validation of Koshland's induced-fit hypothesis, too. The binding of highly specific substrates influences the distance between His57 and Asp102. The interaction between these catalytic groups is responsible for the function of His57 as a general base catalyst.

Our results suggest that enzyme-ligand-complexes have to be studied in the context of structural changes during the reaction catalysed by a given enzyme, if a physical explanation of sources of observed different substrate reactivities is wanted.

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The Role of Local Molecular Hydrophobicity and Electrostatic Properties in a Cytochrome P450 Substrate Model

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The cytochrome P450 enzyme system is responsible for the induction of oxidative nitrosamine-metabolism. Cytochrome P450 mediated nitrosamine oxidations and subsequent formation of intermediate diazo compounds may lead to DNA-alkylation and ultimately to cancer.

The cytochrome P450-nitrosamine interaction has been studied with the molecular modelling software MOLCAD, using the concept of molecular surfaces. These surfaces were calculated on the basis of Connolly's solvent-accessible surface to determine the three–dimensional size and topology of the molecules. They are also used as maps for a colour coded representation of local molecular properties such as hydrophilicity-lipophilicity or the electrostatic potential. For calculations of the hydrophobicity potential profile, a new algorithm was developed. It is applicable to larger molecular systems, names complete globular proteins like cytochrome P450, where most of the constituent atoms are located in the interior of the molecule. The analysis is performed with 3D structure data of bacterial cytochrome P450cam, which is widely accepted as a model system for cytochrome P450 enzymes. Topological analysis of the P450 surface leads to the identification of a substrate entry/exit channel. These findings made it possible to calculate the interior surface and the local molecular properties for those regions of the active site as well as for the entry/exit channel.

The analysis and the quantitative comparison of selected nitrosamine potential profiles with the activating system leads to the development of a nitrosamine substrate model. It shows the steric requirements together with hydrophilic/lipophilic properties and also electrostatic potential profiles responsible for the activation by cytochrome P450. For a selected number of carcinogenic and non-carcinogenic nitrosamines, it could be demonstrated that only nitrosamines, which are oxidised to the corresponding hydroxy-compounds fit this substrate model. Non-carcinogenic nitrosamines not oxidised by the P450 enzyme do not match the substrate model.

Force Field Calculations of RNA-Tetraloops

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RNA-Tetraloops are discussed as important structure features of tertiary conformations, as kissing partners in unfolding processes and recently as a base of intramolecular stabilization of spatial distinct molecule parts. Structural information obtained by combined NMR/MD methods are only known for the very stable families UNCG and GNRA. Many other RNA hairpins revealed an unusual high melting point in UV/VIS denaturation experiments. We were interested in structural information, relative enthalpies and stem influence of RNA-tetraloops with the sequences UUCG, UUUG and UUUU. The stem region has the nucleotide succession (rCGC)2 . The known structures of the UUCG-tetraloop and the UUU-triloop allow a test of the structure determination process on the computer.

The above listed sequences were built starting from a stem in A-RNA conformation. The start and end nucleotides of the loop were added to this stem. Different starting geometries with two hydrogen bonds between the first and the fourth base were built.

All these structures were closed with the missing nucleotides 2 and 3 of the loop sequence. Here four different crossovers are possible. Molecular dynamics simulations

with the Amber force field were carried out (100 ps, 280 or 300 K, distance dependent, dielectric constant 4.0). A dynamic run with no interaction of the four nucleotides in the loop is carried out at 400 K. From every dynamic run a set of structures was taken and minimized.

Analysis of the structures shows only one conformation for the sequence rCGC(UUCG)GCG and rCGC(UUUG)GCG in a 15 kJ/mole area starting from the one with the lowest energy. The tetraloop rCGC(UUUU)GCG has several conformations in a 15 kJ/mole area and a higher relative steric energy. This is in agreement with the found melting points of the compounds. All stable hairpins show two hydrogen bonds between the first and the last base of the loop and a preference for a selected crossover.

Calculations with water spheres are in progress.

Molecular Modelling Studies on ß-Lactamases

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ß-Lactamases are defensive enzyme systems, which enable the bacterium to survive the anti-bacterial attack. Very shortly after a new ß-lactam antibiotic is introduced into clinical usage, previously unrecognized ß-lactamases are identified. Original ß-lactamases were primarily exclusively effective in hydrolyzing penicillins. Nowadays many related enzymes with a wide range of substrate specifities are known. One of these extended-spectrum ß-lactamases (ESBL) is the MEN1 ESBL of E.Coli [1]. The MEN1 ß-lactamase is a very interesting species, because this enzyme is able to cleave one of the clinically most used extended spectrum ß-lactam-antibiotics, the cefotaxime.

In the work presented here a model of MEN1 ESBL was constructed based on two crystal structures from the penicillinases of Staphylococcus aureus and E.Coli, respectively, by employing the HOMOLOGY [2] Software. The generated model has been checked for consistency. One test controls the absence of forbidden torsional angles of the polypeptide backbone by creating RAMACHANDRAN [3] plots. . The validity of the model further was checked by measuring the compatibility of the modelled structure with the respective protein sequence using PROFIL 3D [4] . In addition, the configuration of amino acids as well as the hydrogen bond network was examined. Molecular dynamics simulations were performed to prove the stability of the model.

Due to many failures of antimicrobial therapy of clinically important, formerly ß-lactamase-stable penicillins, it is of great interest to elucidate the molecular differences between penicillinases, ESBL and Cephalosporinases. For this purpose it is indispensible to create a good alignment of the three classes of ß-lactamases.This was generated taking into account results of different secondary structure prediction studies using e.g. EMBLPRED [5] or PREDICT [5], respectively. Also the observed mutations at each position in the sequences of related ß-lactamases were considered. Very recently the coordinates of the cephalosporinase from Enterobacter cloacae became available and the structural alignment supports our previous results. Only one helix at the N-terminal end of the protein had to be moved slightly.

Conclusion: The MEN1 model satisfies all validity tests. Only small deviations in the torsional angles of the protein backbone of three amino acids at the surface of the protein were necessary. The alignment seems to be realistic and points out some clues for differences between ESBL and originally penicillinases on one hand and the similarities between ESBL and cephalosporinases on the other hand. Further comparative investigations of molecular electrostatic potentials of all three classes of lactamases using DELPHI [6] are in preparation.

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Construction and Evaluation of a Model of the Binding of a Lipoyl Domain to the E3-component of the Pyruvate Dehydrogenase Multienzyme Complex by Molecular Modeling and Energy Minimization Techniques

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Dihydrolipoamid dehydrogenase is a component of the pyruvate dehydrogenase multienzyme complex, where it is called E3-component. In a previous work [manuscript in preparation] we demonstrated on the basis of the known X-ray structure of the enzyme from Azetobacter vinelandii [1] by protein-modelling techniques, that the observed dimer can build a tetrameric structure with intensive contact between the building blocks.

We show how the active site of each dimer is completed by complementary structure in the tetramer and how the coenzyme FAD is additionally stabilized. Since now also the 3-dimensional structure of the exible lipoyl domain connected to the core-component E2 of the PDC complex is known [2], we extend our model to the binding of this additional domain, where we make use of the binding-site of the catalytic active lipoyllysine arm to the dihydrolipoamid dehydrogenase described in Lit. [3]. It turns out, that the exible lipoyl domain binds in the contact-area of two dimers forming the tetrameric complex, at the state of binding being highly covered by surrounding protein structure.

The constructed model of binding reveals, that the lipoyl domain has a surprising additional function besides the well-known transfer of the substrate lipoyllysine into the active sites: The coenzym NAD of one of the dimers building the tetramer is stabilized by parts of the binding lipoyl domain, whereas the catalytic active lipoyllysine arm of the same lipoyl domain occupies the active site of the other dimer. By energy-minimization techniques we compute binding-energies, RMS-values, solvent-accessible surfaces and contact-areas between the building blocks to quantify the interaction and compare it with already known protein-protein interactions. The consequences for the whole pyruvate dehydrogenase complex and the relative content of its components will be discussed.

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Molecular Modelling of G-Protein Coupled Receptors: A Useful Approach to SAR Studies of Selected 5-HT 1A /D2-Agonists

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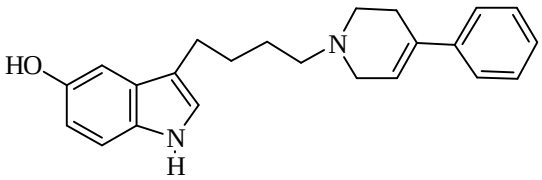
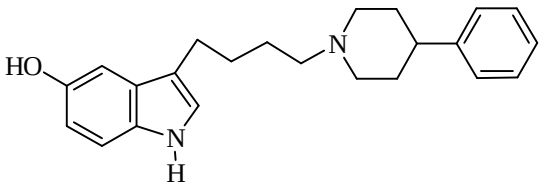
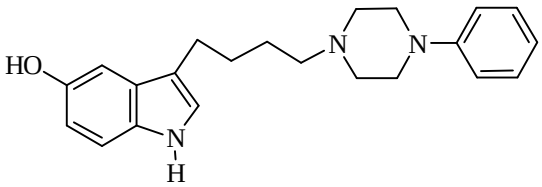
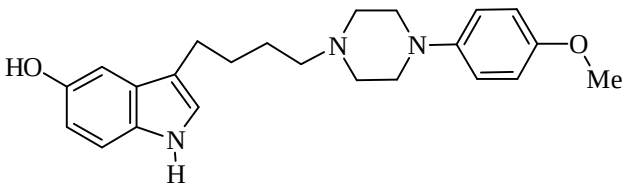
Roxindole is a presynaptic dopamine agonist showing affinity to both the D2 and the 5-HT_{1A} -receptor in the nanomolar range and additionally 5-HT reuptake inhibition. These combined activities make roxindole an interesting new tool in clinical research to treat various forms of depression. Roxindole consists of two heterocycles which are linked by a 4-carbon chain spacer. As shown in the table below, the structural differences among the agonists are small, but largely different activities were found for 5-HT_{1A} - and D2-receptor binding. Thus Roxindole and its analogues represent a challenge to analyse the molecular interaction with these receptors in order to obtain an explanation for the differences in affinities. To this end, the transmembrane region of the 5-HT_{1A} - and D2-receptor was modeled. Mutagenesis data and known ligands were used to refine the model. These models were taken as the basis for studying the interactions of indolalkylamines with the 5-HT_{1A} - and D2-receptors and to explain the specific structure-activity relationships in this series.

