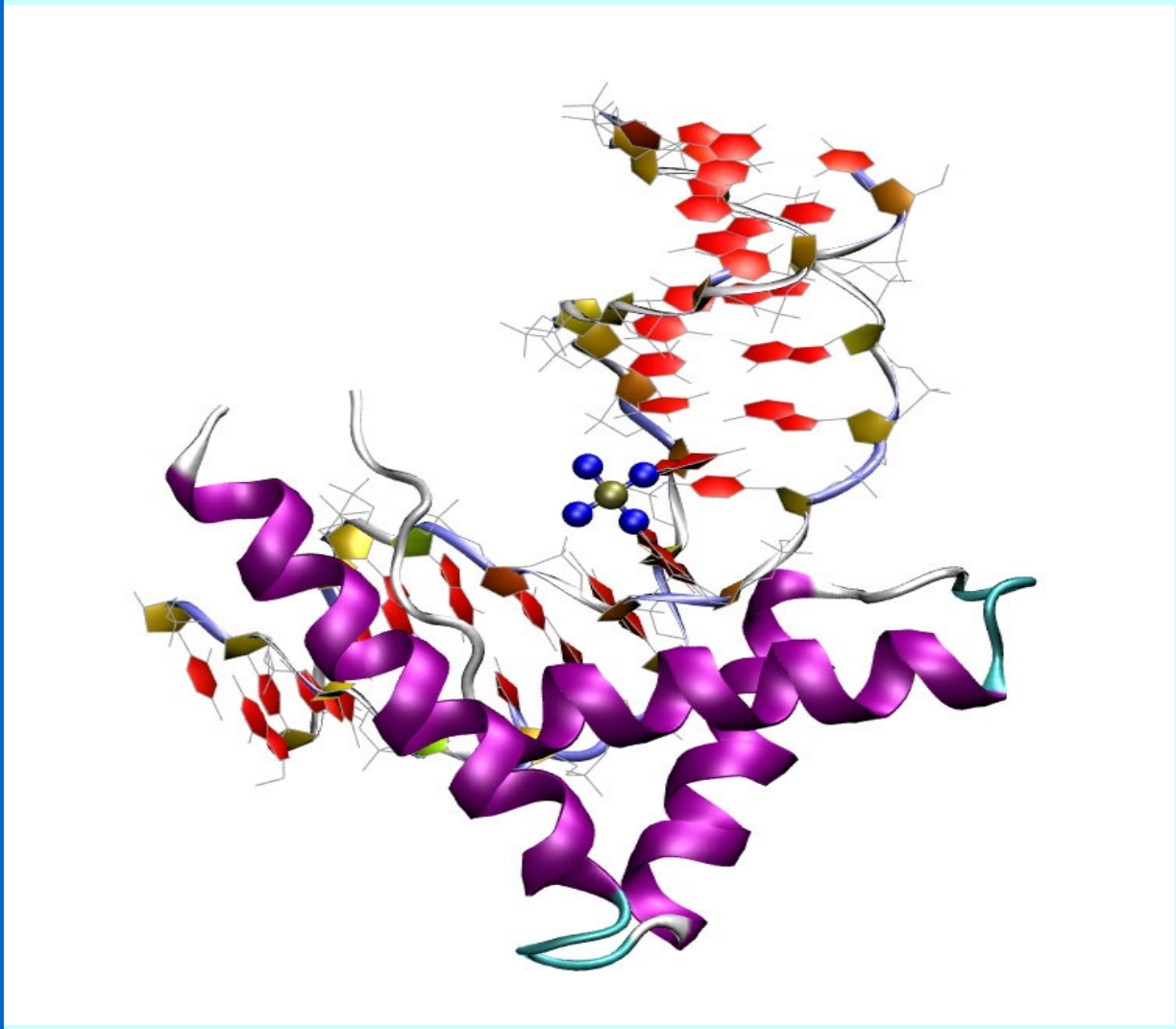
Modeling Interactions in Biomolecules IV

Hrubá Skála, September 14th-19th, 2009



Program & Book of Abstracts

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Acknowledgement

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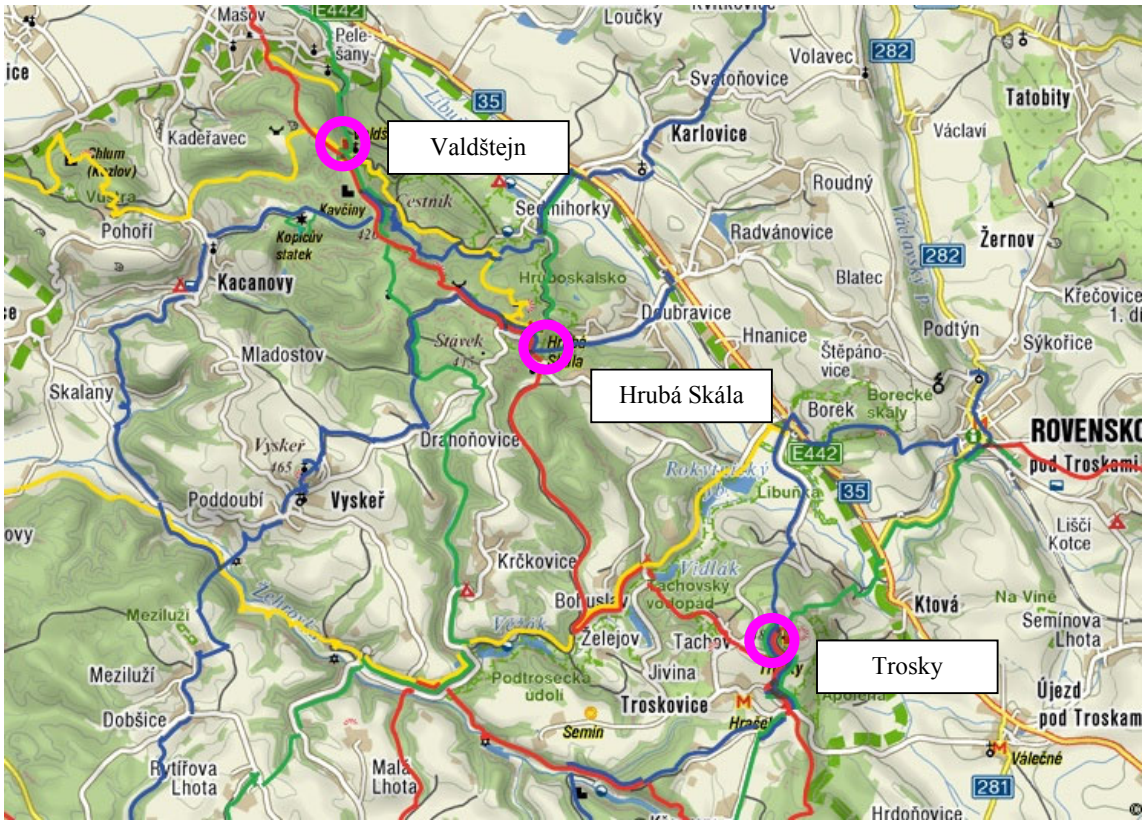
Hrubá Skála and Rock town

Chateau Hrubá Skála is built on the sandstone rocks at the place of the original gothic castle from the 14th century, reconstructed into a renaissance chateau, then in the middle of the 19th century again re-gothicised. Nowadays a private hotel.
Hrubá Skála is the starting point for visits to the area of the *Hrubá Skála rock town*. This area was proclaimed Natural Preserve at the occasion of The Earth Day in 1998. One of the most popular tracks is The Golden Trail of the Bohemian Paradise which is full of fine view points. The most popular one is Mariánská vyhlídka, showing the panorama of the Hrubá Skála Chateau and the Trosky Castle.



Walking trip to **Trosky or Valdštejn** is planned on **Thursday afternoon**. *Valdštejn* (cca 2,5 km from Chateau Hrubá Skála), considered to be the oldest castle in the Bohemian Paradise, was established approximately around 1260 by Jaroslav of Hruštice from the Markvartic family who were the ancestors of the lords of Valdštejn. The Valdštejn family owned the castle until about 1380 and the following owners, the lords of Vartenberk, until the break-out of the Hussite wars.
Trosky Castle was founded by the knight Cenek of Vartenberg at the end of the 14th century as a beautiful and impregnable residence. After Cenek's death the castle became the property of the king Wenceslas IV. The castle several times changed the owner and by the end of the Thirty-year War burnt up. The observation platform offers a grand view not only of the Czech Paradise area, but also of more distant mountain ranges, even of Prague landmarks.

Travel Information

Below are printed departures some buses and trains from Turnov to Prague. All these buses and trains departure from Turnov train station, buses arrive to Prague Černý most (terminal station of Metro B line) and trains to Prague Main station (center of the city, direct bus line to the airport). Chatea Hrubá Skála is located about 7 km far from Turnov and you can get there by train from village Sedmihorky or Hrubá Skála. Please ask organizators for more information or check the time tables on web page http://www.idos.cz

Bus/Train	Departure	Arrival
Bus	7:00	8:20
Bus	8:25	9:55
Bus	9:20	10:45
Bus	10:05	11:20
Train	10:44	12:38
Train	12:44	14:38
Bus	13:55	15:15
Bus	14:35	15:55
Train	14:44	16:38
Bus	15:15	16:35
Train	16:44	18:38
Bus	17:35	18:55

Scientific Program

Monday		
10:00 – 16:00	**registration**	
15:00 – 15:20	**opening**	
chairlady	J. S. Murray	
15:20 – 15:50	L. Skála	Heisenberg Uncertainty Relations Can Be Replaced by Stronger Ones
15:50 – 16:40	M. Olivucci	Towards a Computational Photobiology
	coffee break	
17:00 – 17:50	W. A. Lester	Selected Directions in Quantum Monte Carlo
17:50 – 18:40	J. Vaníček	Using Feynman Path Integrals to Describe Nuclear Quantum Effects
18:50	L. Benda	*Piano Concert – C. Franck, M. Bruch, P. Hindemith*
20:00	**reception**	

Tuesday		
chairman	M. Šíp	
9:00 – 9:45	W. A. Sokalski	Modeling Interactions in Catalytic Sites
9:45 – 10:30	R. Ettrich	Molecular Mechanism of Allostery in Hexameric E. Coli Arginine Repressor
	coffee break	
10:50 – 11:35	T. Clark	The Interplay Between DNA and Regulatory Proteins
11:35 – 12:20	F. J. Luque	Ligand-Receptor Interaction: From First-Principles to Application in Drug Discovery
	lunch	
chairman	J. Urban	
14:20 – 14:50	S. Fairchild	Computational Characterisation of Human Serum Paraoxonase's Binding Mechanisms for the VX Nerve Agent
14:50 – 15:20	E. Hajjar	Probing the Molecular Mechanism of Antibiotics Diffusion Through Bacterial Porins
15:20 – 15:50	B. Minofar	Molecular Dynamics Study of the Effect of Organic Solvent on Structure and Activity of Haloalkane Dehalogenase
	coffee break	
16:20 – 16:45	P. Kulhánek	Computational Study of MutH Recognition and Catalysis
16:45 – 17:10	C. Baldauf	Shear-Induced Unfolding Activates von Willebrand Factor A-type Domains
17:10 – 17:30	R. Meier	ParaDocks – A Framework for Molecular Docking with Population-Based Metaheuristics
17:30 – 17:50	L. Olivieri	Study of Protein-Ligand Interaction Mechanism: Example of FKBP12 with a Nanomolar Affiinity
	dinner	
20:00	**poster session**	*P01-P34*

Wednesday		
chairman	M. Olivucci	
9:00 – 9:45	P. Bouř	Molecular Dynamics and Environment in Simulations of Molecular Spectra
9:45 – 10:30	M. Hall	Modelling Metalloenzymes: Hydrogenases
	coffee break	
10:50 – 11:35	E. Broclawik	Activity of Iron Sites in Enzymes: Spin States and Electron Density Deformation
11:35 – 12:20	C. Lim	Physico-chemical Priciples Governing Biological Processes
	lunch	
chairman	P. Mach	
14:20 – 14:50	J. S. Murray	Non-Hydrogen Bonding Intramolecular Interactions: Important Yet Often Unrecognized
14:50 – 15:20	T. Andruniów	TD-DFT Calculation on Photodissociation of Co-C Bond in Cobalamin
15:20 – 15:50	S. Kamerlin	Accelerated QM/MM Free Energy Calculations: Theory and Applications
	coffee break	
16:20 – 16:45	D. Řeha	Implementation of Molecular Mechanics Polarization in QM/MM Calculation
16:45 – 17:10	Z. Flisak	Phenoxyimine Complexes as Precursors of Coordinative Olefin Polymerization Catalysts: A DFT Study
17:10 – 17:30	D. Rinaldo	QM/MM methods: From Understanding Metalloprotein's Reactivity Toward Improving the Drug Design Process.
17:30 – 17:50	F. Chen	Spectral Responses of 3'-Substitutions in Dideoxythymidine Nucleosides.
	dinner	
19:30 – 21:00	D. Rinaldo	*A short workshop/demo for an interested Jaguar/QSite audience.*

Thursday		
chairman	S. Roszczak	
9:00 – 9:45	S. Zaric	Classification of Amino Acids Based on Their Propensities Towards a Particular Secondary Structure
9:45 – 10:30	R. Lindh	The Emission Modulation of the Chemiluminiscence in the Luciferin-Luciferase System
	coffee break	
10:50 – 11:35	T. Mančal	Role of Coherence in Relaxation of Excitation Energy in Molecular Complexes
11:35 – 12:20	D. Sundholm	Coupled-Cluster and Density Functional Theory Studies of Excited-State Potential Energy Surfaces of Polyenes and Protonated Schiff Bases
	lunch	
14:00	**trip**	*"Rocky Town"*

Friday		
chairman	M. Straka	
9:00 – 9:45	P. Politzer	The Average Local Ionization Energy: A Fundamental and Multi-Faceted Property
9:45 – 10:30	A. Toro-Labbé	Elucidating the Mechanism of Complex Chemical Reactions through the Use of the Reaction Electronic Flux
	coffee break	
10:50 – 11:35	T. A. Wesolowski	Orbital-Free Effective Embedding Potential: The Basis for a Family of Computational Methods for Modeling Electronic Structure in Condensed Phase
11:35 – 12:20	A. Michalak	ETS-NOCV – A Combined Charge and Energy Decomposition Scheme for Bond Analysis
	lunch	
chairlady	S. Zaric	
14:20 – 14:50	S. Záliš	Electron Transfer Reactions in Proteins Labeled with ReI(CO)3(a-diimine)(imidazole)
14:50 – 15:20	T. Dudev	Determinants of K+ vs Na+ Selectivity in Potassium and Sodium Ion Channels from DFT/CDM Calculations
15:20 – 15:50	A. Robertazzi	Copper-1,10-Phenanthroline Complexes Binding to DNA: Structural Predictions from Molecular Simulations
	coffee break	
16:20 – 16:45	M. F. Lucas	Haemoglobin: Can We Understand a Bit More?
16:45 – 17:10	M. Johansson	A Vibrational Electron-Shovel Mechanism for Charge Transfer Between Haems a and a3
17:10 – 17:30	L. Johannissen	H-Tunnelling in Enzymes: The Role of Promoting Vibrations and Barrier Compression
17:30 – 17:50	J. Pang	Computational Study of Enzyme Catalysed H-tunnelling Reactions
17:50 – 18:10	A. M. Ferrari	DFT Periodic Study of the Conformational Behaviour of Glycine Helical Homopolypeptide
	dinner	
20:00	**poster session**	*P01-P34*

Saturday		
chairman	W. A. Sokalski	
9:00 – 9:45	N. Gresh	Polarizable Water Molecules in Ligand-Macromolecule Recognition
9:45 – 10:30	J. Leszczynski	Challenges in Modeling Properties of Nanomaterials
	coffee break	
10:50 – 11:35	P. Cysewski	Many-body Contributions to Base-Base Interactions in B-DNA d(XpY) Dinucleotide Steps
11:35 – 12:10	V. Sychrovský	Probing the Molecular Flexibility with NMR Spectroscopy
12:10 – 12:20	**closing remarks**	
	lunch	

Poster Presentations

Poster session takes place in the "Medieval Pub" near the Lecture Hall on Tuesday and Friday evening.

Poster/Abstr. No.		Name	Poster Title
P01	3	L. Benda	Theoretical Modeling of the Metal Ion Effects on NMR Parameters in Nucleic Acid Backbone
P02	4	T. Borowski	Glycosylasparaginase – Insight into Reaction Mechanims of Modelling Studies
P03	7	E. Broniatowska	Electron and Geometric Effects in a Ligand Molecule in Different Protein Environment
P04	8	M. Chawla	Structural Analysis and Ab Initio Quantum Chemical Studies of Protonated Base Pairs in RNA
P05	10	E. Chudyk	Catalytic Activity of Fatic Acid Amine Hydrolase: Non-empirical Analysis of Differential Transition State Stabilization
P06	13	P. Czelen	The Post-SCF Quantum Chemistry Study on the Structural and Energetic Heterogeneities of Canonical and Oxidized Basepairs Found in Telomeric Complexes
P07	15	E. Dyguda-Kazimierowicz	Molecular Basis of Phenylalanine Ammonia-lyase Inhibition: Ab Initio Prediction of the Binding Affinity
P08	16	A. Dzielendziak	Analysis of Atypical Protonation States in Enzyme Active Sites via Theory of Intermolecular Interactions
P09	21	Z. Futera, J. V. Burda	Interaction of "Piano-Stool" Ruthenium Complexes with DNA; QM/MM Study
P10	25	J. Hladyszowski, P. Ordon	Analytic Evaluation of Hellmann – Feynman Forces
P11	26	P. Jayapal	Modeling the DNA-Protein Interactions: MD Simulation Studies
P12	27	Z. N. Jiroušková	Solvation Energy Calculations Based on Electronegativity Equalization Method's (EEM) Charges, Internal Coordinate Mechanics's (ICM) Charges and Charges Based on Partition Coefficients
P13	30	P. Kadlubanski, S. Roszak	Designing New Materials for the Hydrogen Storage
P14	32	P. Kedzierski	Model of Transition State Stabilization by Aminoacid-tRNA Synthethases

P15	33	W. Kolodziejczyk	Probing the Role of P=O Stretching Mode Enhancement in Nerve-Agent Sensors: Simulation of the Adsorption of Nerveagents on the Model MgO and CaO Surfaces
P16	34	K. Kopec-Harding	Atomistic Insight from Computational Simulation into How Enzymes Catalyse Tunnelling Reactions
P17	40	P. Lipkowski	Structural Variability and the Nature of Intermolecular Interactions in Watson-Crick Guanine-Cytosine Base Pairs
P18	43	P. Mach, J. Urban	Interaction of DNA Model Compounds With Low Energy Electrons
P19	44	T. McGrory	Probing Enzyme Catalysis Using High Pressure Molecular Dynamics
P20	47	M. Melichercik	Allosteric Mechanism for Hexameric E. Coli Arginine Repressor Based on Competition Between Resident Arginine Residues and L-Arginine Ligands
P21	51	A. Nowakovska	The Structural, Ionization and Optical Properties of Oligomers Building Fragments of Conducting Polymers
P22	55	Z. Pokladek	Modelling of Intermolecular Interactions of Amino Acids with Phosphonic or Carboxylic Unic
P23	61	M. Skorsepa	In Silico Study of Interactions Between VEGFR2 and Inhibitors Based on Triazole Linkers
P24	62	D. Slepienczuk	DFT Calculations of Structural Properties of B12-retro-riboswitches
P25	64	S. Standara	Understanding the NMR Chemical Shift for 6-halopurines: Role of Structure, Solvent and Relativistic Effects
P26	65	M. Straka	Computational Studies of NMR Parameters in Endohedral Fullerenes. The role of Intra-Molecular Dynamics
P27	68	B. Szefczyk	Molecular Dynamics Simulations of Mouse Ferrochelatase Variants
P28	69	B. Szefler	Environment Imposed Alternations of Aromatic Character of Canonical Nucleobases and Aromatic Amino Acids
P29	70	S. Taubert	Assessing Aromaticity Using the Gauge Including Magnetically Induced Currents (GIMIC)-Method

P30	73	Z. Vokáčová	Structural Interpretation of J-Coupling Constants Calculated in Guanosine and Deoxy-Guanosine
P31	74	E. Walczak	Structural Parameters of Zoanthus Yellow Fluorescent Protein Chromophore in Terms of Molecular Dynamics Methodology
P32	76	L. Wolanski	MCQDPT2//CASSCF Calculations for zFP538 Protein Chromophore – Structure and Spectral Properties in vacuo
P33	79	A. Zawada	Evaluation of DFT Methods for the Calculations of the Interaction-Induced Electric Properties of Molecular Complexes
P34	80	T. Zimmermann	Path Integral Evaluation of Equilibrium Isotope Effects

Jaguar/QSite Workshop

Workshop for an interested Jaguar/QSite audience will be given by Dr. D. Rinaldo on Wednesday evening in Lecture Hall.

