22nd Darmstädter Molecular Modelling Workshop

Computer-Chemie-Centrum
Nägelsbachstr. 25, 91052 Erlangen
Germany

Tuesday, April 29th - Wednesday, April 30th 2008

Once again, we in CCC are happy to welcome you to the 22nd Darmstädter Molecular Modelling Workshop. The goals of the Workshop are to give graduate students and young postdocs an opportunity to present their work, to provide a forum for molecular modeling and to give young researchers the opportunity to meet established researchers, both industrial and academic. The Molecular Graphics and Modelling Society – German Section (MGMS-DS) is, as always the organizer of the Workshop and provides financial support to enable students to attend the workshop.

We especially thank our sponsors, who have not only this year enabled us to provide an excellent program at a very low price, but many of whom have supported the Darmstädter Molecular Modelling Workshop consistently and generously over its entire history.

Coordination of scientific program

PD Dr. Wolfgang Brandt

Leibnitz Institut für
Pflanzenbiochemie

Weinberg 3
06120 Halle (Saale)

Tel.: +49 (0) 345 5582 1360
Fax: +49 (0) 345 5582 1309
Mail: wbrandt@jpb-halle.de

Technical coordination

Prof. Dr. Tim Clark

Computer-Chemie-Centrum
Universität Erlangen-Nürnberg

Nägelsbachstr. 25
91052 Erlangen

Tel.: +49 (0) 9131 85 22948
Fax: +49 (0) 9131 85 26565
Mail: clark@chemie.uni-erlangen.de

Dr. Claus-Wilhelm "Willi" von der Lieth († 16.11.2007)

Willi von der Lieth leitete die Gruppe 'Molecular Modelling' in der Abteilung Zentrale Spektroskopie des Deutschen Krebsforschungszentrums und war ein grossartiger, sehr hilfsbereiter und selbstloser Wissenschaftler, der von allen, die ihn kannten, hoch geachtet wurde. Er studierte Chemie in Hannover, promovierte in Heidelberg und kam 1980 als Wissenschaftler ans DKFZ um ein computergestütztes Informationssystem für Spektren zu entwickeln. Bereits 1984 führte er Molecular Modelling Methoden im DKFZ ein. Nach einem Aufenthalt in Schweden, wo er sich mit Moleküldynamik Simulationen von Peptiden befasste, kehrte er 1987 ans DKFZ zurück, wo er seither viele Kollegen durch computergestütztes Modellieren von 3D Strukturen unterstützte. Die Visualisierung von räumlichen Molekülstrukturen war für ihn von Anfang an nicht l'art pour l'art, sondern ein nützliches Medium für den Erkenntnisgewinn in der Wissenschaft sowie für die verständliche Darstellung wissenschaftlicher Erkenntnisse, welches er in der Öffentlichkeit zu nutzen und nutzbar zu machen verstand.

Willi war Mitglied im GDCh, CIC und über viele Jahre Schatzmeister der Molecular Graphics Society. Willi gilt weltweit als einer der führenden Wissenschaftler und Pionier im Zukunftsgebiet Glycomics. Willi von der Lieth war Koordinator des EUROCarbDB projects, Co-Director im HGPI/HUPO und Mitglied im US Consortium for Functional Glycomics. *'Willi was an inspiration to the evolution of the glyco-bioinformatics field and an emerging leader in the mission to develop standardized glycan databases and bioinformatics tools world-wide. He will be missed tremendously.'* (Rahul Raman, CFG Core Director B, MIT). Seine Arbeiten auf dem Gebiet des 3D Modelling von Kohlenhydratstrukturen haben weltweite Anerkennung gefunden.

Die über das Web-portal http://www.glycosciences.de frei zugänglichen Programme, wie „Carbohydrate Structure Suite“ und „Sweet 2“, die in seiner Arbeitsgruppe entwickelt wurden, sind als wichtige Werkzeuge zur Berechnung komplexer Kohlenhydratstrukturen nicht mehr wegzudenken. Willis Projekte wurden vom BMBF, DFG und der EU durch Drittmittel gefördert. Willi war im Editorial Board von Carbohydrate Research und hat selbst weit über 100 Artikel in wissenschaftlichen Journalen und Büchern publiziert. Die Wissenschaft verliert mit ihm einen wunderbaren Menschen und Visionär.

Seine intensive Zusammenarbeit sowohl mit Kolleginnen und Kollegen im Deutschen Krebsforschungszentrum als auch weltweit erstreckte sich auf fachlich eng verwandte Felder, jedoch auch und besonders auf die Bereiche der Klinischen Chemie und der Medizin. Selbst schon in jungen Jahren persönlich betroffen, war ihm die Krebsforschung ein Anliegen, dem er sich mit unvorstellbarem Einsatz an Kraft und Zeit widmete. Mit seinen Forschungsergebnissen und der Mitwirkung in Projekten und Konsortien erreichte er in den letzten Jahren zunehmend gebührende Aufmerksamkeit. Viel umfangreicher noch dürften seine zahllosen und unschätzbaren Beiträge zu vielen Arbeiten von Kolleginnen und Kollegen sein, die er durch Modellierung und Visualisierung unterstützte und dadurch den Dienstleistungscharakter der Arbeitsgruppe im besten Sinne manifestierte.

Nach reiflicher Überlegung strebte er selbst keine Professur an, hat jedoch derartige Ambitionen nach Kräften unterstützt und maßgeblich zur Habilitation und erfolgreichen Berufung von mindestens zwei seiner Mitarbeiterinnen und Mitarbeiter beigetragen.

Sein plötzlicher Tod verursacht einen großen fachlichen und menschlichen Verlust bei allen, die mit ihm zusammenarbeiten durften. Seine hohe Kompetenz, sein unermüdlicher Fleiß, seine besondere Gabe zum interdisziplinären Arbeiten und seine einzigartige Weise, als Primus inter pares aufzutreten und auf formale Autorität zu verzichten, werden unauslöschbare Spuren hinterlassen.

Er wurde von der Krankheit aus dem Schaffen gerissen, deren Bekämpfung er sein Leben gewidmet hat. Jeder Mensch ist zu ersetzen – aber bei manchen ist es besonders schwierig.

Dear colleagues,

The Darmstädter Molecular Modelling Workshop takes place every year on its traditional dates of the Tuesday and Wednesday before Christi Himmelfahrt (Ascension Day); this year April 29th and 30th. This is the sixth time that the Workshop has taken place in Erlangen after 16 years in Darmstadt. The Workshop is organized by Prof. Tim Clark's group from the Computer-Chemie-Centrum (CCC) at the Friedrich-Alexander-Universität Erlangen-Nürnberg. The organization of the scientific program traditionally alternates between scientists from industry or academia. In this year, PD Dr. Wolfgang Brandt from the Leibniz-Institut für Pflanzenbiochemie in Halle is responsible for the scientific program.

The goal of the Workshop is to allow young scientists, especially graduate students, to present their work to an audience that consists of modeling specialists from industry and universities.

Contributions from all branches of modeling, from life-sciences to materials modeling, are welcome.

Our Plenary Speakers this year are

Pavel Hobza
Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic and Centre for Biomolecules and Complex Molecular Systems
Prague, Czech Republic

Hans-Jörg Hofmann
Institute of Biochemistry, University of Leipzig

The official language of the Workshop is English.

Awards

As in the past years, there will be two Poster Awards of EUR 100 each and three Lecture Awards for the best talks:

Winner: Travel bursary to the Young Modellers Forum in the United Kingdom (travel expenses are reimbursed up to EUR 500)
2nd Winner: EUR 200 travel expenses reimbursement
3rd Winner: EUR 100 travel expenses reimbursement

Only undergraduate and graduate research students qualify for the poster and lecture awards. A Web Award for WWW-based scientific applications in the field of molecular modelling will not be awarded this year.

Program: Tuesday, April 29th 2008

8:00-9:15	Registration
9:15-9:20	Welcome remarks / Agenda review
	Session 1, Chair: W. Brandt
9:20-10:20	**Plenary Lecture: Hans-Jörg Hofmann** *Institute of Biochemistry, U Leipzig* Prediction of Foldamer Structures Employing Theoretical Methods
10:20-10:50	Coffee break
10:50-11:15	**Karel Berka** *Institute of Organic and Biochemistry, Prague* Amino acid side-chain interactions in proteins. Comparison of ab-initio and empirical methods
11:15-11:40	**Diana Schulze** *Leibniz-Institute of Plant Biochemistry, Halle (Saale)* Structural Models of Membrane Bound Aromatic Prenyltransferases
11:40-12:05	**Christophe Jardin** *Institute of Biochemistry, U Erlangen* The phosphoryl transfer between the IIA and IIB proteins of the Escherichia coli Glucose Phosphotransferase System
12:05-12:30	**Jana Selent** *Computer-Assisted Drug Design Laboratory, U Pompeu Fabra, Barcelona* Multi-Receptor Profiling of Antipsychotic Drugs. A Structural Study Based on the new β2 Adrenergic Receptor Template
12:30-13:30	Lunch break
	Session 2, Chair: H. Bögel
13:30-13:55	**Lothar Terfloth** *Computer-Chemistry-Center, U Erlangen* Isoform Specificity of Cytochrome P450 Substrates
13:55-14:20	**Sebastian Kruggel** *Institute of Pharmacy, U Hamburg* P-gp substrate differentiation by pharmacophore modelling

Program: Tuesday, April 29th 2008

14:20-14:45 **Tobias Lippert**
Center for Bioinformatics, U Hamburg
Fast Optimization of Hydrogen Bond Networks in Protein-Ligand Complexes

14:45-15:10 **Andrea Straßer**
Institute of Pharmacy, U Regensburg
3D-QSAR-Models of four Histamine H_1-Receptor Species Isoforms and a Hypothesis for a ligand induced activation mechanism of the H_1-Receptor

15:10-15:40 Coffee break

Session 3, Chair: I. Thondorf

15:40-16:05 **Christian Kramer**
Computer-Chemistry-Center, U Erlangen
A compound model for hERG blockade

16:05-16:30 **Frank Broda**
Institute of Biochemistry/Biotechnol, U Halle (Saale)
Molecular Dynamics Simulations of Dimeric Tetraurea Calix[4]arene Capsules

16:30-16:55 **Christof Jäger**
Computer-Chemistry-Center, U Erlangen
Structured Micelles – Guiding experiments with MD simulations

16:55-17:20 **Justin J. Finnerty**
Institute for Pure and Appl Chemistry, U Oldenburg
Theoretical Study on the non-linear optical properties of phenylenes and influencing factors

17:20-18:00 Annual MGMS-DS Meeting

18:00-22:00 **Poster Presentations / Buffet**

Program: Wednesday, April 30th 2008

Session 4, Chair: M. Krug

9:15-9:40 **Mateusz Wielopolski**
Computer-Chemistry-Center, U Erlangen
Modeling of Electron-Transfer Properties in Organic π-Conjugated DONOR-WIRE-C_{60} Systems

9:40-10:05 **Rene Meier**
Inst for Pharmaceutical Chemistry, U Halle (Saale)
ParaDockS – An Extensible Framework for Parallel Molecular Docking

10:05-10:30 **Tim ten Brink**
Department of Chemistry, U Konstanz
Automated Ligand Preparation for Protein-Ligand-Docking

10:30-11:00 Coffee break

11:00-11:25 **Michael Hutter**
Center for Bioinformatics, U Saarland
In silico screening of drug-like compounds online: eDrugScan

11:25-11:50 **Sina Kazemi**
Computational Pharmaceutical Chemistry, U Kiel
Elastic potential grids - A new paradigm for fully flexible docking

11:50-12:00 Conference photo in front of the building

12:00-13:15 Lunch break

Session 5, Chair: T. Clark

13:15-14:15 **Plenary Lecture: Pavel Hobza**
Institute of Organic and Biochemistry, Prague
Benchmark Quantum Chemical Calculations on Stabilization Energies in the DNA Base Pairs

14:15-14:40 **Jindrich Fanfrlík**
Institute of Organic and Biochemistry, Prague
Interactions of Metallacarboranes with Biomolecules: QM/MM Calculations Refine the Crystal Structure of HIV-1 Protease-Metallacarborane Complex

Program: Wednesday, April 30th 2008

14:40-15:05	**Wolfgang Wenzel** *Department of Physics, U Dortmund* Free-energy based all-atom protein modelling with worldwide distributed computational resources
15:05-15:20	Coffee break
15:20-15:45	**Sebastian Radestock** *Institute of Pharmacy, U Kiel* Constraint network analysis: Exploiting the link between protein rigidity and thermostability
15:45-16:10	**Jan Řezáč** *Institute of Organic and Biochemistry, Prague* “On the fly” ab initio MD simulations of complex molecular systems
16:10-16:30	**Poster & Lecture awards / Closing remarks**

Poster

P1	**Susanne Aust**	A Novel Class of Inhibitors for Prolyl Endopeptidase derived from Docking Analysis and CoMSIA studies
P2	**Kristin Engels**	Cyclin-Dependent Kinases of Apicomplexan Parasites as Target Proteins for the Rational Design of Antiparasitic Drugs
P3	**Stephanie Gulde**	Application of MOE´s virtual screening for new ligands of a steroid hormone receptor
P4	**Anselm H. C. Horn**	Dynamics and Binding to a Model Inhibitor of Alzheimer Disease-Related Peptides Aβ40 and Aβ42
P5	**A. Bauer-Mehren**	Combination of direct and indirect approaches to study the D2/5-HT2A selectivity of antipsychotic drugs
P6	**Monika Nocker**	Flexibility of Aldose Reductase: Opening of a novel subpocket upon ligand binding
P7	**Mario Dejung**	Web interface with advanced query properties for the Binding Interface (BIF) database
P8	**Alexander Entzian**	Classification of the Amino Acids on the basis of structural data
P9	**Volker Hähnke**	PhAST – Pharmacophore Alignment Search Tool
P10	**A. Koch**	Experimental and calculated NMR parameters
P11	**Tobias Heintz**	Comparing Natural Product (NP) and non-NP Datasets at an Atomic Scale
P12	**Anica Lämmermann**	NMR and theoretical investigations of intramolecular hydrogen bonding
P13	**Björn Loeprecht**	Prediction of Blood Brain Distribution with KNIME
P14	**Frank Beierlein**	QM/MM Binding Free Energy Calculations
P15	**Marcel Youmbi Foka**	Prediction of the Solvation Free Energy using a Combination of Semiempirical Self-Consistent Reaction Field Calculations and the Local Energy Properties

Poster

P16	**M. Hennemann**	CypScore: A Quantum Chemistry based Approach for the Prediction of Likely Sites of P450-Mediated Metabolism
P17	**Hakan Kayı**	Parameterization of Bromine and Iodine for AM1*
P18	**Robert Klein**	Fast access to total energies
P19	**M. Kreim**	Simulation of Ion Transport Through a Potassium Channel under Realistic Transmembrane Potentials in a Double Lipid Bilayer System
P20	**Heike Meiselbach**	Protein Dynamics Simulations of HIV-1 Protease to Investigate the Effects of Single or Multiple Mutations
P21	**Anja Fettke**	Solution-state Conformational Study of Thio-glycosidic carbohydrates by NMR Spectroscopy and Molecular Modelling
P22	**Gudrun M. Spitzer**	Different Handling of a Hydrophobic Pocket and Consequences for Screening Results in Catalyst, Phase and MOE
P23	**Gudrun M. Spitzer**	Analysis of DNA Minor Groove Binding Patterns
P24	**Florian Haberl**	Molecular Dynamics Studies on the TIP - Tet Repressor System
P25	**M. Hartenfeller**	Reaction-driven Combinatorial Library Design
P26	**Nadine Homeyer**	Towards a detailed understanding of the mechanisms associated with HPr phosphorylation
P27	**Christophe Jardin**	The phosphoryl transfer between the IIA and IIB proteins of the Escherichia coli Glucose Phosphotransferase System
P28	**Hai-Shun Wu**	Structures and Energies of $(CF)_{60}$ and $(CH)_{60}$ Cages and Tubes – Effect of Fused Five-Membered rings
P29	**Gül Altınbaş Özpınar**	A plausible pathway for nucleophilic addition of trichloronitroethylene to aniline through cis-trans isomerization
P30	**Carsten Wittekindt**	COSMO*mic* – a Novel Tool for fast Access to Membrane-Water Partition Coefficients and Internal Distribution within Biomembranes

Poster

P31	**Sabine Werner**	Molecular dynamics simulations of macrocyclic anion receptors
P32	**Volker Kuntermann**	Surface-modified Silicon Quantum Dots
P33	**Sebastian Kruggel**	Generation and evaluation of a homology model of *Pf*GSK3
P34	**C. Higgs**	Probing Flexibility in the Activation Loop of Kinases
P35	**W. Sherman**	Glide XP fragment docking and structure-based pharmacophores
P36	**Sebastian Schenker**	Theoretical approach to the thiourea-guanidine catalyzed nitro-Michael reaction
P37	**René Wölfel**	Molecular-Dynamics Simulations of an Ionic Liquid between Gold Electrons
P38	**Erika Nerini**	Towards pteridine reductase inhibitors with anti-parasitic action
P39	**Domantas Motiejunas**	Protein-protein docking guided by biochemical data
P40	**Wielopolski M.**	Molecular Wire Behavior of Organic π-conjugated Systems in DONOR-WIRE-C_{60} Conjugates

Lectures

Tuesday, April 29th 2008

Prediction of Foldamer Structures Employing Theoretical Methods

Hans-Jörg Hofmann
Institute of Biochemistry, University of Leipzig, Brüderstraße 34, D-04103 Leipzig

The notation "foldamers" is applied for conformationally ordered synthetic oligomers.[1] The monomers for such oligomers can be selected from a wide variety of different structure classes. Foldamers have attracted considerable attention during the last decade. In particular, oligomers of homologous amino acids, which form definite secondary structures mimicking those of the native peptides, have essentially stimulated foldamer research. Some of these foldamers show interesting biological effects. Others could be interesting for material sciences.[2-6]
In this lecture, an overview is given on the application of theoretical methods, in particular ab initio MO theory and molecular dynamics, for the description of the structure of numerous foldamer classes. It is shown that theory is able to predict reliably the possible conformational alternatives in foldamers and their stabilities and to derive rules, which can be applied in a rational structure design to prefer special secondary structure types.
It is demonstrated that the theoretical predictions have considerably stimulated experimental work in this field.