Model building studies of selected serotonin and dopamine receptors suggest that large, flexible ligands like roxindole might bind in an extended conformation, although a U-shaped conformation cannot be excluded entirely. In the extended conformation, the ligands fill two distinct pockets. One pocket is bordered by helices III, IV and V. This pocket is likely to hold the natural ligands, i.e. serotonin or dopamine, as demonstrated by mutagenesis studies, and, by analogy, also the

indole part of roxindole. Another pocket is formed by helices VI, I, II and III. This pocket holds the aryl-piperazine ring system in our models.

All four compounds are potent 5-HT $_{1A}$ -receptor agonists. However, their activity on the D2-receptor differs largely. The structural differences in the model-built receptors were used to rationalize the differences in activities. Volume difference maps were used to identify the major differences in spatial requirements. In the D2-receptor model the cavity which accomodates the aryl-piperazine ring system is considerably smaller than in the 5-HT $_{1A}$ -receptor. This is due to a number of larger inward pointing side chains in the D2-receptor relative to the 5-HT 1A -receptor on helices I (Thr in D2/Gly in 5-HT $_{1A}$), II (Met/Leu), III (Met/Cys) and VII (Gly/Tyr, Ala/Ser, Ile/Phe, Thr/Asn). Therefore, this site is structurally much more demanding in the D2 receptor. Especially, there is no space for a terminal extension at the phenol ring in the D2-receptor, because the site is filled by Thr on helix I (Gly in 5-HT $_{1A}$), Met and Val on helix II (Leu and Ala in 5-HT $_{1A}$). This explains the difference in activity of compound 4 on the two receptors. Compound 2 is almost inactive on the D2-receptor, although there is no terminal substitution on the phenol ring. However, in this compound there is a large angle between the piperazine ring and the phenol ring. Active compounds on the D2 receptor seem to have an almost parallel orientation of the planes of the ring systems. In compound 1, this is achieved by the double bond conjugated to the aromatic system. In compound 3, the nitrogen next to the phenyl ring has the character of an aniline nitrogen, and hence the orientation of the rings is parallel here, too. The relative orientation of the rings is critical in the D2-receptor only, as all compounds are highly active on the 5-HT $_{1A}$ -receptor. The angle dependence might again be a consequence of the sterical crowding in the D2-receptor. Especially Tyr and, probably less important, Phe (Gly and Ile in 5-HT $_{1A}$) hold the piperazine ring in a firm grip, thus orientating the attached aromatic ring precisely in the tight pocket.

	5-HT$_{1A}$-binding [3H]-8-OH-DPAT IC_{50} [nmol·L^{-1}]	**D2-binding** [3H]-Spiperone IC_{50} [nmol·L^{-1}]
 **Roxindole**	1	5.2
	1	100
	0.8	4.2
	0.1	120

Sindo1 Calculations of the Cu,Zn Superoxide Dismutase Active Site

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Copper, zinc superoxide dismutase (SOD) is a dimeric enzyme containing a copper and a zinc ion in each subunit [1]. In each of the two active sites a copper ion is coordinated by four histidine residues in a distorted square-planar geometry. One of them (His 61) acts as a bridge between the copper and the zinc ion.

The physiological function of SOD is the dismutation of the superoxide radical anion, that is produced during the oxygen metabolic cycle. The reaction takes place at the copper ion, which is essential for the enzyme activity. Since the discovery of the enzymatic activity in 1969 by McCord and Fridovich [2], several research groups have investigated SOD extensively, both experimentally and theoretically [3]. Two mechanisms have been proposed, the first being the most widely accepted.

$$Cu^{2+} + O_2^{\bullet -} \rightarrow Cu^{+} + O_2$$

$$Cu^{+} + O_2^{\bullet -} + 2H^{+} \rightarrow Cu^{2+} + H_2O_2$$

In this case the enzyme copper ion is repeatedly reduced and oxidized in a two-step process. Within this scheme, it has been suggested that the bond between copper and His61 breaks down in the first step, the His61 then takes a proton from the solvent, which is transferred to a second superoxide molecule in the second step, while regenerating the copper-His61 bond.

$$Cu^{2+} + O_2^{\bullet -} \rightarrow (CuO_2)^{+}$$

$$(CuO_2)^{+} + O_2^{\bullet -} \rightarrow (CuO_2) + O_2$$

$$(CuO_2) + 2\,H^{+} \rightarrow Cu^{2+} + H_2O_2$$

In the alternative mechanism based on quantum-mechanical calculations a stable copper-superoxide intermediate, that is able to oxidize a second superoxide molecule, is proposed. In this case no bond-breaking between copper and His61 takes place.

We present here a theoretical description, of the active site of SOD and the interaction with the superoxide as well as a hypothetical reaction between the superoxide complexed SOD and methane, using the semiempirical method SINDO1 [4].

Computational Procedure

SINDO1 is an all-valence SCF MO method developed by K.Jug and coworkers [4]. SINDO1 makes use of symmetrically orthogonalized AOs, takes into account the core-valence electron interactions through pseudopotentials, and includes d-orbitals in the basis set for second row atoms.

The molecules under study were completely geometry optimized at the SCF level. The structures were optimized with tolerance limits for convergence at 0.001 Å for bond lengths and 0.1° for bond angles and dihedral angles.

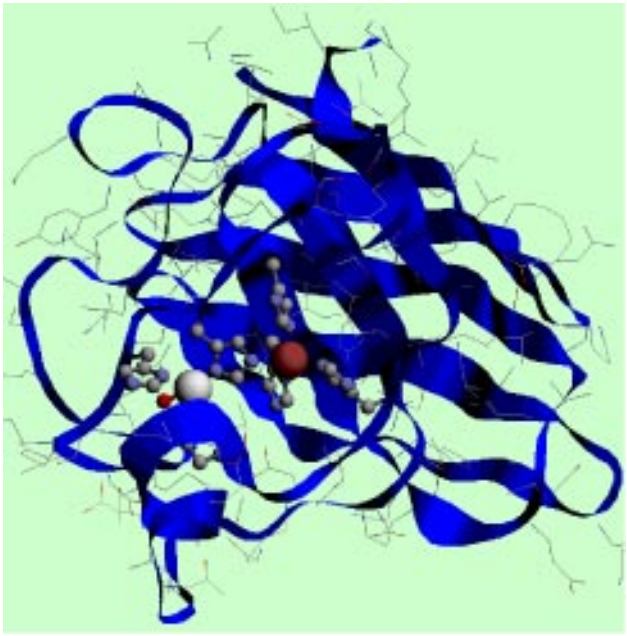

Fig. 1 *Active Site of the copper zinc superoxide dismutase (SOD)*

The preliminary calculations show that SINDO1 is a suitable method for describing enzymatic reactions, where copper is involved as metal centre. The geometry optimized structures are in good agreement with experimental and other theoretical studies. This gives us a good starting point to perform further calculation wiht the goal to find an explanation for the reaction mechanism. The calculation of the total energies of the complexes leads to reaction energies of about

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20 kcal·mol^{-1} for both alternatives making the calculation of the full reaction path for both mechanisms inevitable.

The modelled reaction of the protonated superoxide radical anion at the copper centre of the SOD with methane is an indication that from a thermodynamical point of view the superoxide radical anion or its protonated form could follow other pathways leading to its decomposition.

Further calculations are dealing with the role that Arg141 plays during the catalytic reaction, since several groups have proposed that the electrostatic influence is essential leading to the final electron transfer between the copper, zinc SOD and the superoxide radical anion.

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α-Helical Transmembrane Topology of the SS1-SS2 Region? Secondary Structure Prediction of Voltage-Gated Calcium Channels

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Voltage-gated calcium channels (VGCC) are integral proteins, which are modulated by changes in the transmembrane voltage. A depolarization of the membrane opens calcium selective pores, calcium permeats into the cytosol and activates other second messenger systems. This mechanism is important in the regulation of many physiological functions like excitation-contraction (E-C) coupling or insulin secretion. The specific inhibition of this functions by calcium channel antagonists is used therapeutically in the treatment of hypertension and angina pectoris.

In spite of many investigations the α1-subunit topology of the four repeats (I-IV) with their six membrane spanning segments (S1-S6) and especially the SS1-SS2 region (short segment) as linker from S5 to S6 is still not enlighted. Hydropathy plots, which give evidence about the lipophilicity of amino acid sequences, confirm the experimental findings of six transmembrane segments per repeat. Using the software programs ALB [1], GOR [2], CHOU-FASMAN [3], JAMSEK [4] and SIMPA [5], however, the secondary structures of this domains are equivocally predicted as α-helical, β-sheet or turn structures.