Content of the workshop:

- How to use Jaguar efficiently, for which tasks, and limitations.
- How to use Jaguar in Parallel: Setup, optimal number of processors.
- Pure QM tasks with Jaguar: Building molecules with Maestro, Methods/basis sets available, optimization, single point calculations, transition state search, frequency calculations, pKa calculations).
- Biomolecules and QM/MM: Protein Preparation, Choosing optimally the QM and MM regions, choosing how to treat the QM/MM interface, running calculations.
- Analysis of the results using Maestro.
- How to run calculations: Using Maestro/Job control, running batch jobs, creating batch scripts to run calculations using different settings.
- Tips and tricks to solve issues regarding SCF convergence, Geometry optimization, how to treat metals, using your known basis sets etc…

Book of Abstracts

(all contributions are presented in alphabetical order)

TD-DFT CALCULATIONS ON PHOTODISSOCIATION OF CO-C BOND IN COBALAMINS

T.Andruniów

Molecular Modelling and Quantum Chemistry Group, Institute of Physical and Theoretical Chemistry, Wroclaw University of Technology, Wyb. Wyspianskiego 27, 50-370 Wroclaw, Poland

It has been demonstrated that under nonenzymatic conditions, the cleavage of Co-C bond in cobalamins can be induced either thermally or photochemically. While the thermally induced scission probes only the lowest electronic state, photocleavage involves manifold of low-lying excited states.

In the present work, the mechanism of photolysis has been explored by means of timedependent denisty functional theory (TD-DFT). Precisely, the detailed picture of low-lying excited states as well as their changes along the elongated Co-C coordinate was investigated to shed some light on relevant excited states involved in the photolytic cleavage of the Co-C bond.

SHEAR-INDUCED UNFOLDING ACTIVATES VON WILLEBRAND FACTOR A-TYPE DOMAINS

Carsten Baldauf[1], Reinhard Schneppenheim[2], Tobias Obser[2], Antje Pieconka[3], Sonja Schneppenheim[3], Ulrich Budde[3], Wolfram Stacklies[1], Jing Zhou[1], and Frauke Gräter[1]

[1]CAS-MPG Partner Institute for Computational Biology, SIBS, CAS, Shanghai, P.R. China and EML Research, Heidelberg, Germany, [2]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Germany, and 3Coagulation Lab, AescuLabor Hamburg, Hamburg, Germany.

The von Willebrand factor (VWF) is a shear-flow sensitive multimeric protein of the blood plasma. Under normal flow conditions VWF is in a globular state, it unfolds at high shear rates and is activated for adhesion at the blood vessel wall [1]. This elongation of multimeric VWF results in a force pulling along the VWF length axis. Based on a model of the VWF A domain organization, we performed force probe molecular dynamics simulations. We reveal the basis of two force-sensing VWF functions, and test the results by experiments:
Our results indicate a competition between VWF A2 domain and glycoprotein Ib (GPIb) for the same binding site of the VWF A1 domain. When the stretching force along VWF reaches a critical point, the A1 A2 interaction is lost. The domains remain connected by a linker that gives space for GPIb to bind to the A1 domain. We thus suggest a force-dependent platelet binding to VWF as mediated by GPIb, which is experimentally testable and represents an alternative mechanism to recently published studies [2].
We show how proteolysis of the VWF is activated under shear conditions. The specific proteolytic site is buried in the VWF A2 domain [3]. At extreme forces as present in high molecular weight VWF multimers, the A2 domain C terminus unfolds until the ADAMTS13 cleavage site is uncovered. Introducing a disulfide bond by mutagensis prevents VWF cleavage [4]. This explains the size regulation of VWF by ADAMTS13: larger multimers involve higher pulling forces and therefore higher unfolding rates under shear flow. Larger VWF is cleaved faster, preventing blood clots and thrombosis.

Acknowledgements: CB is grateful for a Feodor Lynen Fellowship by the Alexander von Humboldt foundation.

[1] Schneider, S. W.; Nuschele, S.; Wixforth, A.; Gorzelanny, C.; Alexander-Katz, A.; Netz, R. R.; Schneider, M. F. Proc. Natl. Acad. Sci. U. S. A. 2007, 19 (104), 7899–7903.
[2] Lou, J. Z.; Zhu, C. Proc. Natl. Acad. Sci. U. S. A. 2008, 37 (105), 13847–13852; Chen, Z. Z.; Lou, J. H.; Zhu, C.; Schulten, K. Biophys. J. 2008, 3 (95), 1303–1313.
[3] Zhang, X. H.; Halvorsen, K.; Zhang, C. Z.; Wong, W. P.; Springer, T. A. Science 2009, 5932 (324), 1330–1334; Zhang, Q.; Zhou, Y. F.; Zhang, C. Z.; Zhang, X.; Lu, C.; Springer, T. A. Proc. Natl. Acad. Sci. U. S. A. 2009, 23 (106), 9226–9231; Sutherland, J. J.; O'Brien, L. A.; Lillicrap, D.; Weaver, D. F. J. Mol. Model. 2004, 4 (10), 259–270.
[4] Baldauf, C.; Schneppenheim, R.; Stacklies, W.; Obser, T.; Pieconka, A.; Schneppenheim, S.; Budde, U.; Gräter, F. arXiv:0904.3951v1 [physics.bio-ph], 2009.

THEORETICAL MODELING OF THE METAL ION EFFECTS ON NMR PARAMETERS IN NUCLEIC ACID BACKBONE

Ladislav Benda[1,2], Bohdan Schneider[3], Vladimír Sychrovský[1]

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[2]*Faculty of Mathematics and Physics, Charles University Prague, Ke Karlovu 3, 12116 Praha 2, Czech Republic,*
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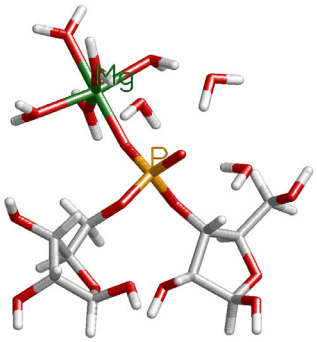
The negatively charged phosphate group of nucleic acid backbone interconnecting two (2-deoxy)ribose units represents one of the most important solvation sites in nucleic acids. An impressive amount of work has been done on characterizing the structure of the solvation shell of canonical DNA as well as of other backbone patterns found in RNA. Surprisingly localized water occurrences due to the direct contact (H-bond) with phosphate group have been observed in the structures obtained from X-ray diffraction. The presence of physiological monovalent and divalent cations in the phosphate first solvation shell was also confirmed [1].

The X-ray identification of biologically essential Na+ and Mg2+ metal ions is not a straightforward task since these ions and the water molecule possess the same number of electrons. In many cases, the methods of molecular spectroscopy can be used for the metal ion recognition [2-4]. We investigated the possibility of characterizing the specific interactions of metal cations with phosphate group by NMR spectroscopy. On the basis of ab-initio calculations of chemical shielding tensors and indirect spin-spin coupling constants we propose several options for monitoring the nucleic acid metalation. The molecule on Figure 1 is an example of molecular model used for calculation of NMR parameters.



Acknowledgements: Support from grant No. IAA400550701 is acknowledged.

[1] Schneider, B.; Kabeláč, M. J. Am. Chem. Soc. 1998, 120, 161.
[2] Tanaka,Y.; Taira, K. Chem. Commun. 2005, 2069.
[3] Halle, B.; Denisov V. P. Proc. Natl. Acad. Sci. USA 2000, 97, 629.
[4] Morrissey, S.R.; Horton, T. E.; De Rose, V. J. J. Am. Chem. Soc. 2000, 122, 3473.

GLYCOSYLASPARAGINASE - INSIGHTS INTO REACTION MECHANISM FROM MODELLING STUDIES

Tomasz Borowski[1], Marcin Krol[2]

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[2]*Department of Bioinformatics and Telemedicine, Medical College, Jagiellonian University, ul Sw. Lazarza 16, 31-530, Krakow*

Glycosylasparaginase (GA) is an amidase involved in degradation of Asn-linked glycoproteins. It belongs to an enzyme superfamily called N-terminal nucleophile hydrolases, since to catalyze its reaction it uses a processed N-terminal group (threonine) as both polarizing base and a nucleophile. GA can effectively hydrolyze a variety of glycoasparagines that contain L-asparagine, including its natural substrate N^4-(β-N-acetylglucosoaminyl-L-asparagine (NAcGlc-Asn) (see Figure).

What makes GA an interesting subject of modelling studies is the fact that several key questions about the mechanism of GA hydrolysis still remain to be answered. Moreover there is a possibility that GA, in its native or engineered form, could be a useful anticancer drug (a substitute for bacterial asparaginase)[1].

Several crystal structures are currently available, including a structure of a Michaelis complex for a slowly reacting mutant of GA [2]. Side directed mutagenesis studies have provided important insights into the reaction mechanism [3]. For example, substitution of the catalytic threonine by serine or cysteine dramatically reduces hydrolase activity (k_{cat} is reduced by one to five orders of magnitude), suggesting that precise positioning of the hydroxyl group in the Michaelis complex is critical for GA catalysis. Besides the N-terminal Thr, the active site also hosts another threonine group (Thr170), which is properly placed to mediate interaction between the amino and hydroxyl groups of the catalytically active N-terminal residue. Substitution of Thr170 by Ala reduces k_{cat} by four orders of magnitude.

The aim of this project it to provide a detailed description of the GA reaction mechanism as well as explanation of the kinetic data available for WT and mutated forms of GA. To this purpose, classical molecular dynamics simulations are performed in order to equilibrate the structures and also to calculate potential of mean force (PMF) profiles for conformational changes of the nucleophilic residues. MD trajectories are clustered and the centre of the largest cluster is selected for investigations of reaction mechanism. Active site models comprising 160-180 atoms are used to investigate the reaction paths with B3LYP method. We kindly invite you to the poster for further information concerning GA and this work.

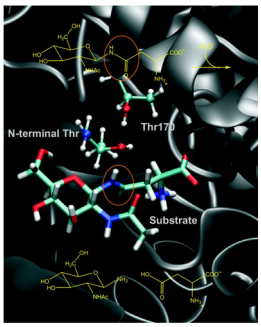

Fig. 1: GA active site and the hydrolysis reaction

[1] Kelo, E.; Noronkoski, T.; Mononen, I. Leukemia 2009, 1–4.
[2] Wang, Y.; Guo, H.-C.J. Mol. Biol. 2007, 366, 82–92.
[3] Liu, Y.; Guan, C.; Aronson, N. Jr. J. Biol. Chem. 1998, 273, 9688–9694.

MOLECULAR DYNAMICS AND ENVIRONMENT IN SIMULATIONS OF MOLECULAR SPECTRA

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Many spectroscopical techniques, such as nuclear magnetic resonance (NMR), vibrational absorption (IR), Raman scattering or ultraviolet absorption, can be significantly enhanced by independent simulations of some of the measured parameters. Typically, quantum chemical methods are used for prediction of molecular spectroscopic properties. These methods can be quite precise and latest computational tools, such as the density functional theory (DFT) or multi-level procedures can handle relatively large systems. This allows us to treat molecules not only in vacuum and equilibrium geometry, but also with inclusion of finer effects caused by molecular motion and molecular environment. Obviously, many approximations still have to be made, depending on the size and nature of studied systems, as well as on particular parameter that needs to be computed.

For example, if we wanted to simulate spectroscopic properties of solvated amide groups in peptide, we could use a relatively simple atomic partial charge model for the vibrational properties [1], while this approximation appeared quite inadequate for the electronic spectra [2]. For NMR, the solvent influences very much the chemical shift, while it has a limited effect on indirect spin-spin coupling constants [3, 4].

To explore some aspect of the molecular motion, we concentrated on anharmonic interactions and vibrational averaging of NMR spectral properties [4]. Such an averaging significantly improved some calculated results, depending on the precision of the equilibrium values. In explicit solvent models many solvent configurations must be averaged (Figure 1). The inclusion of the environmental and dynamic factors thus complicates the computations, but also brings a new information about the solute-solvent interactions and makes the simulations more realistic.

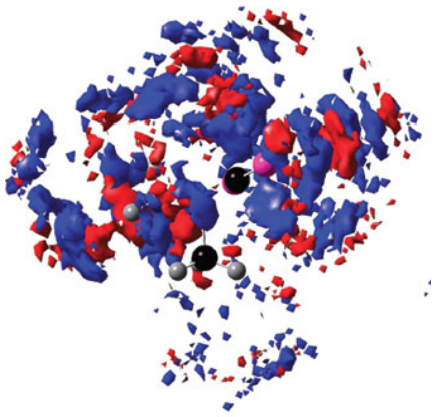

Figure 1: Probability of the water (red-oxygen, blue-hydrogen) distribution around alanine zwitterion as obtained by the Car-Parrinello molecular dynamics and used for the averaging of NMR parameters.

Acknowledgements: Support from GACR (202/07/0732), and GA AV (A400550702) is acknowledged.

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ACTIVITY OF IRON SITES IN ENZYMES: SPIN STATES AND ELECTRON DENSITY DEFORMATION

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Versatility of spin states of iron core embedded in various ligand environments poses a serious challenge to quantum chemical methodologies. At the same time this property seems to be intrinsic for intricate patterns of spin allowed/forbidden enzymatic pathways executed in biological systems. Therefore modeling of iron-catalyzed enzymatic reactions inevitably involves careful balancing the compromise between computational efficiency and high-level reliability of computational tools. In this presentation we will address few examples of DFT/CASPT2 calculations for iron sites interacting with demanding biological ligands like O, O_2 and NO.

Enzymatic iron sites activated by molecular oxygen to form Fe=O (iron-oxo) form are responsible for a variety of oxidation reactions. In the first part we wish to adress the following query: what is quantum methodological reliability in describing radical character in the ground state active form of CYP450 (Cpd I), located either on the porphyrine ring, or on a lone pair of the axial S from cysteine, which is crucial for predicting and understanding cytochrome reactivity. In the same spirit we will briefly mention the query of O_2, CO and NO binding to the hemes (benchmarking DFT versus CASPT2 calculations).

In the second part we will address the coordination of nitric oxide (NO) to iron(II), receiving both experimental and theoretical interest, partially for its biological importance, but also for the complicated electronic structure of the resulting $\{FeNO\}^7$ complexes. Here we will discuss fiveand six-coordinate heme–NO models (S = ½ experimental spin state), a spin-crossover (S = ½→3/2) Fe(salen)NO complex and two other non-heme complexes (with the S = 3/2 ground state). Theoretical calculations of these properties are very challenging, especially that the reliability of DFT is in question. There are important controversies about the electronic structure of the $\{FeNO\}^7$ complexes where the interaction with a noninnocent NO ligand puts spin populations and effective oxidation states on Fe and NO under debate.

		CAS SCF			BP86			B3LYP		
A	S=1/2	q^S_{Fe} 0.96	q^S_{NO}	0.03	q^S_{Fe} 0.95	q^S_{NO}	0.06	q^S_{Fe} 2.05	q^S_{NO}	-0.99
	S=3/2	3.42		-0.59	3.34		-0.69	3.83		-1.19
B	S=1/2	0.66		0.33	0.59		0.40	0.20		0.80
	S=3/2	3.41		-0.57	3.23		-0.51	3.87		-1.20

Mulliken spin populations for spin states of Fe(Por)NO (A) and $FePNH_3NO$ (B)

Acknowledgements: Support from Polish MNiSWgrant N N301 09 3036 is acknowledged.

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ELECTRON AND GEOMETRIC EFFECTS IN A LIGAND MOLECULE IN DIFFERENT PROTEIN ENVIRONMENTS

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Proteins manifest their biological function via interaction with small non-protein molecules called ligands. In many cases the electron structure of ligand molecules changes after binding to protein in reference to the electron structure of isolated ligand. However, there are also such ligands for which the electron structure of the molecule bound to protein resembles that of isolated molecule. The main purpose of this work is to study the changes which undergo in the electron structure after creating the complex with protein on the example of the (1R)-1-(2-thienylacetylamino)-1-(3-carboxyphenyl)methylboronic acid molecule (sm2).

Molecule sm2 is a boronic inhibitor of b-lactamase [1], the enzyme hydrolizing the b-lactam ring. The b-lactamases are important in antibacteria therapy because the presence of these enzymes casues the resistance to b-lactam antibiotics like i.e. penicylins.

The structures of all the complexes (protein with sm2) were extracted from the Protein Data Bank (PDB) [2]. The calculations were lead for four protein-ligand molecular systems available in the PDB: 1mxo, 1nxy, 1pi5, 1ym1. The electronic structure for isolated sm2 was taken from the ligand database [3] whereas for sm2 bound with protein directly from PDB. The geometry of sm2 molecules bound with proteins is different according to root means sqare deviation (RMSD) ranging from almost 0 value to 2.26. The Muliken and electrostatic potential fitting partial atomic charges were calculated for the isolated and complexed electronic structures of sm2. Comparing the data for isolated sm2 with protein bound sm2 allows the investigation of the electron charge flow. The biggest differences in electron charge are mainly observed for both rings and on the oxygen atom coming from the carboxyl group for these two methods. The maps of electron densities for isolated and complexed sm2 were compared as well.

The detailed analysis of electron and geometric changes would help reveal the mechanism of the interaction between boronic inhibitors and b-lactamases which is still unclear [4].

Acknowledgements: Calculations were performed at the Cracow Academic Computer Centre Cyfronet AGH.

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STRUCTURAL ANALYSIS AND AB-INITIO QUANTUM CHEMICAL STUDIES OF PROTONATED BASE PAIRS IN RNA

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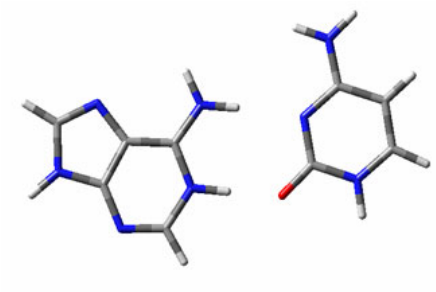
Protonated base pairs constitute an important class of RNA base pairing systems, several of which nucleate higher order structures and participate in tertiary interactions joining distant regions in RNA structures. These base pairs are involved in the formation of functionally important regions of RNA such as ribozyme cleavage sites, protein recognition sites, and rRNA motifs. Our earlier report [1] on Hartree Fock level quantum chemical studies on the geometries and interaction energies of a few protonated base pairs, in crystal contexts and gas phase optimized geometries, shows that these base pairs have high interaction energies and display stable geometries. Here we report results of higher level ab initio studies on an extended set of protonated base pairs. The structures of 18 systems, with one of the bases being protonated, were optimized at B3LYP/cc-pVTZ level and their interaction energies were calculated at MP2/aug-cc-pVDZ level. To mimic the solvent effect COSMO calculations have also been carried out on some the systems. The interaction patterns of protonated base pairs are highly diverse, with gas-phase optimized interaction energies in the range from -24 to -49 kcal/mol. The interaction energy values, for all base pairs studied, were found to be dominated by the HF term. This suggests that, in contrast with observations on nonprotonated base pairs, interaction energies of protonated base pairs have higher electrostatic contribution with noticeably reduced electron correlation component. As is also indicated by Mulliken population analysis, Morokuma decomposition analysis of interaction energies shows charge transfer as one of the dominant components in these base pair systems.