[1] S. H. Gellman, *Acc. Chem. Res*., **1998**, *31*, 173.
[2] D. Seebach, J. L. Matthews, *J. Chem. Soc., Chem. Commun.* **1997**, 21, 2015.
[3] D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, 101, 3893.
[4] R. P. Cheng, S. H. Gellman, W. F. DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
[5] T. A. Martinek, F. Fülöp, *Eur. J. Biochem.* **2003**, *270*, 3657.
[6] D. Seebach, A. K. Beck, D. J. Bierbaum, *Chem. & Biodiv.* **2004**, *1*, 1111.

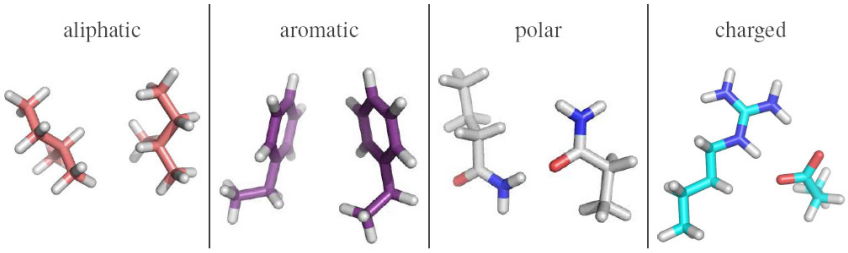
Amino acid side-chain interactions in proteins. Comparison of ab-initio and empirical methods

K. Berka[1], *K.E. Riley*[1], *R. Laskowski*[2], *J. Vondrášek*[1], *P. Hobza*[1]
[1]*Institute of Organic Chemistry and Biochemistry, Centre for Complex Molecular Systems and Biomolecules, Flemingovo nam. 2, Prague 6, 166 10, Czech Republic*
[2]*EMBL Outstation - Hinxton, European Bioinformatics Institute, Welcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SD, UK*

The knowledge of the precise interaction hyper-surface for side-chains of amino acids (AA) is a desirable characteristic providing relationship between the energy minimum geometry of AA side-chains and those we can find in real proteins. First step toward this knowledge should be the establishment of a reliable theoretical method, which is necessary for a good description of AA side-chains interaction in proteins with a respect to their actual energy minima and a character of the interaction. In this study we focused on evaluation of 24 selected pairs of interacting side-chains covering all 20 naturally occurring amino acids in a different interaction environment taken from Protein Side-Chain Atlas[1] (Fig. 1). The energy stabilization for the representative set of AA-AA pairs has been calculated at several levels of the theory:

- ab-initio methods covering CCSD(T), MP2, DFT-SAPT;
- empirically augmented density functional theory DFT-D and
- empirical methods utilizing OPLS-AA/L and Amber03 force-fields.

Figure 1 – Typical side-chains contacts found in Protein Side-Chain Atlas[1].



[1] http://www.biochem.ucl.ac.uk/bsm/sidechains/

Structural Models of Membrane Bound Aromatic Prenyltransferases

Diana Schulze, *Wolfgang Brandt, Lars Bräuer, Svetlana Zakharova, Ludger Wessjohann*
Leibniz-Institute of Plant Biochemistry
Department of Bioorganic Chemistry, Weinberg 3, D-06120 Halle (Saale), Germany

The membrane bound enzyme 4-hydroxybenzoic acid oligo-prenyltransferase (ubiA) from E. coli is crucial for the production of ubiquinone, which is the essential electron carrier in pro- and eukaryotic organisms. Based on previous modeling analyses, amino acids identified as important in two putative active sites (1 and 2) were selectively mutated. All mutants but one lost their ability to form geranylated hydroxybenzoate, independent of being from active site 1 or 2. This suggests that the two active sites are interrelated or in fact one site only. Based on the experimental results and a new structure based classification of prenylating enzymes, a relevant 3d-model could be developed by threading. The new model explains the substrate specificities and is in complete agreement with the results of site directed mutagenesis. The high similarity of the active fold of UbiA-transferase to that one of 5-epi-aristolochene synthase (Nictotiana tabacum) despite low homology allows a hypothesis on the evolution of these enzymes[1].
A corresponding plant protein (UniProtKB/TrEMBL entry: Q8W405) from Lithospermum erythrorhizon was modelled based on the same fold and nicely supports the previous results.

[1] Bräuer, L., Brandt, W., Schulze, D., Zakharova, S., Wessjohann, L., A Structural Model of the Membrane Bound Aromatic Prenyltransferase UbiA from E. coli, *ChemBiochem*, **2008**, in press.

The phosphoryl transfer between the IIA and IIB proteins of the *Escherichia coli* Glucose Phosphotransferase System

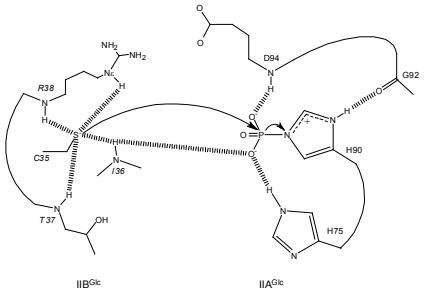
Christophe Jardin, *Anselm Horn, Gudrun Schürer, Heinrich Sticht*
Bioinformatics, Institute of Biochemistry and Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Phosphoryl transfer is a key reaction in many aspects of metabolism, gene regulation, and signal transduction. One prominent example is the phosphoenolpyruvate:sugar phosphotransferase system (PTS), which represents an integral part of the bacterial sugar metabolism. The transfer between the enzymes IIA^{Glc} and IIB^{Glc} in the glucose-specific branch of the PTS is of particular interest due to the unusual combination of donor and acceptor residues involved in phosphoryl transfer. The phosphoryl group is initially attached to the Nε2 atom of His90 in IIA^{Glc} and is transferred to the Sγ atom of Cys35 in IIB^{Glc}.

To get insight into the details of the transfer mechanism, we have performed both MD and QM/MM simulations. Our simulations show a strong dissociative character for the transfer. The Nε2-P bond gets immediately destabilized after complex formation by numerous interactions formed between residues of IIB^{Glc} and the phosphoryl group. The fact that the Arg38 sidechain of IIB^{Glc} is directly involved in the transfer process is particularly interesting, since this residue was previously considered to play only an indirect role for the transfer by stabilizing the Sγ-thiolate and by forming an intermolecular salt-bridge. Thus, our simulations reveal an additional important role for Arg38 consistent with the strict conservation of this amino acid.

The final formation of a tight Sγ-P bond is accompanied by a reorientation of the sidechain of the phosphoryl donor (His90). This reorientation results in the loss of interaction between the imidazole ring of His90 and the phosphate group and might thus be important to impede the reverse transfer. Notably, the resulting sidechain conformation of His90 is highly similar to that observed in the structure of free IIAGlc.

A comparison of the transfer to protein tyrosine phosphatases, which also use a cysteine as acceptor of the phosphoryl group, reveals significant similarities both in the conformation of the active sites and in the pattern of interactions that stabilize the phosphoryl group during the transfer.



Multi-Receptor Profiling of Antipsychotic Drugs. A Structural Study Based on the New β2 Adrenergic Receptor Template.

J. Selent, *L. López, A. Bauer-Mehren, F. Sanz and M. Pastor*
Computer-Assisted Drug Design Laboratory, Research Unit on Biomedical Informatics (GRIB), IMIM, Universitat Pompeu Fabra, Barcelona, Spain

The atypical antipsychotic drug clozapine, which is still considered the gold standard in the treatment of schizophrenia, is not a „clean drug" and exhibits affinities to serotonin, dopamine, alpha-adrenergic, muscarinic and histamine receptors, among others. This complex pharmacological profile seems to be a requirement for the therapeutic action but probably it is also responsible for adverse side-effects. In the present study we propose the use of in silico tools in the context of multi-receptor profiling for the design of novel atypical antipsychotics. 3D structural models of a series of aminergic receptors were generated by homology modeling, using a highly consistent protocol based on the structure of the recently published structure of the β2 adrenergic receptor [1, 2]. Docking simulations using the new homology models result in binding complexes diverse from previously reported complexes for clozapine-like ligands due to a slightly different architecture of the binding pocket.

A comparative analysis of the binding sites for all the receptor set reveals the presence of two homology groups: (I) serotonin, dopamine and alpha-adrenergic receptors, and (II) muscarinic and histamine receptors. Remarkably, group I contributes to the antipsychotic effect (target) whereas the second homology group has been related to weight gaining and metabolic side effects (anti-target). Exploitation of the obtained multiple receptor structure by computer-aided profiling, the availability of better structural templates as well as more reliable experimental data will lead to the design of more useful and safer antipsychotic drugs.

[1] V. Cherezov et al., *Science*, **2007**, *318*, 1258-65.
[2] D. M. Rosenbaum et al., *Science*, **2007**, *318*, 1266-73.

Isoform Specificity of Cytochrome P450 Substrates

L. Terfloth [1,2], *B. Bienfait [1,2], J. Gasteiger [1,2]*
[1]Molecular Networks GmbH, Erlangen,Germany
[2]Computer-Chemie-Centrum and Institute of Organic Chemistry, University of Erlangen-Nuremberg, Erlangen, Germany

In silico prediction of ADMET (absorption, distribution, metabolism, elimination, toxicity) properties is of special interest in the drug discovery process in order to detect and eliminate compounds with inappropriate pharmacokinetic properties at an early stage. A central step in the ADMET profiling of potential drug candidates is the assessment of drug metabolism. Some enzymes involved in the detoxification process show polymorphism and have multimodal binding sites. The majority of the oxidation reactions in phase I metabolism are catalyzed by cytochrome P450 enzymes.
Here, we report on the isoform specificity for CYP3A4, CYP2D6, and CYP2C9 substrates.[1] The influence of the descriptors used for structure representation and the impact of the modeling method on the predictability of the models will be discussed. A thorough CV (cross-validation) scheme is presented to assess the reliability of the models. Furthermore, the prediction of a more diverse and larger external validation data set with an accuracy of up to 83% underlines the validity of the models.
It will be shown that the random selection of a test set can be rather misleading to assess the predictability of a classification model.
A classification model for the isoform specificity is implemented in the application isoCYP.[2,3]

[1] L. Terfloth, B. Bienfait, J. Gasteiger. Ligand-Based Models for the Isoform Specificity of Cytochrome P450 3A4, 2D6, and 2C9 Substrates. *J. Chem. Inf. Model*. **2007**, *47*, 1688-1701.
[2] The software package isoCYP is available from Molecular Networks GmbH, Erlangen, Germany. http://www.molecular-networks.com (accessed Feb 24, 2008).
[3] A Web service of isoCYP is available from Molecular Networks GmbH, Erlangen, Germany. http://www.molecular-networks.com/online_demos/cyp450 (accessed Feb 24, 2008).

P-gp substrate differentiation by pharmacophore modelling

S. Kruggel[*], *A. ter Laak*[+], *H. Briem*[+], *R. Franke*[#]
[*]Universität Hamburg, Institut für Pharmazie, Bundesstraße 45, 20146 Hamburg
[+]Bayer Schering Pharma, Müllerstraße 178, 13342 Berlin
[#] Consulting in Drug Design GbR, Gartenweg 14, 16348 Wandlitz OT Basdorf bei Berlin

Besides MRP1 (ABCC1) and BCRP (ABCG2), P-glycoprotein (P-gp, ABCB1) is one of the most important ABC-Transporters responsible for chemoresistance in general and multi drug resistance (MDR) in particular.[1] To avoid problems with potential P-gp substrates several molecular modeling approaches[2] have been proposed to identify P-gp substrates in early stages of drug design (for instance Penzotti et al.[3], Cabrera et al.[4] or Xue et al.[5]).

The three dimensional structure of P-gp still remains unknown, so our ligand based approach relies on the construction of pharmacophores, which were developed from 178 published structures with PHASE.[6] Because of the extraordinary broad substrate spectrum, multiple binding sites are assumed.[7] Hence, we developed a pharmacophore ensemble model, building decision trees to differentiate substrates from nonsubstrates. The model with 87 pharmacophores performs with 80% accuracy on an independent test set.

By selecting pharmacophores with a discriminant analysis we could even improve the result to an accuracy of 84% relying on a discriminant function composed of just seven pharmacophores. In addition to the prediction of a crucial ADME characteristic, important structural information is derived the calculated pharmacophores, which subsequently can be of special interest for the development and synthesis of drug candidates.

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"Fast Optimization of Hydrogen Bond Networks in Protein-Ligand Complexes"

Tobias Lippert, *Matthias Rarey*
ZBH Hamburg

Pharmaceutical research focuses in finding novel ligands to known proteins that are disease-modifying, i.e. proteins that cause or perpetuate disease phenotypes. "Docking" calculations can aid chemists in this search by providing in-silico estimations of the binding mode and the binding affinity of putative ligand molecules and the protein. Protein structures of potential drug targets can easily be obtained from the publically available "Protein Data Bank", which currently contains over 50.000 structures, most of which have been determined by X-ray crystallography. Although very powerful, this experimental method has some limitations which result in ambiguities in the obtained data. Most importantly, the resolution makes it difficult to detect hydrogen atoms, which results in a lack of information relevant for estimating binding affinities.
In this work, we present a novel, fast algorithm for hydrogen placement in the interface of protein-ligand complexes.

Electrostatic interactions, to which hydrogen bonds belong, are one of the major factors that influence non-covalent protein-ligand interactions. In order to correctly identify and assess these interactions, one has to know the correct positions of the involved atoms. A wrong assumption on the hydrogen atoms' positions will lead to mistakes in subsequent calculations, for example, the correct binding mode of a putative ligand might not be found because a hydroxyl group of the protein faces into the wrong direction.