The SS1-SS2 region as postulated pore lining and binding site for calcium channel antagonists of nifedipine type is predicted as a random structure. Utilising multiple sequence alignments [6] and a new alignment strategy for transmembrane proteins [7] the membrane spanning segments and their secondary structures could be unequivocally determined. The three dimensional structures of the transmembrane proteins bacteriorhodopsin (obtained by high-resolution electron cryomicroscopy) and the photosynthetic reaction centers from Rhodobacter sphaeroides and Rhodopseudomonas viridis (each with H-, L- and M-chains; obtained by X-ray diffraction) served to validate the methods. As negative controls the a-helical, not membrane lining segments of this proteins and the β-barrel membrane channel porins of Escherichia coli and Rhodobacter capsulatus have been used.

Results

- the segments S1-S6 and the SS1-SS2 regions are characterized as transmembrane peptides,
- the segments S1-S6 are predicted as α-helical structures and
- the SS1-SS2 regions are predicted as helix-turn-helix domains.

These results, also found for potassium [8] and sodium channels, may serve as tools to create new channel models that will allow the rational design of new therapeutically useful drugs.

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Pathways and Intermediates of Conformatinal Transitions of 11-Alanine

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In a series of recent works dealing with short polypeptides in particular the transition of alpha to 3/10 helix was investigated by simulations. It is a model case for studying the technique of pathway generation, the influence of the force field, and the influence of solvent, which are of interest for application to large molecules. We have applied the method of targeted molecular dynamics simulation (TMD) for an investigation of 11-alanine. TMD is a variant of molecular dynamics simulation which produces a dynamical pathway from a starting configuration to a given target configuration.

Using a special form of thermodynamic integration (thermodynamic distance integration, TDI) each TMD run yields simultaneously also the profile of free energy. A suitable projection technique yields a two-dimensional representation of pathways and stable intermediates. As shown by numerical calculations, the force fields OPLS and GROMOS differ in the strengths of H-bonds. Therefore the simulations were performed with H-bond potentials from either force field. The alpha helix is always stable at room temperature, the 3/10 helix only at extremely low temperatures.

A further stable intermediate was found which is a partially unfolded alpha helix.The results of our simulations are presented as a map containing pathways and stable intermediates of 11-alanine. The free energy profiles were used to calculate equilibrium constants and transition rates.

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Theoretical Studies on Chiral 1,2–Diol Systems

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The structures and stabilities of 1,2–propanediol (PDL1,2) monomers, dimers and monohydrates were investigated by the force field versions PIMM91 [1] and GROMOS87 [2] as well as the semiempirical PM3 method.

Diols are important structure units of amphiphilic molecules which are suitable as model systems for the study of bilayers. In the process of molecular self-organization the formation of a hydrogen-bridge network under participation of water molecules plays an essential role. By comparison of the results of both PDL1,2 and PDL1,3 systems [3] the influence of the different diol head groups on the formation of intramolecular and intermolecular hydrogen bonds were studied in a systematic way. The results of the monomers are in agreement with ab initio data as well as gas phase experimental findings and support the different tendency of hydrogen bonding in both diol systems.

Especially for the chiral PDL1,2 system it was of interest if there are some hints for a different stabilization on the formation of dimers from the same (R-R) and different (R-S) enantiomers within these methods. MD simulations using the GROMOS87 package were performed on PDL1,2 in the gas phase and in the water box in order to investigate the dynamics of intramolecular and intermolecular hydrogen bonding.

The results are visualized by a graphics tool for workstations developed in our group. Moreover, first results of quantum chemical and molecular dynamics calculations on biamphiphilic tetrol systems are presented which are also structure units of an interesting class of amphotropic liquid crystals.

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PM3 Study on β-N-Acetyl-Muramic Acid

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The energetically favored conformations of β-N-acetyl-Muramic acid, a component of Murein, have been investigated using the semiempirical PM3 method [1] implemented in SPARTAN (Wavefunction Inc.). The Murein single strand model of Barnickel et al.[2] has been used as starting set. The cartesian coordinates were kindly provided by the authors. As a first step one single β-N-acetyl-Muramic acid molecule has been cut off from the strand model, followed by a PM3 minimization. This conformation served as starting point for a grid search by scanning all sidechain torsional angles with exception of the N-acetyl group, which was held in cisoid position (i.e. N-H bond is parallel to C1-H and C3-H bond).

The stepsize was set to 120°. The PM3 method with an additional amide correction potential was used. The calculations were performed on the IRIS/INDIGO (Silicon Graphics Inc.) cluster of our institute under the operating system IRIX System V.4 using SPARTAN, SGI version 3.1.1 GL. The results are compared to earlier studies on the same molecule by Yadav et al. [3,4] who were using the MNDO and PCILO methods.

Survey of results

The pyranose ring is in 4 C1-conformation. The two lowest energy conformers are characterized by distinct hydrogen bonding patterns. Conformer 1 shows a hydrogen bond between O4-H4 and the carbonyl-oxygen of the acid function, the N-acetyl group is strictly cisoid. The C6 side chain is in gauche position. Energy of conformer 1 is -353.6 kcal/mol.

Conformer 2 shows two hydrogen bonds, one between N-H of the N-acetyl group and the carbonyl-oxygen of the acid function. The other one between O1-H1 and the carbonyl-oxygen of the amide function. As a consequence the amide plane of the N-acetyl group is slightly rotated out of the cisoid position. The C6 sidechain is in gauche position. The energy difference to conformer 1 is only +0.32 kcal/mol. The ether linkage shows three favoured torsional angle regions in the distribution plot of the 40 lowest energy conformers. Conformer 1 is the lowest energy representant of region I, conformer 2 that of region II. The energy surface of each favoured torsional region has been calculated using the corresponding lowest energy representant as a starting conformer.

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Detailed Analysis of the Solvatochromism of Acetone

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The nπ* energy of carbonyl compounds strongly depends on the solvent polarity. Thus acetone shows a blue shift of 1.56kK in water and a redshift of -0.46 kK in cyclohexane compared to the gasphase [1]. This effect cannot be studied by standard QC calculations.

This solvent dependence of the excitation energy will be analysed by a combined QC/MM approach [2]. The time consuming QC method is used for calculating the electronic properties of acetone and the solvent molecules are incorporated as MM-Centers using special coupling terms. These coupling terms consist of ordinary and special interactions (Coulomb, van der Waals, hydrogen bonding terms).

The electronic excitations are calculated by the semiempirical MNDOC-CI method [3] for isolated acetone and for solvated acetone in water and in cyclohexane at geometries obtained from MD-Simulation trajectories. Fourier-Analyses (PSD-Spectra) for excitation energies and oscillator strengths are performed to analyse their dependence on certain geometrical parameters.

The calculations reveal a blueshift in water of about 1kK, while the breaking of the hydrogen bonds leads to a further increase of 0.6kK. The redshift in cyclohexane is calculated to be -0.2 kK. The fourier-transformations show a strong dependence of the excitation energy on changes in the CO bond length and the CCC bond angle, whereas the oscillatorstrength varies with the out-of-plane vibrational mode.

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Quantum Chemical 6-31G* *Ab Initio* Calculations of Nifedipine

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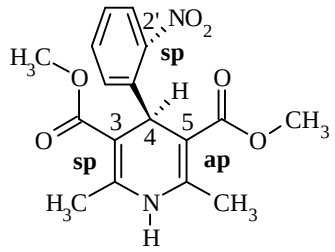
Nifedipine (Tab. 1) - as prototype of the so-called calcium channel antagonists - is widely used in the therapy of cardiovascular disorders like angina pectoris, certain types of arrhytmia and hypertension. Chemically, nifedipine represents a 1,4-dihydropyridine derivative (DHP), whose bioactive conformation at the binding site is still unknown.

Using quantum chemical *ab initio* calculations, the energetically most favourable conformation should be determined as starting point for a pharmacophore model. Examination of 34 X-ray structures from the Cambridge Cristallographic Database [1] yielded information about conformational characteristics of DHP derivatives. Beside the unusual boat form of the DHP ring the ester groups roughly show a coplanar orientation. The 4-aryl substituent pointing in a pseudoaxial direction approximately bisects the DHP ring. In relation to the double bonds of the DHP ring the carbonyl groups of the ester side chains can be oriented in (Z)-configuration (synperiplanar = sp) or (E)-configuration (antiperiplanar = ap). Also for the relative spatial orientation of the 2'-nitro group and the hydrogen atom linked to C4, the terms synperiplanar and antiperiplanar are used. If both are pointing to the same (or opposite) directions this is called a sp- (or ap-) configuration. The rigid character of the nifedipine molecule causes the situation that a relevant rotatory variability only exists at three bonds. In effect, among all X-ray structures only two conformers per rotatable bond (sp- and ap-configuration) are existent.

This results in 23 theoretical structures. Since two stereomeric pairs are identical, there remain six different conformations. After generation of the six conformations, each of the structures was geometry optimized in a stepwise manner firstly using molecular mechanics (CVFF/Discover [2]) then the semiempirical AM1 [3] method. The minimized conformations served as input for an ab initio calculation [4] using the 3-21G* basis set with complete geometry optimization. In order to deduce the potential energy and the molecular electrostatic potential (MEP) of the resulting structures, the wavefunction was calculated using the 6-31G* basis set.

