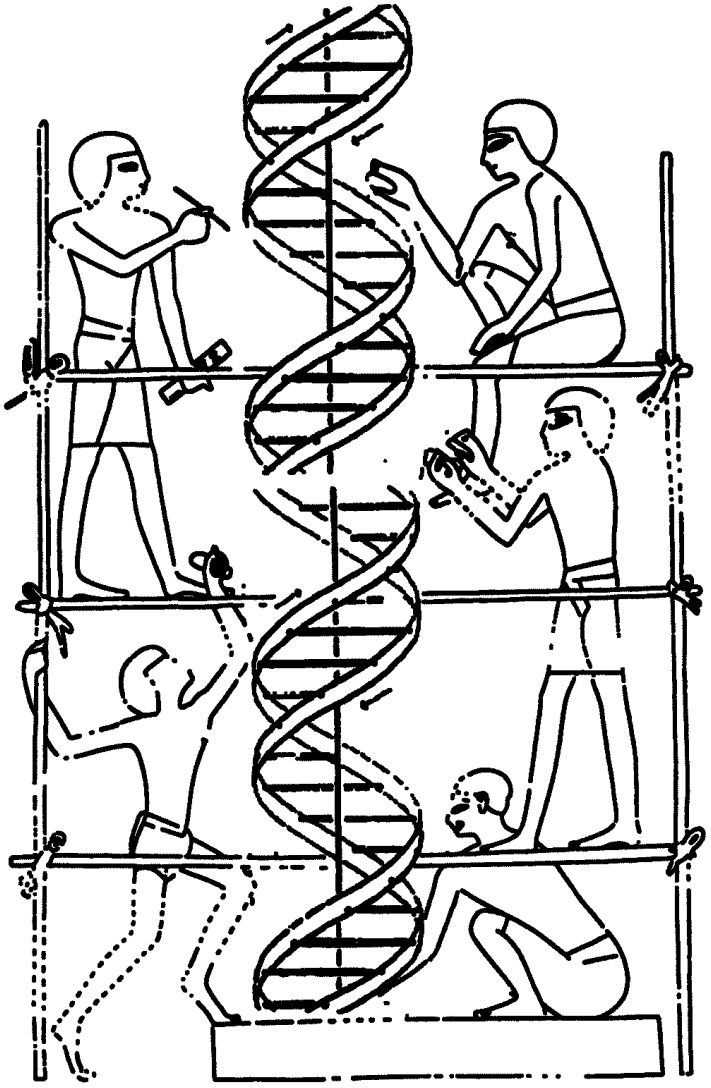
Modeling & Design of Molecular Materials '08

Piechowice, 23-28 June 2008



Conference information & abstracts

Modeling & Design of Molecular Materials 2008

a meeting organized by

Molecular Modeling & Quantum Chemistry Laboratory
Wrocław University of Technology (WUT), Wrocław, Poland

NSF Computational Center for Mol. Structure & Interactions,
Jackson State University (JSU), MS, USA

Charles University in Prague, Czech Republic

Wrocław Center for Supercomputing and Networking (WCSS)

Conference website: www.mml.ch.pwr.wroc.pl/mdmm2008

an event sponsored by

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Bartłomiej Skwara - posters
Krystyna Zając - accountant

Conference program

June 23, 2008 (Monday)

14:00-21:00 Registration - lobby of LAS Hotel

June 24, 2008 (Tuesday)

8:00-9:00 Registration - lobby of LAS Hotel
9:00-9:15 Conference opening

Session I **Advances in computational methods** (chair: J. Sauer)

9:15-9:55 **L1:** T. Wesołowski (Geneva, Switzerland)
Embedding quantum chemical system in orbital-free environment: recent formal developments and applications in multi-level simulations
9:55-10:35 **L2:** M. Meuwly (Basel, Switzerland)
Atomistic simulations for complex systems with chemical accuracy
10:35-10:50 Cofee break

Session II **Modeling zeolite materials** (chair: Z. Latajka)

10:50-11:30 **L3:** R. van Santen (Eindhoven, The Netherlands)
Molecular recognition in heterogenous catalysis

11:30-12:10 **L4:** J. Sauer (Berlin, Germany)
Hydrocarbon reactions in zeolites by hybrid QM/QM and QM/MM methods

12:10-12:25 **L5:** P. Boulet (Marseille, France)
Adsorption into the MFI zeolite of cyclic molecule of biological relevance. Investigations by Monte Carlo simulations

12:25-12:40 **L6:** B. Szyja (Eindhoven, Netherlands)
Study of the silica-water-SDA interactions during the initial stages of zeolite synthesis

12:40-14:40 Lunch break

Session III **Interactions in molecular materials** (chair: A. Tachibana)

14:40-15:15 **L7:** J. S. Murray (Cleveland, OH, USA)
σ–hole bonding – a widely occurying directional noncovalent interaction

15:15-15:50 **L8:** H. Cheng (Air Products & Materials Inc., Allentown, PA, USA)
Predictive atomistic simulations for design and development of novel materials for semiconductor applications

15:50-16:25 **L9:** O. Shishkin (Kharkov, Ukraine)
Non-conventional intermolecular interactions in molecular complexes and crystals

16:25-17:00 **L10:** S. Grabowski (Łódź, Poland)
The enhancement of X-H..pi hydrogen bonds - the study of cooperativity effects

17:00-17:15 Cofee break

17:15-19:15 Poster session A (P1-P26)

June 25, 2008 (Wednesday)

Session IV **Modeling chemical reactions** (chair: T. Brinck)

9:00-9:35 **L11:** A. Toro-Labbe (Santiago, Chile)
The reaction force analysis. Application to catalytic processes

9:35-10:10 **L12:** P. Politzer (New Orleans, LA, USA)
The reaction force constant

10:10-10:45 **L13:** P. Paneth (Łódź, Poland)
Modeling of enzymatic reactions based on isotope effects

10:45-11:00 **L14:** Z. Flisak (Opole, Poland)
Modeling Multidentate Ligands in Coordinative Olefin Polymerization Catalysts

11:00-11:15 Coffee break

Session V **Protein Dynamics** (chair: A. Liwo)

11:15-11:50 **L15:** T. Clark (Erlangen, Germany)
QM/MM Molecular Dynamics Calculations of Electronic Properties
11:50-12:25 **L16:** A. Koliński (Warsaw, Poland)
Multiscale modeling of protein structure, dynamics and interactions
12:25-12:40 **L17:** A. Sikorski (Warsaw, Poland)
Thermodynamic properties of polypeptide chains. The comparison of some Monte Carlo techniques
12:40-14:40 Lunch break

Session VI **Protein structure prediction** (chair: A. Koliński)

14:40-15:20 **L18:** A. Godzik (La Jolla, CA, USA)
Structural genomics – surveying the unknown regions of protein structure space
15:20-16:00 **L19:** A. Liwo (Gdańsk, Poland)
Prediction of structure and simulation of dynamics of protein folding with the mezoscopic UNRS force field
16:00-16:15 Coffee break

Session VII **Properties of molecular materials** (chair: T. Clark)

16:15-16:50 **L20:** R.A. Poirier (St.John's, Canada)
Interesting properties and applications of the average inter-particle distance
16:50-17:25 **L21:** A. Tachibana (Kyoto, Japan)
Stress tensor description of chemical bonds - formulation of non-classical bond order concept
17:25-18:00 **L22:** Z. Latajka (Wrocław, Poland)
Quantum nature of proton transfer in H-bonded mono- and di-carboxylic acid crystals - path integrals molecular dynamics studies
18:00-18:35 **L23:** B. Kuchta & L. Firlej (Marseille, France)
Modeling of alkanes adsorbed on graphite
18:35-18:50 **L24:** J. C. Wojdeł (Barcelona, Spain)
Influence of cations and water molecules on electron structure of Prussian blue analogues
19:00-21:00 Conference grill

June 26, 2008 (Thursday)

9:00-15:30 Excursions (A – Szrenica mountain, B – uranium mines & Wang temple)