There are two reasons why an automated procedure is desirable to solve the problem of hydrogen atom orientation:
1. Different ligands may develop different hydrogen bond networks. If hydrogen atoms are assigned statically from the crystal structure, the correct binding mode may not be found for all ligand molecules.
2. Hydrogen bonds may form "networks" of interacting residues. Because of the exponentially growing search space, the problem can easily become too hard for manual assignment or brute-force methods.

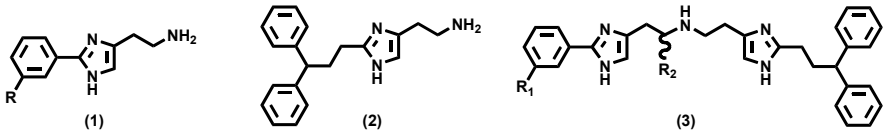
Our approach tackles the problem of finding an optimal hydrogen bond network in protein-ligand complexes with a dynamic programming technique. Also, a branch and bound heuristic has been implemented in case cyclic dependencies prevent the application of dynamic programming.
We validated our predictions with two datasets from a publication by L. Forrest and B. Honig. The first dataset contains eight manually confirmed positions for hydrogen atoms in proteins. Our method was

able to reproduce all hydrogen atom positions within a deviation of 0.6Å. The second dataset was automatically compiled and contains 34 hydrogen atoms that are considered to be buried in the protein. We reproduced correct positions for 85% of the complete dataset, and 93% of all residues that did not have contact to solvent molecules – determined by visual inspection.

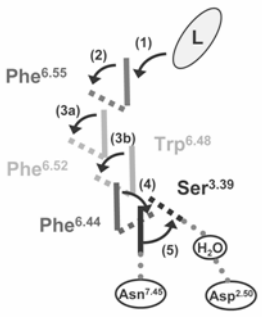
3D-QSAR-Models of four Histamine H_1-Receptor Species Isoforms and a Hypothesis for a ligand induced activation mechanism of the H_1-Receptor

Andrea Straßer, *H.-J. Wittmann*
Institut für Pharmazie, NWF IV-Chemie und Pharmazie, Universität Regensburg, Universitätsstraße 31, D-93053 Regensburg

Histamine H_1-receptor (H_1R) agonists are useful and powerful tools to study the functionality and pharmacology of the H_1R species isoforms at a molecular level. Phenylhistamines (**1**), histaprodifens (**2**) and hybrid molecules (phenoprodifens) (**3**), consisting of one phenylhistamine and histaprodifen partial structure are H_1R (partial) agonists. Some of this derivatives show species differences between human, bovine, rat and guinea-pig H_1R. Because of the symmetrical structure of some derivatives, two orientations in the binding pocket are possible for the phenoprodifens.



Based on the crystal structure of the adrenergic β_2 receptor we constructed inactive and active state models of these four H_1R species isoforms. We used experimentally determined pK_i values of about 40 histaprodifens and phenylhistamines for 3D-QSAR studies with the active state model of all four species isoforms. An analysis of the resulting data showed, that the predicted orientation of the phenoprodifens (**3**) in the binding-pocket is substitution (R_1, R_2) and species dependent.
Besides we implemented an algorithm to calculate the binding pathway of a ligand into the GPCR, including the activation pathway of the receptor. The calculations showed that the penetration of H_1R ligands into the binding pocket of the H_1R, accompanied by the receptor activation is energetically preferred. A hydrophobic contact between a phenyl moiety of the histaprodifen and $Phe^{6.55}$ seems to activate an activation cascade including the highly conserved amino acids $Phe^{6.52}$, $Trp^{6.48}$, $Phe^{6.44}$, $Ser^{3.39}$, $Asn^{7.45}$, $Asp^{2.50}$ and internal water molecules as given in the following picture. This reaction cascade results in a hydrogen bond switch of $Ser^{3.39}$ from $Asn^{7.45}$ to $Asp^{2.50}$, bridged by one internal water molecule.



A *compound* model for hERG blockade

Christian Kramer[*,‡], *Bernd Beck*[‡], *Timothy Clark*[*]

[‡] *Boehringer-Ingelheim Pharma GmbH Co KG, Department of Lead Discovery, Biberach, Germany and*

[*] *Computer-Chemie-Centrum der Friedrich-Alexander Universität Erlangen-Nürnberg, Nägelsbachstrasse 25, 91052 Erlangen, Germany*

hERG Blockade is one of the major toxicological problems in lead-structure optimization. Reliable in silico models for predicting hERG blockade therefore have considerable potential for saving time and money, as patch-clamp measurements are very expensive and no crystal structures of the hERG-encoded channel are available.

We built a predictive QSAR model for hERG blockade that differentiates between specific and non-specific binding. Specific binders are identified by preliminary pharmacophore scanning.[1] In addition to descriptor-based models for the compounds selected as hitting on of two pharmacophores, we also use a model for non-specific binding that reproduces blocking properties of molecules that do not fit into the pharmacophore well. PLS-models based on easily interpretable quantum-mechanically derived descriptors on a literature dataset of 113 molecules reach overall R^2 values of 0.72 for the validation sets and R2 values in between 0.62 and 0.81 for the partitioned datasets. Our findings suggest that hERG blockade may occur via different binding modes, so that several different models may be necessary in order to assess hERG-toxicity.

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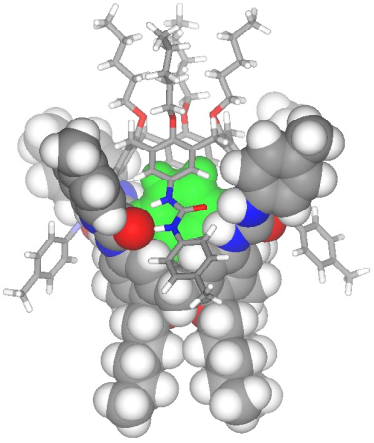
Molecular Dynamics Simulations of Dimeric Tetraurea Calix[4]arene Capsules

Frank Broda, *Iris Thondorf*
Martin-Luther-Universität Halle-Wittenberg, Institut für Biochemie und Biotechnologie, Kurt-Mothes-Str. 3, 06120 Halle (Saale)
fbroda@ipb-halle.de / iris.thondorf@biochemtech.uni-halle.de

The noncovalent synthesis of molecular capsules from self-complementary subunits is one of the current issues in supramolecular chemistry. Tetraurea calix[4]arenes constitute a class of synthetically easy accessible compounds, which form dimeric capsules in apolar solvents if suitable guest molecules are present. Adequate guests are for instance small organic molecules like benzene and many of its derivatives as well as cations like tetraethyl ammonium. Depending on the size of the guest, the capsule interior imposes constraints on the guests degrees of freedom.



The structural and dynamic properties of the capsules are studied predominantly by NMR spectroscopy and in rare cases also by X-ray crystallography. AMBER molecular dynamics simulations were used to clarify the causes of experimentally observed phenomena at the molecular level. Differences in the binding affinity of certain guests were also addressed by GIBBS free energy perturbation simulations. The predictions of the simulations are generally in good to excellent agreement with the experiment. Examples presented include the observation of orientational preferences of encapsulated aromatic guests and the massive consequences which arise for the capsule structure, dynamics and stability from the inclusion of a tetraethyl ammonium cation. Special emphasis is placed on a sophisticated analysis of the MD trajectories. The examinations included not only averaged structures but also hydrogen bonding patterns, guest orientation, interaction energies for individual particles and some geometric parameters of special interest. To accomplish this, the analytical framework of AMBER was extended and also new analysis tools were developed.

Structured Micelles – Guiding Experiments with Molecular Dynamics Simulations

Christof Jäger[a,c], *H. Lanig*[a], *A. Hirsch*[b,c] *and T. Clark*[a,c]
[a] *Computer-Chemie-Centrum, Nägelsbachstr. 25; Friedrich-Alexander-Universität Erlangen, D-91052 Erlangen*
[b] *Lehrstuhl Organische Chemie II; Henkestr. 42, Friedrich-Alexander-Universität Erlangen, D-91054 Erlangen*
[c] *Interdisciplinary Center for Molecular Materials (ICMM), Nägelsbachstr. 25; FAU Erlangen, D-91052 Erlangen*

Long time scale molecular-dynamics simulations have been used to investigate the structure and dynamics of structurally persistent micelles consisting of seven or twelve specifically designed T-shaped amphiphilic calix[4]aren derivatives[1].
Experimental investigations by NMR, cryo-TEM techniques and subsequent 3D-reconstruction[2] confirmed a highly developed topological arrangement of the micelles in water. However, other experiments such as ultrasonification of the micelles together with hexane and water caused a different topology of twelve monomers.

The results presented allow the cryo-TEM 3D-reconstructions of the micelles to be interpreted in detail and several fascinating details of the structure of the solvent around the micelles and of the factors that affect the structure of the micelles. Predictions made on the basis of the simulations have been tested experimentally.

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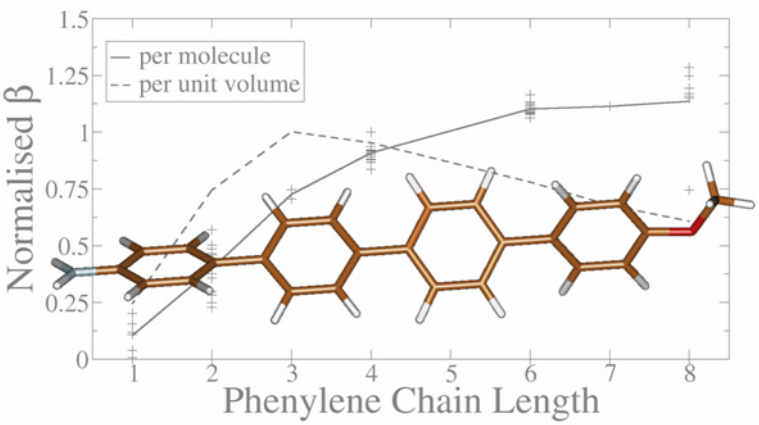
Theoretical Study on the non-linear optical properties of phenylenes and influencing factors

Justin J. Finnerty, *Rainer Koch, Torsten Bruhn*
Institut für Reine und Angewandte Chemie und Center of Interface Science, Carl von Ossietzky Universität Oldenburg, PO Box 2503, 26111 Oldenburg, Germany. justin.finnerty@uni-oldenburg.de

Nanofibres formed from p-poly-phenylenes possess interesting non-linear optical properties that give them potential as new nano-scaled optoelectronic devices. A quantum mechanical investigation of the first hyperpolarisabilities (β) of substituted phenylenes aims to allow the design of functionalised phenylenes as molecular building blocks for nanofibres with tailored non-linear optical properties. The optimal phenylene chain length and the influence of phenylene geometry and para-substituents on non-linear optical properties are presented. Several methods (DFT, HF, MP2) and medium-sized basis sets are compared and a theory level that gives reliable results at moderate computational cost is suggested.
Recent experimental data from phenylene monomers and their nanofibres are being used to further refine the theoretical methodology. Comparison shows that the theoretical approach used for monomers is reliable, though some work is under way to improve accuracy. The future direction is to evaluate clusters of monomers (initially pairs) as a theoretical model of phenylene nanofibres.



Lectures

Wednesday, April 30th 2008

Modeling of Electron-Transfer Properties in Organic π-Conjugated DONOR-WIRE-C_{60} Systems

M. Wielopolski[a], *T. Clark*[a], *D. M. Guldi*[b]
[a] *Computer Chemistry Center University of Erlangen, 91052 Erlangen, Germany*
[b] *Department of Chemistry and Pharmacy, Interdisciplinary Center for Molecular Materials (ICMM), Friedrich-Alexander-Universität Erlangen-Nürnberg, Egerlandstr. 3, 91058 Erlangen, Germany*

The investigation of charge-transfer properties of tailored nanoscale molecules affords novel molecular materials with systematic variation of functionality (e.g. redox, electron-transfer or photo-switching behavior). To address charge transport through single molecules, we have replaced conventional electrode leads with organic donors and acceptors. In the resulting **donor | C_{60} and donor | wire | C_{60}** assemblies, the transport of electrons was triggered either photochemically (i.e., charge separation) or thermally (i.e. charge recombination) and examined by various spectroscopic characterization techniques.[1][2]
Detailed quantum chemical investigation – including density functional theory and semi-empirical methods – provided insight into the nature of charge-transfer processes between different donors and C_{60} mediated by π-conjugated bridges, i.e. ***o*PPV**, ***o*PPE** or ***o*FL**, and ascertained the formation of **DONOR $.^+$ / C_{60}-** radical ion pair states. Both ground- and excited-state properties have been computed in order to yield a comprehensive description of the experimental trends. Further, a practical methodology was developed to describe the electron-transfer pathway in such systems, which provides a fast and efficient way for the systematic acquisition of potential organic structures capable of photo-induced electron-transfer reactions. It was found that besides π-conjugation, which is undoubtedly the sine qua non for efficient charge-transfer processes, the relative energies of donor, wire and acceptor play a decisive role in governing these electron-transfer features.[3][4][5]
Financial support through the Deutsche Forschungsgemeinschaft (DFG) is greatfully acknowledged.

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ParaDockS – An Extensible Framework for Parallel Molecular Docking

Rene Meier[1], *Frank Brandt*[2], *M. Teresa Pisabarro*[2], *Carsten Baldauf*[2] *and Wolfgang Sippl*[1]
[1]*Institute for Pharmaceutical Chemistry, Martin-Luther-University Halle-Wittenberg*
Wolfgang-Langenbeckstr. 4, 06120 Halle (Saale)
rene.meier@pharmazie.uni-halle.de
[2]*Structural Bioinformatics, Biotec TU Dresden*
Tatzberg 47-51, 01307 Dresden

The molecular docking problem is a twofold problem. On the one hand the optimization and on the other the scoring problem. In this study we present the new molecular docking program ParaDockS. ParaDockS is designed to offer a well structured interface to allow the easy integration of different metaheuristics and scoring algorithms.
As an example, we present a Particle Swarm Optimization (PSO) algorithms to address the optimization part of the problem. PSO is a general-purpose iterative heuristic search algorithm. It utilises a population of individuals to probe promising regions of the search space in an effective manner. In this context, the population is called a swarm, and the individuals are called particles. Each particle moves within the search space and retains in its memory the best position that it has encountered and the overall best position. The velocity of each particle is adjusted during each iteration toward the personal best position as well as the overall best position, thus mimic swarm intelligence.
The fitness landscape is modelled by a modified version of the binding-affinity prediction algorithm X-Score.[1] X-Score is an empirical scoring function which shows a good correlation between score and the RMSD of a docking pose.

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Automated Ligand Preparation for Protein-Ligand-Docking

Tim ten Brink, *Thomas E. Exner*
Fachbereich Chemie, Universität Konstanz, D-78457 Konstanz, Germany

Ligand structure preparation is an essential step during the setup of protein-ligand docking or virtual screening (VS) experiments. In most cases only the crystal structure of a protein-ligand complex is known. Thus, the protonation of the ligand and the binding site is largely unknown and often only limited information about hybridization and connectivity in the ligand structure is provided by the pdb[1]. While manual preparation of the ligand structures is the most accurate method, it is by far too time consuming for bigger datasets. In VS experiments the large number of structures which are often obtained from different sources, leads to additional problems. A consistent treatment of all active and inactive structures is needed to prevent a preferential treatment of some of the structures, which could lead to artificial enrichments. Additionally, changes in the protonation of the ligand (and the protein), when binding in the active site, have to be considered.
To overcome these problems, an automated method for ligand preparation was developed. This method does not require any previous knowledge of the receptor and is only based on the 3D coordinates of the ligands' heavy atoms and possibly available hydrogen atom positions. In the first step the hybridization and bond orders are assigned and missing hydrogen atoms are added, leading to the "standard" ligand structure. Additional to the standard structure different protonation states, keto-enol-tautomers and stereo isomers can be generated automatically.
Docking studies with GOLD[2] and PLANTS[3] showed good results for the standard structures compared to the manually revised ligand structures form the ASTEX dataset[4]. In further docking studies, the influence of different protonation states was estimated. Different stereo isomers were generated and docked for selected ligands where no clashes between atoms occurred in the newly generated structures.