Table1. *Energy differences ΔE [kJ·mol^{-1}] of the calculated nifedipine conformations [6-31G* basis set]*

C3 / C5 / C4	ΔE	C3 / C4 / C5	ΔE
sp / sp / sp	0.0	sp / sp / ap	7.3
ap / ap / sp	25.2	ap / ap / ap	15.1
sp / ap / sp	9.6	sp / ap / ap	8.9



Nifedipin

The results clearly indicate a preference of the sp/sp-configuration at C3 and C5, which are in comparison with the ap/ap-configuration 25.2 kJ·mol^{-1} (C4 = sp) and 7.8 kJ·mol^{-1} (C4 = ap) energetically favoured. The sp/ap-orientations take a medium energy level. The configuration at C4 has different effects on the potential energy of the molecules. While the sp/sp/sp-configuration - as the global minimum - has a 7.3 kJ·mol^{-1} lower energy than the sp/sp/ap-structure, the ap/ap-configuration shows inverse effects. Here the C4 ap-conformation is 10.1 kJ·mol^{-1} energetically more favoured than the C4 sp-configuration. The results are in good agreement with the statistic distribution of the X-ray structures. The ap/ap/sp– as well as the ap/ap/ap-conformation - as the most unfavourable structures -have not been observed. The calculated global minimum of the sp/sp/sp-conformation is the most common configuration in the solid state (crystal). The relevance of the different configurations with regard to the binding at the receptor site will be discussed by comparison of the MEP's of all conformations.

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Transferable Electronic Structure in Molecular Density Functional Calculations

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The transferable properties of localized molecular orbitals are a well–studied topic in quantum chemistry. We have developed a method to decompose the density-functional electronic structure of molecules into rigorously localized, nonorthogonal orbitals and to reassemble these orbitals to construct the approximate electronic structures of different, but chemically similar molecules.

It was found that in some cases, this type of orbital transferability reaches the intrinsic accuracy level of state-of-the-art density functional codes and can eliminate the self-consistency cycle. In cases where transferability is imperfect because of mismatches of geometries and chemical environments, the Harris functional can still be used to furnish highly accurate total energies.

The method has been applied to saturated hydrocarbons, systems with conjugated double bonds and systems containing peptide bonds. We also discuss generic types of molecular deformations, such as twisting and stretching of individual bonds.

Typical total energy errors do not exceed a few meV/bond, compared to fully self-consistent calculations. We argue that this opens the way for the construction of comparatively small localized-orbital data bases from which approximate electronic structures can be recovered for a large class of systems and molecular geometries. Applications within the Hartree-Fock framework should be possible with almost no modifications.

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Ab Initio Study and Semiempirical Calculations of Keto-Enol Tautomerism of Triazolopyrimidines

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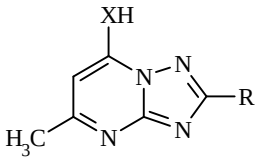
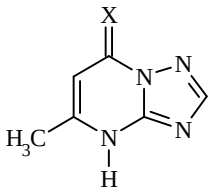
The determination of the equilibria of keto-enol tautomerism is quite more difficult than the determination of the equilibria of different conformations. The relative stability of the different tautomers is of interest because several positions of substitution are possible. The tautomeric equilibrium determines the possible positions of later substitutions.

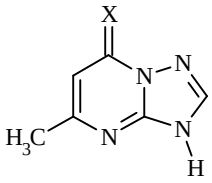
5-methyl-4H-[1,2,4]triazolo[1,5-α]pyrimidin-7-one (**1**), 5-methyl-4H-[1,2,4]triazolo[1,5-α]pyrimidin-7-thione (**2**), and 5-methyl-4H-[1,2,4]triazolo[1,5-α]pyrimidin-7-ylamine (**3**) can occur as four tautomers (**a-d**). The keto forms of compounds **1–3** have the imino-keto form (**b-d**), whereas the enol form (**a**) shows a hydroxy group (**1**), thiohydroxy group (**2**), or a amino group (**3**). The relative energies of each of these four tautomers were calculated using semiempirical and *ab initio* methods.



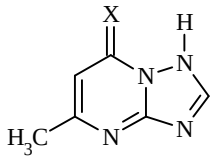
a



b



c



d

X = O (**1**), X = S (**2**), X = NH (**3**)

The semiempirical calculations were performed with the MOPAC 6.0 program package, using the MNDO/PM3 hamiltonian and the AM1 hamiltonian. The *ab initio* calculations were carried out with the HONDO 8.4 program package, using the 3-21G, 4-31G, 6-31G, and 6-31G* basis sets at the Hartree-Fock level.

All the structures were completely geometry optimized. Additonally, MP2/6-31G*//6-31G* pertuberation calculations were performed. The computed energy values show that the keto-tautomer (**b**) of compounds **1** and **2** is the most stable. The imino-group is positioned in the pyrimidine ring. However, the semiempirical methods (AM1, PM3) prefer the enol-tautomer for compound **2a**. The differences in energy values of the tautomers for compound **1** and **2** depend strongly on the used basis set. The graduation of energy of the tautomers for compound **3** is nearly independent of the methods and basis set used. All calculations show that the 'enol-form' (**a**) with a amino-group is the most stable tautomer for compound **3**. The results are in agreement with NMR-spectroscopic data.

MO–Calculations on Photo–induced Electron Transfer Reactions

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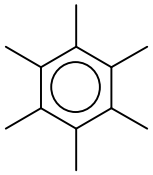
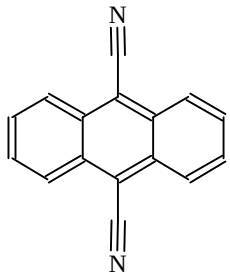
NDDO-based (AM1) configuration interaction (CI) and self consistent reaction field (SCRF) calculations have been used to calculate the reaction path of a photo induced electron transfer reaction.
In this work we describe the charge transfer system hexamethylbenzene (donor (D)) and 9,10-dicyanoanthracene (acceptor (A)) [1].



Hexamethylbenzene



9,10- Dicyanoanthracen

The idea was to calculate the hypersurfaces of the ground state (D-A), the contact-radical-ion pair (CRIP) ($A^{\bullet-}D^{\bullet+}$) and the exciplex (A*-D) relative to the distance of the central aromatic ring of dicyanoanthracene and the aromatic ring of hexamethylbenzene in acetonitrile as solvent.

In order to calculate the excited states we consider a singles plus pair doubles CI-expansion (PECI=n) within the VAMP program [2]. A numerical self-consistent reaction field (SCRF) technique for the calculation of the solvent effects has been used for ground and excited states.

As a first approximation, the SCRF calculations assume infinitely fast solvent relaxation (i.e. equilibrium solvation at every point and for each state). The ground state donor-acceptor complex shows a distinct minimum at a ring-ring distance of about 2.5 Å. The exciplex, on the other hand, is found

to be dissociative at this level of theory. The CRIP state is strongly stabilized by solvation with a well-defined minimum at 2.5 Å. We do not, however, find a crossing between the ground and CRIP states. This suggests that the conventional Marcus theory picture of electron transfer in the inverted region may not be correct, as already suggested on the basis of experimental results for related systems [3].

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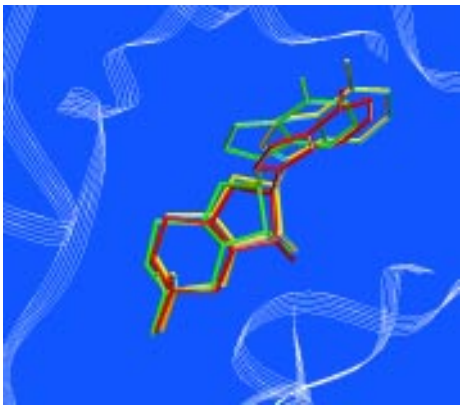

Figure: *CAP complexed with cAMP. The geometries obtained (cyan= PCM; green = GA ; yellow = combination of both) of the ligand are in very good agreement with the X-ray data (red), especially for the ribose-monophosphate subunits. Even the largest deviations are within experimental refinement accuracy (2.5 Å).*

A Combined Genetic Algorithm - QM/MM Approach for Solving the Docking Problem

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Understanding the principles whereby macromolecular biological receptors recognise small molecule substrates or inhibitors is the subject of a major effort. This is of a paramount importance in rational drug design, where the receptor structure is known (docking problem).

Current theoretical approaches utilise models of the steric and electrostatic interaction of bound ligands and recently conformational flexibility has been incorporated. We use two different approaches and a combination of both.

The first method is a genetic algorithm (GA) that uses an evolutionary strategy in exploring the full conformational flexibility of the ligand with partial flexibility of the protein. The second procedure is a semiempirical one in which the atoms of the protein are described as point charges (PCM) to form an environment in which the substrate is fully optimised. To verify our results we compare them to X-ray structures of the calculated systems.

Comparison Between STM-investigations and Force Field Calculations of the Self-assembly Phenomena of Organic Molecules on Graphite

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Self-assembly of alkanes and polysilanes on graphite is known from STM-investigations [1,2]. In order to understand the adsorption of polysilanes we calculated the adsorption behaviour of dodecane, permethyldodecylsilane and dodecasilane. The MM+ force field [3] from the HYPER CHEM [4] program was used.

The graphite model, shown in figure 1, was also optimised with the MM+ force field and contains 1888 atoms in two layers.