An example of protonated base pair. + sign indicates protonation at Watson-Crick edge

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SPECTRAL RESPONSES OF 3'-SUBSTITUTIONS IN DIDEOXYTHYMIDINE NUCLEOSIDES

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2', 3'-dideoxythymidine nucleoside analogues [Fig.1 (a)], such as azido-thymidine (AZT), are important reverse transcriptase (RT) inhibitors of human immunodeficiency virus (HIV). It is suggested that the inhibitory properties are relevant to the substituents at the 2' or 3' positions on the sugar ring, and also are closely related to their electronic structures. It has been demonstrated that it is possible to accurately produce molecular spectra of nucleosides [1] using density functional theory (DFT). The challenge becomes how to appropriately interpret the results. The present study reveals the responses of electronic structures and spectra of 2', 3'-dideoxythymidine nucleoside derivatives to the substituent R on the 3' position. Molecular spectra, such as X-ray photoelectron spectroscopy (XPS) and ultraviolet photoelectron spectroscopy (UPS) [Fig.1 (b)] are simulated in both inner shell and valence shell, through chemical shifts (in core shell) and orbital alternations (in valence shell). The structures and properties will be demonstrated through a recently developed 3D-PDF technique. (Adobe Acrobat 8 is needed to view 3D pictures.)

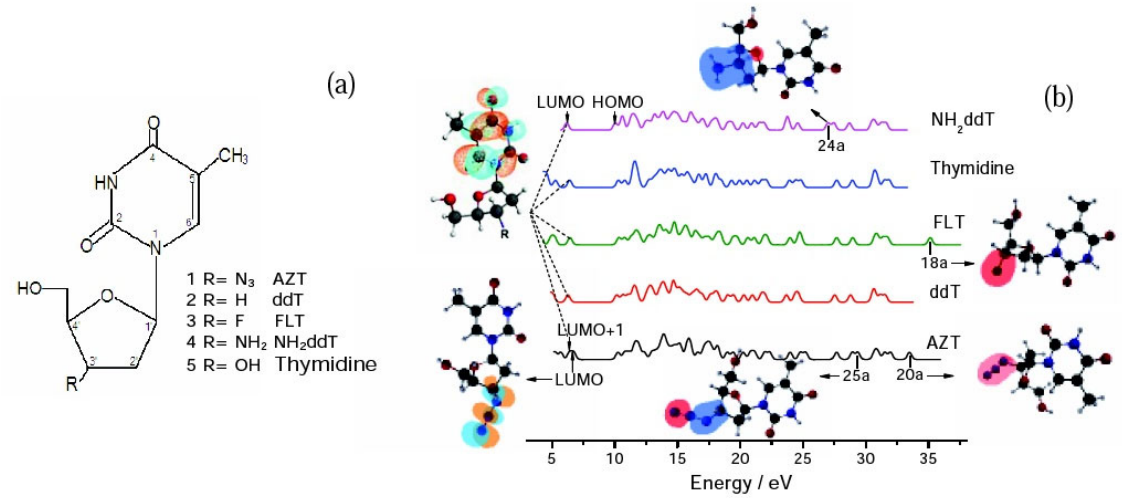

Figure 1: Structure and UPS of 2',3'-dideoxythymidine nucleoside analogues with 3D orbital pictures. 3D pictures can be activated by clicking in the PDF file.

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CATALYTIC ACTIVITY OF FATTY ACID AMIDE HYDROLYSE: NON-EMPIRICAL ANALYSIS OF DIFFERENTIAL TRANSITION STATE STABILIZATION

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Fatty acid amide hydrolase (FAAH), an enzyme first discovered during the research on marijuana influence on a human brain, deactivates neurotransmitters responsible for numerous symptoms present in nervous system diseases. One of its substrates is oleamide, the activity of which is associated with sleep-inducing, antianxiety effects, inflammatory and pain states, and others. Because of such a crucial role in living organisms, a more detailed knowledge of the molecular basis of FAAH-catalyzed oleamide hydrolysis is required to allow for a rational control over the latter.

In this contribution, the factors determining FAAH catalytic activity are analyzed within the framework of Differential Transition State Stabilization (DTSS) theory [1]. Following the DTSS approach, the stronger binding of an enzyme with transition state relative to reactants results in the lowering of activation energy barrier and in the overall reaction rate increase. The differential transition state stabilization energy could further be partitioned according to variationperturbation scheme [2] into the electrostatic, exchange, delocalization and correlation contributions. Thus, both the catalytically important active site residues and the physical nature of the preferential transition state binding can be determined, providing a detailed insight into the enzyme catalytic mechanism, especially useful when planning the mutagenesis experiments and/or for the rational inhibitor design. Finally, the approximate, yet well-founded models can be constructed, guiding the prediction of an influence of enzyme mutations on the enzymatic activity. Wherever electrostatic effects are dominant, these results could be generalized in the form of catalytic fields [1,3].

DTSS analysis of the first step of the FAAH-catalyzed oleamide hydrolysis was performed based on the mechanism proposed in Ref. 4. In addition to the reactive conformation of an enzyme-substrate complex, three conformations described as unreactive [4] were also considered. Remarkably, the height of the respective reaction barriers coincides with the amount of DTSS energy calculated herein. These results along with the catalytic contribution of particular FAAH residues will be discussed.

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THE INTERPLAY BETWEEN DNA AND REGULATORY PROTEINS

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Biological processes are often controlled by regulatory proteins that complex to DNA in order to prevent or promote expression of proteins. These regulation systems must meet stringent requirements as they must be insensitive to environmental variation and must be highly selective for the correct DNA-sequence.

In this lecture, two regulatory systems will be discussed. The first is the tetracycline repressor protein, TetR, a system that is switched by a small molecule (tetracycline antibiotics) and that regulates expression of an efflux pump to remove tetracyclines from bacterial cells. The second is a C-protein that regulates the expression of the two enzymes necessary for the restriction-modification (RM) system that protects bacteria from foreign DNA (e.g. from phages).

Molecular dynamics calculations show that the characteristics of these two systems are very different, but that in both cases a dynamic view of the molecular ensemble is necessary in order to understand regulation mechanisms, specificity of binding etc. The signal-transduction protein TetR is itself very flexible, whereas the C-protein is quite rigid. In the case of the C-protein, its unique binding characteristics can be traced back to its effect on the DNA structure and flexibility.

MANY-BODY CONTRIBUTIONS TO BASE-BASE INTERACTIONS IN B-DNA D(XPY) DINUCLEOTIDE STEPS.

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The non-additivities of base-base interactions in all ten possible model dinucleotide steps were analyzed on MP2/aug-cc-pvDZ quantum chemistry level. The conformations of four nucleobases exactly matching to ones occurring in B-DNA crystals were prepared according to procedure successfully applied for polymorphism-related heterogeneities of guanine stacking in B- and ADNA forms1, characteristics of inter- and intra-strand stacking interactions in d(CpG) and d(GpC) steps found in B-DNA, A-DNA and Z-DNA crystals2, description of energetic heterogeneities in canonical and oxidized central guanine triad of B-DNA telomeric fragments3 and quantification of all possible intra-strand stacking interactions between nucleobases4. In most of 162 analyzed tetramers, which were schematically presented in Fig.1 both three- and four-body contributions are negligible except of d(GpG) steps. Interestingly, even then these contributions always are of opposite signs and in all cases the sum of all non-additive part of intermolecular interactions do not exceed 2.6 kcal/mol. This stands for less than 4% of the overall binding energy of dinucleotide steps. Besides, there is observed linear relationships between values of the total binding energy obtained in the tetramer basis set and estimated energy with assumption of pairwise additivities in dimer basis sets. For all analyzed dinucleotides steps there are also linear correlations between amount of non-additive contributions and pairs interactions. Based on these relationships, three distinct classes of dinucleotide steps were identified. The explanation of this fact is related to differences in electrostatic contribution to the total binding energy of four nucleobases.

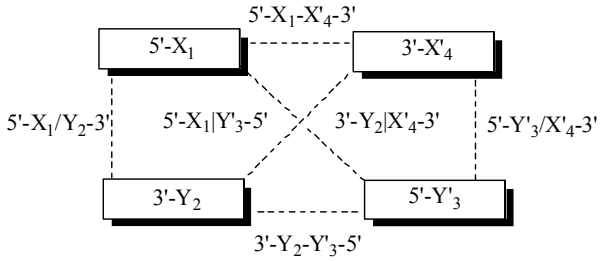

Figure 1: The schematic representation of intermolecular interactions in model d(XpY) dinucleotide steps. There are three distinct types of contacts, namely intra-strand stacking (5'-X_1/Y_2-3', 5'-Y'_3/X'_4-3'), inter-strand stacking (5'-X_1|Y'_3-5', 3'-Y_2|X'_4-3') and hydrogen bonding (5'-X_1-X'_4-3', 3'-Y_2-Y'_3-5'), where X,Y denotes one of four nucleobases and X',Y' stands for corresponding complementary base.

Acknowledgements: The results were partly obtained based on computational grants from PCSS (Poznań Supercomputing and Networking Centre, Poland).

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THE POST-SCF QUANTUM CHEMISTRY STUDY ON THE STRUCTURAL AND ENERGETIC HETEROGENEITIES OF CANONICAL AND OXIDIZED BASEPAIRS FOUND IN TELOMERIC COMPLEXES

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Telomers play a crucial role in keeping genomic stability. It has been proven that this structures are very sensitive to oxidative damages [1]. Presence of 8-oxo-guanine lesions in telomeric sequence have profound influence on binding process [1]. Significantly reduced affinity of TRF1 to oxidized telomers may be imposed by structural, energetic and electrostatic alterations of modified strand [2].
In this work set of structures of central telomeric fragment (d(GpXpG), where X={G or 8oxoG}) was generated in 2ns molecular dynamic (AMBER) run and assessment of intermolecular interaction energies were performed on DF-MP2/aug-cc-pvDZ level according to previously presented method [2,3]. The impact of 8oxo-guanine on the structure of GG dimers was characterized by analysis of distribution of base pair and base step parameters [4].
We have observed significant impact of TRF1 ligands on structural and energetic properties of central telomeric triad. Largest effects ware noticed for structures containing 8-oxo-guanine. Figure 1. shows that interactions between protein and DNA can drastically changed values of IIE and base step parameters. For example the twist values have distinct distributions for free and complexed telomeric fragments and corresponding IIE populations also have bimodal character. Similar features were identified also for other structural parameters characterizing canonical, oxidized telomeric fragments in free form and attached to TRF1.

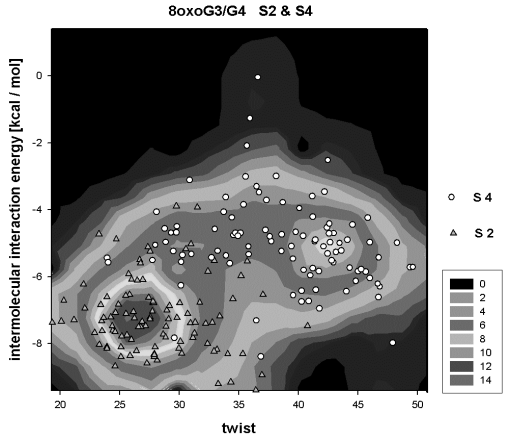

Figure 1: The mutual dependence of intermolecular interaction energy and twist for 8oxoG3/G4 dimers founded in S2 (free oxidized) and S4 (in complex with TRF1 and oxidizeed) structures .The contours colours correspond to magnitude of population of stacked dimers.

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DETERMINANTS OF K^+ VS. Na^+ SELECTIVITY IN POTASSIUM AND SODIUM ION CHANNELS FROM DFT/CDM CALCULATIONS

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Ion channels are indispensable component of the nervous system and play crucial role in regulating the cardiac, skeletal and smooth muscle contraction. Among those, the monovalent ion channels (conducting K^+ or Na^+) are of particular importance since they control the action potential of a number of excitable cells by polarizing/depolarizing the cell membrane. Selective potassium or sodium channels are characterized with a remarkable ability to discriminate quite efficiently between cations with the same charge and similar ionic radii favoring the native ion. Although the molecular basis for this striking ion selectivity has been a subject of extensive investigations using both experimental and theoretical methods, the following outstanding questions remain: (a) To what extent is the permeating ion hydration number important for the K^+/Na^+ competition? (b) Is the chemical type and number of coordinating groups lining the pore critical for the selectivity process? (c) Apart from providing cation-ligating groups, do the channel walls play any other role in the selectivity process? Here, by combining density functional theory (DFT) with continuum dielectric method (CDM) calculations, we evaluate the free energies of $K^+ \rightarrow Na^+$ exchange reaction, $\Delta G(K^+ \rightarrow Na^+)$, in both the gas phase and protein environment:

$$[Na(aq)]^+ + [K^+\text{-channel}] \rightarrow [Na^+\text{-channel}] + [K(aq)]^+ \quad (1)$$

where $[Na(aq)]^+$ and $[K(aq)]^+$ stand for the hydrated sodium and potassium cations, respectively, whereas $[Na^+$-channel] and $[K^+$-channel] denote the respective sodium and potassium-bound ion channels. We systematically study the effect of different factors, such as the number, type and protonation state of ligating groups, cation hydration number, pore dielectric constant, and rigidity of the selectivity filter, on $\Delta G(K^+ \rightarrow Na^+)$. Their role in governing the ion channel selectivity is assessed.

MOLECULAR BASIS OF PHENYLALANINE AMMONIA-LYASE INHIBITION: *AB INITIO* PREDICTION OF THE BINDING AFFINITY.

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Phenylalanine ammonia-lyase (PAL) is a crucial plant enzyme redirecting the carbon flow from primary metabolism to the synthesis of phenylpropanoid compounds involved in mechanical support, signaling and protection against biotic and abiotic stress. Accordingly, PAL has been extensively studied as a possible control site of desirable product accumulation and potential target for herbicides.

Despite the abundant experimental data regarding structure-activity relationships of PAL inhibitors, there exists no experimental or theoretical evidence explaining the molecular basis of PAL inhibition. To gain insight into the mode of PAL inhibitors binding, the *in silico* docking of 11 parsley PAL inhibitors with known experimental binding affinity [1] was performed, followed by a detailed analysis of the *ab initio* binding energy. These results show an energetic preference for the axial binding conformation of 2-aminoindane-2-phosphonic acid and its derivatives, in agreement with the observation that only axial placement of inhibitor phosphonic group allows for a specific interaction with PAL active site [2].

The physical nature of an inhibitor binding was revealed by means of the variation-perturbation interaction energy partitioning into the electrostatic, exchange, delocalization and correlation components [3]. Significant correlation with experimental inhibitory activity was found between the interaction energy at gradually decreasing levels of theory (MP2, SCF) down to the first order Heitler-London term. Three PAL active site residues responsible for the observed inhibitory activity were identified leading to a minimal active site representation. Further approximation yielded a valid model of the ligand activity based exclusively on the molecular electrostatic potential of the inhibitors generated at the closest atomic contacts with five PAL atoms.

Computational protocol applied herein illustrates how a systematic analysis of both the physical nature of interactions and binding contribution of receptor site residues allows for a rational derivation of simple yet sufficiently accurate models of inhibitory activity. Such models, employing the first principles of quantum mechanics (in contrast to, e.g., QSAR approach) provide a rapid and straightforward estimation of the binding affinity without using any empirical parametrization.

Acknowledgements: This work was partially funded by the L'Or´eal Poland-Unesco For Women in Science Fellowship.

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ANALYSIS OF ATYPICAL PROTONATION STATES IN ENZYME ACTIVE SITES VIA THEORY OF INTERMOLECULAR INTERACTIONS

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Aminoacids constituting enzyme active sites may experience significant pKa shifts reaching sometimes 5 units, which may lead to atypical protonation states. Unexpected proton positions resulting from interactions with neighbouring residues as well as docked reactants or inhibitors can be rarely confirmed via neutron diffraction experiments [1-2] and available structures from X-ray diffraction can not be conclusive. Such non standard protonation i.e., a protonated acid or deprotonated base) may occur in the active site of the selected enzymes (HIV-1 protease) strongly influencing the catalytic mechanisms of analyzed protein. Czodrowski et al. [2] reported that DMP-323 induces a protonation change of the catalytic dyad: from the apo state with one of the two aspartates protonated to a doubleprotonated state with both aspartates uncharged. Two different form of the enzyme: one with typical protonation states of active site residues (ASP-25 and ASP-125) and second with atypical protonation states have been analyzed here within variation-perturbation partitioning of interaction energy [3]. Analogously different protonation states of TYR159 in D-alanyl-Dalanine peptidase interacting with RE1 ligand have been studied in this work indicating preferred TYR 159 deprotonation [4].

Acknowledgements: Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

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MOLECULAR MECHANISM OF ALLOSTERY IN HEXAMERIC E. COLI ARGININE REPRESSOR

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Molecular dynamics simulations with ArgRC, the ~50 kDa C-terminal hexamerization and L-arginine-binding domain of *E. coli* arginine repressor, reveal the proteins range of motions with and without bound L-arg. Simulations starting from the nearly identical apo- and holo-ArgRC X-ray crystal structures evolve distinctly during 20 ns. The two trimers of apoArgRC rotate freely with respect to one another between two limiting ensembles, one essentially like the starting state derived from the crystal structure and the other rotated in one direction by a mean of ~13 degrees. Simulations with holoArgRC having six L-arg ligands bound reveal essentially no rotational motion. The crystal-like ensemble of apoArgRC states is visited much less frequently than the rotated ensemble, consistent with bond occupancies and entropies in the two ensembles that likewise imply the crystal traps a high-energy state. Detailed analysis of the trajectories reveals that the motion of apoArgRC is unidirectional because the single arginine residue of each polypeptide chain faces one side of the L-arg-binding pocket and extends its sidechain into the pocket, mimicking the ligand. Simulations with the apoArgRC hexamer after adding six L-arg ligands confirm that, as in holoArgRC, rotational dynamics are suppressed and the most populated states are more crystal-like. Simulations with incremental additions of individual L-arg ligands reveal that a single bound L-arg is sufficient to suppress rotation and favor a more crystal-like ensemble. The proposed mechanism is corroborated by recent crystals of *Mycobacterium tuberculosis* ArgR, which present an arginine sidechain on the opposite side of the pocket and which trap a state that is rotated in the opposite direction. The results enable structure-based interpretation of the multiphasic thermodynamic profile of L-arg binding and predict its long-range structural consequences in intact ArgR.

Acknowledgements: Access to METACentrum supercomputing facilities was provided under the research intent MSM6383917201. Support from the Ministry of Education, Youth and Sports of the Czech Republic (MSM6007665808, LC06010), Academy of Sciences of the Czech Republic (AVOZ60870520), Grant Agency of the Czech Republic (203/08/0114 to R.E), and joint Czech - US National Science Foundation International Research Cooperation (INT03-09049 and ME09016) is acknowledged.

COMPUTATIONAL CHARACTERIZATION OF HUMAN SERUM PARAOXONASE'S BINDING MECHANISMS FOR THE VX NERVE AGENT

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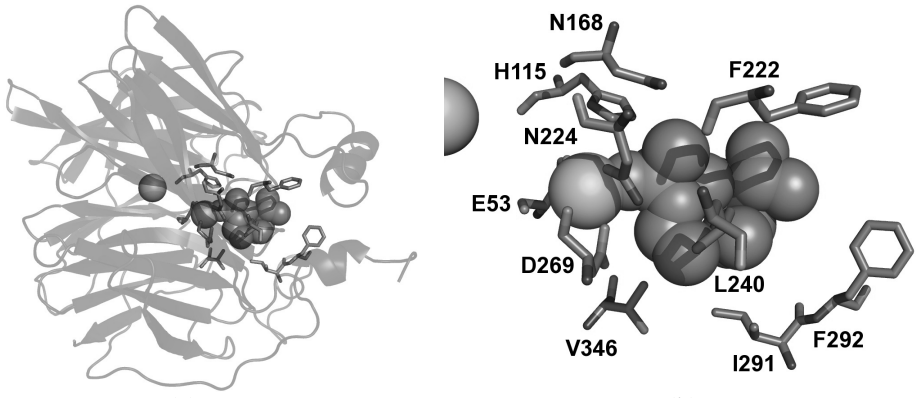
Human serum paraoxonase (HuPON1) is a potential bioscavenger of organophosphorus nerve agents (OPNAs) such as VX. While the enzyme has inherent activity towards OPNAs, the ezymatic rates are not sufficient to make HuPON1 an effective OPNA countermeasure. Recent studies have shown that computational engineering can improve an enzyme's activity by multiple orders of magnitude towards a given substrate. For HuPON1, such increases could make the enzyme an effective countermeasure against the VX nerve agent.