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In silico screening of drug-like compounds online: eDrugScan

Oliver Frings, **Michael Hutter**
Center for Bioinformatics, Building C 7.1, Saarland University, Germany

Selecting potentially suitable compounds for experimental testing from the vast chemical space is still a challenge in computer-aided drug design. Corresponding prediction methods comprise individual ADME properties as well as drug-likeness criteria and indices.[1] We have investigated the suitability of decision trees and support vector machines for the classification of chemical compounds into drugs and nondrugs.[2] To account for the requirements upon screening virtual compound libraries, schemes for successive filtering steps with gradual increasing cost were derived. We found that a decision tree approach that uses a minimum of rapidly computable descriptors including Hutter's drug-likeliness index,[1] molar refractivity, molecular weight, and XlogP is most efficient for this purpose.[2] Together with other drug-likeness criteria this filtering scheme has been included in the online tool eDrugScan.[3] To also enable customized step-wise screening including other criteria such as SMARTS provided by the user, the sequence of the filter modules can be arranged interactively. They also allow to specify upper and lower margins for a series of descriptors such as molecular weight, XlogP, and number of rotatable bonds. Currently, eDrugScan accepts uploaded compounds in the .hin file format of HYPERCHEM.[4]

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[4] HYPERCHEM, HyperCube Inc, Gainsville, FL, http://www.hyper.com

Elastic potential grids - A new paradigm for fully flexible docking

Sina Kazemi[*§], *Dennis M. Krüger*[*], *Holger Gohlke*[*]
[*]*Computational Pharmaceutical Chemistry, Christian-Albrechts-University, Kiel*
[§]*Molecular Bioinformatics, Johann-Wolfgang-Goethe-University, Frankfurt*

Structural information of a target is widely used in different steps of the lead finding process. The most commonly used tool to include structural information in computer-aided drug design is molecular docking. To increase computational speed, sophisticated scoring functions are often mapped to potential grids. This allows using them as table lookup functions.

For many targets, it has been shown that protein flexibility plays a crucial role in molecular recognition[1]. At a first glance, this finding does not seem to be compatible with the use of potential grids, as the grids have to be precalculated from a single conformation. As a first attempt to circumvent this problem, lookup tables have been introduced that combine features of grids calculated for single conformations of bound targets, thereby representing an "average" grid[2]. These "average" grids include information about the conformational ensemble in an implicit way.

Here we present a new docking approach to tackle the fully flexible docking problem by using a flexible-grid based approach. The main idea is to deform a precalculated grid, which was calculated for one conformation of the target, to other target conformations. That way we are able to sample protein conformations during a docking run at high computational efficiency due to the fact that the grid does not need to be recalculated for every sampled conformation. Since the precalculated energy value of every grid point is derived from the atomic environment of the grid point, this value will remain approximately valid if we are able to preserve the atomic environment of the grid point during the induced fit process. Thus, grid points are moved along with their atomic environment, which moves due to conformational sampling. We propose two techniques to allow for the reasonable movement of the grid points. First, the grid is simulated as an elastic body deforming according to the conformational change of the target. Second, grid points are connected with the surrounding atoms of the target such that the movements of the atoms trigger the elastic deformations. Scope and limitations of the approach will be discussed.

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Benchmark Quantum Chemical Calculations on Stabilization Energies in the DNA Base Pairs

Pavel Hobza
Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic
pavel.hobza@uochb.cas.cz

Stabilization energies of noncovalently bound DNA base pairs are investigated. Specifically, we consider H-bonded and stacked structures of methylguanine... methylcytosine, methyladenine... methylthymine and uracil dimer in the gas phase.. Structures of pairs are either optimized or taken from experiment. Benchmark stabilization energies of complexes studied are determined at the Complete Basis Set (CBS) limit of the CCSD(T) calculations. The role of CCSDT level is also discussed. Resulting stabilization energies of H-bonded and stacked pairs are very larger, much larger than considered before. This is especially true about stacked DNA base pairs. Stabilization energies of these structures originate exclusively in the London dispersion energy and only high-level wave function theories can be applied. The partitioning of the total interaction energy to the components is performed using the DFT-SAPT method. The use of density functional theories, including the recently introduced hybrid meta GGA functionals, is discussed.

Interactions of Metallacarboranes with Biomolecules: QM/MM Calculations Refine the Crystal Structure of HIV-1 Protease-Metallacarborane Complex

Jindrich Fanfrlík, *M Lepšík, J Řezáč, J Brynda, P Řezáčová, J Konvalinka, and P Hobza**

Gilead Sciences and IOCB Research Center, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic and Center for Biomolecules and Complex Molecular Systems, Flemingovo nam. 2, 166 10, Prague 6, Czech Republic, Fax: +420-220 410 320, E-mail: hobza@uochb.cas.cz

Polyhedral metallacarborane compounds have recently been discovered as potent, specific, stable and nontoxic inhibitors of HIV1 protease (PR), the major target for therapeutic intervention against AIDS (Cigler P et al., 2005). The 2.15 Å-resolution crystal structure has shown a nonsymmetrical binding of the parental compound **1**, [Co-bis(dicarbollide)]$^-$, into PR tetramer (Fig. 1) (Cigler et al., 2005). In order to explore structural and energetical details of the inhibitor binding, we utilize hybrid QM/MM approach. We first calculate energy profiles for rotation of **1** in position Cb1 and subsequently in position Cb2. Second, we determine whether and how much are these rotation profiles influenced by a specified rotamer in other positions. By combining these results we delineate energetically favorable and unfavorable positions for carbon atoms in the four molecules of **1** in the complex with PR tetramer. These results will be crucial in calculating interaction energies of each of the four molecules of **1** with each other as well as with amino acids of PR active-site.

Fig. 1: Structure of [Co-bis(dicarbollide)]$^-$, compound **1**.

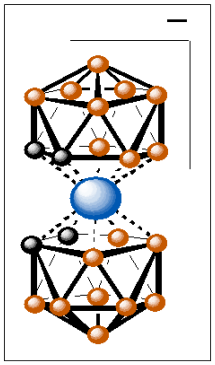
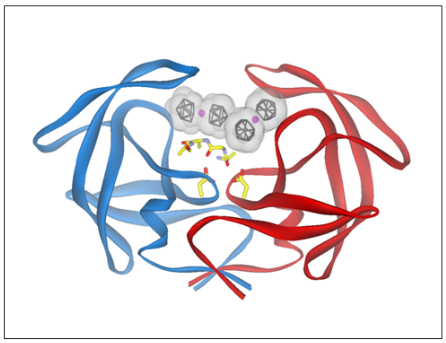


Fig. 2: Crystal structure shows binding of compound **1** into HIV-1 protease.



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Free-energy based all-atom protein modelling with worldwide distributed computational resources

Timo Strunk[1,2],Srinivasa Murthy Gopal[2], Konstantin Klenin[2] and **Wolfgang Wenzel[1,2]**
[1]Fachbereich Physik, Universität Dortmund, 44227 Dortmund, Germany
[2]Forschungszentrum Karlsruhe, Institut für Nanotechnologie, PO Box 3640, 76021 Karlsruhe, Germany

Following Anfinsen's thermodynamic hypothesis we have implemented massively parallel stochastic optimization methods for all-atom de-novo protein folding using our free-energy forcefield PFF02[1]. We have implemented this approach (POEM) using a world-wide volunteer computation a grid to predictively and reproducibly folded several proteins with up to 57 amino assets, including the engrailed homeodomain and protein A, from completely unfolded conformations.

POEM identifies the native conformation of the protein as the global minimum of the protein free-energy forcefield PFF02, which stabilized the native conformation of all 32 monomeric proteins (without cofactors) against all decoys in the Rosetta decoy set[2]. In addition we could fold a set of 13 proteins with helical, sheet and mixed secondary structure from completely unfolded conformations to near-native conformations, to an average 2.87 Å resolution[1-3].

In this investigation, we deployed a BOINC server implementing an evolutionary strategy[4], which explores the free-energy landscape in many parallel dynamical processes, which communicate with one another through a central server. The overall computational work is thus segmented into medium size work-units, which can be processed independently. The algorithm evolves a population of conformations towards the global optimum of the free-energy surface by balancing energy improvement with population diversity. POEM@HOME (http://boinc.fzk.de) thus implements a complementary approach to existing distributed computational proteomics initiatives, such as Folding@Home or Rosetta@Home, to help analyze structure and function of large, experimentally relevant proteins.

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Constraint network analysis: Exploiting the link between protein rigidity and thermostability

Sebastian Radestock, *Holger Gohlke*
Mathematisch-Naturwissenschaftliche Fakultät, Pharmazeutisches Institut, Christian-Albrechts-Universität, Kiel, Germany

The molecular basis of stability relates closely to contemporary issues in protein science such as the protein folding problem, protein-protein interaction and protein-ligand binding. In addition, protein stability has industrial importance. The identification or the development of enzymes with higher stability will increase the adoption of biocatalytic syntheses in industrial production.[1] Understanding and exploiting the relationship between microscopic structure and macroscopic stability is important for developing strategies to improve protein stability in the reaction media used in industrial processes.

Thermostability of proteins has been repeatedly linked to an enhanced structural rigidity of the folded native state. Here, we directly probe the rigidity of protein structures from mesophilic and thermophilic organisms along a thermal unfolding trajectory. For this, protein structures were modeled as constraint networks, and the rigidity in these networks was quantified using the Floppy Inclusion and Rigid Substructure Topography (FIRST) method.[2] By the dilution of non-covalent contacts in the network, FIRST has been employed to simulate thermal unfolding.[3] In going from a rigid to a flexible network, a phase transition can be observed that defines the rigidity percolation threshold and corresponds to the folded-unfolded transition in protein unfolding. Here, thermal unfolding simulations were applied to a dataset of 20 homologous proteins from thermophilic and mesophilic organisms.

Using concepts from percolation theory and network science, a higher phase transition temperature was observed for approximately two-thirds of the proteins from thermophilic organisms compared to their mesophilic counterparts. Direct support was found for the "corresponding states" concept, which states that mesophilic and thermophilic enzymes are in corresponding states of similar flexibility at their respective optimal temperature. Our approach allowed for identifying structural features from which a destabilization of the structure originates upon thermal unfolding. These predictions show a good agreement with experiment. The information might thus be exploited in data-driven protein engineering by pointing to residues that should be varied to obtain a protein with higher stability.

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„On the fly“ ab initio MD simulations of complex molecular systems

Jan Řezáč, *Pavel Hobza*
rezac@uochb.cas.cz
Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic and Center for Biomolecules and Complex Molecular Systems, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

Recent development in computational methods and hardware opened the possibility to perform molecular dynamics at ab initio level. What is more important, it can be done on rather large molecular systems and reasonable timescales can be reached.
For the most accurate simulations, density functional theory with empirical dispersion correction (DFT-D) is our method of choice. We use this method to study dynamical nature of benzene dimer and for calculation of infrared spectra of even larger molecules, up to tripeptides. Extracting the results from trajectories 20 – 40 ps long requires use of advanced analysis and careful interpretation. The promising method of calculation of anharmonic vibrational spectra from molecular dynamics fails in applications where we got close to the border between classical and quantum description of vibration.
When longer trajectories are needed, semiempirical methods can be used where molecular mechanics fails. In our study of peptides[1], we use the SCC-DFTB-D method, which was found to be surprisingly accurate in this application. The goal of molecular dynamical simulations is to evaluate free energy surface of conformation changes in the peptides. Timescale accessible to our simulations (nanoseconds) is too short for use of conventional methods, we use metadynamics to enhance sampling of selected coordinates and evaluate the free energy surface. Results are in good agreement to selected points on the surface calculated using accurate correlated QM methods, while force field calculations fail to describe the delicate balance between different types of conformers.

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Posters

A Novel Class of Inhibitors for Prolyl Endopeptidase derived from Docking Analysis and CoMSIA[1] studies

Susanne Aust, *André J. Niestroj, Ulrich Heiser, Wolfgang Brandt*, and Hans-Ulrich Demuth*
Probiodrug AG, Weinbergweg 22, 06120 Halle, Germany
** Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle, Germany*

Prolyl endopeptidase (PEP; EC 3.4.21.26; also prolyl oligopeptidase) is a serine peptidase and is characterized by an oligopeptidase activity at the C-terminal side of proline containing substrates. It is supposably involved in the degradation and maturation of peptide hormones and neuropeptides like substance P, vasopressin and the thyrotropin-releasing hormone. A relation to a physiological function in learning and memory processes is still in the discussion. It is therefore commonly assumed that PEP is a promising target for the development of drugs. Starting from a screening hit, derivatives were synthesized and tested for inhibitory potency against PEP. Activities of $K_i > 10^{-5}$ M for were detected. Docking studies (GOLD[2]) and a superposition study with a known potent inhibitor (S17092[3]) suggested a point for a distinguished extension of the molecular core. Basing on that modified structure, a new class of inhibitors was suggested leading to potent compounds.
In order to establish a 3D QSAR model, the best ranked conformations of 41 inhibitors resulting from GOLD docking studies were superposed followed by the calculation of the 5 CoMSIA fields. The 41 membered training set was used for the generation of a cross-validated QSAR model leading to values for r^2 and q^2 of 0.878 and 0.735 respectively. The model utilized three COMSIA-components.
The model was applied for the prediction of a test dataset of 10 compounds. As a result, the IC_{50} values could be predicted with an R^2=0.702.

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Cyclin-Dependent Kinases of *Apicomplexan* Parasites as Target Proteins for the Rational Design of Antiparasitic Drugs

Kristin Engels[1,2], *Maria L. Suárez Fernández[1,2], Carsten Beyer[1,3,5], Richard J. Marhöfer[1], Frank Bender[1], Michael Gassel[1], Jeremy C. Mottram[4], Gottfried Unden[2], Paul M. Selzer[1,3]*

1) Intervet, Zur Propstei, Schwabenheim, Germany

2) Institut für Mikrobiologie und Weinforschung, Johannes Gutenberg Universität Mainz, Germany

3) Interfakultäres Institut für Biochemie, Eberhard Karls Universität Tübingen, Germany

4) Wellcome Centre for Molecular Parasitology, University of Glasgow, United Kingdom

5) Current address: Computational Chemistry & Biology, BASF Aktiengesellschaft, Germany

Apicomplexan parasites enclose several human-pathogenic as well as animal-pathogenic protozoans, like *Eimeria tenella*, *Toxoplasma gondii* and *Plasmodium falciparum.* The animal-pathogenic representative *E. tenella* provokes coccidiosis a poultry disease, which causes tremendous economic losses to the world poultry industry. Considerable increase of drug resistance makes it necessary to develop and pursue new therapeutic strategies. Cyclin-dependent kinases (CDKs) are key molecules in the regulation of the cell cycle and are therefore prominent target proteins in parasitic diseases. To date several proteins from *apicomplexan* parasites, which are homologous to *mamalian* CDKs have been characterized using classical molecular biology techniques. Our extensive bioinformatics analysis revealed additional candidate proteins and especially three new CDK-like proteins were identified for *E. tenella*. Using an x-ray crystal structure of human CDK2 as template, protein models were built by comparative homology modelling. A structural comparison of the resulting protein models, especially within the active site, revealed structural differences and could be used for the optimization of specific CDK inhibiting compounds for *apicomplexan* parasites. A virtual screening campaign on EtCRK2, a CDK of *E. tenella* resulted in hits, which have been verified *in vitro*. These verified hit compounds were used for a substructure search in an in house compound database leading to a set of potential inhibitors. In order to select inhibitors of higher potency and selectivity, docking studies were performed and the ligand-receptor binding interactions were analyzed in detail. Linear interaction energy (LIE) calculations provide the opportunity to accurately predict the relative potencies of the selected substructures. Furthermore the usability of this method for binding-pose prediction will be discussed.