Session VIII **General session** (chair: S. Roszak)

15:30-16:45 Fujitsu Poland workshop session
Tools for computational chemistry
16:45-17:00 Coffee break
17:00-19:00 Poster Session B (P27-P53)

June 27, 2008 (Friday)

Session IX **Protein design** (chair: P. Paneth)

9:00-9:40 **L25:** M. Ramos (Porto, Portugal)
Computational mutagenesis and drug discovery

9:40-10:20 **L26:** T. Brinck (Stockholm, Sweden)
Computational search and design of new enzyme activities

10:20-11:00 **L27:** J. Koca (Brno, Czech Republic)
In silico mutagenesis to improve protein binding affinity and selectivity

11:00-11:15 Coffee break

Session X **Modeling biomaterials** (chair: P. Tchounwou)

11:15-11:55 **L28:** P. Kozłowski (Louisville, KY, USA)
The Co-C bond cleavage in cobalamin-dependent methioninine synthase: a theoretical study

11:55-12:15 **L29:** D. Plewczyński (Warsaw, Poland)
Evaluation of various protein-ligand docking programs

12:15-12:30 **L30:** P. Sharma (Hyderabad, India)
Modelling the noncovalent interactions at the metabolite binding site in purine riboswitches

12:30-12:45 **L31:** S. Sharma (Hyderabad, India)
Design of laser pulses for selective vibrational excitation of amino N-H bond of adenine and A-T base pair using Optimal Control Theory

12:45-14:45 Lunch break

Session XI **Drug design I** (chair: P. Kafarski)

14:45-15:20 **L32:** P. Tchounwou (Jackson, USA)
Molecular pharmacology of arsenic trioxide and the cure of acute promyelocytic leukemia

15:20-15:55 **L33:** S. Guccione (Catania, Italy)
Identification of novel scaffolds leading to small molecule DNA polymerase-beta inhibitors with potential in neurodegenerative and oncology disorders

15:55-16:30 **L34:** V. Kuzmin (Odessa, Ukraine)
The hierarchical QSAR technology for virtual screening and drug design

16:30-16:45 Coffee break

Session XII **Drug design II** (chair: V. Kuzmin)

16:45-17:20 **L35:** J. Burda (Prague, Czech Republic)
Electronic Properties and Reaction Mechanisms of Selected Anticancer Metallodrugs

17:20-17:45 **L36:** L. Berlicki (Wroclaw, Poland)
Computer-aided design of inhibitors of amino acids biosynthesis

17:45-18:00 **L37:** T. Zimmermann (Praha, Czech Republic)
Reaction of cisplatin aquation products with cysteine and methionine at constant pH

18:00-18:15 **L38:** E. Muratov (Odessa, Ukraine)
Consensus prediction of aqueous solubility of military compounds

Session XII **Special lecture folowed by conference dinner** (chair: J. Leszczyński)

18:30-19:00 **L39:** P.Drożdżewski (Wrocław, Poland)
Normal vibrations and music harmony

June 28, 2008 (Saturday)

Session XIV **Nucleic acids I** (chair: J. Murray)

9:00-9:40 **L40:** P. Hobza (Prague, Czech Republic)
Accurate stabilization energies of DNA base pairs

9:40-10:20 **L41:** J. Rak (Gdansk, Poland)
Single strand breaks in DNA induced by low energy electrons. Possible mechanisms

10:20-11:00 **L42:** J. Sponer (Brno, Czech Republic)
RNA base pairing and RNA building blocks

11:00 -11:15 Coffee break

Session XIV **Nucleic acids II** (chair: J. Burda)

11:15-11:50 **L43:** P. Cysewski (Bydgoszcz, Poland)
The post-SCF complete basis set quantum chemistry characteristics of the energetic heterogeneity of stacking interactions in crystallographic DNA.

11:50-12:05 **L44:** Z. Vokáčová (Praha, Czech Republic)
Probing the structure and dynamics of RNA dinucleoside monophosphates (ApA, ApC, CpA, CpC) with NMR spectroscopy)

12:05-12:45 **L45:** J. Leszczyński (Jackson, MS, USA)
Common convenient misconceptions: theory versus experiment

12:45-13:00 Conference closing

Conference posters

No.	Presenting authors	Title
P1/A	Ferenc Bogár Gábor Paragi	*Structural motifs and H-bonding patterns of homo-oligopeptides consisting of Ala and Gln residues*
P2/A	Ferenc Bogár	*Structure of chiral peptide nucleic acids (cPNAs)*
P3/A	Elżbieta Broniatowska	*Quantum chemistry calculations in pharmacology*
P4/A	Michael A. Cato, Jr. Jerzy Leszczyński	*"The Origins Project": a closer look at formamide dimers*
P5/A	Piotr Cysewski	*The structural aromaticity alteration of para substituted benzene analogues imposed by solvent: implicit versus explicit models*
P6/A	Piotr Cysewski Przemysław Czeleń	*The post-SCF quantum chemistry study on the structural and energetic properties of stacked pairs found in central triad of telomeric B-DNA fragments*
P7/A	Żaneta Czyżnikowska	*Nucleic acid bases complexes: elucidation of the physical origins of their stability*
P8/A	Piotr Drożdżewski	*DFT modeling of the structure and vibrational spectra of 4-hydroxybenzhydrazide*
P9/A	Agnieszka Dybała–Defratyka	*To tunnel or not to tunnel? The methylmalonyl-CoA mutase story, part II*
P10/A	Edyta Dyguda–Kazimierowicz Jerzy Leszczyński W. Andrzej Sokalski	*Phosphotriesterase-catalyzed hydrolysis of sarin: modeling of the enzyme-substrate complex*
P11/A	Krzysztof Ejsmont	*Topological analysis of the electron density in model compounds containing nitrogen-nitrogen bonds*
P12/A	Mikołaj J. Feliks W. Andrzej Sokalski	*Towards the design of asymmetric organocatalysts*
P13/A	Jason Ford–Green Jerzy Leszczyński	*Conformational studies of organophosphorus pesticides towards the discernment of their esterase inhibition*
P14/A	Jaroslav V. Burda Zdenek Futera	*Computational study of ruthenium(II) complexes with biological activity*
P15/A	Andrzej J. Gorączko	*Prediction of double-charge ion pattern by modeling of the high- and low-resolution isotopomeric forms*
P16/A	Andrzej J. Gorączko	*Detection of symmetrical decomposition of the molecules - isotopomeric analysis of the M/2 ions clusters*
P17/A	Tomasz Grabarkiewicz Tomasz Kubacki	*In search of potential peptidomimetic HCV protease inhibitors*
P18/A	Katarzyna E. Hejczyk	*The importance of molecular polarization for crystal structure prediction of multicomponent crystals*
P19/A	Marcin Hoffmann	*Chameleonic ligand in self-assembly of grid-type copper(I) and zinc(II) complexes*