Here we present two key pieces of information required for engineering HuPON1 to have increased VX hydrolase activity. First, we characterize HuPON1's tertiary structure using two computational methods (I-TASSER and MODELLER) combined with energy minimization and molecular dynamics (MD) simulations. Second, based on the predicted structures, we determine how VX binds to HuPON1 using three docking packages (DOCK, AutoDock, and OpenEye) combined with MD and steered MD.

The resulting bound conformations indicate various aspects of how VX binds to HuPON1. All four predicted bound conformations indicate that VX's lone oxygen atom forms a strong interaction with HuPON1's active site calcium. Additionally, VX's phosphosulfur (P-S) bond is found to have multiple favorable orientations within HuPON1's active site. However, none of these orientations places the H115/H134 histidine dyad in a position to coordinate a water-based SN2 attack on VX's P-S bond. Instead, the results show that residue D269 is better aligned for accepting a proton from the attacking water molecule. Together, these findings support recent experimental studies that show H115 and H134 are not required for HuPON1 activity on all substrates. Additionally, we find that residue D183 is a likely proton donor to VX's sulfur atom given D183's location within the active site and its predicted pKa value. Altogether, the study provides valuable information required for further enhancing HuPON1's VX hydrolase activity.



(a) (b)

Fig. 1: Figure (a) illustrates the VX binding mode determined through steered molecular dynamics. Figure (b) highlights key HuPON1 residues involved in VX binding.

DFT PERIODIC STUDY OF THE CONFORMATIONAL BEHAVIOUR OF GLYCINE HELICAL HOMOPOLYPEPTIDE

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Representative helicoidal conformations of polyglycine polymorphs have been investigated by using periodic calculations, large basis sets and a density functional theory DFT approach. The exploitation of the helix roto-translational symmetry permits to optimize at a relatively low cost the structure of systems whose unit cell contains more than 300 atoms, much larger than the one investigated till now. The helix symmetry is exploited at three levels in the CRYSTAL[1] code, that has been used for the present calculations. First, for the automatic generation of the structure. Second, for the calculation of the mono- and bi-electronic integrals that enter into the Fock matrix definition. Only the irreducible wedge of the Fock matrix is computed. Finally, for the diagonalization of the Fock matrix, where each irreducible representation is separately treated. The efficiency and accuracy of the computational scheme is documented, by considering cells containing up to 47 glycine residues. Results are compared with previous calculations and available experimental data.
The dependence of the computed properties on the choice of the functional is accurately addressed. This includes the most popular hybrid and gradient corrected functionals. The inclusion of dispersive forces (through an empirical correction as suggested by Grimme and modified for solid states [2]) on the computed properties is also considered.
Vibrational properties (IR and RAMAN spectra) and thermodinamic stability are also analyzed.

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PHENOXYIMINE COMPLEXES AS PRECURSORS OF COORDINATIVE OLEFIN POLYMERIZATION CATALYSTS: A DFT STUDY

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Post-metallocene coordinative olefin polymerization catalysts offer new possibilities in controling the properties of resulting polymers, maintaining high activities that are characteristic for metallocenes [1]. The presence of multidentate ligands (e.g. phenoxyimines) generates several isomeric structures of precursors, transition states and products that can be modeled by octahedral complexes. In the theoretical study, all such structures have to be considered in order to obtain the adequate description of the process.

Dichloro-bis[(salicylidene)iminato]titanium(IV), a complex that contains two molecules of a bidentate phenoxyimine ligand, can form three pairs of enentiomers and two separate diastereomers. For the structural reasons, the potential precursor of the efficient catalyst should contain the chlorine atoms arranged cis with respect to each other. Therefore, the latter two species can be rejected and the number of isomers to be analyzed in the theoretical study is limited to six. Additionally, if no prochiral monomer is used in the model, the enantiomeric forms can be excluded and the number of species is further reduced to three.

NMR and X-ray experiments clearly indicate that one of the isomers is prevalent. However, the other two forms can also exist [2, 3] and this is determined by numerous factors, mainly the kind of substituents in the phenoxyimine ligand. The origin of the isomeric preference can be explained and quantified by theoretical calculations. We have found that the most important factor that determines the relative stability of the isomers is the steric hindrance exerted by the substituent at the imine nitrogen atom of the ligand, expressed in terms of the molar volume. Based on these findings, preliminary calculations of the polymerization energetic profiles were also performed in order to study the influence of these substituents on the catalytic activity.

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INTERACTION OF "PIANO-STOOL" RUTHENIUM COMPLEXES WITH DNA; QM/MM STUDY

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Ruthenium(II) "piano-stool" complexes $[Ru^{II}(\eta^6\text{-arene})(en)Cl]^+$ (en = ethylendiamine) were reported by Sadler's group [1,2] as promising anticancer drugs. Their behavior in biological environment is similar to well known chemotherapeutic cisplatin, i.e. first the chlorine is replaced by water molecule and after this hydration reaction the aqua ligand is exchanged by nucleic base.

We have shown in our previous computational study that the most preferable site in DNA for bonding Ru is N7 position on guanine which is well accessible from major groove of DNA. Guanine replacement reaction passes complex two-step mechanism. DFT/MP2 calculations on this system were performed both *in vacuo* and in COSMO regime. Thermodynamic parameters and rate constants were determined and compared with experimental results.

Possibility of intrastrand cross-link formation was investigated by QM/MM methodology. We use model where Ru complex is bound to 6-base-pair DNA oligomere. QM part of system is evaluated by program Turbomole while the MM surrounding is treated by Amber program package. These programs are governed by script-based interface called ComQum [3,4]. AIM and NBO analysis were calculated. Investigated process of the cross-link forming is exothermic and the piano-stool structure is lost during the reaction.

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POLARIZABLE WATER MOLECULES IN LIGAND-MACROMOLECULE RECOGNITION

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We present a short overview of the SIBFA polarizable molecular mechanics/dynamics procedure, along with recent validation tests against parallel ab initio quantum chemistry computations. We then present applications to the modeling of the complexes of inhibitors with protein targets: FAK (focal adhesion kinase) involved in cancer processes, and PMI (phosphomannoisomerase), a Zn-metalloenzyme involved in bacterial and parasitic illnesses. The ranking of relative affinities of competing inhibitors is done by energy balances which include the solvation energy of their protein complexes on the one hand, and their desolvation energies prior to complexation on the other hand. For both FAK and PMI targets, and along with bulk solvation energies using a Continuum reaction field methodology, it is found indispensable to include discrete structural, highly polarized water molecules in the recognition site. These waters mediate the ligand-protein interactions, and can play a decisive role in the relative energy balances.

PROBING THE MOLECULAR MECHANISM OF ANTIBIOTICS DIFFUSION THROUGH BACTERIAL PORINS

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Gram-negative bacteria are protected by an outer membrane and to function, antibiotics have to diffuse passively through outer membrane porins, such as OmpF. Bacterial strains can modulate their susceptibility to antibiotics by under-expressing or mutating porins and today we are facing an alarming situation due to the increasing bacterial resistance to antibiotics. A key feature in the structure of OmpF is the presence of a constriction zone, characterized by both spatial and electrostatics restrictions. To study the process of antibiotics translocation at a molecular scale, we performed molecular dynamic simulations accelerated with the metadynamics algorithm. We studied the diffusion of antibiotics with different structural and chemical properties through OmpF wild type and variants that are mutated at the constriction region. The calculated energy barriers suggest faster translocation for the cephalosporins compared to the penicillins antibiotics, and also for OmpF mutants compared to the wild type. We reveal for the first time the rate determining interactions that govern translocation and the specific affinity sites of antibiotics inside the OmpF channel.
The simulations results compare remarkably well with the electrophysiology measurements and liposome swelling assays from our collaborators. This study demonstrates how theory and experiments can be combined to reveal the structural determinants and molecular mechanism of antibiotics diffusion through a nanometer-sized channel. Our methodology, which can be conveniently employed to study other porins/antibiotics, will benefit the rational design of antibiotics with improved transport properties.

Acknowledgments: This study was supported by EU-grant MRTN-CT-2005–019335 (Translocation) and by the computer center and consortiums: Cybersar, CASPUR and CINECA through CPU-hours.

MODELLING METALLOENZYMES: HYDROGENASES

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Density functional theory (DFT) calculations on active site models for the catalytic cycles for [NiFe]-, [FeFe]-, and [Fe]-hydrogenases have been helpful in defining the nature of the active site. By comparing calculated CO frequencies from the DFT calculations with the measured IR frequencies, the redox states and structures of the active site can be predicted.

In the $(CO)(CN)_2Fe(\mu\text{-}SMe)_2Ni(SMe)_2$ model for the [NiFe] active site, the unconstrained optimized geometries for high-spin Ni^{II} species appear to be better structural models than low-spin Ni^{II} species. High-spin Ni^{II} and Ni^{III} species involved in the H_2-cleavage reaction, especially the transition state, show remarkable structural resemblance to the active site in the enzyme crystal structure. Dihydrogen activation on the Fe^{II}-Ni^{III} species is more favorable than on the corresponding Ni^{II} or Ni^{I} species. Recent calculations with additional protein residues included in the model suggest that both high- and low-spin Ni^{II} species may be involved. This would be the first example of "two-state" reactivity in hydrogenases.

In modeling the [Fe]-hydrogenase, the calculations have been used to develop a "trigger" mechanism. The first reported crystal structure suggested that the active site had two open Fe coordination sites. The calculations baded on this model predicted that the barrier for H_2 cleavage in the presence of MPT^+ is about 18 kcal/mol lower than in the absence of MPT+, a result that explains why the isotopic D_2/H_2O exchange catalyzed by Hmd is strictly dependent on the presence of MPT^+. This difference is a result of the MPT^+ triggering the pyridone to provide electron density to allow the Fe to take a proton while transferring a hydride to the MPT^+. In models based on a revised crystal structure of this active site, which shows only one available coordination site on Fe, a different role is predicted for the pyridone that involves it in a very stable Fe-H --- H-O(pyridone) dihydrogen bond which prevents D_2/H_2O exchange before the arrival of the MPT^+.

ANALYTIC EVALUATION OF HELLMANN – FEYNMAN FORCES

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We derive analytical formula for electric potential and Hellmann – Feynman forces for the system described by the wavefunction generated from primitive gaussians without any approximations. Our construction permits evaluation of Hellmann – Feynman forces arising from any particular orbital. Studying forces appearing due to the HOMO (LUMO) we can obtain insight into chemical reactivity and interactions. This way we expect to get best approximation for Fukui Function. This incorporates the fundamental idea from Nakatsuji but without any approximation except from the chemistry model used to get the molecular wavefunction. Input values are density matrix elements and contraction coefficients for primitive Gaussians. We are inspired by beautiful work of J. F. Rico, R. Lopez, I. Ema and G. Ramirez and their program DAM. However their approach is based on spline functions approximation of the electron density. Our derivation of explicit form of electric potential at any point of the molecule uses analysis of special function namely gamma function, Bessel Ij+1/2 function, Whittaker function M and Clebsch – Gordan decomposition of the products of spherical functions into irreducible components. The analytical formula is then differentiated to obtain the exact formula for Hellmann – Feynman forces.

MODELING THE DNA-PROTEIN INTERACTIONS: MD SIMULATION STUDIES

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15-mer ssDNA anti-thrombin aptamer plays a vital role in the blood clotting mechanism1. It is of high importance to explore the structural factors controlling the inhibitory nature of the aptamer2. We investigated the structure-function relationship of 15-mer ssDNA anti-thrombin aptamer, as well as its 'caged' variant (2-(2-nitrophenyl)-propyl group (NPP)) 3 by molecular dynamics simulations. The stability of the unmodified aptamer at different temperatures is examined in 2ns all-atom simulations and compared to experiment. The change in structure when introducing the photo-labile cage compound is analyzed, and the regiospecificity of this modification explained on atomic level. Removal of the cage compound leads to the re-formation of the active aptamer structure from its inactive state4. The mechanism for this formation process is a concerted movement of the aptamer backbone and some highly important bases. The binding of the aptamer to thrombin with regard to the 'caged' group is studied in an explicit simulation with the aptamer-thrombin complex and the reason for the binding / unbinding nature of the aptamer shown.

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SOLVATION ENERGY CALCULATIONS BASED ON ELECTRONEGATIVITY EQUALIZATION METHOD'S (EEM) CHARGES, INTERNAL COORDINATE MECHANICS'S (ICM) CHARGES AND CHARGES BASED ON PARTITION COEFFICIENTS

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Partial atomic charge is a molecular property which is very often used in chemistry, particularly for clarification of differences in structure or reactivity between molecules. The most common approach for charge calculation in a molecule is to use some quantum mechanical method. Although there is no absolutely precise method for charge determination, quantum mechanical methods are considered to be sufficiently accurate, but they are also quite timedemanding and therefore some alternative approaches appeared.
One of the alternatives, Electronegativity Equalization Method (EEM) [1], was developed as a semi-empirical approach based on the Density Functional Theory [2] and it is able to provide partial charges in a fast and appropriate way. Due to its semi-empirical character it is necessary to parameterize it before the first usage, but once parameterized, EEM can be used for fast charge calculation using eem_Solver which is available free of charge at [3].
Internal Coordinate Mechanics (ICM) approach [4] provides a general modeling and structure prediction framework. ICM allows using MMFF force field including atomic charge assignments in combination with a fast procedure for accurate electrostatic calculation using the boundary element solution of the Poisson equation and thus ICM is able to provide electrostatic energy for any particular molecule in aqueous solution.
Based on the charges determined using EEM and ICM methods, solvation energies were determined and compared with solvation energies calculated from experimentally measured octanol-water partition coefficients.

Acknowledgements: Support from grant No. ME 08008 is acknowledged. Calculations were performed at the Supercomputing MetaCentrum in Brno.

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H-TUNNELLING IN ENZYMES: THE ROLE OF PROMOTING VIBRATIONS AND BARRIER COMPRESSION

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The prevailing picture of enzyme catalysis is that transition state stabilisation lowers the reaction barrier and thus enhances the rate. A more controversial proposal is that enzymes can also enhance rates through barrier compression, an idea that has emerged from studies of the kinetic isotope effects (KIEs) of enzymic H-tunnelling reactions and their temperature-dependencies. This concept is intimately linked to that of "promoting" vibrations which decreasing the donor-acceptor distance and therefore increase the tunnelling probability. The role of promoting vibrations has been largely inferred from so-called "vibronic" models of H- tunnelling, where the tunnelling probability depends on the proton wavefunction overlap between the reactant and product, and over-the-barrier (classical) transfers are ignored.
We explore the effect of barrier compression on the rates and the partitioning between tunneling and classical reaction paths through theoretical and computational studies of model systems and enzymic proton transfer systems, and conclude that barrier compression, either through promoting vibrations or by other means, may be important for the rates of not only tunneling, but also classical reactions. We also investigate the validity of the vibronic model, and find that it adequately reproduces KIEs within realistic ranges of H-transfer distances. Promoting vibrations in enzymic H-tunnelling reactions are studied using molecular dynamics simulations, and hybrid molecular mechanical / quantum mechanical methods are used to analyse how these affect the Htransfer barrier.

A VIBRATIONAL ELECTRON-SHOVEL MECHANISM FOR CHARGE TRANSFER BETWEEN HAEMS A AND A_3

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Cytochrome c oxidase (CoC) is the terminal enzyme in the electron transfer pathway of cell respiration. The enzyme contains four redox-active metal centres, all intermediately called by the reducing electrons on their path towards reduction of molecular oxygen. The first stop for the electron, after being delivered by cytochrome c, is the dinuclear Cu_A centre. From here, the electron moves forward to haem a, the "electron pump" of CcO. From haem a, the electron is subsequently transferred to the binuclear site of the two remaining metal centres, haem a_3 and Cu_B, where it is finally consumed in the reactions transforming oxygen into water, the by-product being a force for maintaining the principal action of the enzymeI proton pumping across the membrane.

Here, a possible connection between molecular vibrations and electron transfer in the coupled haem a/a_3 system of CcO is investigated. fn the low frequency regionI several normal modes occasion structural distortions spanning large portions of the connected haems. Of these, only few vibrations lead to a shift of the electron density from one haem to the other. A common feature of these vibrations is the shovel-like movement of the phenylalanine covalently linking the haem-ligating histidines to each other. It is suggested that the vibrations involving this highly conserved residue could play a role in the electron transfer mechanism of the enzyme.

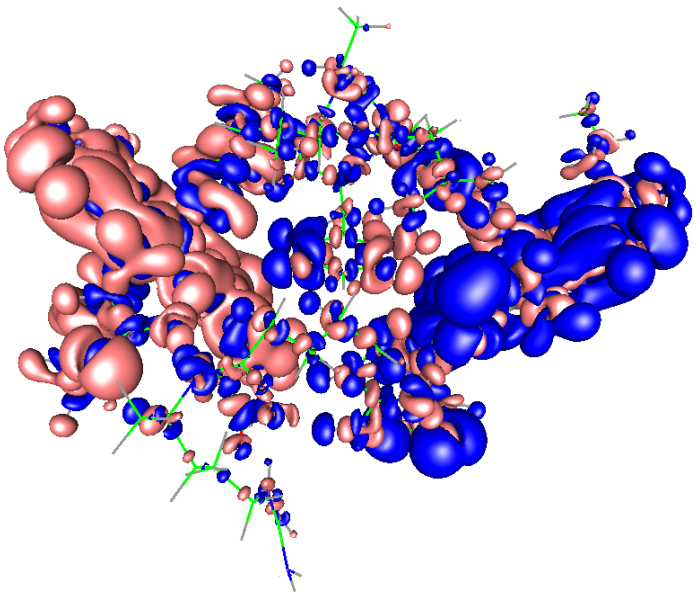

Figure 1. Electron density difference occasioned by eT from haem *a* (left) to a_3.

DESIGNING NEW MATERIALS FOR THE HYDROGEN STORAGE

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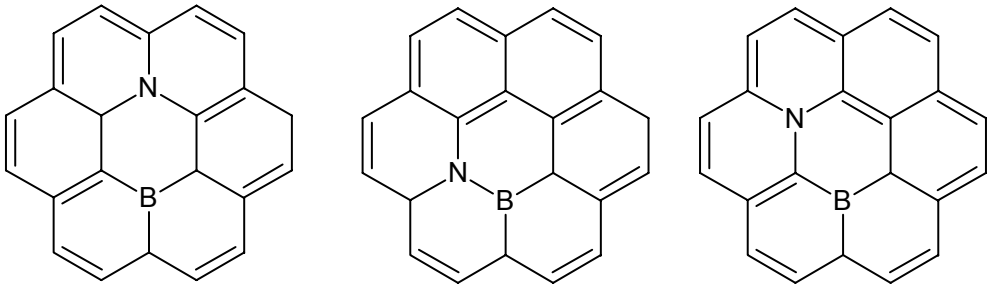
The theoretical studies of interactions between modified graphene and molecular hydrogen are presented. The graphene (figure 1) was modified by replacing carbon atoms {(4,8); (4,9); or (4,10)} by boron or nitrogene atoms. The structure of modified graphene was optimized and used to construct the H2 complex with optimized hydrogen molecule position. The calculations were performed at DFT and MP2 levels of theory applying standard ecp SBKJC atomic basis set supplemented by d polarization functions.



(4,10) (4, 8) (4, 9)

Figure 1.