See also poster and presentation by Suárez Fernández *et al.* and Selzer *et al.*

Application of MOE´s virtual screening for new ligands of a steroid hormone receptor[1]

Stephanie Gulde, *Claudia Bobach, Wolfgang Brandt, Ludger A. Wessjohann**
Leibniz Institute of Plant Biochemistry, Department of Bioorganic Chemistry, 06120 Halle, Germany
** e-mail: Ludger.Wessjohann@ipb-halle.de*

Steroid receptors play an important role in the regulation of ontogeny, sexual maturation, and cell differentiation, as well as in various metabolic processes.
In this study, it was attempted to identify ligands with high affinity to known steroid hormone receptors. Three pharmacophore models were established, based on the ligand binding site, known agonists and antagonists. The models were analysed for there relevance for virtual screening. The enrichment in the top percent of the database using different docking programs and different scoring functions were improved.
At this point a three-step virtual screening route is available using prefiltering for non-reactive and presumably non-toxic compounds as first screening, two pharmacophore models as second screening, and PLANTS software for docking and scoring as third screening.[2] After a screening of our in house database which includes 6000 structures and the MOE database which contains 930.000 structures of commercially available compounds, 40 compounds were predicted to have a high affinity for one of the steroid hormone receptors.
A enzymatic assay was performed, and as a result, two compounds with an IC_{50} below 10µM and one compound with an IC_{50} around 1nM were identified.

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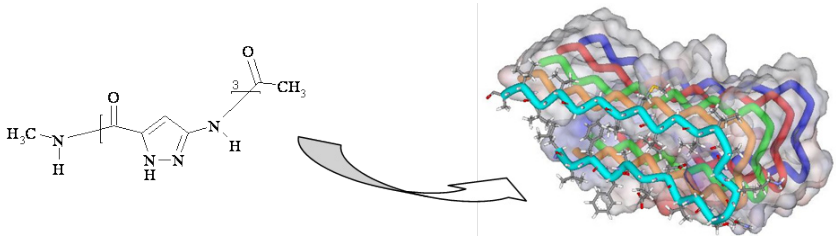
Dynamics and Binding to a Model Inhibitor of Alzheimer Disease-Related Peptides $A\beta_{40}$ and $A\beta_{42}$

Anselm H. C. Horn, *Heinrich Sticht*
Bioinformatik, Institut für Biochemie, Emil-Fischer-Zentrum
Friedrich-Alexander-Universität Erlangen-Nürnberg
Fahrstraße 17, 91054 Erlangen, Germany

The high standard of living in the industrial nations has been generating an increasing average life expectancy, which is, unfortunately, followed by an increase of age-related diseases, of whom one of the most grave is the Alzheimer disease (AD). The 39- to 42-residue-long amyloid-β (Aβ) peptide, generated from the amyloid precursor protein, is the major component of AD-associated amyloid plaques consisting of pathological protein fibrils.
In order to develop a rationally designed medication against Alzheimer's disease, a detailed knowledge of the dynamical behaviour and properties of already toxic Aβ oligomers developing into amyloid fibrils is mandatory.
In a first step we wanted to elucidate the different propensity for forming fibril structures of the two most abundant amyloid peptides, $A\beta_{40}$ and $A\beta_{42}$, the shorter of which is known to be much less prone to amyloid formation. Starting from a pentamer of Aβ1-42's structured peptide region (NMR-structure, pdb code 2beg [1]) molecular dynamics simulations were performed for both species using the Amber9 suite of programs. Differences in global structural flexibility as well as energetic contributions of key residues were analysed.

Our second aim was to shed more light on the dynamics of the binding mode of a new class of non-peptidic β-sheet ligands on amino-pyrazole basis. Several such compounds were experimentally shown to prevent Aβ aggregation,[2] although their exact mode of action is still unclear. We thus parameterised the pyrazole subunit for the parm99 force field, validated the final parameter set by molecular dynamics simulations, and investigated its binding to a model amyloid fibril.



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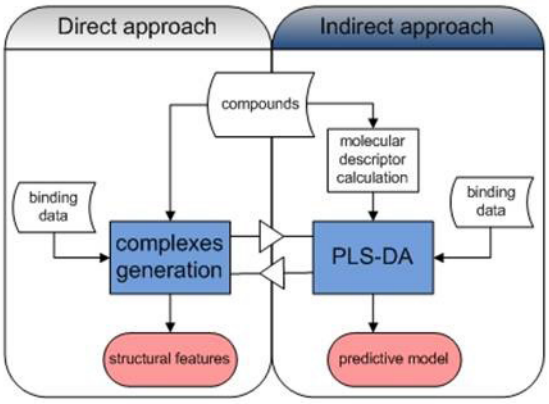
Combination of direct and indirect approaches to study the D2/5-HT2A selectivity of antipsychotic drugs

A. Bauer-Mehren, *J. Selent, L. López, F. Sanz and M. Pastor*
Computer-Assisted Drug Design Laboratory, Research Unit on Biomedical Informatics (GRIB), IMIM, Universitat Pompeu Fabra, Barcelona, Spain

Schizophrenia is a debilitating psychotic disorder, affecting up to 1% of the general population. Most antipsychotic drugs have a multi-receptor profile exhibiting affinities to serotonin, dopamine, alpha-adrenergic, muscarinic and histamine receptors, among others. The serotonin 5-HT_{2A} and the dopamine D_2 receptor have received particular attention, and their binding affinity ratio (5-HT_{2A}/D_2), also know as Melzer index, has been used as screening criterion for atypical antipsychotics.
The goal of this work is (i) to elucidate structural features of a new series of compounds[1] which are associated with the required 5-HT_{2A}/D_2 selectivity and (ii) the generation of a predictive model for novel compounds. In the present study we apply the combination of direct and indirect approaches with the advantage of complementing each other (figure). In the direct approach ligand-receptor complexes based on the new ß2-adrenergic structure[2] are generated, providing valuable input data such as molecular interaction fields of the ligand-receptor complexes for the indirect approach. The gained information serves as feedback for the direct approach and the modeling of ligand-receptor complexes in order to draw a complete image of the 5-HT_{2A}/D_2 selectivity.



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Flexibility of Aldose Reductase: Opening of a novel subpocket upon ligand binding

Monika Nocker, *Christoph A. Sotriffer*
Institute of Pharmacy and Food Chemistry, Julius-Maximilians-University Würzburg

Aldose Reductase is the first and rate limiting enzyme in the polyol pathway and in this context an interesting therapeutic target for the treatment of late-onset diabetic complications. The enzyme's binding site can be divided into two main subpockets distinguished by their amount of flexibility. The specificity pocket can be observed in a closed as well as in an open state showing induced-fit adaptations, while the catalytic pocket is rather rigid.

Recently designed Aldose Reductase inhibitors of a series of naptho[1,2-d]isothiazole acetic acid compounds[1] leave the specificity pocket in a closed state. This is in contrast to the initial design hypothesis as analogues of the well-known ligand tolrestat, which binds to the protein with an open specificity pocket[2].

One of these new inhibitors demonstrates the opening of a completely new subpocket never observed before in crystal structures. This new binding-site conformation is characterized by the rotation of an indole moiety of Trp 20 by about 35°. Trp 20 belongs to the usually rigid catalytic pocket, and motion in this part of the binding site is therefore unexpected. The rotation is further accompanied by the displacement of Lys 21 that normally forms two charge-assisted hydrogen bonds to a phosphate group of the cofactor NADPH and the carboxylate side-chain of Asp 216.

The ligand itself also shows an interesting property in the crystal structure as the nitrogen can be seen in a pyramidal geometry instead of the planar structure expected to be more favorable for an imide-type nitrogen. Quantum-mechanical calculations were used to determine the energy barrier between these two geometries.

MD simulations were carried out to investigate the binding-pocket flexibility of Aldose Reductase. Starting point were the crystal structures of the protein in complex with the new naptho[1,2-d]isothiazole acetic acid inhibitors and the uncomplexed state resulting from the removal of those. These simulations should help to determine the key features of inter- and intramolecular interactions responsible for the opening of the mentioned new subpocket.

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Web interface with advanced query properties for the Binding Interface (BIF) database

Mario Dejung, *Sebastian Radestock, Holger Gohlke*
Mathematisch-Naturwissenschaftliche Fakultät, Pharmazeutisches Institut, Christian-Albrechts-Universität, Kiel, Germany

The amount of structural and energetic data on biomacromolecules and their complexes is constantly growing. The data is of great value for applications such as molecular modeling, drug discovery, or chemogenomics.[1] Currently, the data is distributed over many different databases. To integrate the information, the Binding Interface (BIF) database has been developed in our group as a MySQL-based relational database system.[2] At the heart of the BIF is the structural information from the PDB. This information is augmented with additional relations based on a hierarchical molecule model and a mol2 atom type classification. Ligands, potential binding pockets, and binding interfaces are identified and integrated. Energetic information from the PDBbind database and the BindingDB, DrugScore potential fields, and information from the catalytic site atlas (CSA), the SCOP and the CATH database are added.

To fully exploit the large amounts of available data in the BIF database, an efficient data handling capability is crucial. To this aim, a web interface is currently under development that provides a powerful, yet intuitive tool for accessing the data. The interface can be queried by PDB code, or by any structural or energetic property of the molecules. The search results can be saved as pdb- or mol2-file, or as tabular report in a text file. In addition, statistical analyses will be possible. To visualize the results, the retrieved data can directly be piped to Pymol, where the hierarchical molecule model will be kept.

We expect the BIF – in conjunction with its new interface – to be a valuable tool for drug discovery and structural bioinformatics. It will be possible to generate datasets for testing or developing new docking tools and scoring functions, and to extract various types of knowledge from the data. In addition, the BIF is believed to be an interesting tool for chemogenomics applications, such as analyzing the similarity between different binding pockets. The BIF and its interface are designed and implemented in such a way that the database can easily be expanded.

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Classification of the Amino Acids *on the basis of structural data*

Alexander Entzian, *Horst Bögel*
Institute of Organic Chemistry, Martin-Luther-University Halle-Wittenberg, D-06120 Halle (Germany)

The considered 20 canonical amino acids show a complicated spectrum of their properties; they are traditionally divided according to their acid and bases strength, the hydrophobicity, and qualities of the substituent of the side chain, as well as other qualities. These divisions are based on the chemical experience which leads to numerous overlapping of possible separations into classes.

In this work additional characteristic features obtained by theoretical calculations are considered, such as stabilization energy, electron densities (or atomic charges), partial charges areas on the molecule surface and front orbital energies. The most stable conformation of amino acids were calculated by structural optimization and conformation analysis, assuming the molecular mechanics on the basis of proven force field parameter (MMFF94x). These structures were re-optimized with semi-empirical methods (MOPAC) by MOE [1]. From these calculation we have analysed the electronic structure and the sequence of the orbital energies. In case of a chiral centre only the S-configurations were considered owing to their biological meaning.

A suitable set of features were selected from the calculated qualities by means of Principal Component Analyse (PCA). We used an agglomerative hierarchical clustering using the software program XLSTAT [2]. This is an unbiased classification achieved with mathematical-statistical methods. In contrast to traditional divisions the degree of the resemblance of the amino acids gets more apparent.

The best classification could be reached by using 7 features in ordered to divides to 20 amino acids into 4 classes which could be compared to the Venn diagram drawn by K. Giles [3]. We hope to use this classification for comparing with the BLOSUM62 matrix [4].

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PhAST – Pharmacophore Alignment Search Tool

Volker Hähnke, *Gisbert Schneider*
Johann Wolfgang Goethe-Universität, Beilstein Endowed Chair for Cheminformatics, Institut für Organische Chemie und Chemische Biologie, Siesmayerstr 70, D-60323, Frankfurt am Main, Germany

We developed the Pharmacophore Alignment Search Tool (PhAST), a text-based method for the comparison of molecules that can be used for ligand-based virtual screening. For each molecule, a two-dimensional graph of potential pharmacophoric points (PPPs) is created, that has an identical topology as the original molecule with implicit hydrogen atoms. Each type of PPP has an associated symbol. The vertices of the graph are labelled canonically. The symbols associated with the vertices are combined to a so-called PhAST-Sequence beginning with the vertex with the lowest index. Due to the canonical labelling, there is only one possible PhAST-Sequence for each molecule. For similarity assessment, PhAST-Sequences are compared using the sequence identity[1] in their global pairwise alignment[2]. The similarity score lies between 0 (no similarity) and 1 (identical PhAST-Sequences). In order to use global pairwise sequence alignment, a score matrix for pharmacophoric symbols was developed and gap penalties were optimized. PhAST performed comparably and sometimes superior to other similarity search tools in retrospective Virtual Screenings using the COBRA[3] molecule library.

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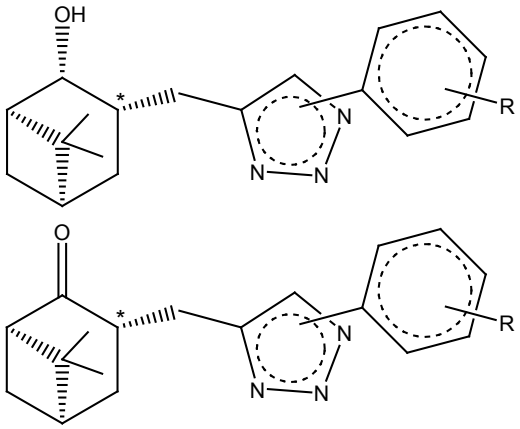
Experimental and calculated NMR parameters

A. Koch, *M. Heydenreich, E. Kleinpeter*
Universität Potsdam, Institut für Chemie, Karl-Liebknecht-Str. 24-25, D-14476 Potsdam

In a series of 3-substituted 6,6-dimethyl-bicyclo[3,1,1]heptan-2-ols and 3-substituted 6,6-dimethyl-bicyclo[3,1,1]heptan-2-ones large differences in ^{1}H and ^{13}C NMR chemical shifts of methyl groups bound to C-6 were observed. Additionally, the value of the $^{1}J_{(C\text{-}3,H)}$ coupling constants (see Scheme, position marked by *) depend on the substitution pattern (hybridization) in position 2.



A conformational search using B3LYP/6-31G* level of theory determined local and global minima of these compounds. Calculations of chemical shifts are in good agreement with experimental values. The analysis of structural features and calculation of the anisotropic effects of the carbonyl group and the aryl moieties were employed to determine reasons for the differences in ^{1}H and ^{13}C chemical shifts of the C-6 methyl groups.
The differences in direct $^{1}J_{C,H}$ coupling constants between the two series could be reproduced too, however, this is caused by electronic influences.
Calculations were done using Gaussian03[1] program package and SYBYL7.3[2] modelling software were used to analyse the results.

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Comparing Natural Product (NP) and non-NP Datasets at an Atomic Scale

Heintz, T.[a,b], *Brandt, W.*[b], *Weber, L.*[a], *Wessjohann, L.A.*[a,b]
[a] *OntoChem GmbH, Heinrich-Damerow-Str. 4, D-06120 Halle/S.*
[b] *Leibniz Institute of Plant Biochemistry (IPB), Weinberg 3, D-06120 Halle/S.*

Understanding the basic chemical composition of secondary natural products (NP) will help to design NP like agents more efficiently. This should lead to an elaborated comprehension of the biosynthetic origin of natural products and to an efficient way to simulate and to imitate these structures in research and development, especially since it is known that natural and natural like products provide an evolutionary advantage towards protein binding and thus differ from non natural synthetic compounds to some extent.[1]
Initial research regarding the comparative analysis of natural products, synthetic compounds, and drugs has already been done in 1999,[2] and more recently this year.[3] Additionally, a statistical analysis of natural macrocycles has been performed lately,[4] ring systems were examined with respect of their structural similarities[5] by charting natural products in general.[6] A different analysis concerning natural products versus molecules from combinatorial synthesis with respect to drug design was done in 2003.[7]
In order to capture the evolutionary advantage of NPs, it is of high relevance to develop methods for their differentiation from chemical molecules in general, separating NPs and NP-like compounds out of the set of all chemical structures. Despite of the previously done comparisons between natural product compounds and synthetic ones, here a general comparison of all elements and atom types for an advanced classification of compounds from different resources is presented. These results will be the basis for further, more detailed analyses with regard to drug alikeness and development. Cheminformatic analysis of the frequency of selected structural elements occurring in natural products in comparison to compounds of synthetic origin should gain more insight in essential differences between both classes of compounds. For this purpose, a JAVA application was developed to examine eight datasets of various vendors, with three among them containing natural products only. These data were analysed to understand - on an atomic scale - the differences between compounds synthesised by nature and compounds synthesised by man.