P20/A	Tim Clark Christof Jaeger	*Controlling micelle structures by included molecules*
P21/A	Gábor Janzsó	*Conformational study of cyclic disulphide-bridged nonapeptides, Arg- and Lys-conopressins*
P22/A	Henryk Chojnacki Iwona Jaroszewicz	*Non-empirical quantum chemical studies on platinum(II) – cysteine systems*
P23/A	Adrian Jasiński	*Theoretical models of nitrile hydration*
P24/A	Piotr Cysewski Katarzyna Kozłowska	*Accurate gas phase basicities of hydroxyl radical modified pyrimidines estimated by advanced quantum chemistry methods*
P25/A	Bartłomiej Krawczyk Karol M. Langner W. Andrzej Sokalski	*Comparison of interaction energy decomposition schemes for small dimers, revisited*
P26/A	Wojciech Bartkowiak Przemysław Krawczyk	*Theoretical and experimental study of UV-Vis spectra of functionalized carbazole-azo dyes*
P27/B	Marcin Hoffmann Adam Kubas	*Quantum chemical studies on substitution effects in the reaction of the silylative coupling of olefins*
P28/B	Vitalina Kukueva	*Modeling phosphorus oxide immobilization on the silica surface*
P29/B	Tadeusz Kuliński	*New antisense/antigene agents with pirydylphosphonate internucleotide bonds: ab initio characterisation*
P30/B	Victor E. Kuz'min	*Estimation of equivalence of molecular graph vertexes on the basis of topological model of the informational field*
P31/B	Karol M. Langner W. Andrzej Sokalski	*Analysis of interaction energies for molecular systems of unprecedented size*
P32/B	Danuta Leszczyńska Jerzy Leszczyński	*Application of QSAR technique to prediction of properties and activities of selected nanomaterials*
P33/B	Paweł Lipkowski	*Aromaticity and tautomeric equilibrium study of hydroxyphenyl and naphthalene Schiff bases*
P34/B	Paweł Lipkowski	*Proton transfer and intramolecular hydrogen bonding in o-hydroxyaryl ketimines*
P35/B	Marcin Lorkowski	*Quantum-chemical and molecular dynamics study of Cu2+ and Mn2+ complexes with a neurotoxic fragment (106-126) of human PrPC protein*
P36/B	Victor E. Kuz'min Jerzy Leszczyński Eugene N. Muratov	*2D QSAR analysis of toxicity of nitroaromatics against rats, tetrahymena pyriformis and vibrio fischeri*
P37/B	Ferenc Bogár Zoltán Násztor Gábor Paragi	*Folding kinetics of implicitly solvated alanine oligomers*
P38/B	Ferenc Bogár Gábor Paragi	*3- and 5-methyl-6-aminouracils with natural DNA bases: a computational study*
P39/B	Ferenc Bogár Gábor Paragi	*Computational model of the interaction of small peptides and its modifications with an amyloid fibril*
P40/B	Piotr Romiszowski Andrzej Sikorski	*The structure of polymer systems in a confinement - a Monte Carlo study*
P41/B	Szczepan Roszak	*Theoretical investigations of mono- and biradical forms of 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine*

P42/B	Wojciech Bartkowiak Bartłomiej Skwara	*On the basis set superposition error in supramolecular calculations of interaction-induced electric properties - many-body components*
P43/B	Monika Srebro	*Theoretical description of bonding in the Co, Rh, Ir complexes with NHC ligands*
P44/B	Monika Srebro	*Theoretical study on the copolymerization of ethylene with polar monomers: bonding of the monomer by the catalyst's metal center*
P45/B	Magdalena J. Ślusarz Rafał Ślusarz	*Molecular modeling of the δ and μ opioid receptor interactions with cyclic deltorphin analogues containing urea bridges*
P46/B	Magdalena J. Ślusarz Rafał Ślusarz	*Molecular dynamics of vancomycin and representative peptidoglycan fragment.*
P47/B	Piotr Paneth Katarzyna Świderek	*Modeling properties of iridium complexes*
P48/B	Borys Szefczyk	*Molecular dynamics of self-assembled monolayers of functionalized alkanethiols for protein adsorption*
P49/B	Marcin Hoffmann Mieczysław Torchala	*Search for inhibitors of aminoacyl-tRNA synthases by virtual click chemistry*
P50/B	Borys Szefczyk Elżbieta Walczak	*Theoretical modelling of the reaction mechanism of phosphonoacetaldehyde hydrolase*
P51/B	Małgorzata Wołcyrz	*Positron binding systems*
P52/B	Wojciech Bartkowiak Mikołaj Mikołajczyk Agnieszka Zawada	*Influence of the solvent on the interaction induced first-order hyperpolarizability of H-bonded HF dimers*
P53/B	Tomasz Ringel	*Modelling of the aggregation superphosphate particles*

Lecture abstracts

in chronological order

Embedding quantum chemical system in orbital-free environments: recent formal developments and applications in multi-level simulations

Georgios Fradelos, Jakub Kamiński, Tomasz A. Wesołowski

Department of Physical Chemistry, University of Geneva, Switzerland

Our work deals with such types of problems in which the primary interest concerns the change of the electronic-structure of an embedded molecule arising from the interactions with its environment. To this end, we apply orbital-free embedding strategy, in which a reference system of non-interacting electrons is used to obtain a selected component of the total electron density [1]. Embedded orbitals obtained from one-electron equations (Eqs. 20-21 in Ref. [1]) can be used to derive a range of properties including electronic excitation energies [2, 3]. In the first part, examples using one-electron equations for embedded orbitals implemented into the Amsterdam Density Functional code to derive various properties of embedded molecules will be overviewed. We will focus on our own works dealing with: i) electronic excitation energies in molecular clusters used as models of hydrogen-transfer chains in biological systems and ii) electronic excitations for dye molecules inside zeolite-L framework used in the construction of artificial antennae systems. Practical applications of one-electron equations for embedded orbitals rely, however, on approximants to explicit functionals of electron density for various components of the total energy. Our recent works on exact properties of such functionals and reflecting them in the corresponding approximants will be summarized [4]. Time permitting, recent formal developments concerning universality of the orbital-free effective embedding potential will be outlined [5, 6].

[1] Wesolowski, T. A; Warshel, A., *J. Phys. Chem.* **1993**, *97*, 8050.
[2] Casida, M.; Wesolowski, T. A., *In. J. Quanum. Chem.* **2004**, *96*, 577.
[3] Wesolowski, T. A, *J. Am. Chem. Soc.* **2004**, *126*, 11444.
[4] Garcia Lasta, J.-M.; Kaminski, J.; Wesolowski, T. A; *in preparation.*
[5] Wesolowski, T. A, *Phys. Rev. A* **2008**, *77*, 012504.
[6] Pernal, K.; Wesolowski, T. A; *in preparation.*

Atomistic simulations for complex systems with chemical accuracy

Markus Meuwly

Chemistry Department, University of Basel, Switzerland

With recent advances in both, experiment and computer simulations, it has become possible to investigate the dynamics of small molecules in heterogeneous environments. This is of particular interest because small ligands can be used as an experimental probe to investigate the interior of proteins or other disordered materials. Atomistic Simulations are an established computational method to investigate gas- and condensed-phase systems. Recent extensions to force fields incorporate more details in capturing electrostatic interactions and allow to more quantitatively understand particular processes. In this seminar I will describe some of these methods and their use to understand the energetics, [vibrational]spectroscopy and reactions in biological and physico-chemical systems. For myoglobin interacting with diatomic ligands the vibrational spectroscopy of the ligand [1] and its rebinding kinetics are long-standing problems in biophysics which continue to attract the attention of experimentalists and computational chemists. The relationship between spectroscopy and structure is an interesting problem in the physical chemistry of doped ices which play an important role in astrophysics [2].

[1] Plattner, N.; Meuwly, M. *Biophys. J.* **2008**, *94*, 2505.
[2] Plattner, N.; Meuwly, M. *ChemPhysChem*, *in print.*

Molecular recognition in heterogeneous catalysis

Rutger A. van Santen

Eindhoven University of Technology, Eindhoven, The Netherlands

Two reaction systems will be chosen to discuss theoretically the relation between catalyst structure and catalytic performance.

For transition metal catalysis we select for discussion the Fischer-Tropsch reaction that converts synthesis gas into higher hydrocarbons. We will discuss the quantum-chemical aspects of CO activation as well as CH_4 formation and C-C bond formation. This catalytic reaction is of interest theoretically, because selectivity strongly depends on choice of metal as well as particle size and shape. Reactivity-free energy relations can be formulated that enable a rational analysis of reactivity trends.

A heterogeneous catalytic system with steric constraints is the microporous zeolite. In protonic form these materials are widely used. We will address the question of the interplay between the reactivity of these protons and the size and shape of zeolite cavity.

More recent is the use of reactive cations or cationic clusters to activate hydrocarbons. Chemical interaction between the zeolite channel wall and the cationic systems in the zeolite micropore determine the relative stability of cationic clusters and hence their catalytic activity. This will be discussed for Zn and Ga cationic clusters.