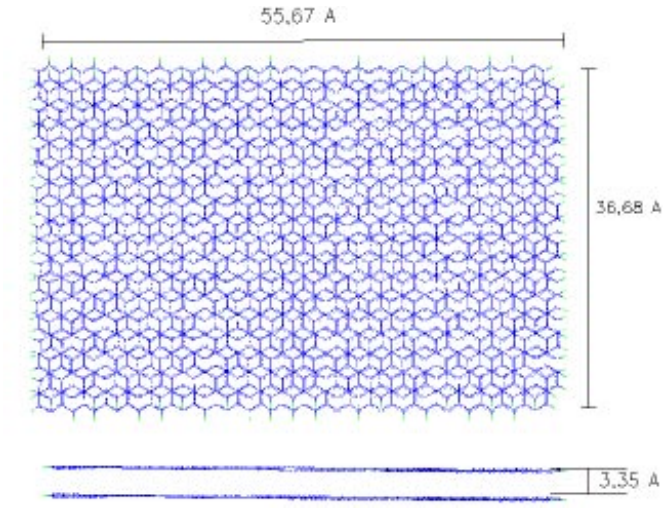

Figure 1 *shows the graphite lattice used for the simulations. The lattice constant is 2.42 Å and the distance between the two layers is 3.35 Å, in agreement with the experimental values.*

The methyl(ene)groups are responsible for the adsorption of alkanes. In case of the permethylpolysilanes either the Si-backbone or the methyl groups can be responsible for the adsorption. The intermolecular van der Waals interactions and the heat of adsorption are dependent on the relative orientation of the backbone to the substrate as shown in table 1.

Table 1. *Calculated heats of adsorption of dodecane (**1**), dodecasilane (**2**) and permethyldodecylsilane (**3**) depending on the relative orientation of their backbone to the graphite.*

	Heats of adsorption [kcal/mol]	
compound	**Parallel**	**Perpendicular**
1	25.56	22.43
2	26.69	38.96
3	53.78	54.27

For the dodecasilane a large difference between the perpendicular and parallel orientation of the dihedral angle of the Si-backbone was calculated. The dodecane and the permethyldodecylsilane show only a small difference in the relative orientation of the backbone to the substrate.This suggests that the methyl–groups are responsible for the adsorption of permethylpolysilanes. This is supported by the fact that the heat of adsorption and the number of methyl(ene) groups of the permethyldodecylsilane is about twice that of dodecane.

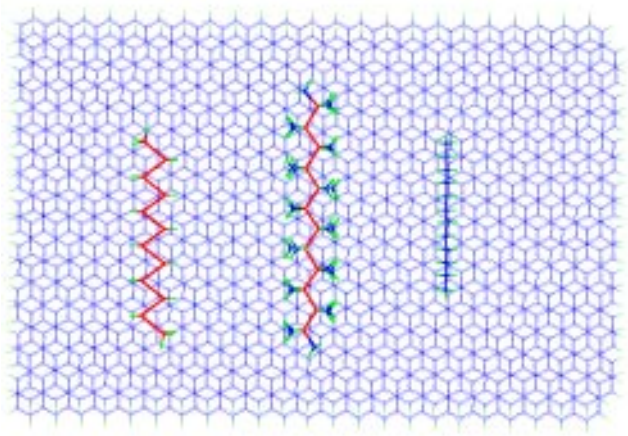

Figure 2 *shows dodecane, permethyldodecylsilane and dodecasilane on the basal plane of graphite. The silanes are lying, i.e. with the dihedral angle of the Si-backbone parallel to the graphite. The alkane is standing, i.e. the dihedral angle of the C-backbone is perpendicular to the substrate. (Si-atoms: red; C-atoms: blue; H-atoms: green)*

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Semiempirical Calculations on the Structures and Electronic Properties of $[CpFeP]_4$- and $[CpFeS]_4$-Clusters

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The program package AMPAC5.0 includes the new semiempirical Hamiltonian SAM1, which is now parametrised for iron. However, since the parameters are not final, this is only a first test.

The structures calculated were $[CpML]_4$-Clusters with M = Fe (or Co, Ru, Os in x-ray-investigations) and L = S, P. Some experimental and calculational work on these systems has been done in the last ten years. All these compounds are vertex dodecahedra with an ideal or distorted M_4-tetrahedron, only depending on the number of electrons in the metal-metal antibonding MO's.

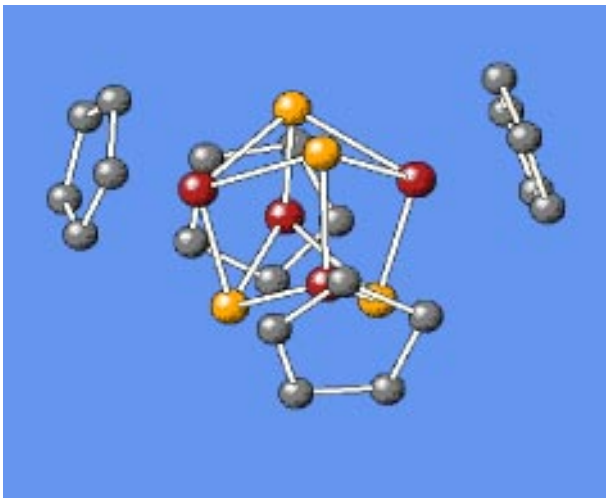

Fig. 1: *SAM1 calculated structure of* $[CpFeS]_4$

It can be shown that SAM1 is able to reproduce the structure of $[CpFeS]_4$ and to a smaller extent the one of $[CpFeP]_4$. Both have D_{2d} symmetry (a distorted M_4-Tetrahedron) as expected from the number of electrons. The structure for $[CpFeCl]_4$ with T_d symmetry can also be obtained. These compounds are isoelectronic to $[CpCoS]_4$. For this compound an X-ray structure with T_d-symmetry is known. $[CpFeSi]_4$ should also exhibit T_d symmetry.

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Journal of Molecular Modeling – The Beginning of a New Era in Scientific Publishing

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The *Journal of Molecular Modeling* is the first fully electronic journal in chemistry. What started as an idea at an ACS meeting is now officially "up and running", operated by the Computer-Chemie-Centrum at the Institut für Organische Chemie of the Friedrich-Alexander Universität Erlangen-Nürnberg in cooperation with Springer.

The aim is to produce a high quality chemistry journal that takes advantages of modern electronic communication technology. The use of electronic media in every step of the publication process should lead to unprecedentedly short publication times.

The journal is made accessible through FTP-servers to subscribers with a minimum availability time for individual papers of one year. The servermode of publication however does not mean that we do not provide for the longevity of the published material, which will be guaranteed by issuing a CD-ROM version.

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The *Journal of Molecular Modeling* accepts papers from all areas of molecular modeling, both applications and method development, including classical and quantum mechanical modeling, QSAR, biochemical research topics, de novo ligand design, neural nets, genetic algorithms, expert systems, information retrieval and management.

The goal is to convert the *Journal of Molecular Modeling*, which has now in the beginning a conservative "book-like" format, into something approaching an interactive journal in which the reader will have the possibility to rotate graphics, extract diagrams etc. The technology for this kind

of application is under continual developement over the years and we will try to keep pace with its progress.

Today the *Journal of Molecular Modeling* gives scientists the possibility to publish sophisticated presentation material without extra costs. Full colour graphics are incorporated directly in the text and are not grouped together on extra pages. Videos can be delivered together with the text and no limits are set to supplementary material, everything can be incorporated, e.g. source code, program executables etc.

The *Journal of Molecular Modeling*
– the advanced way of publishing–

A Molecular Mechanics Study of an Organometallic Tinkertoy

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A fairly new and rapidly growing field of polymer science is targeted at the synthesis and characterization of molecular compounds beyond the sizeof conventional organic molecules. Apart from the dendrimers, currentinterest centers on extended planar structures that can be viewed as excentric alternatives to the familiar structure of graphite. These can be synthesized from ethynyl-substituted carbocycles such as cyclobutadienyl and cyclopentadienyl derivatives that are stabilized by complexation with a metal carbonyl or metal cyclopentadienyl moiety. The comparative rigidity of the triple bond gives rise to a number os isomers with respect to the relative orientation of these metal-organic groups in the oligomeric molecule.

In order to study the structural and energetic features of the isomeric oligomers, we have incorporated parameters for Fe(0) and Co(+) as well as the CO ligand in our PIMM force field. All interactions between the metal and its organic ligands are calculated without resorting to pseudoatoms or static bonds. This ensures a maximum of flexibility in our approach that should allow its application to problems beyond those presented here.

Modified Cyclodextrins as Chiral Selectors - A Molecular Modelling Study

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Modified cyclodextrins diluted with polysiloxanes have become powerful tools in the enantioselective capillary gas chromatography. One very recent and successful application is the enantioselective analysis of aroma-relevant dihydrofuranones [1].

The aim of our Molecular Modelling study is to get insight into the mechanism of this separation process by construction of a corresponding interaction model of the host-guest complexes. On the basis of this model the forces which are responsible for enantiomeric separation shall be described.

In the first step we have modified the CVFF force field of INSIGHT/DISCOVER [2] so that the special geometrical properties of carbohydrates are more correctly reflected. The results of the calculations using the modified force field are in good agreement with experimental data [3] and ab initio calculations [4]. A conformational analysis of heptakis (2,3-di-O-methyl-6-tert-butyldimethylsilyl)-ß-cyclodextrin was performed, using annealed molecular dynamics starting at 1000 K and annealing to 0 K. For each of the received energetically reasonable structures, favourable binding sites for the host-guest interaction have been determined using the programme GRID [5]. The results of these calculations are used as starting points for the generation of the host-guest complexes between cyclodextrins and dihydrofuranone derivatives.

In order to investigate the flexibility of the diastereomeric complexes a molecular dynamics simulation of 200 ps for each of the generated starting geometries of the complexes was performed. During the molecular dynamics simulations the complex geometries have been saved at regular time intervals resulting in 800 different complex states. For each of these states the interaction energy was determined.