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NMR and theoretical investigations of intramolecular hydrogen bonding

Anica Lämmermanna[a], *István Szatmárib[b] and E. Kleinpeter[a]*
[a]University of Potsdam, Department of Chemistry, Karl-Liebknecht-Str. 24-25, 14476 Potsdam/Golm
[b]University of Szeged, Istitute of Pharmaceutical Chemistry, PO Box 427, H-6701 Szeged

Hydrogen bonds (HB) are very important interactions for a wide range of chemical and biological systems (e.g. RNA, protein folding and crystal engineering). A hydrogen bond (D-H • • • A) is an interaction wherein a hydrogen, which is covalently linked to D, is attracted to another atom A.[1] This special kind of non-covalent interaction could be studied on the *ab initio* level of theory, especially the natural bond orbital (NBO) method has developed to be a powerful tool in this respect. The population analysis of NBO showed that the major contribution to the hyperconjugative interaction of HBs is the LP(A) → σ*(D-H).[2] Furthermore, the strength of a hydrogen bond depends strongly on the relative orientations of the bond D-H and the lone pair of A. [3]
To investigate the influence of substituents on a certain hydrogen bond, especially on the hyperconjugative interaction energy (mentioned above) and on the ^{1}H chemical shift of the involved proton, a number of aminonaphthol derivatives with different substituents R (R_1 = H, *p*-OMe, *p*-F, *p*-Br, *m*-Br, *m*-NO_2, *p*-Me; R_2 = *p*-Me, *p*-F, H, *p*-Br, *p*-OMe, *p*-Cl, *p*-NO_2, *m*-Br; R_3 = Me, Pr, *i*-Pr, Et, H) have been investigated (**Figure 1)**. Geometry optimizations were done with GAUSSIAN03 on a B3LYP//6-311+G** level of theory. 2D potential energy scans were performed by rotating the corresponding dihedral angle to find the right direction of the hydrogen bond, because two possible pathways exist.
We will show that there is a linear dependence between the distance of a hydrogen bond and the hyperconjugation energy of the LP(N) → σ*(O-H) contribution and that there is also a linear dependence between the distance of a HB and the substituent induced chemical shifts (SCS) of the involved hydrogen.

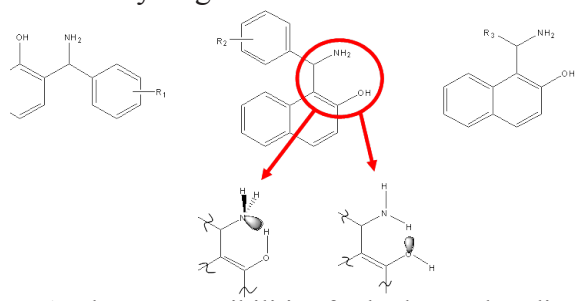

Figure 1: The two possibilities for hydrogen bonding in aminonaphthol derivatives.

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Prediction of Blood Brain Distribution with KNIME

Björn Loeprecht
Tripos International Spain S.L., Martin-Kollar-Str. 17, 81829 Germany

The Konstanz Information Miner (KNIME) [1] is used to create a model for predicting the ability of a compound to pass the blood brain barrier. 82 structures with known experimental logK_{BB} values were derived from literature [2,3] and classified into three groups: penetrating, weakly penetrating or not penetrating the brain. The decision tree mining node of KNIME identifies molecular 2D properties which classify compounds according to these three classes. Compound preparation, duplicate checking, classification of logP_{BB} values, partition into training and test set and molecular property calculations were all performed within KNIME enhanced by the Tripos chemistry extensions. For a test set consisting of 25 structures the prediction accuracy is 84%. Several other interactive analysis tools in KNIME are discussed.

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QM/MM Binding Free Energy Calculations

Frank Beierlein[1,2], *Jonathan Essex*[1]
[1]*School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom*
[2]*Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany*

We present a combined DFT-QM/MM-Monte Carlo protocol which provides a QM/MM correction to include polarisation in the context of rigorous classical free energy techniques. The phase space of the system is sampled using classical Monte Carlo and relative MM free energies are calculated using replica exchange thermodynamic integration. Snapshots of the configurations at the endpoints of the perturbation are then selected for subsequent DFT-QM/MM single point calculations, which provide a QM/MM correction for the MM free energies, thereby incorporating polarisation. The method has been validated by calculating relative free energies of hydration of methane and water; closed thermodynamic cycles are obtained. The approach is now being extended to the calculation of relative free energies of binding of protein inhibitors.

Prediction of the Solvation Free Energy using a Combination of Semiempirical Self-Consistent Reaction Field Calculations and the Local Energy Properties

Marcel Youmbi Foka, *Timothy Clark*
Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany

A new QSAR method, based on Self-Consistent Reaction Field (SCRF) and local properties at the molecular surface of a compound has been developed for the free energies of solvation in water, n-octanol and chloroform. SCRF[1] technique using Tomasi´s treatment of the reaction field within an arbitrarily (Van der waals) shaped cavity, performed with VAMP 9.0, is used for the calculation of the solvent effects. As Coulomb interactions are usually the major contribution to intermolecular interaction energies[2] , within SCRF theory using numerically derived cavities, the molecular electrostatic potential (MEP) which determines the quality of the reaction field and the electrostatic interaction free energy was calculated using our zero-differential-overlap based atomic multipole technique.

Multiple linear regressions were performed in Tsar 3.3[3] and the linear regression coefficient r, the square r^2 , and the cross validation r^2_{cv} were used to select the best regression performance. The statistical descriptors derived from the MEP and new local properties[4] calculated by the AM1 semiempirical method were used to build surface integral models. A parameterized function of four local properties calculated at the isodensity surface (molecular electrostatic potential, local ionization energy, electron affinity, and polarizability) is integrated over the triangulated surface area to obtain the target quantity[5] . The resulting models give results only slightly less accurate than those reported for parameterized generalized Born/polar surface area models despite relying only on gas-phase calculations.

In our approach to determining the solvation free energies, the electrostatic energy has been used as the apropriate correction factor. The water and octanol free energy models were validated by calculating the water-octanol partition coefficient for a test set of organic compounds with moderate success.

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CypScore: A Quantum Chemistry based Approach for the Prediction of Likely Sites of P450-Mediated Metabolism

M. Hennemann,[#] *A. H. Göller,*[*] *A. Hillisch,*[*] *T. Clark*[#]
[#] *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany.*
[*] *Bayer HealthCare AG, Bayer Schering Pharma, Global Drug Discovery - Chemical Research, Aprather Weg 18a, 42096 Wuppertal, Germany.*

Unfavorable ADMET properties are among the major reasons for the termination of lead optimization and development projects in pharmaceutical research. Metabolism via first-pass clearance in the liver frequently leads to low bioavailability of compounds. Additionally, toxic metabolites and metabolites that alter the overall metabolism via inhibition or induction of CYP enzymes cause severe side effects. It is therefore highly desirable to have a tool to predict the lability of specific atomic positions and the metabolites of any compound in silico.

With CypScore, we have developed in silico prediction software for small molecule metabolic oxidations mediated by cytochrome P450 enzymes. CypScore has specific models for all important P450 mediated oxidative reactions, such as aliphatic hydroxylation, aromatic and alkene epoxidation, N-oxidation and S-oxidation. The models are based on ParaSurf[1] atomic reactivity descriptors derived from VAMP[2] AM1 quantum chemically calculated wave functions. The models were fitted to reproduce the metabolic patterns from an in-house established literature database of 850 compounds with 2,400 metabolic transformations.

Since the models are derived from quantum-chemical descriptors, CypScore is not just an interpolative QSAR or a knowledge-based approach but is able to predict metabolism at an atomic position under explicit consideration of the 3D neighborhood effects of the rest of the molecule.

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Parameterization of Bromine and Iodine for AM1*

Hakan Kayı, *Timothy Clark*
Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany

An extension of AM1 [1] semiempirical molecular orbital theory, named AM1* [2], uses the original AM1 parameters and theory unchanged for the elements H, C, N, O and F and *d*-orbitals for the elements starting from second long row on the periodic table [2,3,4]. In this work, bromine and iodine have been parameterized using a set of *d*-orbitals and with two-center core-core parameters. The typical errors of AM1* for bromine and iodine are discussed. Now AM1* parameters are available for H, C, N, O and F (which use the original AM1 parameters), Al, Si, P, S, Cl, Ti, Cu, Zn, Zr, Mo (slightly modified Voityuk and Rösch's AM1(d) [5] parameters for Mo), Br and I [6].

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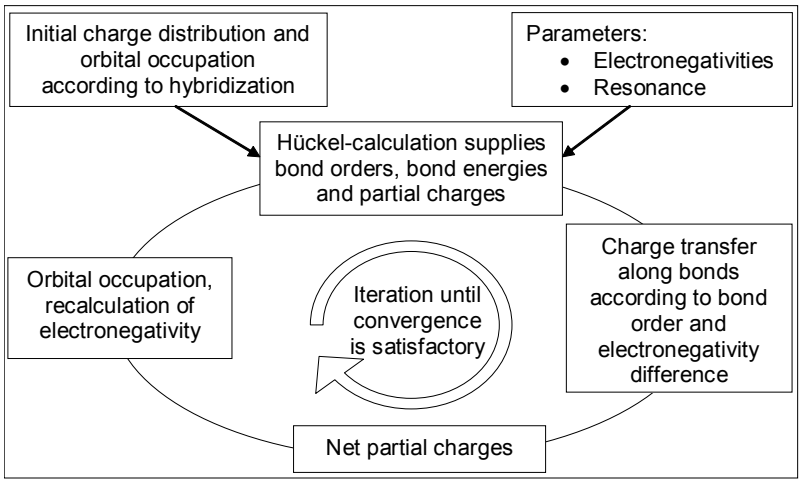
Fast access to total energies

Klein, R.[a], *Brandt, W*[b]*., Wessjohann, L. A.*
Leibniz-Institut für Pflanzenbiochemie, Weinberg 3, 06120 Halle (Saale); [a] *rklein@ipb-halle.de,* [b] *wbrandt@ipb-halle.de*

A computational method for the fast calculation of total energies is presented. Using a combination of classical Hückel molecular orbital (HMO, [1]) theory and the partial equalization of orbital electronegativity (PEOE, [2]), it could be shown that heats of formation of large molecules might become accessible in a very efficient way.
The new approach uses classical HMO calculation for the determination of bond orders, partial charges and bond energies in π-conjugated components. Furthermore, 2-dimensional Hückel problems are formulated and solved for isolated σ- and π-bonds. Assuming no charge interaction between σ- and π-orbitals, all non-conjugated parts of the considered molecule are iteratively allowed for charge transfer according to PEOE which leads to the following scheme:



Correlating results from this procedure for a set of 201 organic molecules with total energies calculated by PM3 [3] lead to a very good agreement and a stability index of $R^2 \approx 0.991$. An incorporation into force fields for the inclusion of steric terms is planned.

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Simulation of Ion Transport Through a Potassium Channel under Realistic Transmembrane Potentials in a Double Lipid Bilayer System

M. Kreim[1,2], *S. Tayefeh*[2], *G. Thiel*[1], *S. M. Kast*[2]
(1) Institut für Botanik, Technische Universität Darmstadt, Schnittspahnstr. 3, 64287 Darmstadt, Germany
(2) Eduard-Zintl-Institut für Anorganische und Physikalische Chemie, Technische Universität Darmstadt, Petersenstraße 20, 64287 Darmstadt, Germany

Progress is reported on the first steps toward modeling a potassium channel in a realistic environment under the influence of an external voltage. To this end, a solvated double lipid bilayer system is constructed. The channel protein is embedded in only one of the membranes. In this way, even under periodic boundary conditions for the total system, it is possible to separate physically the two baths corresponding to the intracellular and extracellular compartments. Ionic concentration can be controlled individually as well as, in analogy to ref. [1], the cation-anion balance which controls the external voltage. In comparison with earlier simulations at constant external electric field across the membrane, the present setup leads to a more realistic model of the transmembrane potential. Together with a virtual transport mechanism that is triggered once species pass the channel, the simulation scenario can be used to study stationary electroosmotic flow that can be compared with experimental current/voltage data. As an example, we use a model of the Kcv potassium channel in a DMPC membrane established by us earlier [2,3], which has been shown to exhibit repetitive single-file ion transitions under constant field conditions. Preliminary simulation results and analyses of transmembrane potentials are presented and discussed.

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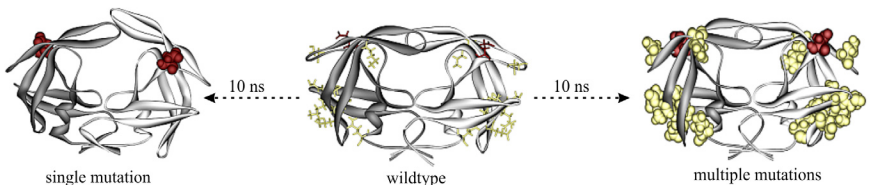
Protein Dynamics Simulations of HIV-1 Protease to Investigate the Effects of Single or Multiple Mutations

Heike Meiselbach, *Anselm H. C. Horn, Heinrich Sticht*
Bioinformatik, Emil-Fischer-Zentrum
Fahrstraße 17, 91054 Erlangen, Germany

Despite the efforts undertaken during the last decade, AIDS still remains a pandemic threat to the world health situation. One of the main reasons for this is the HI virus' ability to develop resistance via versatile mutations. These mutations frequently occur in the protease of reverse transcriptase, which represent essential enzymes form viral replication. The mutations either arise as consequence of drug treatment mediating resistance to the respective drugs, or they arise to allow escape from detection by the immune system.

Residue Glu35, for example, is located in an epitope which is recognized by the immune system and mutation of Glu35 to aspartic acid (E35D) hampers this recognition process, thereby suppressing an immune system response [1, 2]. Using molecular dynamics simulations we were able to show that this mutation has a significant effect on the dynamics of the free protease and on its substrate and inhibitor binding properties [1]. In particular the enhanced flexibility of two loops ('flaps') in the mutant protease compared to the wildtype leads to a weaker binding of the substrate suggesting a decreased enzymatic activity [1].

Recent experimental studies have shown the existence of additional mutations in HIV-protease, which occur in conjunction with E35D. We found that these mutations allow additional stabilizing interactions thus compensating the destabilizing effect of the E35D mutation. As a consequence, the overall dynamics of the multiple-mutant protease is highly similar to that of the wildtype enzyme. Thus, the emergence of additional mutations in HIV-protease restores wiltype-like properties resulting in an active protease that is still capable to escape from the immune system.