Progress in these two topics illustrates the great advances in catalytic science due to access to efficient high quality computer codes as well as hard ware computer performance. The complexity of model systems we can discuss today was unthinkable only ten years ago.

[1] van Saten, R.A.; Neurock, M., Molecular Heterogeneous Catalysis, Wiley-VCH, 2005.

Accurate modeling of adsorption and reactions of hydrocarbons in zeolites by hybrid QM:force field, hybrid MP2:DFT and DFT+dispersion calculations

Joachim Sauer

[1]Institut für Chemie, Humboldt-Universität zu Berlin, Berlin, Germany

Currently used density functionals do not properly account for dispersion interactions which limits the use of density functional theory (DFT) in applications that involve both bond rearrangements and van-der-Waals interactions. Moreover, currently used functionals underestimate energy barriers. We present a hybrid approach which combines MP2 calculations for the reaction site with DFT calculations for a large system under periodic boundary conditions. We apply it to catalytic hydrocarbon reactions in zeolites [1], specifically to the methylation of alkenes in H-ZSM-5, a reaction that is crucial in methanol-to-gasoline and methanol-to-olefine processes [2]. Adding a semiempirical dispersion term to DFT improves adsorption energies significantly, but not the barriers [3]. Hybrid QM:force field methods (using the QMPOT code) are a computationally more affordable alternative [4].

[1] C. Tuma and J. Sauer, Phys. Chem Chem. Phys, **2006**, *8*, 3955.
[2] S. Svelle, C. Tuma, X. Rozanska, J. Sauer, *in preparation.*
[3] T. Kerber, M. Sierka, J. Sauer, J. Comput. Chem., s*ubmitted.*
[4] V. Nieminen, M. Sierka, D. Yu. Murzin, J. Sauer, J. Catal. **2005**, *231*, 393.
[5] B. De Moor, M.-F. Reyniers, M. Sierka, J. Sauer and G. B. Marin, J. Phys. Chem. C, *accepted for publication.*

Adsorption into the MFI zeolite of cyclic molecules of biological relevance - investigations by Monte Carlo simulations

Narasimhan Loganathan, David Berge-Lefranc, Oliver Schäf, Renaud Denoyel, Christelle Vagner, Bogdan Kuchta, Pascal Boulet

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Uremia is a syndrome where the human renal system becomes unable to purify blood from metabolism products. Urea is the main uremic toxin which is removed up to 75% during conventional dialysis process (polymeric membrane materials). Unfortunately, dialysis is not selective enough, and e.g. some metabolites (for instance vitamins) and mineral salts are also eliminated. By contrast, other toxins, such as paracresol, are not efficiently eliminated and may cause critical cellular hurts. Paracresol ($CH_3C_6H_4OH$) is a protein bound solute that is responsible for the intoxication of patients, the decrease of immune defenses, and vascular hurts, when the molecule is not properly removed.

Our project, developed in collaboration with the Regional Centre for Uremia, aims at elaborating porous materials, and studying, both experimentally and theoretically, the adsorption capability of these materials for uremic toxins. In this presentation we will report on our theoretical results, using Monte Carlo simulations, about the adsorption of paracresol and water into the hydrophobic silicalite zeolite (Table 1).

Materials	Unit cell stoechiometry	Cell parameters (Å) and symmetry group
Silicalite	$Si_{96}O_{192}$	20.0220 x 19.8990 x 13.3830, orthorhombic, Pnma

Table 1: Structural parameters of the silicalite zeolite.

Grand-canonical Monte Carlo simulations using a configurational biased algorithm [1] were first used to locate the sites of adsorption of p-cresol into the zeolite. Subsequent simulations were performed in the canonical ensemble to obtain reliable energetics which were compared to experimental measurements. Finally, the adsorption of water in the p-cresol-containing silicalite were investigated. All these results will be presented in this communication.

Acknowledgements: Part of the calculations were performed at the Centre Informatique National de l'Enseignement Supérieur (Montpellier, France). The CNRS and the Région Provence-Alpes-Côte d'Azur are acknowledged for providing financial support.

[1] MCCCS - Towhee: A Monte Carlo molecular simulation program. Copyright (C) 2004-2007 Marcus G. Martin, http://towhee.sourceforge.net

The role of different intermolecular interactions in silicalite synthesis

Bartłomiej Szyja[1,2], Antonius Jansen[1], Rutger A. van Santen[1]

[1]Eindhoven University of Technology, Department of Chemical Engineering and Chemistry
[2]Wrocław University of Technology, Department of Chemistry

This study aims to unravel the elementary reactions of silicalite formation. We address the question how the interactions between silica precursor species and tetrapropylamonnium ions/water evolve during the nucleation process. The analysis is based on some of the precursor species proposed by Kirschhock et al. [1, 2]. The relevance of electrostatic interactions in initial stage of synthesis has been discussed by Catlow et al. [3]. We focus our work on studying the interactions between larger silica oligomers and tetrapropylamonnium ions during the formation of the initial channels of silicalite structure (i.e. early stage of nucleation).

We have carried out the Molecular Dynamics simulations in the system containing three Si_{11} oligomers as well as the tetrapropylamonnium ions and water. We have used the Universal forcefield to describe the energy of the system. In order to study the electrostatic interactions, charge has been assigned to some of the oxygen atoms belonging to silica oligomers and all nitrogen atoms from TPA ions.

We have found that charge on the atoms is not static, and transferring it to the other atoms (i.e. OH^- groups) allows the system to relax. In the system containing fully formed channel, where 2 or 4 out of total 6 negative charges present on the Si_{22} cluster has been transferred to the hydroxyl ions in the solution, the calculated Coulomb component decreased from 566.54 kcal/mol to 288.12 and 197.57 kcal/mol respectively.

Before the channel is formed, the structures have a wide enough gap to fit a TPA ion between two Si_{11} parts. That situation changes after the channel is formed. Although the TPA ion is able to fit inside the channel of system, this causes too much strain, and its preferable position is outside – the interaction energy between TPA and Si_{22} is then close to zero. The template appears to move outside of a channel into the direction of the channel cross-section.

Acknowledgements: Calculations were performed at the Wroclaw Center for Networking and Supercomputing (WCSS) and at the Department of Chemical Engineering and Chemistry (TU/e). Software used was Cerius2 and Materials Studio (Accelrys Inc.).

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$\boldsymbol{\sigma}$-hole bonding: a widely-occurring directional noncovalent interaction

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A σ-hole is an electron-deficient outer (noninvolved) lobe of a p-type bonding orbital. For example, the bromine in 4-bromopyridine has an electron deficiency along the extension of its CBr bond and the sulfur in 1,3-thiazole has two such regions of electron deficiency along the extensions of its two CS bonds; these electron deficiencies result in regions of positive electrostatic potential along the extensions of the covalent bonds to the bromine and sulfur. σ-hole bonding is the resulting highly directional noncovalent interaction that can result when these localized positive regions of electrostatic potential on Group V, VI and VII atoms interact with nucleophilic sites on other molecules. The importance of σ-hole bonding, in areas ranging from molecular biology to crystal engineering, is increasingly being recognized. After a brief discussion of the origin and some features of σ-hole bonding, this talk will focus upon examples involving cyclic and oxygen derivatives of Group V and VI atoms, e.g. thiazole, selenazole, $POCl_3$ and DMSO.