Considering the evaluated interaction energy between the cyclodextrin and the dihydrofuranone derivative as a measure of complex stability the S-complexes are energetically favoured over the R-complexes. This is in good agreement with the experimental determined elution sequence [1]. The R-enantiomer of the dihydrofuranone derivative, which forms the less stable complexes elutes before the corresponding S-enantiomer.

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Best Poster Award

3D Investigations of Sandalwood Fragrances

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The structure activity relationship of sandalwood fragrances is mostly unknown until today, this may be caused by the large structural inhomogenity, the lack of knowledge of the olfactory process and of the properties of the aromatic substances [1,2].

With the help of osmophorical hypothesis relationships the structure of biological active compounds is scanned with the goal to find key structure elements out of a large amount of aromatic substances [3,4].

A fast and reliable method to prove the pharmacophor- or osmophor hypothesis and to find active conformations (i.e. the binding conformation of the molecule to the receptor) is the *ACTIVE ANALOG APPROACH* [5]. Beginning with the coordinates of active aromatic substances of sandalwood taken from a data bank a conformation analysis of the different molecules is performed with *SYSTEMATIC SEARCH* [6] and *RANDOM SEARCH* [7] to give the starting geometries [8] for the *ACTIVE ANALOG APPROACH.*

With the help of systematic searching algorithms the 3D-arrangements of the osmophoric groups of the fragrances taken from the data base are searched for the similarity towards sandalwood aromatic fragrances. The 3D orientation of the osmophoric groups of the active conformations plays an important role.

In the next step a receptor mapping [5] is performed and through addition of van der Waals volumina to the biological active molecules a negative model is generated, leading to the properties of a possible receptor. To validate the method, inactive aromatic substances of sandalwood with similar structure are bound to the receptor model according to the molecular surface, proving the missing effect of the test molecules.

To locate binding sites in the surroundings of the osmophoric groups an optimization and a comparison of the complete surface or definite segments is performed [9–11] and the results are analysed with quantitative methods. These methods are based on the construction of points of intersection through the centre of mass of the reference molecule. The criterion to qualify the degree of similarity of the compared molecular surfaces is scaled corresponding to the sum of squares of the deviation of the included surface points.

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Efficient Modeling Protocols for Oligosaccharides; from Maltose to Cyclodextrin

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The determination of conformational preferences of oligosaccharides is best approached by describing their preferred conformations on potential energy surfaces as a function of the glycosidic linkage torsional angles Φ and Ψ. Besides the conformational transitions in the Φ,Ψ space, the flexibility of the rotable pendant groups must be analyzed, which, in the case of title compounds, is a multidimensionality problem of 10 for maltose and 28 for β-cyclodextrin. On a molecular mechanics level, the so called "adiabatic maps", which partially mimics the flexibility within the 10 dimensional conformational space of the pendant groups, are considered to be the state of the art of the maltose Φ,Ψ potential energy surface recently calculated [1].

The computation protocol, based on the RAMM [2] (*RA*ndom *M*olecular *M*echanics) methods, is shown to calculate such profiles in an entirely automatic way. The procedure can easily be expanded for larger oligosaccharides, as illustrated by the example of cyclodextrin [3]. The efficiency of the RAMM calculational protocol to locate low-energy conformers on the multidimensional potential energy hypersurfaces of maltose and cyclodextrin is discussed. In addition to molecular mechanics modeling several molecular dynamics simulations have been performed on a 1 ns time scale. The effect of simulation temperature, dielectric constant, integration steps, etc., on the conformational flexibility in the Φ,Ψ space of both molecules have been analyzed. The parametrization of the force field utilized is believed to have key importance to obtain realistic energy profiles for oligosaccharides, but the question as to which is the most appropriate force field to use for carbohydrates has yet to be answered.

Several different force fields (CVFF, CFF91, Amber, MM+,...) were tested for this reason for maltose, illustrating the differences in predicting of the Φ,Ψ regions of the stable conformers. The Φ,Ψ regions theoretically obtained from molecular mechanics and molecular dynamics calculations for both title compounds, cyclodextrin and its maltose subunit, are compared with the statistical analysis of all structural data retrieved for these molecules from the Cambridge Crystallographic Database.

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Conformational Flexibility of β-Cyclodextrin as Revealed from Random-Walk Molecular Mechanics and Long Range (nanosecond) Molecular Dynamics

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Conformational properties of β-cyclodextrins (BCD) are of particular interest, and were also thoroughly investigated during the last few years in several laboratories. Qualitative estimation of the conformational flexibility of BCD can be obtained by monitoring the changes of intramolecular torsional angles. In the case of BCD these can be divided into

two classes. First, the glycosidic torsional angles Φ_i ,Ψ_i (dimensionality 14) describe the orientation of the adjacent glucose units. The second class, ω_i , χ_{i2} , χ_{i3} , χ_{i6} , describes the orientation of the primary and secondary hydroxyl groups on the glucose subunits and has dimensionality of 28 (where i=1 to 7 for both classes).

Complex analysis is required to answer the question what is the relationship between the conformational changes in Φ,Ψ directions and the conformational fluctuation of the substituents. The standard molecular mechanics methods based on regular grid search are not suitable for such an enormous conformational problem. An alternative approach is given here, using the RAMM procedure [1], a molecular mechanics method based on random-walk within the torsional angle space. The results of the analysis of nine stable forms are presented, six geometries of low symmetry [2] and three conformers with higher symmetry. The last were obtained with standard and driven optimization of BCD conformation with Φ_i ,Ψ_i = 0.0° . For all conformers studied, the random sampling within the 28 dimensional ω_i , χ_{i2} , χ_{i3} , χ_{i6} conformational space improved the molecular energy. In the case of all the studied forms the primary hydroxyl groups have larger conformational freedom than the secondary ones. In the case of the symmetric forms the secondary hydroxyls are involved into a homodromic O2...O3 hydrogen bond network.

The results of the RAMM modeling were confirmed with long range molecular dynamics simulations, using the Discover program of Biosym. Simulations at 300 and 400 K (1ns and 2ns) and at 1000 K (1ns) were calculated. At low temperature simulations the molecule fluctuates within the Φ,Ψ space at values around 0.0° . The occupancy profile, drawn in two-dimensional Φ,Ψ plot, is similar for each of the seven combinations of Φ_i ,Ψ_i and has a characteristic half-moon like shape. The stabilizing hydrogen bond network between O2(i)....O3(i-1) is present during the entire simulation with consequent decrease of the mobility of HO2 and HO3 (oscillating around χ_{i2} » -60° , χ_{i3} » -60°). No conformational transitions of these groups were observed at 300 K and, the first and only reorientation occurred (χ_{i2} » 180° , χ_{i3} » 180°) at approximately 1.7 ns at 400 K.

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Molecular Dynamics Simulations of 1,2-Diol Water Clusters

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Investigations of the structure, stability and dynamics of amphiphilic 1,2-octanediol as well as phenyl and cyclohexyl substituted 1,2-ethanediols were performed within MD simulations using the program package GROMOS87 [1-3].

These diols are suitable as model systems for the study of structural formation in amphotropic liquid crystals and bilayers. The applicability of the GROMOS87 force field was tested by calculations on the isolated molecules.First results of MD simulations on monomers, dimers as well as clusters with 4 and 16 molecules of the 1,2 diols in the gas phase and in the water box are presented. The influences of the GROMOS87 parameters, e.g. step width, cut-off radii and boundary conditions on the results were investigated. Especially, the role of intramolecular and intermolecular hydrogen bonding as well as the function of water molecules in the process of association of the hydrophilic head groups was studied in more detail. Moreover, by structural variations in the amphiphilic molecular units, the formation of the energetically preferred arrangements of clusters and bilayers was investigated in a systematic way.For the visualization of the molecular dynamics results a graphics tool was created for SGI and IBM RISC 6000 workstations. With the help of this tool the results of MD runs are illustrated and analyzed in a useful way including trajectories of energy, significant distances and torsion angles as well as the representations of molecular structures and the water box.

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A new Modeling Tool for Sybyl to Calculate LOG P and Visualize Atomic and Molecular Lipophilicity

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Despite the importance of hydrophilicity for structure activity relationship and the availability of published data sets from Broto es al [1] and Crippen et al [2], reproduce lipophilic properties of atoms and molecules, there is still no adequate tool at hand for this purpose within the Sybyl basic command set. LIPOP is a simple Sybyl programing language macro written for the SYBYL-BASIC module.

The main concept for such a computational quantification of lipophilicity by atomic fragmental contributions has been established as Molecular Lipophilic Potential (MLP) by Croizet et al [3] and Heiden et al [4]. The only input data LIPOP asks for is the molecule itself. The algorithm is derived from the fragmental code described by Croizet et al. It applies the empirical finding that each atom contributes additively in a constant way to the molecular lipophilicity. LIPOP-2 will be able to switch to another data set of Crippen et al. LIPOP automatically calculates and displays the following informations on the screen:

- LOG P value based on the Broto and/or Crippen data set- molecular lipophilic potential (MLP) map using Broto or Crippen data
- colored molecular surface (VAN DER WAALS) visualizes lipophilic and hydrophilic properties using Broto or Crippen data on a transparent
- CONNOLLY surface.

A Sybyl DEMO has been set up to show the usefulness of LIPOP in the comparison of anti-lepra Dapsone to other sulfonamides. Experimental LOG P values of several compounds are gathered and compared to the results of CLOGP and LIPOP.