ACCELERATED QM/MM FREE ENERGY CALCULATIONS: THEORY AND APPLICATIONS

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In recent years, hybrid quantum mechanical / molecular mechanical (QM/MM) approaches have been used to provide a general scheme for chemical reactions in solution and in proteins. However, reliable studies of enzymatic reactions by QM/MM approaches with an ab initio description of the quantum region present a major challenge to computational chemists, due to the need for very large computer time to evaluate the QM energy, which in turn makes performing proper configurational sampling extremely challenging. Here, we will introduce an approach to accelerate QM/MM calculations by means of a classical reference potential and an updated mean charge distribution [1]. We recently demonstrated that this approach is not only able to reproduce experimental free energies for reactions in solution with high accuracy, but it is also able to reproduce the pKas of ionisable groups in proteins within an accuracy of 3 kcal/mol (which is well within the 7 kcal/mol energy difference observed in studies of enzymatic catalysis), while providing computational time savings of up to a factor of 1000 relative to calculations that evaluate the QM/MM energy at every time step [2]. We also provide an overall perspective of the potential of QM/MM calculations in general evaluations of electrostatic free energies, suggesting that our approach should provide a very powerful and accurate tool to predict the electrostatics of not only solution but also enzymatic reactions, as well as the solvation free energies of even larger systems, such as nucleic acid bases incorporated into DNA.

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MODEL OF TRANSITION STATE STABILIZATION BY AMINOACID-tRNA SYNTHETHASES

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The family of aminoacid-tRNA synthethases (aa-tRS) performs the same reaction and is divided into two distict classes. The arrangement of charged residues within their active site environments is a good example of the electrostatic lock-and-key concept by N´aray-Szabó [1], and the simple electrostatic model of the transition state stabilization has been used to predict the catalytic role of various aminoacids [2] and to compare the electrostatic environment of the active sites [3]. In this work, an extended model of the active site is used for a similar analysis, aiming at evaluation of the most important contributions to the transition state stabilization by aa-tRS.

Acknowledgements: Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

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PROBING THE ROLE OF P=O STRETCHING MODE ENHANCEMENT IN NERVE-AGENT SENSORS: SIMULATION OF THE ADSORPTION OF NERVEAGENTS ON THE MODEL MGO AND CAO SURFACES

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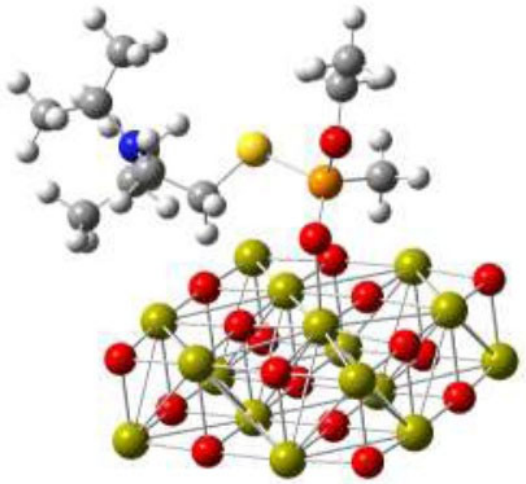
The interactions of nerve gases with model MgO and CaO surfaces have been investigated using density functional theory (DFT) and Møller-Plesset second order perturbation techniques. The geometries were fully optimized at the DFT level. Analyses of the calculated IR and Raman spectra point to the enhancement of the P=O stretching mode with respect to the isolated nerve agents and this property could be used to detect these toxic gases using surface-enhanced Raman spectroscopy.



ATOMISTIC INSIGHT FROM COMPUTATIONAL SIMULATION INTO HOW ENZYMES CATALYSE TUNNELLING REACTIONS

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The rate determining step in many enzyme catalysed reactions is a proton, hydride or hydrogen transfer, a process which can take place by quantum mechanical tunnelling. Tunnelling in enzymes can be probed experimentally by measuring the size and temperature dependence of the kinetic isotope effect (KIE) on the transfer step. It is currently thought that large (>7), temperature dependent KIEs indicate that a protein promoting motion (PPV) facilitates tunnelling.[1]

However, it has been suggested that large temperature dependent KIEs could also arise in tunnelling enzymes due to the population of multiple reactive substrate configurations within the active site. [2] This hypothesis is being examined through computational studies of methylamine dehydrogenase with substrate ethanolamine (MADH/EA). In this enzyme, the rate determining step is a proton transfer from an iminoquinone intermediate to an aspartate residue. [3]

Molecular dynamics simulations of the MADH/EA system revealed that the iminoquinone substrate adopts a variety of unique hydrogen bonding patterns in the enzyme active site. Preliminary QM/MM calculations on structures sampled from some of the most populated patterns have not revealed any significant differences with respect to classical barrier height or reaction energy for the proton transfer. However, geometry analysis showed that in some cases, different hydrogen bonding patterns are associated with different modal donor-acceptor distances and donor-hydrogen-acceptor angles. Calculations are in progress to determine whether the different patterns give rise to distinct KIEs on the rate determining proton transfer step.

Once complete, this study should provide valuable atomistic insight into the origin of the temperature dependent KIE of MADH/EA. An atomistic understanding of catalysis in tunnelling enzymes is essential if they are to be exploited successfully in the future.

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COMPUTATIONAL STUDY OF MUTH RECOGNITION AND CATALYSIS

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MutH enzyme participates in methyl-directed DNA repair together with two other enzymes MutS and MutL. Their joint choreography is conceptually known but a lot of details are still elusive. As a specific example, MutH is known to recognize specific DNA sequence [d(GATC)], which is cleaved by the enzyme in the close vicinity of dG base if the second strand is hemimethylated. This makes MutH a perfect biochemical machine with a unique function. Although this function is experimentally well-characterized, the underlying mechanism still remains to be unraveled.

We aim to resolve to two challenging questions related to the recognition and catalytic activity of MutH by utilizing computational techniques. 1) How a single methyl group attached to a far-lying adenine base from the active site can determine the activity of MutH? 2) Is Lys-77 residue serves to couple recognition to catalysis ("linchpin")? To answer these questions various models were constructed based on the recently solved crystallographic structures of MutH in free form and in complex with two DNA substrates using different protonation states for the active site residues. Using molecular dynamic simulations, we investigated the influence of the ionization/neutralization of Lys-77 as well as the nucleophile (water/hydroxyl ion) on the geometry of the active site. Then several reaction pathways were probed by the means of hybrid quantum mechanics/molecular mechanics methods to elucidate the most probable reaction mechanism.

SELECTED DIRECTIONS IN QUANTUM MONTE CARLO

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The quantum Monte Carlo (QMC) has become recognized as an accurate method for the electronic structure of atoms, molecules, and solids. In the most accurate variant of QMC, diffusion MC, algorithm modifications have led to the method scaling favorably compared to other ab initio methods as N2 where N denotes system size. This talk shall briefly summarize the approach and indicate current projects underway including a QM-MM adaptation and graphene structure, among others.

CHALLENGES IN MODELING PROPERTIES OF NANOMATERIALS

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Industrial applications of various nanomaterials have been increasing appreciably in the last decade. This progress is paralleled by the investigation of fundamental properties of nanostructures by chemists, biochemists and medicinal chemists. Usually such experimental investigations can be augmented by the results of advanced computational studies. Among various computational approaches the quantitative structure – property / activity relationships (QSPR/QSAR)-based methods by combination of experimental data with theoretical descriptors provide useful tools to supply necessary information assisting development of novel nanomaterials.

This talk highlights the most significant achievements and challenges related to our recent studies on nanomaterials. Among studied species are, fullerenes, carbon nanotubes, metal and metal oxide clusters. Application of computational techniques allows obtaining detailed information on various properties of these nanostructures. Among studied properties are molecular structures, solubility, and Young modules. Also novel developments of Quantitative Structure – Activity Relationships (QSAR) approach in prediction properties of nanospecies and in the risk assessment of nano-size materials will be reviewed.

PHYSICO–CHEMICAL PRINCIPLES GOVERNING BIOLOGICAL PROCESSES

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Our research interests are to

(i) unravel the underlying physico–chemical principles governing biological processes,
(ii) develop new methods, as required, along the way and
(iii) use the above principles and methods to design molecules with potential therapeutic utility.

This talk will provide an example of work in these three areas by unraveling the physical basis underlying structural and catalytic Zn−binding sites in proteins.

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THE EMISSION MODULATION OF THE CHEMILUMINESCENCE IN THE LUCIFERIN-LUCIFERASE SYSTEM

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The color modulation of the bioluminescence of the North-American and Japanese fireflies is achivied by mutations of residues in the active site of the luciferase enzyme. To understand this process we have initially studied the parent process in 1,2-dioxetane and 1,2-dioxetanone at the molecular orbital level of understanding. The use of the complete active space SCF (CASSCF) and the multi-state multi-configurational reference second order perturbation theory (MS-CASPT2) was demonstrated to be required for qualitative and quantitative understanding of the process, which involves inter-state crossings, conical intersections and entropic trapping. The importance of chemical induced electron-exchange luminescence (CIEEL) was explored in gas phase investigations on a thiazole-dioxetanone complex and the luciferin molecule. These studies show that protonation or not was critical to facilitating CIEEL. Finally, the complete complex of luciferin-luciferase complex was modelled with quantum mechanical/molecular mechanical (QM/MM) methods. Here the effects of mutations studied.

STRUCTURAL VARIABILITY AND THE NATURE OF INTERMOLECULAR INTERACTIONS IN WATSON–CRICK GUANINE-CYTOSINE BASE PAIRS

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Many computational studies characterizing hydrogen bonding and stacking interactions between native and modified nucleic acid bases were performed till now and the number of computational studies grows rapidly every year. Various aspects of intermolecular interactions in nucleic acids such as base pairing, interactions with metal cations, base triples and quadruples creation and water connected pairs formation were the main subject of interest. Relatively small atenttion, however, was paid to the nature of intermolecular interactions of biologically important complexes. The majority of studies concerned with the physical origins of stabilization was performed for stacked configurations of native and oxidized complexes of nucleic acid bases. The nature of interactions in hydrogen–bonded Watson–Crick base pairs has attracted much less attention. In the present study the impact of conformational variability of Watson–Crick guanine–cytosine base pairs on intermolecular interaction energy and its components has been analyzed at the *ab initio* level of theory for almost 50 crystallographic guanine–cytosine complexes. We used second–order Møler–Plesset pertutbation theory and coupled cluster with singles and doubles method to account for electron correlation effects. We have found that the crystallographic structures of the nucleic acid bases are mainly stabilized by delocalization component of the intermolecular interaction energy. In most considered cases, however, the first–order electrostatic energy is found to be canceled out by exchange repulsion. Correlation corrections to the intermolecular interaction energy were found to be important stabilizing components for large majority of studied complexes. Among structural parameters describing mutual orientation of bases in Watson–Crick pairs, *shear, stagger, stretch* and *opening* were found to have particularly significant influence on intermolecular interaction energy and its components.

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HAEMOGLOBIN: CAN WE UNDERSTAND A BIT MORE?

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The exploration of slow (long range) conformational changes remains a great challenge. Many biologically relevant processes, involving large domain motions or quaternary rearrangement, occur in the millisecond time scale, out of the reach of Molecular Dynamic techniques. PELE (Protein Energy Landscape Exploration), combines protein structure prediction techniques with a metropolis algorithm able to map the slow motion energy landscape.[1] The combination of PELE with QM/MM techniques has already been applied, in simple systems, and a good description of the conformational changes, in myoglobin, upon ligand ligation has been obtained.[2]

Human haemoglobin, an iron-containing protein is essential in oxygen transport and storage. It is known that the oxygenation process in haemoglobin is cooperative, that is, the binding of the first oxygen molecule enhances the following O2 binding affinity (and so on). Before oxygenation the protein adopts a low-affinity T-state conformation while when fully liganded it presents a high-affinity R-state. Although, this is one of the most studied proteins, the molecular details accompanying the T-R transition are not yet known and hence the allosteric mechanism. The main problem, in modelling this process is, of course, the time scale which is outside the reach of, for example, Molecular Dynamics.

In this contribution, we will present a series of studies, performed with PELE, that include:

- A detailed, conformational and energetic, exploration of the CO migration in and out of the protein active site.
- CO binding energies calculated with QM-MM performed following the ligand migration.
- The preliminary results on the T to R transition at the atomistic level.

Acknowledgements: This work was supported by startup funds from the Barcelona Supercomputer Center and by the Spanish Ministry of Education and Science through the project CTQ2007-62122/BQU.

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LIGAND-RECEPTOR INTERACTION: FROM FIRST-PRINCIPLES TO APPLICATIONS IN DRUG DISCOVERY

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One of the current challenges for computational chemistry is the accurate prediction of the solvation free energy, which is relevant for the thermodynamics of transfer between gas phase and solution and a key parameter to understand chemitry in solution. This interest explains the intense ongoing efforts invested in developing theoretical solvation models based on both explicit and implicit treatment of solvent and in either classical or quantum mechanical description of the solute. In this framework, this talk pursues to show new computational strategies based on quantum mechanical continuum and classical solvation models designed to gain insight into the molecular determinants of ligand-receptor interaction, paying attention to their impact in drug discovery. In particular, three topics will be considered. First, the MST continuum model [1] will be used to derive hydrophobic descriptors to be used in the context of ligand-based drug design for molecular similarity and pharmacophore studies [2]. Second, an MST-based multilevel approach will be used to explore the conformational landscape of flexible molecules in aqueous solution and to discern the energy penalty associated with selection of the bioactive conformation of ligands. Third, the use of molecular dynamics simulations of proteins in binary solvent mixtures to estimate the druggability of binding sites in pharmacologically relevant targets [3].

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INTERACTION OF DNA MODEL COMPOUNDS WITH LOW ENERGY ELECTRONS

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3-hydroxytetrahydrofuran (3HTHF, C4H8O2) and a-tetrahydrofurfuryl alcohol (THFA, C5H10O2), wich are related to some extent to deoxyribose molecule, have been studied both experimentally and theoretically. Crossed electron/molecule beams technique together with quadrupole mass spectrometer has been used for electron induced positive ion formation studies. The mass spectra of 3HTHF and THFA determined at incident electron energy 70 eV were analyzed and for number of mass-charge ratios (m/q) the ionization efficiency curves have been measured. Due to the lack of structural information about fragments theoretical calculations can help with interpretation of experimental findings. Actually, 18 different m/q channels were experimentally analyzed for 3HTHF, from which 6 were selected for deeper investigation on DFT level of theory and finally 5 for the G3MP2 method. The same was performed for THFA with 15 m/q channels experimentally, 5 on DFT and 4 on G3MP2 levels of theory. Theoretical calculations led to more than 160 fragmentation reactions on B3LYP/6-311+G(2d,2p), from which only those energetically comparable to experimental appearance energies were recomputed on G3MP2.

The experiment showed that although there were 18 and 15 m/q channels observed for 3HTHF and THFA respectively, only 10 (6) of them possess intensity at least 10% of the ionic yield of most intensive fragment for 3HTHF (THFA). Contrary to 3HTHF where parent ion is relatively abundant, for THFA its signal is very weak. Our theoretical conformational studies of neutral and cationic 3HTHF and THFA agree well with this experimental observation, for $3HTHF^+$ at least 2 stable conformers were found while for the $THFA^+$ partial dissociation of the CH2OH group occurred. However the later process, dissociation of CH2OH, seems to be a common feature for the most abundant fragment ion of both molecules, the corresponding structures are the furanose ring cation (with m/q=71) for THFA and $CH2=CH-CH-OH^+$ (with m/q=57) for 3HTHF fragment. Additionally, fragmentations to cations with m/q=70, 58, 43 and 31 were studied theoretically for both molecules, except the 58 for THFA which was not observed.

There is also the possibility of the oxidation of fragmented cationic structures which results in the structures containing single or two oxygen atoms. ($C2H2O2^+$ with m/q=58 from 3HTHF as well as CH2OH + CO from THFA)

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ROLE OF COHERENCE IN RELAXATION OF EXCITATION ENERGY IN MOLECULAR COMPLEXES

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Discussion about the role of coherence in biologically relevant excitation energy relaxation in multi-chromophoric aggregates, which was started by recent advances in non-linear spectroscopy [1], raises fundamental questions about the validity of our understanding of primary processes in photosynthesis. In Ref. [1], surprisingly long living oscillations in two-dimensional (2D) Fourier transformed photon echo spectrum were observed for photosynthetic protein-chromophore complex FMO. These oscillations, predicted earlier theoretically [2], were assigned to the presence of electronic coherence. Moreover, signs of coherence transfer were demonstrated by the same experiment in energy transfer dynamics of the complex. The conclusion was made that the energy transfer proceeds in a wavelike coherent fashion (as opposed to the incoherent hopping) and it was suggested that quantum entanglement plays a role in increasing energy transfer efficiency [1].
In this contribution, the role of various types of coherence in the dynamics of photo-excited molecular systems will be discussed. It will be demonstrated that coherence transfer has non-trivial consequences for interpretation of even the simplest spectroscopic experiment – the linear absorption [3]. The origin of coherent oscillations in 2D spectra and their relation to the dynamics of excited states of molecular aggregates and the dynamics of intra-molecular vibrations in small molecules will be analyzed. This analysis shows that vibrational coherence can be experimentally excluded as a source of the oscillations in FMO [4]. Several relaxation theories will be compared and the second order non-Markovian quantum master equation will be identified as the simplest theoretical description where the dynamics of the system exhibits both comparatively long living coherences and significant coherence transfer within the range of parameters relevant to photosynthetic systems. Finally, the question of non-trivial role of quantum effects in excitation energy transfer will be addressed by constructing a reference model of the aggregates which is completely classical. This classical model exhibits many effects usually associated with quantum nature of molecular aggregates, and can be used as benchmark for identification of non-trivial quantum effects.

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PROBING ENZYME CATALYSIS USING HIGH PRESSURE MOLECULAR DYNAMICS

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Enzymes are highly efficient catalysts, achieving rate enhancements of up to 10^{21}, however it is not yet fully understood how they work. The majority of enzyme reactions involve one or more hydrogen transfers, and these transfers can occur by a partial or full quantum mechanical tunneling mechanism. Morphinone reductase (MR) is an enzyme which employs a deep tunneling mechanism in its reductive half-reaction – the hydride transfer from the NADH-C4 atom to the FMN-N5 atom.[1] This mechanism is thought to be assisted by a promoting vibration that decreases the distance between the donor and acceptor atoms. Experimental work using the pressure dependence of kinetic isotope effects as a probe for hydrogen tunneling has suggested an increase in pressure, from 1 bar to 2 kbar, decreases the donor/acceptor distance.[2] Using pressure is a novel approach for probing hydrogen tunneling in enzymes. This complements the established use of temperature dependence. Pressure shifts the equilibrium of the system towards the tunneling ready configuration. To gain atomistic insight, molecular dynamics simulations were carried out to probe the rate of structural changes in MR as a function of pressure. The protein is shown to be stable across the range of pressures used. Trajectory analysis showed a decrease of 0.19 Å in the average distance between the donor and acceptor atoms, as the pressure is increased from 1 bar to 2 kbar.[3] This is due to the pressure restricting the conformational space in which the nicotinamide can move. This work gives the first atomistic insight into the effect of pressure on the tunneling reaction, through a decrease in the tunneling distance.

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PARADOCKS – A FRAMEWORK FOR MOLECULAR DOCKING WITH POPULATION-BASED METAHEURISTICS

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Background: Molecular interactions define all manifestations of life. Therewith, knowledge on such processes is of paramount importance to various fields of current life science research and development in diverse fields like medicine, biotechnology, and crop science. Molecular docking plays a key-role amongst the variety of approaches and techniques, as it offers the chance to gain knowledge on the actual binding pose, the situation at atomic level that defines binding and function [1]. The prediction of a binding pose between a ligand and a receptor is a multidimensional continuous optimization problem that is hardly solvable in an exact way. Molecular docking solves this problem by combining an optimization algorithm with an objective function that describes the interaction.
Methodology: Our approach to molecular docking, the software ParaDockS, is designed to be flexible enough to hold different optimization algorithms and objective functions. At the current stage, an adapted version of the Particle-Swarm Optimizer (PSO)[2] is implemented. Available objective functions are: *(i)* the empirical objective function p-Score, which was inspired by X-SCORE [3], and *(ii)* an adapted version of the knowledge-based potential PMF04 [4].
Results: We tested the docking accuracy in terms of reproducing known crystal structures and we checked the virtual screening efficiency of our software. The results were compared with the state-of-the-art docking program GOLD (CCDC, Cambridge). For the accuracy tests we docked all structures of the PDBbind [5] core set and calculated the RMSD to the crystal structure. For 52% of all structures (GOLD: 62 %) the docking solution with the best score is within a RMSD of 2 Å. For 73% of the complexes (GOLD: 76 %) at least one of the obtained solutions is within 2Å RMSD. The virtual screening efficiency was tested on datasets with inhibitors of acetylcholinesterase and the estrogenreceptor, respectively. On both targets we find a significant enrichment of active compounds; the effciency is comparable to GOLD.
Conclusions: The current release of the software is usable for molecular docking and can be employed for virtual screenings of large compound libraries. The performance in terms of accuracy and enrichment is close to the results of commercial software solutions. ParaDockS offers all advantages of open source software and is free for everyone and everyone is invited to use and further improve the program (http://www.paradocks.org).