Predictive atomistic simulations for design and development of novel materials for semiconductor applications

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As feature size of semiconductor devices continues the trend of shrinkage, design and development of new generation of interconnect materials that are more reliable with higher conductivity to replace the conventional aluminum- based interconnect is a subject of extensive research interests. Copper, in particular, has been widely accepted to be the preferred interconnect material due to its lower electrical resistivity and higher electromigration resistance than those of aluminum. However, the high diffusivity of copper in silicon was found to degrade device performance. To prevent copper diffusion, diffusion barriers using TaN or WN are required. It has been widely recognized that atomic layer deposition is the preferred technology for depositing copper seed layer for the future generation of logical devices. Unfortunately, Cu films were found to agglomerate on diffusion barrier surfaces at typical ALD operating conditions, forming Cu islands on the surfaces that lead to decrease of conductivity. Fundamental understanding of Cu agglomeration processes on barrier surfaces is of essential importance to ensure successful applications of ALD technology. In this talk, I will describe our effort of using ab initio molecular dynamics (MD) simulations to unravel the mechanisms of Cu agglomeration on WN(001) surface. We show that a well aligned Cu film on WN(001) remain stable at near ambient temperatures but can undergo a substantial agglomeration process at a typical ALD operating condition. Our simulation results predict that the Cu film can be stabilized on careful selected "glue" layer materials. The role of "glue" layer materials for the enhancement of copper adhesion on barrier materials will be discussed.

Non-conventional hydrogen bonds and intermolecular interactions in molecular complexes and crystals

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Intermolecular interactions represent some kind of "glue" bonding molecules together in various molecular complexes, supramolecular assemblies and molecular crystals. During last decade it was demonstrated that many of "non-specific" interactions has clear directionality and dependence on nature of interacting molecular fragments and they should be considered as specific interactions.

Analysis of crystal structure of some organic compounds allows to find some new types of specific intermolecular interactions. In particular it is demonstrated that the nitrogen atoms of amino group in aromatic and heteroaromatic amines can form hydrogen bonds as proton acceptor despite of involving of the nitrogen lone pair in n-° conjugation. In the case of 1,2-diamines formation of the N-H...X hydrogen bond is the most favorable way of interactions with water or other proton donating groups.

Results of theoretical investigation of structure of protonated 2'- deoxyribonucleotides reveal the possibility significant strengthening of usually weak C-H...O hydrogen bonds. Characteristics of some such bonds agree well with parameters for conventional strong H bonds.

It is well known that halogen atoms can form stable halogen bonds with electron rich heteroatoms like the oxygen or nitrogen. Some of these bonds are extremely stable even in solutions and complexes with halogen heteroatom bond may be easily isolated and characterized. Investigation of crystal structure of complexes of fluorenonophane with haloforms reveal also the formation of stable halogen...° bond which may be considered as some kind of halogen bonds. Analysis of intermolecular interactions in crystals of halogen derivatives of trityl alcohols demonstrates that halogen bonding provide 30-100% into total energy of interaction between molecules.

Enhancement of X-H...π hydrogen bonds – a study on cooperativity effects

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Strong hydrogen bond (SHB) is the subject of extensive studies since it is very important interaction in numerous chemical and physical processes, among them proton transfer reaction and enzymatic catalysis are often analyzed [1,2]. Hence the problem arises, what kind of interactions may be classified as SHBs, it was pointed out that they are charge assisted hydrogen bonds as well as hydrogen bonds enhanced by cooperativity effects [3]. The latter topic was analyzed very recently for $H_2CO...(HF)n$ complexes, where n=1,..9 [4]. It was found that the binding energy for the complex containing one HF molecule amount to -7.6 kcal/mol, while if n increases to 3 it is equal to -13.7 kcal/mol (the calculations performed at MP2/aug-cc- pVTZ level of approximation, BSSE included).

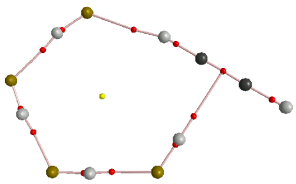

Fig. 1: Molecular graph of C_2H_2 complex.

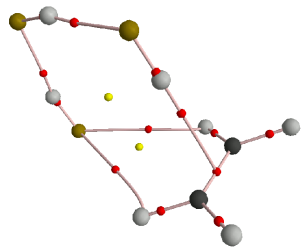

Fig. 2: Molecular graph of C_2H_4 complex

The topological and geometrical parameters confirm the energetic results showing the decrease of the proton-acceptor distance and the increase of the electron density at the corresponding bond critical point if n increases. The similar results were obtained for various π-electron systems interacting as proton acceptors with HF molecules. If the number of HF species increases thus the numerous parameters indicate the enhancement of F-H...π hydrogen bond. The following complexes with π-electrons as a proton acceptor were considered: $C_2H_2...(HF)_n$, $C_2H_4...(HF)_n$ and $C_6H_6...(HF)_n$, n up to four molecules. Figure 1 shows the molecular graph of $C_2H_2...(HF)_4$ complex while Figure 2 presents $C_2H_4...(HF)_3$ system; big circles correspond to attractors attributed to atoms' positions while small circles to bond and ring critical points.

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

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Reaction force analysis - application to catalytic processes

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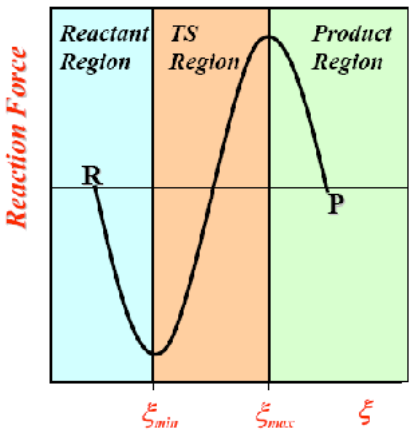
The concepts of reaction force and reaction electronic flux (REF) are presented and discussed in detail [1-4]. For typical processes with energy barriers, the reaction force has a universal form which defines key points along an intrinsic reaction coordinate: the force minimum and maximum. Three reaction regions results along the reaction coordinate, they can be interpreted as involving preparation of reactants in the first, transition to products in the second, and relaxation in the third.

This general picture is supported by the distinctive patterns of the variations in relevant global and local electronic properties such as chemical potential, hardness and electronic charges. The electronic flux associated to a chemical reaction emerges from the change of chemical potential during the reaction. It is shown that the profile of this quantity allows identification of polarization and electronic transfer phenomena that take place along the reaction coordinate. The framework provided by the reaction force is used to analyze different kind of chemical reactions, in particular the polymerization process of ethylene in the presence of a metallocene catalyst is characterized. It was observed that initiation, propagation and termination steps present specific REF patterns that are used to characterize the different steps of the polymerization process.



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Some insights from the reaction force constant

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The reaction force of a chemical process is the negative derivative of the potential energy of the system along an appropriate reaction coordinate, usually the intrinsic reaction coordinate. The minimum and maximum of the reaction force define three phases of the process, each emphasizing different factors. This talk with focus upon (a) the two components of an activation barrier that are identified by the reaction force, and provide insight concerning the roles of catalysts and solvents, and (b) the significance of the position-dependent force constant, the second derivative of the potential energy.

Modeling enzymatic reactions based on isotope effects

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QM/MM techniques are currently the most efficient approaches used in the studies of enzymatic catalysis. They are, however, a trade between the precision of theoretical scrutiny and the computational cost and technical constrains of modern computers. Among several problems that trouble QM/MM calculations are sizes of the QM and MM parts that have to be included in calculations to gain satisfactory description of the modeled system. We illustrate this problem on the example of two reactions catalyzed by enzymes; methylmalonyl-CoA mutase and lactic dehydrogenase. We verify the results of our calculations by comparing isotope effects obtained theoretically with those measured experimentally.

Modeling multidentate ligands in coordinative olefin polymerization catalysts

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The consecutive generations of modern Ziegler-Natta catalysts contain Lewis bases that modify the activities and selectivities of the catalytic systems. Bidentate ligands, such as diesters and diethers are particularly efficient by blocking certain surfaces of the support that might generate active sites of potentially low selectivities [1]. However, these bases can bind both to the support and the transition metal atom, thus increasing the number of species to be considered in the computational analysis.

The tetrahydrofurfuryloxide bidentate ligand, $C_4H_7O–CH_2O^-$, unlike diethers, has two atoms of different donor numbers and it can be forced to remain in the transition metal coordination sphere. To demonstrate how certain isomeric active sites are deemed non-existent, the Bailar method is applied. As a result of this approach, only two diastereomers are selected for further calculations.