Limitations: reproduction of conformational, isomeric, tautomeric, ionic, and dipolar influences. LIPOP is a user-friendly, robust modeling tool giving basic information and intuitive insight to MLP. It constitues a simple introduction to a not yet satisfactorily understood empirical intrinsic structural property: LIPOPhilicity.

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Conformational Analysis of Charged and Uncharged Oligothiophenes

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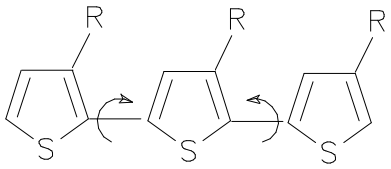
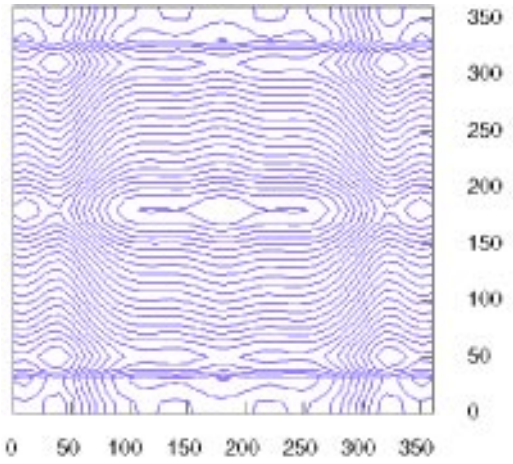
Conjugated organic polymers like polythiophenes have attracted a lot of interest during the last decade. They show interesting properties in their reduced and oxidized (doped) forms, e.g high electrical conductivity. These properties are dependent of the conjugation of the π-system and therefore a thorough investigation of the conformation of oligothiophenes as model systems for the polymers was conducted. Semiempirical calculations give a possible explanation why only doped systems show those extraordinary properties.

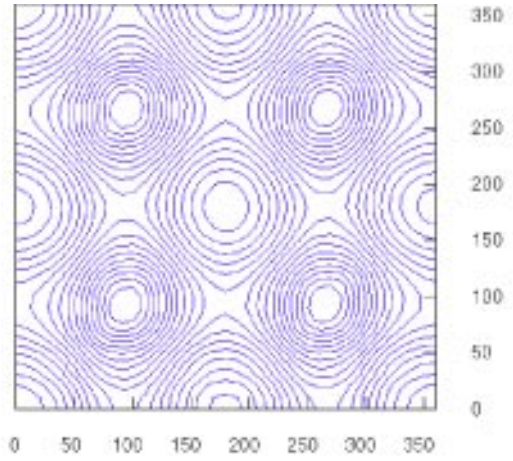
Oligothiophenes **1** and **2** were used as model compounds, the conformational hypersurfaces of the radical anion/cation and of the neutral molecule were calculated by means of the semiempirical methods AM1, MNDO and PM3 [1]. The surfaces shown at the end of the abstract were calculated with the PM3-method.



1 R = H
2 R = CH_3



Compound **1**, Charge 0
(Spacing 0.1 kcal/mol)



Compound **1**, Charge -1
(Spacing 1 kcal/mol)

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Conformational Analysis on Monospirodienone–Derivatives of Calix[4]arenes

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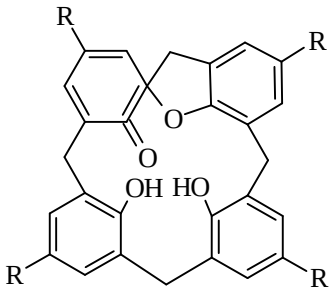
The mild oxidation of p-*tert*-butylcalix[4]arene leads to the chiral monospirodienenone **1**(R = *tert*-butyl) as an intermediate for the synthesis of proximal disubstituted and didehydroxylated calixarenes [1].



1

The X–ray structure of **1** shows a partial cone conformation with both hydroxyl groups in *syn*-position and one possible H-bond between one hydroxyl group and the oxygen of the furan–ring. In contrast to classical calix[4]arenes the inversion of the ring leads to a diastereorisomeric partial cone conformation, where the phenol ring is anti to the dihydroxybezofurane ring, which is stabilized by a H-bond between the hydroxyl group and the carbonyl function.

Temperature dependent ^{1}H-NMR spectroscopy does not show decoaleszenz at 145K, this can be explained by the precence of only one conformer or an activation energy for the ring inversion below 7.5 kcal·mol^{-1}.

A systematic conformational seach of the model compound **1** (R = Me) was performed with the help of high–temperature MD-simulations, followed by an energy minimization to give a set of starting conformations using the TRIPOS [2] and the MM3 force field [3].

19 local minima structures were found and classified as followed (relative energies, TRIPOS–force field [MM3]):

syn partial cone (0.0 [0.4] kcal·mol^{-1})
1.2–alternate (2.6 [0.0] kcal·mol^{-1})
anti partial cone (6.7 [0.6] kcal·mol^{-1})
1.3–alternate (7.5 [2.5] kcal·mol^{-1})

The geometry of the thermodynamically most stable *syn partial cone* conformation is in good agreement with the X-ray structure, the fit with the calixarene ground structure gives RMS values of 0.32 Å (TRIPOS) and 0.27 Å (MM3), respectively.

The reaction paths and the corresponding activation energies of the ring inversion process were calculated with several methods based on the MM3 force field.

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Comparison of Molecular Surface Properties Using a Kohonen Neural Network

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Based on the application of the Kohonen neural network, we would like to present a novel, versatile approach for a comparative analysis of surface properties of molecules, here especially of the electrostatic potential on molecular surfaces. The Kohonen neural network is a self-organizing network, which can be used to generate a non-linear projection of objects into a lower dimensional space, while conserving as much as possible of the topology of the information [1].

The advantage of this method compared to previous approaches is that no superposition of the molecules studied is required.

Applications of the methodology will be presented to show a variety of possibilities for the use of the Kohonen net in SAR and drug design. A template approach will be presented, using several compounds of cardiac glycosides, which bind to the digitalis receptor and inhibit the Na^+/K^+-ATPase[2].

In the template approach the shape is taken into account by a reference molecule within a series of compounds to prepare a template net, which forms a basis for further comparisons.

The template approach can also be used to compare the conformations of a flexible molecule, generated by conformational search with respect to a reference molecule.

The backprojection of the 2D-Kohonen maps into 3D-space allows to identify the areas of the molecular surface where active and inactive compounds differ significantly. This will be shown using the example of ryanodine derivatives, which bind to specific membrane proteins, altering the calcium permeability of the intracellular membrane [3].

A fragment library of small 'functional groups' together with their corresponding Kohonen maps has been generated. The comparison of the electrostatic potential patterns of the maps of such a library can be used to cluster the bioisosteric groups and consequently improve the efficiency of the 3D-design of bioactive molecules.This strategy will be presented for the $5HT_{1A}$-agonists as a group of semiridig analogs of serotonin.

The results indicate that the Kohonen neural network may be a useful tool for the fast and accurate investigation of large datasets of molecules and for the rational design of drugs of biological interest.

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Similarity Analysis of Biologically Active Molecules with Topological Autocorrelation Vectors in Self-Organizing Maps

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Increasingly large databases with hundreds of thousands of compounds, which often only contain the two–dimensional (topological) structure of the molecules have become available in the last few years. The automated search of these databases for substances similar to those with known therapeutic effect is an important method to find new highly specific drugs.

The method presented here uses self-organizing maps on a massively parallel computer (MasPar MP-1 with 16384 processors) for clustering of similar molecules, on the basis of topological autocorrelation vectors. The algorithm of the self-organizing map requires a vector of equal length for every molecule which is used as input vector for an unsupervised network training algorithm. This input vector must code all features of a molecule relevant for the grouping or classification decision of the network. Here, autocorrelation vectors [Moreau80] of features (s-charge, total charge, s-electronegativity, p-electronegativity, lone-pair-electronegativity, atom polarization coefficient, atom identity) of the topological structure of the molecules were used.

The goal of training these Kohonen maps was to separate 112 dopaminergic agonists and 60 benzodiazepine agonists [MDL94] into two clusters of activated neurons. In this application a near perfect class separation (3 misclassifications) could be achieved for a Kohonen map of size 10x7. A smaller subset of 17 dopaminergic agonists and seven benzodiazepine agonists [Martin93] could be separated perfectly with a self-organizing map of size 5x7. For the intended application as a database screening method it is interesting to see what happens if the active substances are buried in a large number of inactive substances or substances whose activity is not known. To answer this question, the 172 active substances were complemented by inactive substances from the Janssen catalogue of chemical substances with 8298 entries [Jansen94]. To see distinctive clusters in this large data set we used a self-organizing map of size 40x30. This data set with its 8470 entries is so large that training the Kohonen map needed several hours even with the very powerful parallel computer used. Surprisingly, these active substances formed disticnt clusters in a small region of the full space of substances. The combination of topological autocorrelation vectors and self-organizing maps is thus a successful approach for the similarity analysis of molecules. Even if the active substances are among a large set of inactive substances, they form distinct clusters.

The use of a massively parallel computer with 16384 processors, which is 200 to 500 times faster than a workstation for this particular problem, enables a rapid training of large self-organizing networks with high resolution. Once the network is trained, however, the resulting network can easily be deployed and used on a workstation.

marvin: A New Platform for QSAR Software Development and a General Molecular Modeling Software Interface

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marvin is a software package that organizes QSAR and molecular modeling algorithms, and applicates them to different types of molecular data sets. In mavin, an algorithm is defined as a list of marvin applications. Every application is a stand alone program designed for the use with marvin. In addition, any existing molecular modeling or

quantum chemistry program (eg. mopac, gamess, gaussian) can be adapted easily to use it as an application.