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ALLOSTERIC MECHANISM FOR HEXAMERIC E. COLI ARGININE REPRESSOR BASED ON COMPETITION BETWEEN RESIDENT ARGININE RESIDUES AND L-ARGININE LIGANDS

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Molecular dynamics simulations with ArgRC, the ~ 50 kDa C-terminal hexamerization and L-arginine-binding domain of E. coli arginine repressor, reveal the protein's range of motions with and without bound L-arg. Simulations starting from the essentially identical apo- and holo-ArgRC X-ray crystal structures evolve distinctly during 20 ns. The two trimers of apoArgRC rotate freely with respect to one another between two limiting ensembles, one resembling the starting state derived from the crystal structure and the other rotated in one direction by a mean of ~ 13 degrees. Simulations with holoArgRC having six L-arg ligands bound reveal essentially no rotational motion. The crystal-like ensemble of apoArgRC is visited much less frequently than the rotated ensemble; bond occupancies and entropies in the two ensembles likewise imply the crystal traps a high-energy state. Detailed analysis and control trajectories reveal that the unidirectional motion of apoArgRC is promoted by the single arginine residue of each polypeptide chain, which extends its guanidino group into the L-arg-binding pocket from one side, mimicking the ligand's interactions with an aspartate sidechain across the pocket. Simulations with the apoArgRC hexamer after adding six L-arg ligands confirm that, as in holoArgRC, rotational dynamics are suppressed, and the most populated states are holo-like. Simulations with incremental additions of L-arg ligands reveal that a single bound L-arg is sufficient to suppress rotation and favor a hololike ensemble, consistent with the multiphasic calorimetric binding profile that reveals negative cooperativity between the first ligand and the remaining five. The proposed mechanism is corroborated by recent crystals of Mycobacterium tuberculosis ArgRC, which present an arginine sidechain on the opposite side of the pocket and which trap a state that is rotated in the opposite direction. Simulations with M. tuberculosis apoArgRC indicate that it can also rotate in the same direction as E. coli apoArgRC, promoted by a second arginine/aspartate sidechain pair on the other side of the pocket. This direct and simple mechanism suggests that amino acid binding in competition with resident sidechains was a founding basis for the evolution of protein allostery.

ETS-NOCV - A COMBINED CHARGE AND ENERGY DECOMPOSITION SCHEME FOR BOND ANALYSIS

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A new scheme for chemical bond analysis by combining the Extended Transition State (ETS) method [1] with the Natural Orbitals for Chemical Valence (NOCV) [2] will be presented. Within the ETS-NOCV [3] charge and energy decomposition analysis it is not only possible to decompose the deformation density, Δρ, into the different components (such as σ, π, δ, etc.), but also to obtain the corresponding energy contributions to the total bond energy. Thus, the ETS-NOCV scheme offers a *compact*, qualitative and quantitative, picture of the chemical bonding within one common theoretical framework. The applicability of the ETS-NOCV scheme is demonstrated for single (H_3X-XH_3, for X = C, Si, Ge, Sn) and multiple (H_2X=XH_2, H_3CX≡XCH_3, for X = C, Ge) covalent bonds between main group elements, for multiple bonds between metal centers (Cr_2, Mo_2, W_2, $[Cl_4CrCrCl_4]^{4-}$), as well as for the agostic bonds between C-H and the metal. Finally, we include the applications involving examples of hydrogen bonding (Figure 1).

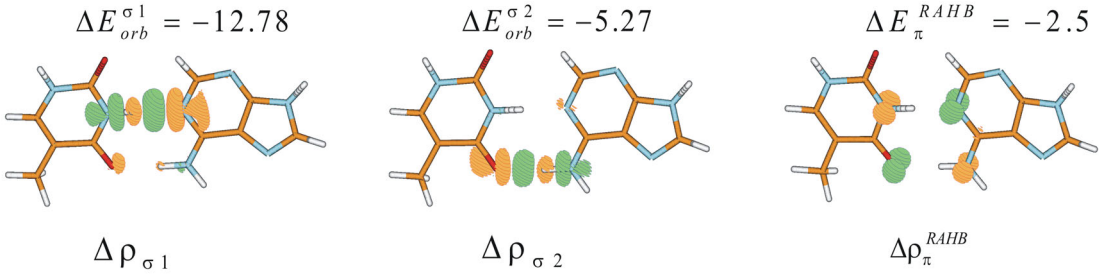

Figure 1: The contours of relevant deformation density contributions describing the hydrogen bonding bonding together with the corresponding energies obtained from ETS-NOCV scheme.

Acknowledgements: This work was supported by a research grant from the Polish Ministry of Science and Higher Education in Poland (N N204 227534).

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MOLECULAR DYNAMICS STUDY OF THE EFFECT OF ORGANIC SOLVENTS ON STRUCTURE AND ACTIVITY OF HALOALKANE DEHALOGENASE

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Haloalkane dehalogenases are enzymes which catalyze the cleavage of the carbon-halogen bond by a hydrolytic mechanism. Solubility of such hydrophobic substrates is limited in aqueous solutions but solubility can can be improved by addition of water soluble organic solvents. Introducing the organic solvents to the environment of enzymes such as LINB and DhaA improves the efficiency of these enzymes than in water solutions. For example haloalkane dehalogenase DhaA, exhibits activity with a broad range of halogenated substrates including 1,2,3-trichloropropane (TCP)[1] and sulphur mustard[2] and its activity can be addition of dimethyl sulfoxide (DMSO) to the solution mixture.

In this work we studied the effect of various organic solvents (e.g., acetone,formamide, Isopropanol) on the structure and activity of haloalkane dehalogenases by molecular dynamis (MD) simulations.

Acknowledgements: This research was supported by the Ministry of Education of the Czech Republic (LC06010 and MSM6007665808), by the Academy of Sciences of the Czech Republic AV0Z60870520) and the Grant Agency of the Czech Republic (203/08/0114)

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NON-HYDROGEN BONDING INTRAMOLECULAR INTERACTIONS: IMPORTANT YET OFTEN UNRECOGNIZED

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Intramolecular interactions are widely-occurring and can significantly influence structures of molecules and their resultant functional behavior. In this talk, I will survey a number of examples of intramolecular electrostatically-driven interactions that involve atoms other than hydrogen as the positive partner. Some of these will involve σ-hole bonding, which is a highly directional noncovalent interaction between a positive region on a covalently-bonded Group IV – VII atom and a negative site on another molecule, e.g. a lone pair of a Lewis base. The discussion will include the neighboring group effects in iodoxybenzoates and related molecules, the effects of sulfur and selenium in thiazole and selenazole nucleoside drugs and 5-selenium-thymidines in stabilizing particular conformations, the β-effect in silicon chemistry, and the extremely short carbon-chlorine bond in chlorotrinitromethane (the shortest C-Cl bond known).

THE STRUCTURAL, IONIZATION AND OPTICAL PROPERTIES OF OLIGOMERS BUILDING FRAGMENTS OF CONDUCTING POLYMERS

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Conjugated donor-acceptor (D-A) copolymer semiconductors are of growing interest for organic optoelectronic and electronic applications, including photovoltaic cells, lightemitting diodes (LEDs) and field-effect transistors (FETs).[1] Structures, electron ionization and exicition energies, and electron density distribution are widely studied for carbazole polymers substituted symmetrically by thiophene. The theoretical studies of the molecules are important for the design of process of polymerization, modeling the final polymers and their conducting properties.[2]

In this study, we observed non typical behavior of conducting polymers. It was found the electron population analysis on connection between two mers, but not, as traditionally on the end of polymers (Fig. 1, 2). Molecular structures and electronic properties of monomers influence on every step of polymerization process and are probably the most important factors shaping the final polymer. Each step of the polymerization is influenced by distinct molecular parameters. The calculated properties of consecutive oligomers indicate their fast convergence to value characterizing polymers. The molecular modeling applied in this work is based on ab initio calculations.[3,4] The optimization geometry was performed applying the DFT method the standard 6-31 G* atomic basis set. This method is shown to be reasonable compromise between quality and cost of calculations for similar size molecules. The results reported here were obtained by utilizing the GAUSSIAN 03 code.

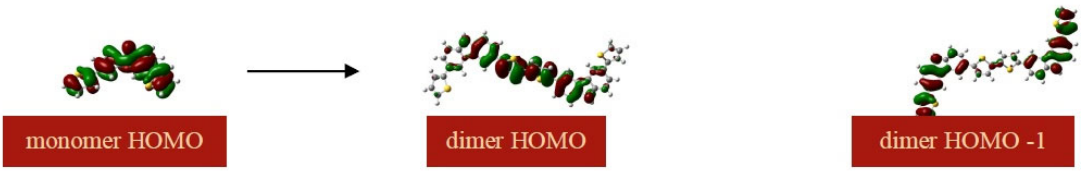

Fig. 1. HOMO molecular orbitals of carbazole and thiophene polymers

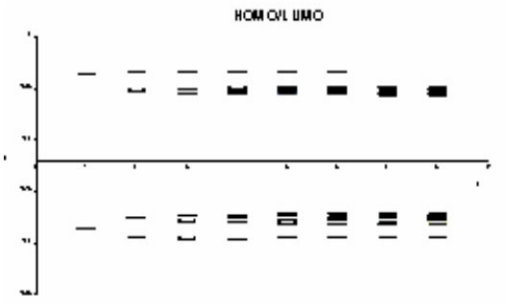

Fig. 2. The arrangement of HOMO/LUMO orbitals for carbazole derivatives (from monomer to octamer)

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STUDY OF A PROTEIN-LIGAND INTERACTION MECHANISM: EXAMPLE OF FKBP12 WITH A NANOMOLAR AFFINITY INHIBITOR

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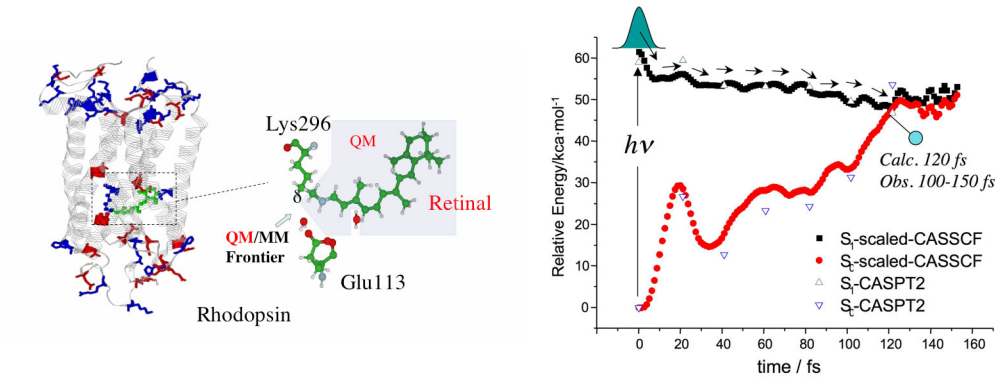
We present the study of FKBP12 in interaction with a rotamase synthetic inhibitor with high affinity ((1R)-1,3-Diphenyl-1-propyl (2S)-1-(3,3-Dimethyl-1,2-Z-dioxopentyl)-2-piperidine-carboxylate). FKBP12 is the 12 kDa mammalian FK506 Binding Protein predominant cytoplasmic isoform in most cells and is the smallest peptidylprolyl cis/trans isomerase (PPIase) in the FKBP family of proteins. This protein has been shown to play important role in cell cycle mediation, signal transduction, calcium channel modulation and may be involved in Parkinson's disease. FKBP12 is therefore an important therapeutic target. This study aims at finding the rules governing the complexation in order to design new potent ligands giving better and/or new abilities to this protein. On the complexation pathway of FKBP12 and its ligand, we have localized an intermediate state whose main features may explain the role played by the peripheral groups bound to the α-ketopipecolinyl-amide core by enhancing the affinity of the ligand. This intermediate state provides a rationale for explaining the relative affinities of a series of ligands. Finally, the precise study of the interactions using molecular orbitals (MO) calculations shows the peculiar importance of aromatic interactions in the mechanism of complexation.

TOWARDS A COMPUTATIONAL PHOTOBIOLOGY

Massimo Olivucci

Dipartimento di Chimica, Universitá di Siena (Italy) and the Chemistry Department, Bowling Green State University, OH (USA)

In this lecture we show how the development of a hybrid quantum mechanics/molecular mechanics computational strategy (see Figure below) based on multiconfigurational perturbation theory and complete-active-space-self-consistent-field geometry optimization has recently allowed for the correct evaluation of the excited-state properties of *chemically different* chromophores *embedded in different protein environments and*In particular we show how it has been possible to investigate the static and dynamics factors responsible for the color and ultrashort excited state lifetime (see Figure below) observed for *rhodopsin proteins* (such as rhodopsin and sensory rhodopsins) featuring a cationic retinal chromophore. The same progress in the field of the computational design of artificial bio-mimetic switches will be revised.



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COMPUTATIONAL STUDY OF ENZYME CATALYSED H-TUNNELING REACTIONS

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It is widely accepted that quantum mechanical tunnelling can significantly influence the rate of hydrogen transfer in many enzyme-catalysed reactions. More controversial at present is the role enzyme dynamical effects play in catalysis. Two systems, hyperthermophilic dihydrofolate reductase (TmDHFR) and morphinone reductase (MR), have been chosen to test the hypothesis of environmentally coupled hydrogen tunnelling. A combined QM/MM method was applied in conjunction with ensemble averaged-variational transition state theory with multidimensional tunnelling (EA-VTST/MT).

In both cases, the computational studies qualitatively reproduced the experimental hydrogen transfer rate and primary (1°) and α-secondary (2°) kinetic isotope effects (KIEs), and allowed us to understand tunnelling dynamics at a level of detail not possible solely based on experimental measurements. In TmDHFR [1,4], H-tunnelling was calculated to contribute to 50-80% of the reaction rate constants at 5-65 °C. Structural and dynamical analysis indicated that the catalytic power of TmDHFR was correlated with motions between domains, as well as within and between its two subunits. In contrast to TmDHFR, the calculations suggest that 99% of hydride transfer reaction proceeds via tunneling in MR [2,3], although the experimentally observed KIE lies below the semi-classical limit. This dominant tunnelling contribution was likely to arise from pre-organisation of the active site towards a "tunneling-ready" configuration and participation of the heavy atom motions in the substrate and cofactor.

Acknowledgements: Financial support from the UK Biotechnology and Biological Sciences Research Council (BBSRC) is acknowledged.

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MODELING OF INTERMOLECULAR INTERACTIONS OF AMINO ACIDS WITH PHOSPHONIC OR CARBOXYLIC UNIT

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The aminophosphonic compounds are intensive examined as a platform widely applied in supramolecular chemistry. They possess useful application in crystal engineering as building blocks in order to create specific engineered molecular materials bearing desired crystallographic architecture and specific chemical/physical properties [1]. Furthermore, the aminophosphonates would be successfully applied as chemical sensor [2,3].
It would be interesting to assess and explore in details how their properties affect the interaction with themselves and with different biologically important compounds.
We investigate interactions in two systems. First of them consisted of phosphonic analogues of glycine, the second one of glycine both with phosphonic and carboxylic moiety.
The molecular modeling was performed using ab initio calculations. The optimization of the geometry was achieved applying the HF and DFT methods with 6-31++G(d,p) basis set. The calculations were conducted in a gas phase and in a solvent - scrf iepcm[6]. The stationary point was confirmed by frequencies analysis. The interaction energy was calculated using DFT and MP2 methods with 6-311++G(d,p) basic set. All the computations were performed using GAUSSIAN 03 code
In system of two aminophosphonates, the formation of two different complexes was observed. In the first one, three hydrogen bonds (Fig.1) were noticed. They were more stable in comparison with the second system where two weaker hydrogen bonds were created (Fig.2).
Additionally, the calculations in system presented in (Fig.3) strongly suggest that interaction energy was significantly less favourable as compared to two phosphonate species complex. These finding could explain reason why these compounds are bad receptor for amino acids.

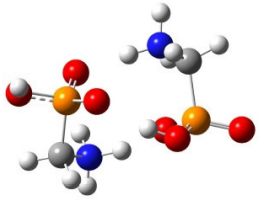

Fig.1

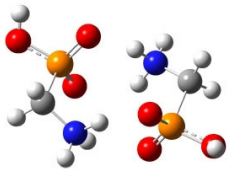

Fig.2

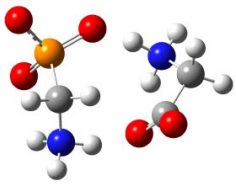

Fig.3

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THE AVERAGE LOCAL IONIZATION ENERGY: A FUNDAMENTAL AND MULTI-FACETED PROPERTY

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The average local ionization energy, $\overline{I}(\mathbf{r})$ [1], is increasingly recognized as an important tool for analyzing and characterizing atoms, molecules and other systems. It is defined by the formula, $\overline{I}(\mathbf{r}) = \sum_i \rho_i(\mathbf{r})|\varepsilon_i| \Big/ \rho(\mathbf{r})$, where $\rho_i(\mathbf{r})$ is the electronic density of the ith occupied orbital, having energy ε_i, and $\rho(\mathbf{r})$ is the total electronic density. $\overline{I}(\mathbf{r})$ is interpreted as the average energy required to remove an electron from the point r in the system under consideration [1,2]; the focus is upon the point in space rather than a particular orbital. The lowest values of $\overline{I}(\mathbf{r})$ computed on an appropriate molecular surface identify the locations of the most reactive electrons, and hence the most favorable sites for electrophilic attack. However the significance of $\overline{I}(\mathbf{r})$ goes much beyond this [2,3]. In atoms, $\overline{I}(\mathbf{r})$ brings out the shell structure, and its average values over their surfaces correlate with their electronegativities. In molecules, it reveals radical sites, localized π bonds and strained bonds. These and other aspects of $\overline{I}(\mathbf{r})$ will be surveyed.

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QM/MM METHODS: FROM UNDERSTANDING METALLOPROTEIN'S REACTIVITY TOWARD IMPROVING THE DRUG DESIGN PROCESS

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Metalloproteins are involved in a great number of fundamental and challenging reactions ranging from the oxidation of methane into methanol to the metabolism of drugs. Yet these systems are challenging to model because standard force fields cannot accurately describe the behaviour of transition metals and these later, often in a high oxidation state, introduce strong polarization effects in the system. Therefore, QM/MM appears to be the method of choice to study these systems.
Schrodinger has developed QSite, a powerful QM/MM program, whose special algorithms to improve speed, initial guesses and to handle the QM/MM frontier made it particularly attractive in the studies of metalloproteins.
We will show this program was successfully used to study the reaction mechanisms of challenging metalloenzymes.
We will also see how the QM-Polarized Ligand Docking (QPLD) protocol which combines docking steps with Glide with QM/MM charge calculation using QSite can be used to improve docking accuracy in systems with important electronic polarization effects.