In the following DFT analysis, the catalyst modified with the tetrahydrofurfuryloxide ligand is compared with a system containing tetrahydrofuran as a monodentate base, discussed elsewhere [2]. Certain properties, such as activity, regio- and stereoselectivity in the polymerization of propylene are assessed, based on the insertion barriers calculated.

	THF	THFFO – site 1	THFFO – site 2
Insertion barrier	7.6	15.3	9.1
$\Delta\Delta E_{regio}$	2.3	2.2	3.4
$\Delta\Delta E_{stereo}$	3.2	4.3	2.3

Table 1: Insertion barriers, regio- and stereoselectivity of catalysts with tetrahydrofuran (THF) and tetrahydrofurfuryloxide (THFFO) in kcal/mol

The results of Bailar analysis and subsequent DFT calculations indicate that the presence of the bidentate ligand in the catalytic system limits the number of possible active sites and slightly increases selectivities at the expense of activity.

Acknowledgements: Calculations were performed at the Wroclaw Center for Networking and Supercomputing as well as Academic Computer Center CYFRONET.

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QM/MM molecular dynamics calculations of electronic properties

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The combination of classical molecular-dynamics (MD) simulations with quantum mechanical calculations of electronic properties of snapshots from the trajectories represents a powerful technique for calculating the electronic or spectroscopic properties of complex systems. We routinely use AM1 semiempirical MO theory [1] with configuration interaction because it is fast enough for us to be able to calculate many thousands of snapshots and generally gives reliable properties. The lecture will illustrate this technique for two applications with a biological background. The first is the calculation of Fluorescence Resonant Energy Transfer (FRET) in proteins. Our calculations [2] demonstrate that the isotropic approximation usually used in "spectroscopic ruler" experiments leads to large errors and that the distribution of energy-transfer rates caused by the dynamics of the system leads to non-exponential fluorescence decay curves.

The second application involves non-linear optics dyes embedded in biological membranes. We were able to predict the second-harmonic generation and its dependence on the action potential across the membrane using the QM/MM technique. [3]

In a third, purely classical study, we were able to provide a new interpretation for the images found in cryo-TEM studies of structured micelles [4] and to suggest further experiments that confirm our interpretation.

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Multiscale modeling of proteins: structure, dynamics and interactions

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Protein structure prediction is now feasible for a significant fraction of newly determined sequences. Computationally more challenging is prediction of protein folding thermodynamics and pathways. Also theoretical prediction of biomacromolecular assemblies and mechanisms of protein aggregation is still very far from a satisfactory solution.

Since global relaxations of protein structures (including protein folding) is a very slow process, typically lasting microseconds to seconds a straightforward approach via classical methods of molecular mechanics remains impractical, except very small systems. Thus, a large spectrum of reduced conformational-space modeling methods [1-5] have been developed and successfully employed to the above mentioned problems of computational biology, especially to the problem of protein structure prediction. The most recent applications provided insights into protein dynamics [5-7] and protein-protein interactions [8].

Obviously, for typical biological applications we need as accurate as possible all-atom models. Therefore, it is necessary to be able to build a reasonable all-atom picture from the reduced structures and trajectories from the lower resolution methods. As it is shown in this contribution, sometimes such multiscale approaches are quite successful.

General assumptions and illustrative applications of a few representative modeling strategies are described. Possible near-future developments are briefly discussed.

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Thermodynamic properties of polymer chains - a comparison of Metropolis, parallel tempering and Wang-Landau Monte Carlo algorithms

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In last decades one observed a rapid development of simulation methods applied to study the properties of polymer and biopolymer systems. However, for the most biopolymer systems, models were rather complicated and contained enormous amount of parameters and, therefore, it is sometimes difficult to judge which of them are really important to obtain proper results. This was the main reason for designing and studying simple models of biopolymers. A coarse-grained model of polypeptide chains was thus designed and studied [1]. In our model we replaced a real polypeptide chain with a sequence of statistical segments connected by united atoms located on the positions of alpha carbons while the remaining atomic details were suppressed. Such a chain was restricted to a lattice of a [310] type, which was frequently used in simulations of biopolymers. Two kinds of amino acids residues were defined: hydrophilic and hydrophobic ones (HP model). The sequence of the residues was assumed to be characteristic for alpha-helical proteins, i.e. the helical septets -HPPHPP-. The force field used consisted of the long-range contact potential between residues and the local potential preferring conformational states, which were characteristic for alpha-helices. In order to obtain the thermodynamic description of our model we used the Multihistogram (WHAM) method (the procedure that relies on a mutual overlap of the probability of states in the neighboring replicas) combined with the Parallel Tempering (the Replica Exchange) Monte Carlo sampling scheme [2]. Optimal set of temperatures for the Parallel Tempering simulations was found by an iterative procedure. The simulations using the Wang-Landau algorithm (Multicanonical Monte Carlo method) were also carried. The influence of the temperature and the force field on the properties of coil-to-globule transition was studied by the above mentioned methods. It was shown that the WHAM and Wang-Landau methods could give more precise results when compared to a Metropolis and Replica Exchange methods.

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Structural genomics – surveying the unknown regions of protein structure space

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One of the most interesting results of genome sequencing projects is that significant part, often over 40%, of the proteins identified in such projects, appears to be completely novel, not homologous to any of the previously characterized proteins. Many of such proteins form large, broadly distributed families that remain uncharacterized simply because they never came into focus of any research group. Various protein classification resources identified several hundred such families and for instance in the PFAM database they are referred to as Domains of Unknown Function (DUF) and current release lists almost 1500 of them. While occasionally some of the DUF families become characterized and loose their DUF status, traditional research groups shun them in favor of well characterized, previously studied proteins. As a result, there has never been a coordinated, large-scale effort to study such families and systematically explore the uncharted regions of the protein space.

This has changed in last several years, as protein structure initiative structure determination centers, in their quest for providing structural coverage to large swaths of protein space have solved first experimental information for almost 300 DUF families. This unprecedented scale of coordinated experimental characterization of new families provides us with many interesting observations. With new experimental information we can show that a vast majority (70%) of these new families can be now recognized as very divergent branches of previously known protein families, illustrating the power of evolution and divergence of proteins in acquiring new functions or modifying the old ones to respond to new needs. In addition, most of the remaining 30%, even that formally characterized as new folds, show significant blocks of structural similarity to other known proteins. While we cannot at this point prove whether such partial similarities are due to an extremely divergent or to the convergent evolution, these results offers a hope that, despite rapidly growing sequence databases, structural coverage of protein space may enter the period where diversity within known protein folds and reshuffling of large structure fragments will become the central theme of structural biology.

Prediction of structure and simulation of dynamics of protein folding with the mesoscopic UNRES force field

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First-principle based prediction of structure and simulations of folding pathways in the all-atom representation are currently possible for small proteins only and, consequently, united-residue models of polypeptide chains are used in the field. The UNRES model [1] and the respective force field developed in our laboratory belong to this class. In the UNRES model a polypeptide chain is represented as a sequence of α-carbon atoms with attached united side chains and united peptide groups located in the middle between the consecutive α-carbon atoms. The force field has been defined as a restricted free-energy function (RFE) of a coarse-grained chain where secondary degrees of freedom have been averaged out. Approximate analytical expressions for the effective energy terms were obtained by cluster-cumulant expansion of the RFE and parametrized by fitting to the numerically calculated RFE's of model systems or from the distribution functions derived from the PDB. Finally, the force field was tuned by optimizing the contributions (weights) of the energy terms to reproduce the native structures and thermodynamics of folding of selected training proteins. UNRES was initially implemented to predict protein structures as global minima of the potential-energy function. Recently its application was extended to mesoscopic molecular dynamics, which resulted in 4,000-time speed-up compared to all-atom molecular dynamics with explicit solvent, thus enabling real-time in silico simulations of protein folding. Implementation of replica-exchange molecular dynamics and multiplexing replica-exchange molecular dynamics extended the application of the method to the thermodynamics of protein folding and enabled us to redefine energy-based protein structure prediction as searching for clusters of conformations with the lowest free energy rather than for a particular conformation with the lowest energy. In this talk the parametrization and application of UNRES to the prediction of protein structure and folding thermodynamics as well as simulation of folding pathways, including recent extensions of the approach to study multi-chain proteins and proteins with disulfide links, which dynamically form and break during folding, will also be discussed.