The interface between the applications is a common data file format that can hold different types of data. Therefore, all applications can be assembled arbitarily without compatibility problems. Consequently, marvin is a modular molecular modeling system with algorithms built up from individual applications. The parameter input for all applications is done in the same input file. This file controls the information flow between the applications as well as the setup for single applications. The algorithm is defined by a list of applications, a second list contains all molecule names to be processed. One input file holds the setup for the whole QSAR investigation that runs automatically, without further engagement of the operator. The format of the input file is very simple: free text format, comments allowed everywhere, inline statement to include files containing default values, hierarchical structure of input files that allows easy definition and change of defaults, etc.

When programming new marvin applications, the functions of the marvin library are used to do all the work related with input, output, error handling and user interface. Therefore, the programmer can focus on the essential algorithm, so that the development of a new application for marvin is very effective. To include the new functionality into a QSAR algorithm, just put the name of the new application into the application list of the marvin input file. There are three main ways of using marvin:

- to organize existing molecular modeling and quantum chemistry software to form specialized algorithms, and run them automatically.
- using marvin as a simple platform, to run single molecular modeling programs. Profit by the user friendly marvin input format for all program setups, instead of using different file formats for each program package.
- to write your own marvin application as a part of new QSAR algorithms, and combine it with all existing and future applications and interfaces.

Structure Activity Relationships in Kappa Opioid Receptor Binding 3,7-Diazabicyclo[3.3.1]nonan-9-ones

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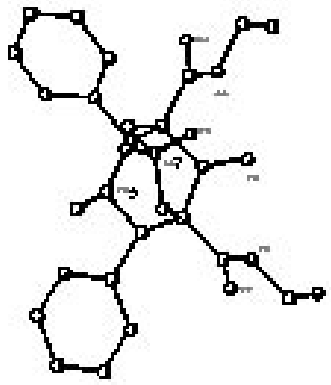
Several 3,7-diazabicyclo[3.3.1]nonan-9-ones (see Fig.) were found to be κ-opioid receptor selective agonists.[1] We analysed the structure-activity relationships of these compounds in different conformations by comparing them with well-known k-selective agonists such as U-62066, U-69593, U-50488 and several isoquinoline derivatives [2]. We performed molecular modelling investigations using SYBYL software as well as PM3 and MM3 calculations. For all compounds a systematic conformational search was carried out. The low energy conformations were compared with regard to spatial similarities of the electrostatic, hydrophobic and hydrogen bonding potentials.

The resulting common features of the very likely pharmacophore conformations of U-62066, U-69593, U-50488 and several isoquinoline derivatives are characterised by identical orientations and positions of the protonated nitrogen atom N7, the carbonyl function as well as the aromatic ring at C2. These characteristics are also found in the κ-antagonist ketocyclazocine.

Based on these studies we determined the pharmacophore conformation of the 3,7-diazabicyclo[3.3.1]nonan-9-ones. Thus, the protonated nitrogen atom, the keto carbonyl func-



** to whom correspondence should be addresse*

tion and one of both aromatic rings agree with corresponding positions found in all other compounds. The other aromatic ring is nearly in the same spatial position as found for the second ring in the isoquinolines.

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Determination and Comparison of μ and δ‐Pharmacophore Conformations of Cyclic ß-Casomorphin Analogues.

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It has been shown that cyclic ß-casomorphin analogues with a D-configurated amino acid residue in position 2, such as Tyr-c[-X-Phe-Pro-Gly-], Tyr-c[-X-Phe-D-Pro-Gly] (X=A_2bu, Orn, Lys) bind to the μ–opioid receptor as well as to the δ–opioid receptor, whereas the L-configurated analogues are nearly inactive at both [1,2]. The very likely μ–opioid receptor binding conformations have already been described for the D-Orn containing ß-casomorphin analogues supported by NMR-spectroscopy [2].

Low energy conformers of both active and nearly inactive compounds have been determined in a systematic conformational search using the TRIPOS force field. The obtained conformations were compared with a μ–opioid receptor pharmacophore model [2,3] as well as with a proposal of the δ–opioid receptor pharmacophore conformations developed by Mosberg et al. [4a,b], and with several rigid δ–opioid antagonists [5]. On the basis of these investigations we were able to propose the until now not described μ–pharmacophore conformations for the A_2bu and Lys derivatives and the δ–pharmacophore structures of all investigated cyclic ß-casomorphins. We did find not only high similarity in the spatial orientations of aromatic rings with regard to the N-terminal nitrogen but also for the overall backbone structure including the carbonyl oxygen atoms in each class of conformations. This is clearly indicated by very similar molecular electrostatic, hydrophobic and hydrogen bonding potentials. Interestingly, for the inactive compounds such conformations could not be detected. Beside, larger distances between the centroids of the aromatics Tyr 1 and Phe 3 for the μ selective conformations (10 to 11 Å) than for the δ-conformations (5 to 7 Å) we found a further main difference in the dihedral angle Ψ 2 to be for μ about -75° but for δ conformations about 160°.

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Quantification and Visualization of Molecular Surface Flexibility

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The surface of a molecule is of special interest when molecular recognition phenomena are investigated. The objective of the work presented here was to improve the widely used *solvent accessible surface* (SAS) model by developing new methods for the quantification and visualization of local surface flexibility.

Information on the dynamics of molecular surfaces can be obtained in many cases from experimental data, e.g., the Debye-Waller temperature factors can be derived from X-ray diffraction studies. However, the thermal fluctuations of hydrogen atoms cannot be quantified using X-ray data. Be-

sides other experimental techniques, computer-aided simulation techniques like *molecular dynamics* can fill this gap. The dynamic behaviour of a molecule may then be described by atomic RMS deviations.

We present a distance weighted incrementation procedure used to project atomic flexibility measures like temperature factors and RMS deviations onto the SAS of a molecule. In addition, we developed another method which allows for a quantification of the flexibility of the SAS itself, which in fact results from a superposition of atomic movements. An important feature of the latter method, which is based on the results of a molecular dynamics simulation, is that an arbitrarily reference direction may be defined for each surface dot during the calculation of the local flexibility values, i.e., the local flexibility of the SAS is described with respect to a well-defined direction.

The numerical data provided by both methods may be visualized via computer graphics. The graphical representation is substantially improved with the help of a recently developed texture mapping procedure which allows for a very sharp and clear display of numerical data on a triangulated surface.

For validation of the methods with respect to biomolecules, local flexibilities for the SAS of two proteins (*pancreatic trypsin inhibitor* (PTI) and *ubiquitin*) were calculated and visualized. Surface domains exhibiting different mobility can be clearly recognized and separated from each other. We are currently working on a new approach to the protein docking problem taking into account surface flexibility quantified with these new methods.

Molecular Modelling on the Responsive Workbench

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Virtual working environments are able to provide Molecular Modelling applications with a highly adapted 3D user interface. The Responsive Workbench (RW) is designed to support end users as scientists, engineers, physicians, and architects working on desks, workbenches, and tables with an adequate human-machine interface [1]. This concept, as an alternative model to the multimedia and virtual reality systems of the past decade, allows users to focus on their tasks rather than on operating the computer.

Virtual objects and control buttons, displayed as computer generated stereoscopic images (seen through shutter glasses) are projected onto the surface of a table. The projection parameters are tuned such that the virtual objects appear to be above the workbench. Users operate within a non-immersive virtual environment. Depending on the application, various input and output modules can be integrated, such as motion, gesture and speech recognition systems.

To get correct stereoscopic rendering from any location around the workbench the system must keep track of the guide's eye positions. This is performed by a Polhemus sensor mounted on the side of the shutter glasses. It delivers position and orientation data for the head, allowing the system to calculate the position of each eye.

The most important and natural manipulation tool for virtual environments is the user's hand. The user wears a data glove with a Polhemus sensor mounted on the back. Gesture recognition and collision detection algorithms compute the user's interaction with the virtual world objects.

Molecular Modelling presents a new field of application besides those which are already embedded in this environment (e.g. a medical training scenario for the examination of a virtual patient, interactive visualization of flow field simulations, and virtual architectural models).

Such applications are basically the examination and/or manipulation of complex molecules like protein complexes or other macromolecular systems. Spatial relations of an enzyme/substrate (or enzyme/inhibitor) or antibody/antigen complex can be examined stereoscopically. On the RW, molecules can actually be touched, grabbed, and moved around manually, which simplifies the detailed examination of distinct molecular regions as well as manual docking. Linked to surface examination algorithms in relation to certain physical and topographical surface properties [2], surface segments can be cut out and viewed separately.

Molecular 3D structures as presented here are PDB X-ray data; Molecular surface generation and processing was performed using the MOLCAD software [3].

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Structure-Property-Relationships of Liquid Crystals based on the Evaluation of the Database LiqCryst

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The database LiqCryst contains chemical structures and physical properties of about 58,000 compounds [1]. Aim of the database is not only the collection of data, but the statistical analysis and the prediction of data as well.

This program uses the "LEGO"-model of liquid crystals. The chemical structure is subdivided into a linear sequence of fragments. These fragments are rings, bridges, terminal groups etc. Two different chemical substructures can be compared by their transition temperatures, e.g. 1,3-dioxane compounds can be compared with the analogous cyclohexane compounds. A similarity between two chemical structures can be defined by one single difference in the code of fragments. The properties of a new structure can be predicted by the extrapolation from known similar compounds.

Examples for statistical analysis and predictions are given.

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