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COPPER-1,10-PHENANTHROLINE COMPLEXES BINDING TO DNA: STRUCTURAL PREDICTIONS FROM MOLECULAR SIMULATIONS

Arturo Robertazzi,[1,2] Attilio Vittorio Vargiu,[2,1] Alessandra Magistrato,[3,1] Paolo Ruggerone,[2] Paolo Carloni,[1,3,4] Paul de Hoog[5] and Jan Reedijk[5]

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Copper complexes of 1,10-phenanthroline (phen) are chemical nucleases employed as footprinting reagents for determining ligand binding sites.[1] The cleavage activity of the parent complex, $Cu(phen)_2$, occurs according to the following mechanism: a) reduction of $Cu(phen)_2^{2+}$ to $Cu(phen)_2^{+}$ b) non-coordinative binding of $Cu(phen)_2^{+}$ to DNA c) $Cu(phen)_2^{+}$ oxidation to $Cu(phen)_2^{2+}$ by H_2O_2, and formation of Cu-"oxo" and/or Cu-"hydroxyl" species d) oxidative attack leading to DNA-cleavage.[1] The potential clinical use of the parent compound is mainly prevented by two drawbacks: i) the low binding constant of the second phenanthroline; ii) the modest sequence selective DNA cleavage.

To improve $Cu(phen)_2$ efficiency, Pitié *et al*.[2] used a serinol bridge to link the two phen rings leading to Cu(2-Clip-phen) and Cu(3-Clip-phen) derivatives, which cleave the DNA 2 and 60 times more efficiently than $Cu(phen)_2$. To address the modest sequence selectivity, the amine group of the serinol link was functionalized with sequence specific DNA minor/major-groove binding ligands such as cisplatin- and distamycin-like compounds, leading to enhanced activity compared to single components.[2,3]

In this work,[4] a combination of theoretical methods, including DFT, Docking and Molecular Dynamics, was employed to i) characterize the DNA binding of these complexes and ii) to determine the origin of their diverse DNA-cleavage efficiency. Our simulations clearly revealed that several factors such as planarity of the ligand, better interaction with DNA and minor-groove fit, contribute to the enhanced efficiency of Cu(3-Clip-phen) compared to the other structurally similar complexes.

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IMPEMENTATION OF MOLECULAR MECHANICS POLARIZATION IN QM/MM CALCULATIONS

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Hybrid quantum mechanical/molecular mechanics (QM/MM) calculation are widely used for the study of biological systems. The effect of polarization on the charge distribution is usually included in the QM part; however this effect is often neglected for the MM part due to difficulties of implementation. However MM polarization can play an important role; furthermore excluding polarization from the MM part is inconsistent with a polarized QM part. Therefore we have introduced simple approach to treat the polarization of the MM part of the model. The approach is based on the treatment of polarization by induced atomic charges instead of induced dipoles.

In this method, the induced dipoles (calculated from atomic polarizabilities) are represented by induced charges on the atom itself plus neighboring atomic sites. This brings considerable simplification, since the expensive evaluation of the charge-dipole and dipole-dipole interactions can be avoided. Therefore standard MM programs can be used, since they already evaluate electrostatic interactions from atomic charges. Thus induced charges can simply be added to permanent MM atomic charges. The induced charges are easily calculated from atomic polarizabilities and electrostatic potentials arising from both the QM part and other MM atoms. Also, the polarization energy and the analytical energy gradients are easily calculated[1].

We have commenced implementation of the method in Chemshell, since Chemshell interfaces with many QM and MM programs and it is readily available. Since analytical gradients are also calculated, it can be used for optimizations and MD simulations. The method has been tested on small molecules and test systems of biological significance. The method has also been applied to the study of effect of polarization on transition state stabilization in the enzyme chorismate mutase since this is relevant to the general question of how enzymes work.

Acknowledgements: Support from BBSRC grant is aknowledged.

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HEISENBERG UNCERTAINTY RELATIONS CAN BE REPLACED BY STRONGER ONES

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Two uncertainty relations, one related to the probability density current and the other one related to the probability density, are derived and discussed. oth relations are stronger than the Heisenberg and Robertson-Schrodinger uncertainty relations. heir generalization to the multi-dimensional case and to the mixed states is also discussed.

IN SILICO STUDY OF INTERACTIONS BETWEEN VEGFR2 AND INHIBITORS BASED ON TRIAZOLE LINKERS

Marek Skoršepa[1], Šimon Budzák[1], Miroslav Medveď[1], Andrej Boháč[2]

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Inhibition of angiogenesis (new blood vessel creation) is a possible way to treat cancer[1,2] by fixing or slowing down the process of tumor neovascularization[3]. Therefore, looking for apropriate inhibitors of VEGFR2, the growth factor that plays a key role in the early stages (initiation) of angiogenesis, is the aim of many recent studies. Linking two (or more) fragments of known molecules with certain inhibitory activities can be a promising method to design new efficient inhibitors.

In our study a series of sixteen inhibitors consisting of molecular fragments of two known inhibitors (1Y6A and 1YWN) linked by a flexible chain based on triazole was designed (Fig. 1). Due to better accommodation of the receptor (VEGFR2) binding site, the stronger interaction with the newly-designed inhibitors compared to the parent inhibitors was expected. The interaction energies for VEGFR2 and two known inhibitors (and their fragments) and then for VEGFR2 and all triazole-based inhibitors have been calculated via the ONIOM approach[4] where the AM1 (or PM3) and DFT (B3LYP/6-31G*) methods have been used to describe outer and inner layers of the system.

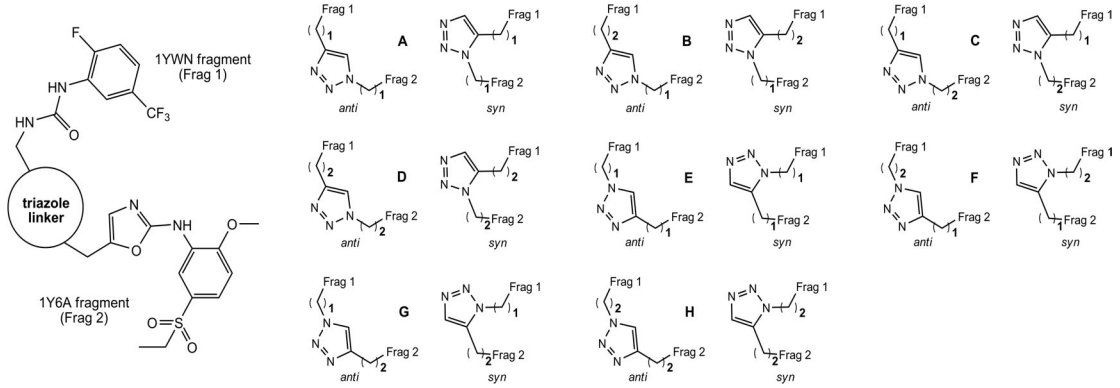

Figure 1: Molecular fragments of two known inhibitors linked by the different triazole linkers

Acknowledgements: Support from VEGA grant No. 1/4467/07 is acknowledged.

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DFT CALCULATIONS OF STRUCTURAL PROPERTIES OF B_{12}-RETRO-RIBOSWITCHES

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It has been discovered that cobalt corrinoids may directly interact with nucleotide environment in covalent models and act as riboswitches. This mechanism of action is based on binding cobalamin by messenger RNA and switching between "based-on" and "based-off" conformation of a molecule [1].
The structural properties of these two forms of cobalamins incorporated with guanine or thymine residue were examined using density functional theory (DFT) method. The optimized structure is in good agreement with experimental data, reproducing the bent-up deformation of the corrin ring as well as the cobalt-ligand bond distances [1].

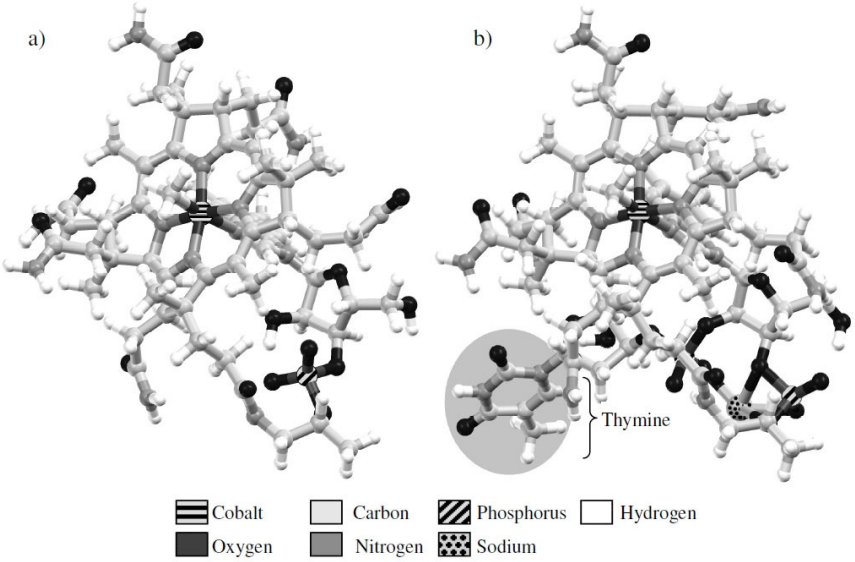

Figure 1. a) methylcobalamin, b) methylcobalamin incorporated with thymine

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MODELING INTERACTIONS IN CATALYTIC SITES

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Recent successful theoretical design of enzymes with new catalytic activity [1] based on transition state stabilization points once again on extraordinary iimportance of interactions in catalytic sites. Such interactions are usually studied by relatively crude methods, employing mostly empirical force fields or in the best case by supermolecular variational methods denying chance to inspect the physical nature of corresponding forces involved. Such interactions can be analyzed using variation-perturbation partitioning of intermolecular interaction energy into electrostatic, exchange, delocalization and correlation terms [2] defining hierarchy of approximate models useful in rational design of new catalyst with desired activities.

One of such models - Differential Transition State Stabilization (DTSS) approach [2] describes catalytic activity of molecular environment allowing to determine the most important residues and energy contributions involved. Corresponding analysis of protein kinase A[3] and fatty acid amide hydrolase [4] catalytic activity will be discussed.

Acknowledgements: Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

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UNDERSTANDING THE NMR CHEMICAL SHIFTS FOR 6-HALOPURINES: ROLE OF STRUCTURE, SOLVENT, AND RELATIVISTIC EFFECTS

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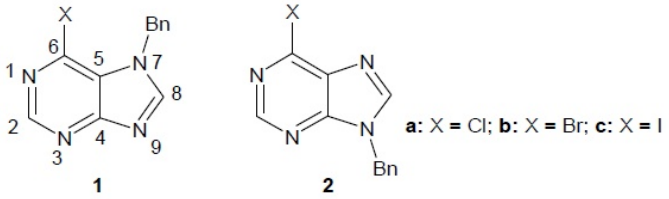
A prototypical study of NMR chemical shifts in biologically relevant heteroaromatic compounds containing heavy halogen atom is presented for the two isomers of halogen-substituted purines (1, 2).

Complete sets of NMR chemical shifts are determined experimentally in solution. Experimental results are completed by quantum-chemical calculations which provide understanding of the trends in the chemical shifts in studied compounds and which show how different physical effects influence the NMR parameters.

Chemical shifts for isolated molecules are calculated using density functional theory methods, the role of solvent effects is studied using polarized continuum models, and the relativistic corrections are calculated using the leading-order Breit-Pauli perturbation theory (BPPT).[1] Calculated values are compared with experimental data and the effects of structure, solvent, and relativity are discussed. We find out that relativistic effects cannot even be neglected in chlorine species to get a good agreement with the experimental data. Solvent effects are of smaller importance for ^{13}C shifts but have been proven to be substantial for particular ^{15}N shifts.

Present contribution seems to be the first real chemical application of BPPT approach to biologically relevant, aromatic molecules.



1 **2** **a:** X = Cl; **b:** X = Br; **c:** X = I

Acknowledgements: Ministry of Education of the Czech Republic (MSM0021622413 and LC0603) and the Czech Science Foundation (No. 203/09/2037).

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COMPUTATIONAL STUDIES OF NMR PARAMETERS IN ENDOHEDRAL FULLERENES. THE ROLE OF INTRA-MOLECULAR DYNAMICS.

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In endohedral fullerenes, atoms, ions, or clusters are enclosed in a fullerene cage. Endohedral fullerenes are promising for applications in materials science such as fuel cells, magnetic resonance imaging, memory devices, spin traps, quantum computing devices, etc. Our recent results from computational studies of endohedral and pristine fullerenes will be presented:
1. Calculations of NMR parameters at real experimental conditions. Xenon chemical shift in Xe@C60 including dynamics and temperature effects [1].
2. Dynamics, bonding and magnetic resonance properties of $Sc_3C_2@C_{80}$ and its monoanion [2].

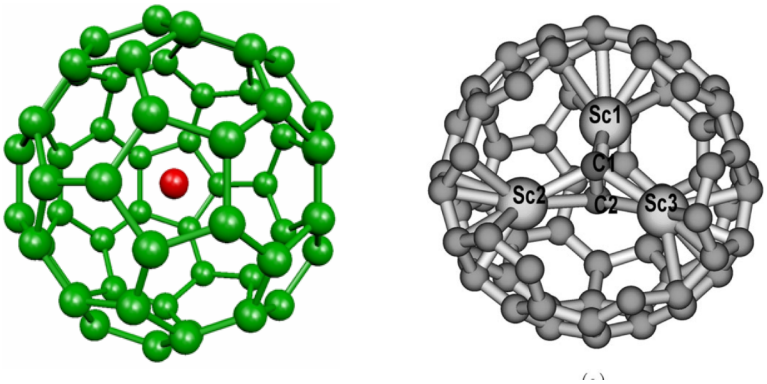

Figure 1. $Xe@C_{60}$ (on the left) and $Sc_3C_2@C_{80}$.

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COUPLED-CLUSTER AND DENSITY FUNCTIONAL THEORY STUDIES OF EXCITED-STATE POTENTIAL ENERGY SURFACES OF POLYENES AND PROTONATED SCHIFF BASES

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The potential energy surface of the ^1B_u and $^1A'$ states of all-*trans*-polyenes and the corresponding protonated Schiff bases have been studied at the time-dependent density functional theory (TDDFT) and linear response coupled cluster (LRCC) levels. The calculations show remarkable differences in the excited state potential energy surfaces of the polyenes and the protonated Schiff bases [1]. The excited states of the polyenes exhibit high torsion barriers for single-bond twists and low torsion barriers for double-bond twists. The protonated Schiff bases are very flexible molecules in the first excited state with low or vanishing torsion barriers for both single and double bonds. The TDDFT and LRCC calculations yield qualitatively similar potential energy surfaces. The electronic excitation spectra of *trans*-1,3-butadiene (CH2=CH–CH=CH2) and *trans*-2-propeniminium (CH2=CH–CH=NH_2^+) have also been studied at LRCC and TDDFT levels employing large correlation-consistent basis sets [2]. The study shows that approximate singles and doubles coupled-cluster (CC2) calculations yield excitation energies in good agreement with experiment for all states except for the two lowest excited A_g states of *trans*-1,3-butadiene which have significant multiconfigurational character. TDDFT calculations employing the generalized gradient approximation and hybrid functionals yield too low excitation energies in the basis set limit. The CC2 calculations yielded excitation energies for 11-*cis*-retinal of 2.14 and 3.21 eV [3] which agree well with the experimental gas-phase values of 2.03 and 3.18 eV [4]. The corresponding B3LYP TDDFT energies are 2.34 and 3.10 eV [3]. Comparisons of CC2 excitation energies with experimental data can be used to assess the multi-reference character of the excited states of the polyenes and protonated Schiff bases. The good agreement with experiment shows that the lowest excited states of retinal protonated Schiff bases can be studied using single-reference approaches such as CC2 and B3LYP TDDFT.

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PROBING THE MOLECULAR FLEXIBILITY WITH NMR SPECTROSCOPY

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Inclusion of molecular flexibility can alter the magnitude of NMR spectroscopy parameters with respect to their magnitudes calculated only for geometry corresponding to the minimum on potential energy surface. The reason for neglecting the effect of molecular motion in theoretical modeling is pragmatic, computational effort needed for its inclusion often can't compensate the gain – relatively small "delta" of the calculated NMR parameters. On the other hand, probing the local molecular motions of molecules with NMR spectroscopy can deepen our knowledge about their basal behavior. Furthermore, the accurate interpretation of experimental data offers probably the only way for reliable validation of empirical force-fields which is nowadays widely used for describing the motional freedom of large molecules. Different computational strategies for calculating the NMR parameters taking into account the vibration/rotation motion in molecules will be presented.

Acknowledgement: This work was supported by the the Grant Agency of the Czech Republic, Grant Agency of the Czech Academy of Sciences, and by the HFSP Grant.

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MOLECULAR DYNAMICS SIMULATIONS OF MOUSE FERROCHELATASE VARIANTS

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Ferrochelatase, the last enzyme in the catalytic pathway of the haem biosynthesis, catalyses the reaction of insertion of a ferrous ion into protoporphyrin IX by distorting the planar geometry of the latter reactant. Based on experimental data, this function has been assigned to residues in the active site. [1] The poster presents molecular dynamics simulations of the wild-type and variant forms of the mouse ferrochelatase in complex with the product (haem). The simulations aim at understanding the role of active site residues in this catalytic process. Analysis of the simulation trajectories explains the consequences of the introduced mutations and sheds more light at the role of the His209 residue in porphyrin macrocycle distortion. The function of residues coordinating propionate groups of the haem molecule is discussed in terms of stability of the substrate and product complexes. [2]

Acknowledgements: This work was supported by Funda c˜ao para a Ciˆencia e a Tecnologia (FCT), Lisbon, grant no. SFRH/BPD/38809/2007. Calculations were performed at the Wrocław Centre for Networking and Supercomputing.

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ENVIRONMENT IMPOSED ALTERATIONS OF AROMATIC CHARACTER OF CANONICAL NUCLEOBASES AND AROMATIC AMINO ACIDS

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Aromaticity is a theoretical concept of practical importance, widely used in organic chemistry and related fields [1]. Among many aromatic systems the basic constituents of DNA, RNA and humans proteins (enzymes) are of particular importance, at least from the point of view of structural biology. One of very important and till now poorly understood aspect is the influence of the environment on the fluctuations of aromatic nature [2]. This project intend to quantify the heterogeneity of different surroundings in terms of structural index of aromaticity, HOMA, of canonical nucleobases and aromatic amino acids in explicit water conditions, proteins imperious and B-DNA crystals. Significant environment influence on HOMA values has been observed as it was demonstrated in Fig.1. In explicit water solutions and B-DNA solids interior it is observed significant increase in aromatic character of pyrimidine rings of most nucleobases, except of adenine. Also aromaticity of imidazole rings of adenine and guanine increases in the presence of water field. Interestingly, B-DNA has almost insignificant impact on HOMA(imidazole). Also only minor influence on aromatic characters was noticed for amino acids, except of histidine. This residue increases its aromaticity both in water and protein environments.

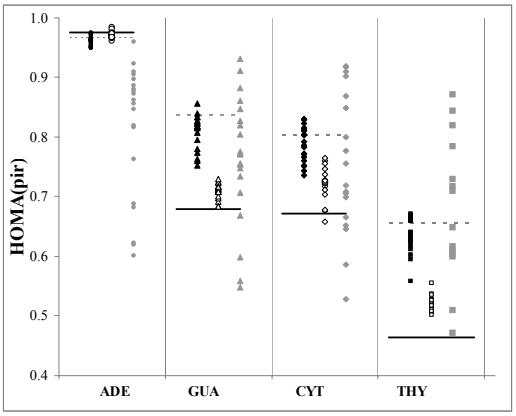

Figure 1: Distribution of HOMA values of pyrimidine ring of canonical nucleobases estimated in explicit water conditions (black symbols), in protein environment modeled by QM/MM method (open symbols) and values estimated on geometries taken directly from PDB files (grey symbols). The HOMA values corresponding to the gas phase and PCM water conditions are represented by solid and dashed lines, respectively.