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Interesting properties and applications of the *average* inter-particle distance

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At the molecular orbital(MO) level, the *average* distance between two electrons in MOs, a and b, is expressed in terms of the first and second moments. When this inter-electronic distance, $(\delta r_{12})_{ab}$, is compared to the corresponding coulomb integral, J_{ab}, an interesting relationship is observed[1]. Analogous to $(\delta r_{12})_{ab}$, an expression for the *average* distance between an electron and a nucleus, δr_{aB}, is defined from the first and second moments of an electron in MO a and a nucleus B. Similar to $(\delta r_{12})_{ab}$ and J_{ab}, this inter-particle distance can be used to model the electron-nuclear attraction potential energy, V_a, where,

$$V_a = \langle a| \sum_{B=1}^{M} \frac{Z_B}{r_{1B}} |a\rangle \tag{1}$$

While for both relationships there are deviations when dealing with delocalized core canonical MOs (CMOs), the relationships are found to be near exact with localized MOs (LMOs).

The application of a scheme similar to that of the *average* interparticle distance to the total electronic first and second moments of a molecule also yields important molecular properties. An origin invariant definition of molecular shape, $\widetilde{S}$, and size, $\widetilde{R}$ and $\widetilde{V}$, are presented[2]. This formulation correlates quite well with existing theoretical measures of molecular size, which are significantly more complicated. Also, this theoretical measure of size performs quite well when compared to experimental measures of molecular size and steric hindrance.

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Stress tensor description of chemical bonds – formulation of non-classical bond order concept

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Recently an examination of bond order gains much attention regarding studies of multiple bonded atoms (especially metals). One has in choice various definitions expressing classical bond order concept by quantum mechanical methods in terms of usual density [1,2] and overlap matrices [3] or natural resonance theory [4]. The bond order concepts have been reviewed recently by Mayer [5]. The original idea trace back to Lewis's shared electrons and the assignment of it to bonding, nonbonding or antibonding orbitals. However, due to disagreement between the experimental and theoretical results with simple Lewis-type structures for multiply bonded metal atoms [6,7], the use of non-classically oriented approaches is advised [8]. The delocalized nature of electron wavefunctions smeared over molecular orbitals makes the assignment of electron pairs to particular bond quite challenging. Besides these pairs might feel different about different elements (due to interaction of initial orbitals at different energy levels) thus a bonding pair between two atoms may not be equivalent to a pair between other two. Presented here, new formulation of bond order [8] refers to the electronic energy rather then electrons it self thus it is more suitable for evaluation of bond strength. Bond order was introduced as an indicator of bond stability and essentially refer to bond strength relative to bonds with order of one, thus new concept of bond order expressed in terms of electronic energy density is formally/naturally better to fulfill this role. Moreover this new indices allow one to have a closer look on redistribution of energy over the molecule and its partition between particular bonds.

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Quantum nature of proton transfer in H-bonded mono- and dicarboxylic acid crystals – Path Integral Molecular Dynamics studies

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Proton transfer in a hydrogen bond is one of the most important phenomenon influencing dynamical behavior in many chemical and biological systems. In many living systems very fast proton transfer processes occur and moreover a proton behaves as quantum particle tunneling through the energy barrier. Despite widespread importance of tunneling effect the quantum character of proton transfer is not frequently use in theoretical models or is restricted only to zero-temperature quantum effects in simple model systems with severe reduced dimensionality of described systems.

The rapid development of computer power with efficient codes gives us an opportunity to study the dynamics of proton transfer processes with a great accuracy. However, the classical Molecular Dynamics with the potential derived from the Molecular Mechanics is not able to take into account large electron density redistribution accompanying the transfer of proton from one subunit to another. The Car-Parrinello Molecular Dynamics (CPMD) is very efficient scheme for description of dynamics of molecular systems. The quantum behavior of proton from a hydrogen bridge can be taken by means of the Path Integral Molecular Dynamics (PIMD).

In the present lecture the results of PIMD calculations will be presented for selected model systems in solid state. Dynamical properties and selected mechanisms of proton transfer in hydrogen bridges will be illustrated on examples of model systems containing of strong and intermediate-strength O-H...O hydrogen bonds in monocarboxylic (acetic acid) and dicarboxylic (fumaric, maleic and glutaric) acids.

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Modeling of alkanes adsorbed on graphite

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Molecular Dynamics (MD) simulations of tetracosane ($C_{24}H_{50}$) monolayer physisorbed on graphite are carried out. $C_{24}H_{50}$ molecules are simulated with explicit hydrogens and the graphite is represented by six graphene layers. We focus our analysis on the microscopic mechanism of melting, experimentally observed at T = 340 K. We are looking for the pre-melting transformations and analyze if there is a correlation between translational disordering of molecules and their internal degrees of freedom. We analyze several order parameters and their fluctuations along the MD trajectories. We show that the all atom representation of $C_{24}H_{50}$ is much more sensitive to the model of intramolecular interactions than united atom model. In particular two components: electrostatic forces and scaled 1-4 internal non- bonded interactions can shift melting temperature by several tenths of degree. A correlation between molecular stiffness and the intermolecular forces causes molecules' footprint reduction during melting which involves a simultaneous lost of intramolecular and translational order. This cooperative mechanism is related to an abrupt increase of gauche defects within the central region of the chain.

Influence of cations and water molecules on the electronic structure of Prussian Blue analogues

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Prussian Blue analogues (PBAs) are a broad family of cyanometallate materials with a face centered cubic crystalline framework with a general formula $A_x M_y^I [M^{II}(CN)_6]_z \cdot nH_2O$ [1]. Depending on the constituent metal sites (M^I, M^{II}), which form the nodes of the cyanide connected framework, these materials contain differing amount of interstitial cations (A), or water filled cavities. PBAs are specifically known for their complex electronic, magnetic and optical properties, which are often interlinked giving rise to opto-electronic, or opto-magnetic behavior.

The prototypical Prussian Blue (PB) salt is formed exclusively of iron sites with alternating oxidation state ($M^I = Fe^{3+}$ $M^{II} = Fe^{2+}$) and potassium interstitial cations ($A = K^+$). Depending on the preparation route, PB can contain between zero ($Fe_4[Fe(CN)_6]_3$) and one potassium ($KFe[Fe(CN)_6]$) atom per formula unit. In the presented study, we show how electronic structure methods can be applied to PB, and what methodology is needed to properly describe its electronic structure [2]. Using state of the art computational methods we show how the electronic structure of PB changes depending on the presence of interstitial cations and water molecules.

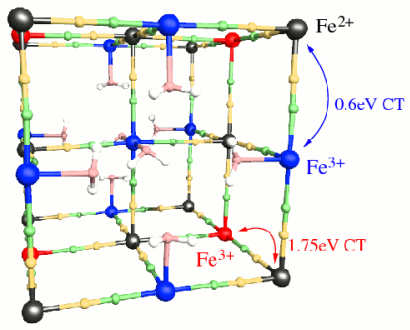

Fig. 1: Optimized unit cell and charge transfer excitations in hydrated Prussian Blue

Our calculations show that even under a constraint of limiting the framework metal type to iron, the formed PBAs exhibit a wide range of interesting physical (and chemical) properties, such as: (i) electrochemically induced changes in band gap [3], (ii) insulator to metal transition, (iii) spin polarized conductivity, and (iv) thermally induced spin crossover [4].

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Computational mutagenesis and drug discovery

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This talk is concerned with computational strategies devised with drug design in mind. Some fundamental stages of rational drug design are addressed, namely computational alanine-scanning mutagenesis of protein- protein interfacial residues, which can be a very important process for drug design since protein-protein interactions form the basis for most biological processes 1; molecular docking using total flexibility of ligand and receptor 2 and the atomic level understanding on disease-related enzymatic mechanisms and inhibition 3, which can be regarded as a pre- requisite to any attempt to rationally design new, better inhibitors.