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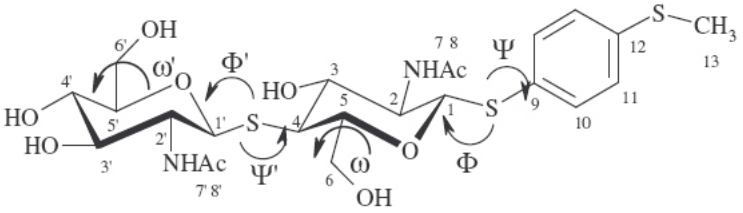
Solution-state Conformational Study of Thio-glycosidic carbohydrates by NMR Spectroscopy and Molecular Modelling

Anja Fettke, *Dirk Peikow, Martin G. Peter and Erich Kleinpeter*
Institut für Chemie, Universität Potsdam,
Karl-Liebknecht-Str 24-25, D-14476 Potsdam (Golm)
afettke@chem.uni-potsdam.de

The solution-state conformation of new β(1-4)-thio-glycosidic[1] N-acetylated carbohydrates were studied by NMR spectroscopy and molecular modelling using force field calculations. NMR spectroscopy has proven to be a good method for assessing the adopted conformation of oligosaccharides in aqueous solution.[2] These oligosaccharides show a high flexibility in solution and therefore the determination of the conformation is limited. On the other hand, it is possible to employ computational methods to assist in interpreting the NMR data. Specific NOE contacts as well as coupling constants corresponding to a particular conformation are only interpretable if this conformation is highly populated in solution. Since oligosaccharides usually populate several conformations at ambient temperature,[3] NOE contacts observed represent a population-weighted average of all participating conformations. Hence, population-weighted average internuclei distances have been calculated for a number of higher populated (>1%) minima conformations (concerning Φ'/Ψ', Φ/Ψ and ω'/ω) with the AMBER force field. Agreement between the experimental NMR data and the theoretical calculations was reached by assessing the structures as population-weighted average conformers on the basis of Boltzmann distributions derived from the calculated relative energies.[4]



Φ = H1' - C1' - O1' - C4, **Ψ** = C1' - O1' - C4 - H4
ω = O5 - C5 - C6 - O6 und **ω'** = O5' - C5' - C6' - O6'

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Different Handling of a Hydrophobic Pocket and Consequences for Screening Results in Catalyst, Phase and MOE

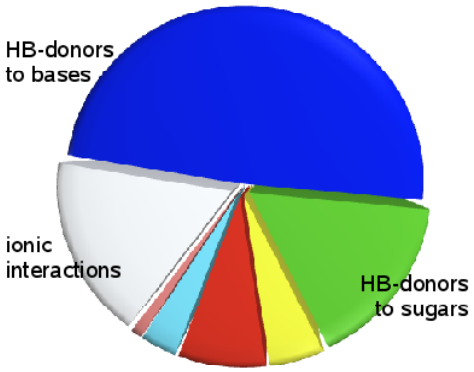
Gudrun M. Spitzer, *Martina Mangold, Theodora M. Steindl, Hannes G. Wallnoefer, Christian Laggner, Thierry Langer, Klaus R. Liedl*
University of Innsbruck, Innrain 52a, 6020 Innsbruck, Austria

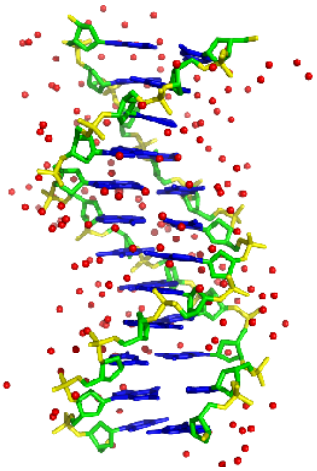
Three pharmacophore modeling programs Catalyst (Accelrys), Phase (Schrödinger), and MOE (Chemical Computing Group) are compared with respect to their virtual screening results relying on a structure based pharmacophore model. We have chosen Human Rhinovirus (HRV) coat protein because of the properties of its binding pocket: there is only one hydrogen bond acceptor at the entrance of the pocket, the remainder of the pocket is mainly hydrophobic and has the shape of a narrow tube. Hydrophobic regions cannot be localized clearly on the ligand in contrast to hydrogen bond acceptors and are therefore especially challenging in the field of pharmacophore modeling. They are suspected to contribute substantially to differences in the screening results. To investigate these differences we tried to find a model which could be translated into every software package and still represents all chemical information obtained by X-Ray structure alignment and thorough literature search. The problem was that descriptors with equivalent names sometimes got assigned to different functional groups. A similar hit list in the test set was considered a good criterion for model similarity.

Analysis of DNA Minor Groove Binding Patterns

Gudrun M. Spitzer, *Bernd Wellenzohn, Patrick Markt, Johannes Kirchmair, Thierry Langer, Klaus R. Liedl*
University of Innsbruck, Innrain 52a, 6020 Innsbruck, Austria

We built up a database of all known 3D structures of minor groove binder - DNA complexes. The database contains a thoroughly collected list of all types of interactions involved in complex formation. It is intended to support efforts towards discovery of new minor groove binding scaffolds. Here we present preliminary results of a statistical analysis with respect to geometric features. Interaction patterns emerging from this investigation and implications of distance and angle distributions are discussed.





Molecular Dynamics Studies on the TIP-Tet Repressor System

F. Haberl, *R. Woelfel, H. Lanig, T. Clark*
Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, D-91052 Erlangen, Germany

The tetracycline-repressor protein (TetR) has achieved immense importance as the archetypical signal-transduction system. It is important both clinically (because it controls expression of the tetracycline-antiporter protein (TetA), which actively pumps tetracyclines out of the bacterial cell) and as a versatile gene-switch in microbiological research.[1] Normally, TetR is induced by a tetracycline complexed with Mg^{2+}. We[2] recently determined the mechanism of induction by this route using long time-scale molecular dynamics simulations. However, Hillen et al.[3] recently discovered that TetR can be induced by small peptides in the absence of Mg^{2+} and Muller et al[4] have been able to determine the X-ray structure of TetR complexed to an inducer peptide. We now report molecular-dynamics simulations designed to determine the mechanism of induction of TetR in this case without Mg^{2+}.

This work was supported by the Deutsche Forschungsgemeinschaft as part of Sonderforschungsbereich 473 “Mechanisms of Transcriptional Regulation” (http://www.biologie.uni-erlangen.de/mibi/sfb473.html).

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Reaction-driven Combinatorial Library Design

Hartenfeller M., *Reisen F., Proschak E., Schneider G.*
Johann Wolfgang Goethe-Universität, Beilstein Endowed Chair for Cheminformatics,
Institut für Organische Chemie und Chemische Biologie,
Siesmayerstr 70, D-60323 Frankfurt am Main, Germany

We developed two complementary methods for rapid fragment-based combinatorial molecule design.
The first approach (COLIBREE®, Combinatorial Library Breeding) generates candidate structures from scratch, based on stochastic optimization. A library is represented by a single scaffold, which remains constant during optimization, and variable linkers and side-chains. Different linkers represent virtual chemical reactions. Side-chain building blocks were obtained from *pseudo*-retrosynthetic dissection of large compound databases. The process of molecule design employs a discrete version of Particle Swarm Optimization (PSO).[1] Assembled compounds are scored according to their similarity to known reference ligands. Distance to reference molecules is computed in the space of the topological pharmacophore descriptor CATS.[2] In a case study, the approach was applied in *de novo* design of potential peroxisome proliferator-activated receptor (PPAR) subtype γ selective agonists.
In a second approach, we focused on the *in silico* representation and application of chemical reactions. Chemical transformation schemes can be represented by functional groups that participate in organic reactions. Therefore, we designed a formal grammar for representing substructure-based reaction schemes, termed *Reaction-MQL*. Chemical substructures are specified by the linear *Molecular Query Language* (MQL).[3] We developed a software package containing a parser for *Reaction-MQL* expressions, which allows an ease application in computational chemistry. The program was used to create a combinatorial library for virtual screening for PPARα agonists.

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Towards a detailed understanding of the mechanisms associated with HPr phosphorylation

Nadine Homeyer[1], *T. Essigke[2], G. M. Ullmann[2], H. Sticht[1]*
[1]Abteilung für Bioinformatik, Institut für Biochemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstraße 17, 91054 Erlangen, Germany
[2]Structural Biology/Bioinformatics, Lehrstuhl Biopolymere, Universität Bayreuth, Universitätsstraße 30, BGI, 95447 Bayreuth, Germany

Posttranslational protein phosphorylation plays a pivotal role in the cellular regulatory network. A protein whose function can be modulated by the addition of a phosphate group is the bacterial histidine-containing protein HPr. Phosphorylation of HPr at His15 yields HPr-His15P, which is essential for the detection and uptake of carbohydrates by the phosphoenolpyruvate:sugar phosphotransferase system.
In previous structural studies of the HPr protein it was found that the active-site residue His15 can adopt two distinct conformations[1, 2] which were termed OPEN and CLOSED. Using molecular dynamics simulations and protonation probability calculations, we were able to show that these two conformations correspond to different protonation forms of the imidazole ring of His15. The CLOSED-to-OPEN transition requires His15 to adopt a conformation with higher energy, which is compensated for by the favorable energetic consequences of protonation. Calculations of the conformational energy of His15 show that HPr exists mainly in the CLOSED form at pH 7.
In contrast to unphosphorylated HPr, the His15-phosphorylated form of the protein exhibits no conformational transitions, and the CLOSED state is stable even for the protonated imidazole ring due to favorable interactions between the phosphate group and the backbone of Ala16 and Arg17.
These results are confirmed by a simple four-microstate model which can explain both the pH dependent conformational change of the unphosphorylated HPr protein and the conformational rigidity of HPr-His15P.
Our study[3] suggests that the predominant CLOSED conformation is relevant for the HPr function in the phosphotransfer reaction, while the OPEN form of unphosphorylated HPr might be important for its additional regulatory function, in which an OPEN conformation of His15 is recognized by the transcriptional regulator CcpA.

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P27

The phosphoryl transfer between the IIA and IIB proteins of the *Escherichia coli* Glucose Phosphotransferase System

Christophe Jardin, *Anselm Horn, Gudrun Schürer, Heinrich Sticht*
Bioinformatics, Institute of Biochemistry and Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Phosphoryl transfer is a key reaction in many aspects of metabolism, gene regulation, and signal transduction. One prominent example is the phosphoenolpyruvate:sugar phosphotransferase system (PTS), which represents an integral part of the bacterial sugar metabolism. The transfer between the enzymes IIA^{Glc} and IIB^{Glc} in the glucose-specific branch of the PTS is of particular interest due to the unusual combination of donor and acceptor residues involved in phosphoryl transfer. The phosphoryl group is initially attached to the Nε2 atom of His90 in IIA^{Glc} and is transferred to the Sγ atom of Cys35 in IIB^{Glc}.

To get insight into the details of the transfer mechanism, we have performed both MD and QM/MM simulations. Our simulations show a strong dissociative character for the transfer. The Nε2-P bond gets immediately destabilized after complex formation by numerous interactions formed between residues of IIB^{Glc} and the phosphoryl group. The fact that the Arg38 sidechain of IIB^{Glc} is directly involved in the transfer process is particularly interesting, since this residue was previously considered to play only an indirect role for the transfer by stabilizing the Sγ-thiolate and by forming an intermolecular salt-bridge. Thus, our simulations reveal an additional important role for Arg38 consistent with the strict conservation of this amino acid.

The final formation of a tight Sγ-P bond is accompanied by a reorientation of the sidechain of the phosphoryl donor (His90). This reorientation results in the loss of interaction between the imidazole ring of His90 and the phosphate group and might thus be important to impede the reverse transfer. Notably, the resulting sidechain conformation of His90 is highly similar to that observed in the structure of free IIAGlc.

A comparison of the transfer to protein tyrosine phosphatases, which also use a cysteine as acceptor of the phosphoryl group, reveals significant similarities both in the conformation of the active sites and in the pattern of interactions that stabilize the phosphoryl group during the transfer.

Structures and Energies of $(CF)_{60}$ and $(CH)_{60}$ Cages and Tubes – Effect of Fused Five-Membered rings

Hai-Shun Wu, *Jia Jianfeng, and Haijun Jiao**
(a) School of Chemistry and Materials Science, Shanxi Normal University, Linfen, 041004, China;
(b) Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany, haijun.jiao@catalysis.de

The structure and energy of $(CF)_{60}$ and $(CH)_{60}$ cage and tubes have been computed and compared. For $(CF)_{60}$, the most stable isomer (F_4@$C_{60}F_{56}$) has tube-like structure with four *endo* C–F bonds and fused five-membered rings at the end of the tube, while the reported most stable cage structure (F_8@$C_{60}F_{52}$) with eight *endo* C–F bonds is higher in energy by 22.6 kcal/mol.[1] For $(CH)_{60}$, tube-like structures are energetically more stable than the cage isomer in I_h symmetry, however, the cage structures with ten endo C–H bonds is most stable.[2]

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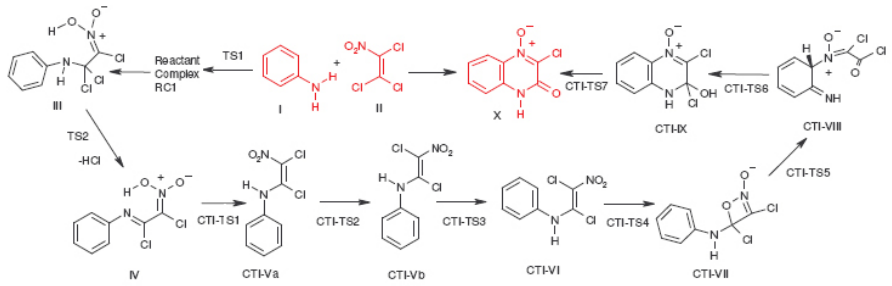
A plausible pathway for nucleophilic addition of trichloronitroethylene to aniline through cis-trans isomerization

Gül Altınbaş Özpınar[*], *Safiye Sağ Erdem*[*], *Christian Meyer*[#], *Dieter E. Kaufmann*[#]

[*]*Marmara University, Department of Chemistry, Goztepe Campus 34722 Istanbul, Turkey*

[#]*Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstr. 6, 38678 Clausthal-Zellerfeld, Germany*

For the first time, the nucleophilic addition of trichloronitroethylene to aniline derivatives was carried out by Kaufmann and Meyer[1,2] in order to synthesize biologically active quinoxalinone-*N*-oxides. The reaction was performed under basic conditions at room temperature. It was reported that *N*-substituted, *N,N*-disubstituted anilines and several phenyl derivatives such as *p*-nitroniline, *m*-aminoaniline do not give the annelation reaction. Since the experimental information about the mechanism of this reaction is limited, we aimed to enlighten the mechanism theoretically. We proposed five different pathways and modelled using DFT (B3LYP)/6-31+G** method. All stationary points were verified with frequency calculations. IRC computations were also carried out for the transition states. The mechanism demonstrated in Figure 1 was found to be the most plausible pathway involving a cis-trans isomerization (CTI-TS2) in the rate determining step. It is interesting that this isomerization has an activation energy of 29 kcal/mol, although it is commonly known that cis-trans isomerizations in alkenes have a high barrier (60-65 kcal/mol) because of restricted rotation around a double bond. We observed that the ethylenic bonds in the structures CTI-Va, CTI-Vb, and CTI-TS2 exhibit partial double bond character because they involve a push-pull effect by the substituents and this accounts for the reduction in the isomerization barrier. The effects of substituent, solvent and the level of computational method on this proposed mechanism are under consideration in our ongoing study.



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COSMO*mic* – a Novel Tool for fast Access to Membrane-Water Partition Coefficients and Internal Distribution within Biomembranes

Carsten Wittekindt, *Andreas Klamt and Uwe Huniar*
COSMOlogic GmbH & Co. KG, Leverkusen, Germany

A vast number of drug candidates fail in the preclinical phase due to poor pharmacokinetic behavior, which is given by the so called ADME properties. In order to reach the site of action, e. g. a protein target, the drug has to cross cell membranes, which is a process of passive diffusion in most cases. The passive diffusion is related to the partition coefficients between the membrane and the surrounding aqueous solvent. But, not only is the overall partition coefficient of importance, but also the internal distribution of the drug within the membrane. A large number of processes like permeability, toxic effects of protonophores and washout rates of drugs [1-3] can be described by the knowledge of the internal distribution within the membrane.

Existing methods take use of the octanol-water partition coefficient, by completely neglecting the anisotropy of the membrane and thus are not able to predict the internal distribution. Molecular dynamic simulations take the atomistic structure of the membrane into account, but are by far too time consuming for in silico screening

Here we present COSMO*mic*, which is a novel extension of our well established COSMO-RS methodology [4,5] for quantum chemically based fluid phase thermodynamics towards the prediction of solvent interfaces, surfaces and micellar properties. Real life examples will demonstrate the performance and applicability of this approach [2,6]. The predictive power of COSMO*mic* has been validated on the partition coefficient between DMPC and water for several data sets of drug and drug like molecules. With a slope close to one from the regression to experimental data, and $r^2 > 0.8$ COSMO*mic* gives very good results without the need to fit parameters to a given training set

COSMO*mic* takes the results of MD simulations of micelles or membranes as an input to describe the radial distribution of the atoms of the micelles. Together with COSMO/DFT calculations of one molecule that builds up the membrane, as well as for the solutes of interest, this is all that is needed for a COSMO*mic* calculation.