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ASSESSING AROMATICITY USING THE GAUGE INCLUDING MAGNETICALLY INDUCED CURRENTS (GIMIC)-METHOD

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Aromatic molecules sustain net diamagnetic ring currents resulting in induced magnetic fields with opposite directions to the external one. For antiaromatic molecules the ring current circles in the opposite direction. Nonaromatic molecules sustain a zero net current, which often is the result of non-zero diamagnetic and paramagnetic currents of the same magnitude. The recently developed Gauge Including Magnetically Induced Currents (GIMIC) method [1] is a versatile tool to assess the extent of electron delocalization in a molecule and the degree of molecular aromaticity. The GIMIC calculations yield quantitative information about the magnetically induced current densities. The current strengths and pathways can be unambiguously determined by numerical integration of the current flow passing chemical bonds. The GIMIC method has been applied to study the magnetically induced currents in, among other studied systems, hydrocarbon nanorings [2], a bianthraquinodimethane-stabilized [16]annulene, [4], the C60 fullerene [3], Polycyclic Antiaromatic Hydrocarbons (PAAH), small open-shell molecules, and a series of small ring-shaped aromatic, antiaromatic and nonaromatic hydrocarbons. Benzene is the archetype aromatic compound, and a qualitative measure of the aromaticity of a compound is obtained by comparing the calculated induced current strength to the benzene value, which is 11.4 nA/T at CCSD(T) level [1]. With the GIMIC program, the current density is computed from the density matrixes obtained calculating the NMR chemical shielding at DFT or ab initio levels of theory. The program also include several options to visualize the calculated current densities.

Acknowledgements: This research has been supported by the Academy of Finland through its Centers of Excellence Programme 2006–2011 and the OPNA research project (118195). The research collaboration is supported by the Nordic Centre of Excellence in Computational Chemistry (NCoECC) project funded by NordForsk (070253). S.T. acknowledges financial support from the Alfred Kordelin Foundation and from the Oskar ¨Oflund Foundation. We also thank CSC – the Finnish IT Center for Science for computer time.

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ELUCIDATING THE MECHANISM OF COMPLEX CHEMICAL REACTIONS THROUGH THE USE OF THE REACTION ELECTRONIC FLUX

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The reaction electronic flux (REF) is a descriptor of the electronic activity that takes place during a chemical reaction [1,2]. The REF is defined as the derivative of the electronic chemical potential μ that describes the escaping tendency of electrons from equilibrium, with respect to the reaction coordinate ξ:

$$J(\xi) = -Q\frac{d\mu}{d\xi} \tag{1}$$

where Q is the transport coefficient. The REF is determined by numerical differentiation of the chemical potential profile along ξ. Then $J(\xi)$ can be expressed in terms of electronic polarization and transfer contributions:

$$J(\xi) = J_p(\xi) + J_t(\xi) \tag{2}$$

The polarization contribution is determined numerically through a *ad hoc* fragmentation procedure and the use of the counterpoise method; the transfer contribution is then determined from $J(\xi)$ and $J_p(\xi)$. It is shown in this talk that, expressed in terms of polarization and transfer effects, the REF becomes a powerful tool to elucidate the mechanism of chemical reactions.

Applications of this new descriptor of electronic activity during a chemical reaction, for elucidating complex reaction mechanisms, will be presented and discussed.

Acknowledgements: Support from FONDECYT through grant No. 1090460 and FONDAP No 11980002 (CIMAT) is acknowledged.

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USING FEYNMAN PATH INTEGRALS TO DESCRIBE NUCLEAR QUANTUM EFFECTS

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For a long time, nuclear quantum effects were believed to be unimportant in the dynamics of large biomolecules. However, recent experiments on hydrogen transfer in enzymes showed extremely strong quantum effects, reflected in so-called "anomalous" kinetic isotope effects (KIEs), observed even at the physiological temperature. Not only was tunneling extremely important, but also the temperature dependence of these KIEs showed a surprising behavior.
Computationally, quantum effects at finite temperatures can be described efficiently by the imaginary-time Feynman path integral formalism, which allows Monte Carlo or Molecular Dynamics implementations, and so is practical for large systems. I will describe how the path integrals can be used to compute the equilibrium and kinetic isotope effects [1, 2, 3].
Unlike standard approaches, ours does not assume the separability of rotational and vibrational motions and does not make the harmonic approximation for vibrations or rigid rotor approximation for the rotations. In particular, many-dimensional tunneling, zero point energy, and anharmonicity effects are described correctly quantum mechanically. The approach is based on the thermodynamic integration with respect to the masses of isotopes, and in the case of the KIEs, on the Quantum Instanton approximation for the rate constant. I will also describe an efficient estimator [2, 3] for the derivative of the free energy whose statistical error is independent of the number of imaginary time slices in the path integral, thus allowing a speedup by two orders of magnitude at room temperature.
I will show applications of the methodology to several organic molecules, make comparisons with other methods as well as with experiments, and describe the implementation of the methodology in Amber 10 [4].

Acknowledgements: This research was supported by the Swiss NSF (grant 200021 124936/1) and by the EPFL.

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STRUCTURAL INTERPRETATION OF J-COUPLING CONSTANTS CALCULATED IN GUANOSINE AND DEOXY-GUANOSINE

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The relationship between the the glycosidic torsion angle χ (Figure 1), the three-bond couplings ^{3}J(C8-H1') and ^{3}J(C4-H1'), and the four one-bond couplings ^{1}J(C8-H8), ^{1}J(C1'-H1'), ^{1}J(C2'-H2') and ^{1}J(C2'-H2'2) in deoxyguanosine and the three one-bond couplings ^{1}J(C8-H8), ^{1}J(C1'-H1') and ^{1}J(C2'-H2') for guanosine has been analyzed using density functional theory - B3LYP /6-31G**. The influence of the backbone conformation, sugar composition and the sugar pucker, and molecular environment including water solvation has been also considered in modeling the structural dependence of the J-couplings on local structure.

New parameterizations of the Karplus equation was calculated for the ^{3}J(C8-H1') and ^{3}J(C4-H1') couplings assigned to the χ torsion angle similar to Munzarová et al.[1] The J-couplings calculated on the geometry grid in the nucleosides were compared with those taking into account the effect of base pairing occurring in the WC/SE RNA base pair family[2] as well as with available experimental data

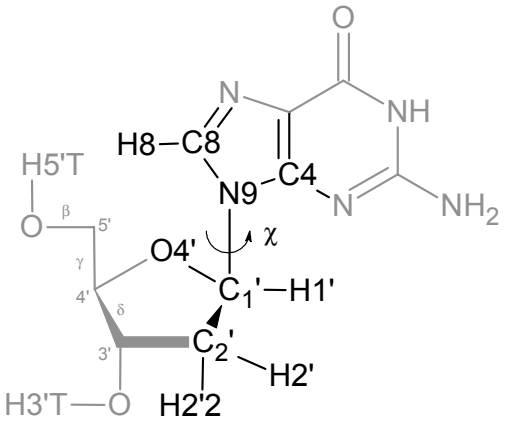

Figure 1: Figure caption

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STRUCTURAL PARAMETERS OF *ZOANTHUS* YELLOW FLUORESCENT PROTEIN CHROMOPHORE IN TERMS OF MOLECULAR DYNAMICS METHODOLOGY

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Fluorescent proteins are very useful in imaging of the localization and dynamics of specific organelles or recombinant proteins in live cells. They are commonly used in multicolour labelling and resonance energy-transfer applications. Due to their significance in extensive range of biological disciplines, it is important to understand the functioning of the protein and its chromophore on the atomic scale, explaining the role of particular atoms, residues and hydrogen bonds.

The best known fluorescent protein is a green fluorescent protein GFP (PDB entry code 1EMB [1]) purified from a jellyfish *Aequorea victoria.* The protein properties, e.g. a structure, chromophore geometry, absorption and emission spectra has been widely investigated for over 40 years. In recent years there has been an increase in publishing results from quantum mechanical (*ab initio* and DFT) analysis of the GFP chromophore *in vacuo* and condensed phase.

The other, less known and poorly examined, fluorescent protein is *Zoanthus* yellow fluorescent protein (zFP538). zFP538 (PDB entry code 2OGR [2]) is a GFP-like protein purified from the coral. It is believed, however, that the zFP538 chromophore comprises of additional 6-membered ring (Fig. 1.), causing a shift of absorption and emission maxima to longer wave lengths in comparison to GFP chromophore.

Both the GFP and zFP538 chromophores were investigated with the use of the molecular mechanical (MM) technique, using CHARMM27 [3] force field. MM energy minimisations and molecular dynamics (MD) simulations were carried out. The calculated structural parameters were compared with *ab initio* and DFT data available from the literature.

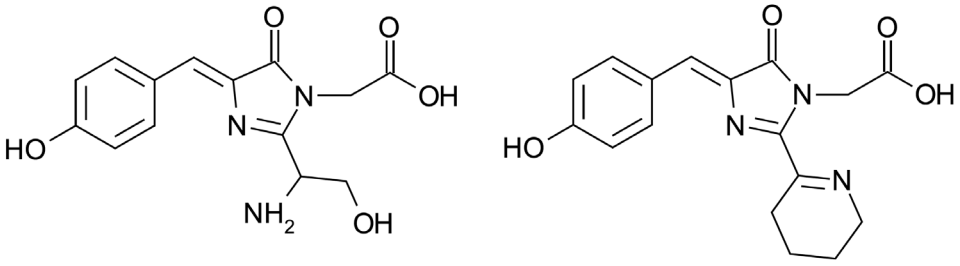

Fig. 1. GFP (left) and zFP538 (right) structures of chromophores

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ORBITAL-FREE EFFECTIVE EMBEDDING POTENTIAL: THE BASIS FOR A FAMILY OF COMPUTATIONAL METHODS FOR MODELING ELECTRONIC STRUCTURE IN CONDENSED PHASE

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The orbital-free effective embedding potential is a local multiplicative potential which can be expressed as is a functional of two electron densities: that of the investigated embedded subsystem (ρ_A) and that of the environment (ρ_B) [1]. The analytic form of this functional is not known although it known for some particular analytically solvable cases [2]. In practical applications, this potential is approximated using some explicit analytical expressions for its the kinetic- and exchange-correlation components of unknown analytic form ($\upsilon_t^{nad}[\rho_A,\rho_B]=\left.\frac{\delta T_S[\rho]}{\delta\rho}\right|_{\rho=\rho_A+\rho_B}-\left.\frac{\delta T_S[\rho]}{\delta\rho}\right|_{\rho=\rho_A}$ and $\upsilon_{xc}^{nad}[\rho_A,\rho_B]=\left.\frac{\delta E_{xc}[\rho]}{\delta\rho}\right|_{\rho=\rho_A+\rho_B}-\left.\frac{\delta E_{xc}[\rho]}{\delta\rho}\right|_{\rho=\rho_A}$, respectively):

$$\upsilon_{emb}[\rho_A,\rho_B;\vec{r}]=\upsilon_{ext}^{B}(\vec{r})+\int\frac{\rho_B(\vec{r}\,')}{|\vec{r}\,'-\vec{r}\,|}d\vec{r}\,'+\tilde{\upsilon}_{xc}^{nad}[\rho_A,\rho_B](\vec{r})-\tilde{\upsilon}_t^{nad}[\rho_A,\rho_B](\vec{r}) \quad (1)$$

where tildas denote analytic expressions approximating the exact quantity. The potential given in Eq. 1 can be used in various computational schemes differing in:

- The choice for the auxiliary quantities to represent the density ρ_A: either orbitals of the noninteracting reference system as introduced in our original work [1], the "wave-function" of the multiconfigurational form [3], or the one-matrix [4]. In all the above cases, the potential given in Eq. 1 assures that a given computational method leads to the density $\rho_A + \rho_B$ which minimized the ground state energy of the total system under the following constraint: $\rho_{total} \geq \rho_B$.
- The way the density ρ_B is generated.
- The subsequent use of the embedded orbitals (or embedded wavefunction or embedded onematrix) to derive observables.

In the present work, we overview applications of the potential given in Eq. 1 in various computational approaches aimed at the electronic structure of molecules or other species in condensed phase.

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MCQDPT2//CASSCF CALCULATIONS FOR *zFP538* PROTEIN CHROMOPHORE - STRUCTURE AND SPECTRAL PROPERTIES *IN VACUO*

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Nowadays, fluorescent proteins are important group of useful proteins, that are often used to label biological specimens or even whole body imaging of small animals. These proteins are useful in a powerful technology, and are intensively investigated by many research teams.
A chromophore of Yellow Fluorescent Protein from *Zoanthus sp.* (*zFP538*) contains a novel three-ring structure [1]. Contrary to *zFP538* protein chromophore, the other fluorescent proteins' chromophores usually contain two-ring chromophores. In that case a comparison of the structural and spectral properties for these two types of chromophores is of great interest.
This work demonstrates the performance of computational MCQDPT2//CASSCF method to determine the structure and stability of *zFP538* chromophore and its basic spectral properties. Two isomeric forms of the *zFP538* chromophore were examined (*cis* and *trans*) – each one in four different protonation states (cation, anion, neutral molecule and zwitterion). The results obtained were compared with the data from DFT calculations [2, 3, 4] and with available experimental values [5]. Additionally, the structural and spectral properties of *zFP538* and *GFP* chromophores [3, 4, 6, 7] were also compared.

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ELECTRON TRANSFER REACTIONS IN PROTEINS LABELED WITH $Re^{I}(CO)_3$(A-DIIMINE)(IMIDAZOLE)

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Long-range electron transfer (ET) reactions in proteins and other complex media often are strongly modulated by donor-bridge-acceptor dynamics. Labeling protein surfaces with $Re^{I}(CO)_3$(N,N)(imidazole)(N,N - α-diimine) opens the way for investigations of relaxation dynamics in the region around one of the redox centers under the same conditions that normally trigger ET. Owing to the high sensitivity of CO stretching vibrations to structural perturbations and changes in electron-density distributions, it is possible to follow relaxation of an electronically excited ReI label using time-resolved IR (TRIR) spectroscopy.[1]
In order to understand the character and dynamics of optically excited states DFT, calculations were performed on several simplified models containing $Re(CO)_3$(dmp) bonded to different part of protein chain (e.g. Fig. 1). Optimized excited-state geometry was calculated for the lowest singlet and triplet states of each complex by TD-DFT. The lowest triplets were also optimized by the unrestricted Kohn-Sham (UKS). The solvent was described by the polarizable conductor calculation model (CPCM) or conductor like screening model (COSMO), solvent molecules within the first solvent sphere were included explicitly. Calculated shifts of CO stretching frequencies were used for interpretation of experimentaly measured FFTIR spectra.

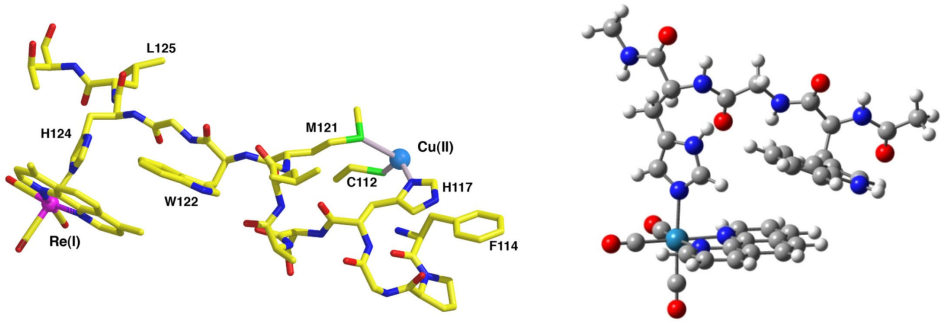

Figure 1: Experimental structure of $Re(CO)_3$(dmp)(H124)|(W122)|AzCu (left) and one of calculation models used (right).

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CLASSIFICATION OF AMINO ACIDS BASED ON THEIR PROPENSITIES TOWARDS A PARTICULAR SECONDARY STRUCTURE

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The preferences of amino acids towards are particular secondary structure are very important for understanding interactions in proteins and can be helpful in predicting secondary and tertiary structures of proteins.

Using a large data set from the Protein Data Bank (PDB) we studied the preferences of amino acids for secondary structures in terms of statistical correlation. Many of our results [1] with this much larger data set are in accord with results obtained in the 1970s on a very small number of proteins [2,3], however, we have identified a number of important differences. It enabled us to determine rules for predicting the preference of an amino acid towards a particular secondary structure type based only on the chemical structure of its substituents at the Cβ or Cγ atoms. This is the first improvement in connecting amino acid preferences with their chemical structures since 1978 [3].

The results show that most amino acids (except His and Cys) have a clear preference to participate in one particular secondary structure type. Based on these preferences, amino acids can be classified in four groups: α-helix preferrers (Ala, Leu, Glu, Gln, Arg, Met, Lys), strand preferrers (Val, Ile, Tyr, Phe, Thr, Trp), turn and bend preferrers (Gly, Asn, Pro, Asp, Ser), and others (Cys, His). These amino acid preferences are caused by structural properties at the Cβ or Cγ atoms, while the rest of the side chain is less important. We can specify the rules that classify amino acids as preferrers of certain secondary structures based only on the structural properties of the Cβ or Cγ atoms. The common structural properties of all α-helix preferrers are: no polar atoms on Cβ and Cγ atoms, no branching on Cβ, and an aliphatic (sp3) Cγ atom. All strand preferrers have aromatic groups or branching on the Cβ atom, while all turn and bend preferrers have a polar heteroatom on Cβ or Cγ atoms, or do not have a Cβ atom. Following these rules, based only on structure, it is possible to determine for which secondary structure type an amino acid will have a preference. Since these rules are based only on the structure of the amino acid, they could help in predicting preferences of non-natural amino acids. The results indicate that polarity, charge and capability for hydrogen bonding do not have a crucial influence on the preference for particular secondary structure types at the same position in the sequence. The polarity of amino acid has significant influence on α-helices and strands at some distance in the sequence [4]. Our data also point out the exchangeability of residues in the proteins; the amino acids with similar properties have similar local folding requirements.

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EVALUATION OF DFT METHODS FOR THE CALCULATIONS OF THE INTERACTION-INDUCED ELECTRIC PROPERTIES OF MOLECULAR COMPLEXES

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In recent years one could have noticed the rapid development of nonlinear optics [1]. It is well known that noncovalent interactions play an important role in determining the electrical properties of molecular complexes and materials [2, 3]. However, the theoretical modeling of intermolecular interactions is still very challenging for quantum mechanical methods.
In this work the interaction-induced optical properties of H-bonded HCHO-HF complex were studied using density functional theory (DFT). We tested a number of DFT methods (B3LYP, LC-BLYP, PBE0, M06-HF, M06-2x and M06). The components of the static electric dipole moment, linear polarizability as well as first-order hyperpolarizability have been calculated and analyzed using different Dunning's correlation consistent basis sets (d-aug-cc-pVXZ, X=D, T, Q). The purpose of the current investigation is to establish the accuracy of DFT by comparison of the interaction-induced optical properties for the HCHO-HF complex with the best available coupled cluster (CCSD(T)) results.

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PATH INTEGRAL EVALUATION OF EQUILIBRIUM ESOTOPE EFFECTS [1]

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A general and rigorous methodology to compute the quantum equilibrium isotope effect is described. Unlike standard approaches, ours does not assume separability of rotational and vibrational motions and does not make the harmonic approximation for vibrations or rigid rotor approximation for the rotations. In particular, zero point energy and anharmonicity effects are described correctly quantum mechanically. The approach is based on the thermodynamic integration with respect to the mass of the isotopes and on the Feynman path integral representation of the partition function. An efficient estimator for the derivative of free energy is used whose statistical error is independent of the number of imaginary time slices in the path integral [2], speeding up calculations by a factor of » 100 at 500 K and more at room temperature. We describe the implementation of the methodology in the molecular dynamics package AMBER 10. The method is tested on three [1,5] sigmatropic hydrogen shift reactions. Because of the computational expense, we use *ab initio* potentials to evaluate the equilibrium isotope effects within the harmonic approximation, and then the path integral method together with semiempirical potentials to evaluate the anharmonicity corrections. Our calculations show that the anharmonicity effects amount up to 30% of the symmetry reduced reaction free energy. Numerical results are compared with recent experiments of Doering and coworkers [3, 4], confirming the accuracy of the most recent measurement on 2,4,6,7,9-pentamethyl-5-(5,5-$^2H_2$)methylene-11,11a-dihydro-12H-naphthacene (see Figure 1) as well as concerns about compromised accuracy, due to side reactions, of another measurement on 2-methyl-10-(10,10-$^2H_2$)methylenebicyclo[4.4.0]dec-1-ene.

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