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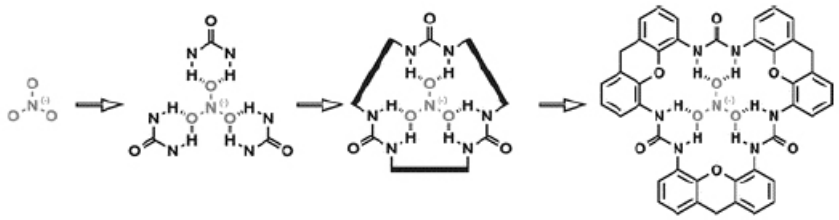
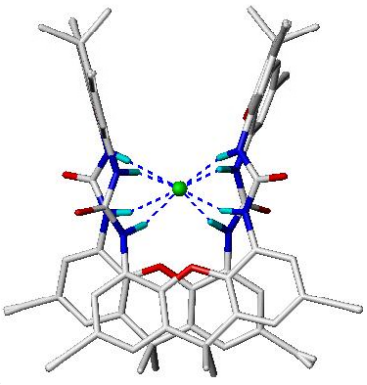
Molecular dynamics simulations of macrocyclic anion receptors

Sabine Werner, *Iris Thondorf*
AG Molecular Modeling, Institut für Biochemie und Biotechnologie, Martin-Luther-Universität Halle

Anion recognition is a field of broad interest in supramolecular chemistry due to the possible applications in ion selective sensors for biological and environmental concerns. The design of efficient and selective synthetic anion receptors is not an easy task because of the specific anion properties as large size, geometric variety and high solvation free energies. A starting point to design neutral macrocyclic receptors are urea functions with their powerful hydrogen bond donors.[1]
The poster shows results of molecular dynamics simulations of macrocyclic tri- and tetraureas both in the free form and as anion complexes in chloroform and acetonitrile. These macrocycles consist of ureas connected by two kinds of spacers, a flexible diphenyl ester and a rigid xanthene unit. Triureas may be preorganised to bind the planar nitrate anion by six hydrogen bonds:
Simulations show that the solvents have a different influence on the



conformation of the free triurea macrocycles. In chloroform the conformation is dominated by intramolecular hydrogen bonds while in acetonitrile the urea groups are solvated. Thus a better preorganisation of the receptor for anion binding is observed in acetonitrile which in turn is counterbalanced by a high desolvation energy. The macrocycles adopt nonplanar conformations, suggesting the complexation of spherical rather than planar anions.[2] Also the tetraureas adopt folded structures which are mostly stabilised by intramolecular hydrogen bonding both in chloroform and acetonitrile. Some are preorganised for the complexation of spherical anions such as chloride, while others may complex tetrahedral compounds such as dihydrogenphosphate.



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Surface-modified Silicon Quantum Dots

V. Kuntermann[1,2], *T. Wölfle[3], W. Hieringer[3], A. Görling[3], T. Clark[1,2], C. Kryschi[1]*

[1]Physikalische Chemie I, University Erlangen-Nuremberg, Erlangen,Germany

[2]Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, University of Erlangen-Nuremberg, Erlangen,Germany

[3]Theoretische Chemie, University of Erlangen-Nuremberg, Erlangen, Germany

This contribution is targeted to the development of surface-modified silicon quantum dots (Si qdots) with tailored luminescence properties. The surface modification of Si qdots with sizes between 1 and 5 nm has been successfully achieved via two different synthesis routes; first, by controlled oxidation followed from silanization and second by thermal hydrosilylation with chromophores. The silanized Si qdots are dispersed in ethanol and are stable over months. Silanized Si qdots were observed to exhibit two kinds of photoluminescence (PL): the blue emission at 380 nm corresponds to localized surface states, the red luminescence is ascribed to Si qdots with sizes larger than 3 nm.[1,2]

A fundamental objective in nanoelectronics is to understand and to control electron flow between semiconductor nanoparticles. This flow is mediated by chromophores attached to the nanoparticle surfaces. Our research activities are focused on developing of Si qdots with optical and electronic properties that can be adjusted by strong electronic interactions with suitable chromophores.[3] Si qdots with covalently bound chromophores were prepared. These exhibit PL in the visible part of the spectrum. The spectral features of the PL strongly depend on both the quantum dot size and the conjugation of the electron system of the chromophores.

Quantum chemical calculations were carried out for a Si qdot modelsystem using density-functional theory (DFT). Based on these electronic excitations were calculated using time-dependent density-functional theory (TDDFT). The main contribution to charge-transfer excitations involves transitions from occupied orbitals located on the chromophore into unoccupied orbitals lying inside the Si core.

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Generation and evaluation of a homology model of *Pf*GSK3

Sebastian Kruggel, *Simon Vogel, Thomas Lemcke*
Universität Hamburg, Institut für Pharmazie, Bundesstr. 45, 20146 Hamburg

To this day more than one million people die of malaria every year, a child dies of malaria every 30 seconds[1]. The infection is caused by different *Plasmodium* species, of which *P. falciparum* is the most vicious one. These facts and the rapid spread of antimalarial drug resistance are making clear the stringent necessity of research for new antimalarial drugs.

Human glycogen synthase kinase-3 β (*Hs*GSK-3β), also known as tau-protein kinase I, is a serine/threonine protein kinase known to be involved in multiple cellular signal transduction pathways.[2] Inhibition of the phosphorylation of glycogen synthase and tau-protein are concepts that can be used in the treatment of diabetes and Morbus Alzheimer. There are several structures of *Hs*GSK-3β published in the RCSB PDB[3] and a number of inhibitors are described.

Droucheau et al. identified and cloned a gene homologue of the glycogen synthase kinase of *P. falciparum* (*Pf*GSK3). Subsequent studies proved partially divergent sensitivity of inhibitors of *Pf*GSK3 and *Hs*GSK-3β suggesting the *Pf*GSK3 as a potential anti-malaria target.[4] Unfortunately structural information about *Pf*GSK3 is lacking. So here we describe the generation and evaluation of homology models of *Pf*GSK3 based on several crystal structures of *Hs*GSK-3β. Models were generated with and without taking information of ligands into account making use of the software MODELLER[5] and MOE (*Molecular Operating Environment*, Chemical Computing Group, Montreal). Models were evaluated with several software tools such as PROCHECK[6], PROSA[7] and ERRAT[8] to build up an optimal ensemble for subsequent docking experiments.

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Probing Flexibility in the Activation Loop of Kinases

Higgs C., *Sherman W.*
Schrödinger, 120 West 45th Street, 29th Floor, New York, NY 10036; US

Since endogenous levels of ATP are high, truly successful kinase inhibitors prevent kinase activation rather than competing for the ATP-binding site. There are over 500 kinases in the human genome; they all have two main lobes with the ATP-binding pocket in-between and a DFG (Asp—Phe—Gly) activation loop. Inhibitors which interact with the DFG motif successfully shift the activation loop conformation toward the ATP-binding site ('DFG-out'), thus mimicking substrate binding and preventing kinase activity.

In this study we show that Prime loop predictions, starting with the DFG-in state of Abelson (Abl), Aurora A, and p38 mitogen-activated protein (MAP) kinases can successfully generate a DFG-out state that is a viable target for structure-based drug design. Further-more, we probe the activation loop of a number of kinases for which the DFG-out state has not yet been observed in an effort to predict the existence of a DFG-out state that can be used for future structure-based drug design efforts.

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Glide XP fragment docking and structure-based pharmacophores

Sherman W.[a], Friesner R.[b]
[a]Schrödinger, 120 West 45th Street, 29th Floor, New York, NY 10036; US
[b]Department of Chemistry, Columbia University, 3000 Broadway, Mail Code 3110, New York, NY 1002; US

In recent years, fragment-based drug design has become increasingly popular. Common computational approaches include building fragments up sequentially, or linking disparate fragments. However, the former approach can restrict the exploration of chemical space and may produce ligands that are not sufficiently drug-like, whereas the latter approach may result in difficulties when linking together the individual fragments.

Here, we describe a third approach that avoids these problems with the use of fragment-derived pharmacophore hypotheses. In our computational workflow a pharmacophore hypothesis is created using fragments docked and ranked by Glide XP, and virtual databases are screened against this hypothesis using Phase [1]. In an initial validation study on P38 Map Kinase, known active compounds were successfully retrieved and good enrichment factors were obtained.

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Theoretical approach to the thiourea-guanidine catalyzed nitro-Michael reaction

Sebastian Schenker[‡], *Tatyana Shubina*[†], *Matthias Freund*[‡], *Svetlana Tsogoeva*[‡], *Timothy Clark*[†]
[‡]*Institut für Organische Chemie, FAU Erlangen-Nuernberg, Henkestrasse 42, D-91052 Erlangen,Germany*
[†]*Computer-Chemie-Centrum, FAU Erlangen-Nuernberg, Naegelsbachstrasse 25 ,D-91052 Erlangen,Germany*

The highly active nitro-Michael addition between nitrostyrene and diethyl malonate is investigated at DFT level.
Based on the results of the calculations, poor enantioselectivity of some of the thiourea-guanidine bifunctional catalysts in comparison to similar thiourea amine catalysts is explained. Our results show that the C-C-bond formation reaction is controlled thermodynamically and high activity of the catalysts results in reduction of the theoretically possible enantiomeric excess.
An improved thiourea catalyst based on cyclic guanidine is proposed.

P37

Molecular-Dynamics Simulations of an Ionic Liquid between Gold Electrons

R. Wölfel, *H. Lanig, T. Clark*
Computer-Chemie-Centrum, FAU Erlangen-Nuernberg, Naegelsbachstrasse 25 ,D-91052 Erlangen,Germany

Ionic liquids are used for a number of industrial applications that vary greatly in character. Besides their established applications as solvents, they show great potential as components of novel electronic devices. Distance-dependent conductance measurements of the ionic liquid 1-ethyl-3-methylimidazolium-bis[(trifluoromethyl)sulfonylamid] between atomic-sized gold electrode pairs were carried out by means of the mechanically controllable break-junction (MCBJ) technique. The experiments showed higher conductance values than for a vacuum for short distances and a sudden change of the conductance value at a certain distance, which could not be explained by experiment. However, molecular-dynamics simulations showed that a vacuum exists between the peak atoms for short tip distances because of the strong electric field. The ionic liquid covering the electrodes, leads to a reduction of the work function in the cathode due to the steep potential gradient, resulting in a higher tunneling current compared to vacuum. The simulations strongly indicate that the sudden change is caused by the disappearance of the vacuum space between the tips for longer distances.

Towards pteridine reductase inhibitors with anti-parasitic action

Erika Nerini, *Domantas Motiejunas, Federica Morandi, Stefan Henrich, Stefania Ferrari, Maria Paola Costi, Rebecca Wade*
EML Research gGmbH, Heidelberg; Dipartimento di Scienze Farmaceutiche, Università di Modena e Reggio Emilia

Protozoan parasites are the causal agents of serious human deseases, including African sleeping sickness, Chagas' desease and Leishmaniasis. The currently available drugs are toxic, expensive and often ineffective, since the parasites have been observed to become resistant upon treatment. The pathway involved in the provision and the use of reduced folate cofactors provides attractive targets for the development of suitable treatments for the trypanosomatid infections. In particular, pteridine reductase (PTR1) is an enzyme essential for the salvage of pterines and folates in tripanosomatids. It is absent in humans and it is the main reason for the failure of classical antifolate drugs, since it provides parasites with the necessary amounts of folates when DHFR-TS is inhibited[1,2]. For these reasons, we focused on the inhibition of PTR1 as a promising treatment of tripanosomatids. In the present study, we performed computational docking and design studies to suggest how to improve the binding affinity of the compounds originally identified as inhibitors of L.major and T.cruzi by virtual screening followed the use of focused compound libraries. We validated a docking procedure to be applied to all compounds for which experimental data were available. Then, based on the docking modes obtained, we suggested extensions of the chemical scaffold of the compounds as well as possible substituents to improve binding.

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Protein-protein docking guided by biochemical data

Domantas Motiejunas[1], *Ting Wang[2], Anna Feldman-Salit[1], Tim Johann[1], Razif Gabdoulline[1], Rebecca Wade[1]*
[1]EML Research gGmbH, Schloss-Wolfsbrunnenweg 33, D-69118 Heidelberg, Germany
[2]UC Davis, Bioinformatics, USA
Email: domantas.motiejunas@eml-r.villa-bosch.de
Phone: +49 6221 533 266

Protein-protein interactions are crucial to numerous cellular processes such as signal transduction, regulation of biochemical pathways, immune response, and enzymatic reactions. Therefore, effective computational methods to model macromolecular complex formation are essential for understanding biochemical systems.

We describe a protocol for computational modeling of protein-protein association and prediction of the structures of complexes. We aim to create a modular procedure with well defined steps which allow this protocol to be used as a protein docking pipeline and as a tool for detailed investigation of association processes of particular macromolecular complexes. Overall, the method can be divided into Rigid Body docking and Flexible Refinement stages.

In Rigid Body docking, we employ Brownian Dynamics based sampling as implemented in a SDA program. An efficient and simple force field is used comprising of electrostatic and shape exclusion terms. Ways to implicitly account for protein flexibility are included at this stage. In addition, we incorporate available biochemical data relevant to complex formation as docking constraints. We cluster the docked solutions based on their structural similarity and score them using cluster population, electrostatic energy and residue propensities. The representatives of these clusters are subjected to flexible refinement stage. For flexible refinement we use Molecular Dynamics with the NPSA implicit solvent model and enhanced sampling techniques.

We tested the protein-protein docking protocol on a number of structurally and functionally different proteins including enzyme-inhibitor, electron-transfer, signal transduction, antibody-antigen and domain peptide complexes. In many cases, already after Rigid-Body docking, we identify structures of complexes with rmsd < 7Å and the number of native contacts > 20%. The results of subsequent Flexible Refinement with MD largely depend on the quality of the protein-protein complex produced by Rigid Body docking. The number of native contacts during the Flexible Refinement increases by several to 60%.

Molecular Wire Behavior of Organic π-conjugated Systems in DONOR-WIRE-C_{60} Conjugates

M. Wielopolski[a], *T. Clark*[a], *D. M. Guldi*[b]
[a]*Computer Chemistry Center University of Erlangen, 91052 Erlangen, Germany*
[b]*Department of Chemistry and Pharmacy, Interdisciplinary Center for Molecular Materials (ICMM), Friedrich-Alexander-Universität Erlangen-Nürnberg, Egerlandstr. 3, 91058 Erlangen, Germany*

Implementing new paradigms for the design of novel hybrid materials requires effective structural integrity of the building blocks, the investigation of charge-transfer properties of tailored nanoscale molecules affords novel molecular materials with systematic variation of functionality (e.g. redox, electron-transfer or photo-switching behavior). To address charge transport through single molecules, we have replaced conventional electrode leads with donors and acceptors. In the resulting **donor** | **wire** | $\mathbf{C_{60}}$ assemblies, the transport of electrons was triggered either photochemically (i.e., charge separation) or thermally (i.e., charge recombination) and examined by various spectroscopic characterization techniques, which were further supplemented by quantum chemical calculations. With respect to the connecting wires, π-conjugated oligomers emerged as the most promising prototypes.[1] Detailed measurements – including femtosecond and nanosecond transient absorption spectroscopy – provided insight into the nature of charge transfer processes between different donors and $\mathbf{C_{60}}$ mediated by π-conjugated bridges, i.e. ***o*PPV**, ***o*PPE** or ***o*FL**, and ascertained the formation of **DONOR** $^{\bullet+}$ **/** $\mathbf{C_{60}}^{\bullet-}$ radical ion pair states. Charge-separation and charge-recombination dynamics were determined in all systems and analyzed as a function of distance and temperature. Particularly small attenuation factors (β), which range from 0.01 $Å^{-1}$ for ***o*PPVs**, to 0.21 $Å^{-1}$ for ***o*PPEs** and 0.09 $Å^{-1}$ for ***o*FLs** guarantee charge transfer processes over distances up to 40 Å. Novel methods for modeling of these charge-transfer features were developed in order to understand the spectroscopic results. Besides π-conjugation, which is undoubtedly the *sine qua non* for efficient charge transfer processes, the relative energies of donor, wire and acceptor play a decisive role in governing these unprecedentedly small attenuation factors.[2][3][4]

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