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Computational search and design of new enzyme activities

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During the last decade it has become evident that many enzymes can use alternate catalytic mechanisms and catalyze more than one chemical transformation. This inherent catalytic promiscuity may be used in the redesign of enzymes by site-directed mutations to obtain new enzyme activities. We have shown, together with experimental collaborators, that it is possible to convert the Candida antarctica lipase B (CALB) into an aldolase by a mutation of a single residue, the catalytic serine [1,2]. It is one of the first examples where a successful redesign of the reactive mechanism has been based on computer modeling. Subsequent studies have shown that the same mutant also is capable of catalyzing Michael Type additions and epoxidations of a−b unsaturated carbonyl compounds [3,4]. These are examples of successful optimization of catalytic promiscuity, since the mutant shows increased efficiency for the promiscuous reactions and essentially no activity for the natural reaction.

Our early design strategy focused on the use of quantum chemical methods to obtain mutants that optimize transition state stabilization. However, the experimental turn-over rates are generally lower than predicted from the computed activation energies. In this lecture we will present an analysis based on experiments and molecular dynamics simulation of the molecular basis for the catalytic performance. We will also outline a new procedure for designing enzyme activities for unnatural reactions. The cornerstone of this approach is to utilize the existing catalytic functionalities of enzyme active sites. Rather than introducing extensive mutations, we search for enzymes that have as many of the required functionalities as possible. The methodology combines the use of chemo- and bioinformatics software with advanced molecular dynamics and quantum chemical calculations.

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In silico mutagenesis to improve protein binding affinity and selectivity

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Protein engineering is a procedure of developing useful or valuable proteins by mutations of residues. It is usually performed in vitro, when the original DNA is mutated, incorporated into host cells (for example, E. coli) and the resulting protein with mutated residues is expressed. It can also be performed in silico, when mutations are performed on a protein model in a computer.

Our effort is to connect both approaches to increase efficiency of the procedure. In our case, the engineered molecules are called lectins, proteins that recognize carbohydrates.

Understanding the intimate details of protein-carbohydrate interactions is gaining more importance due to its capability in deciphering the saccharide code during the process of recognition. This research is also a big challenge for theoretical modeling due to the polar flexible saccharide moieties often interacting with lectins via ions. We will particularly focus our attention on Pseudomonas aeruginosa Lectin II (PA-IIL) [1,2].

The lecture will mainly deal with in silico part of the procedure, which is performed by the program TRITON developed in our laboratory. During this procedure, mutants are automatically generated, refined and their affinity and specificity is predicted. The method is then complemented by in vitro approaches that finish with thermodynamic and kinetic measurements [3].

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The Co-C bond cleavage in cobalamin-dependent methionine synthase: a theoretical study

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B12-dependent enzymes are known to catalyze a variety of difficult chemical reactions in which the first step involves cleavage of the Co-C bond. While it is generally accepted that the strength of the Co-C bond must be significantly reduced by ∼50% in the enzymatic catalysis, the mechanism responsible for such bond dissociation energy (BDE) lowering remains poorly understood. To the extent it has been addressed experimentally, evidence from model systems indicate that steric hindrance around coordinated alkyl ligands leads to a higher hemolysis rate. Different models have been suggested, but none can be considered as fully satisfactory in light of a large body of experimental results.

In my presentation I will summarize recent progress in computational modeling of the catalytic activation of cobalt-carbon bond cleavage. The growing interest in modeling the structure and electronic properties of B12 cofactors has demonstrated that computer simulations, in particular density functional theory (DFT) can be an important part of B_{12} research.

Critical evaluation of protein-ligand docking programs

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Molecular interactions between proteins and small chemical molecules play an important role in various biological processes. Finding a molecule that can potentially bind to a target protein is essential in drug discovery but still remains challenging, expensive and time-consuming task. Since the crystallography and multidimensional NMR provide a wealth of structural information of various biological targets, different protein-ligand docking programs have recently become available [1]. Those *in silico* tools are frequently used for virtual high-throughput screening of large molecular compounds libraries in order to identify new potent inhibitors. The typical aim of the docking procedure is to predict correct poses of a ligand in the binding site of the protein as well as to score them accordingly to the strength of interaction in a reasonable time frame. Since all programs exploit empirically based scoring functions and engines, docking results are sometimes far from reality. Usually receptor is treated as a rigid molecule because of the high computational costs, whereas conformational flexibility of ligands is taken into account owing to different placement algorithms such as evolutionary methods, force field-based methods, fragment-based incremental methods or shape complementary-based methods [2].

The aim of our studies was to evaluate of posing and scoring capabilities of various docking programs on large data set of protein-ligand complexes. Seven commonly used docking programs have been used to re-dock 1200 protein- ligand complexes, which were retrieved from PDBbind database [3]. For those complexes binding affinity data and the precise location of binding sites are available.

We have found that calculated scores do not correlate with experimental pKd values, what indicates that all tested docking programs are not able to predict correctly binding affinities. These results clearly show that we are still lacking the universal scoring function for all kinds of ligands and protein families. Scoring functions often do not rank docked poses in appropriate way, very frequently the best placed molecule is not the highest scored. On the other hand, docking programs can predict with relatively high accuracy the three dimensional structure of the protein- ligand complex. This gives the hope that present advances in docking will at least allow for proper selection of close-to-native decoys.

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Modeling noncovalent interactions at the metabolite binding site in purine riboswitches

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Purine riboswitches constitute a class of highly structured regions within the 5′-untranaslated sequence stretches of mRNAs that specifically bind purines to regulate the gene expression. A unique feature of the ligand binding in these riboswitches is the larger role of hydrogen bonding compared to stacking [1]. In order to study the inherent strength and specificity of molecular recognition involved in these interactions, we have carried out gas phase quantum chemical studies on the metabolite binding pockets of adenine [2] and guanine [2] binding riboswitches, with adenine, guanine and a modified pyrimidine respectively, at the B3LYP/6-31G** level of theory. An analysis of optimized structures reveals that for three conserved residues - C74, U47 and U51, the ligand-base hydrogen bonding pattern remains conserved. On the other hand, the U22 residue deviates from its crystal geometry, suggesting that its is held in the crystal geometry through strong backbone and local environmental constraints.

We have carried out Morokuma decomposition and interaction energy evaluations as well as NBO and AIM analysis to understand the strength and nature of binding of the individual aptamer residues with their respective purine metabolites. The dominant features of these noncovalent interactions have also been analyzed.

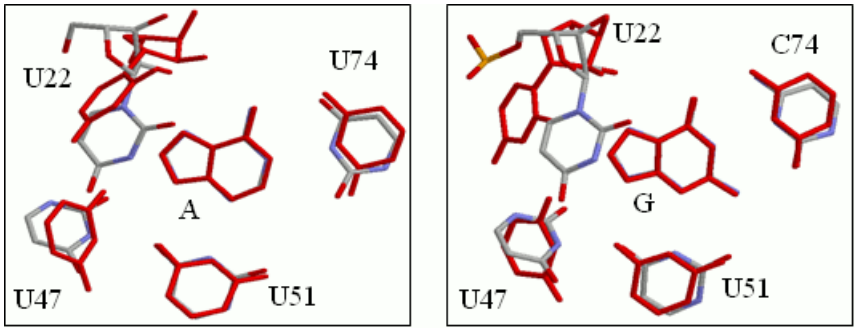

Fig. 1: Superposition of crystal (red) and fully optimized (CPK) geometries of binding pockets of adenine and guanine aptamers.

Acknowledgements: AM thanks DBT for research grant. PS and SS thank CSIR, New Delhi for JRFs.

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Design of laser pulses for selective vibrational excitation of amino N-H bond of adenine and A-T base pair using Optimal Control Theory

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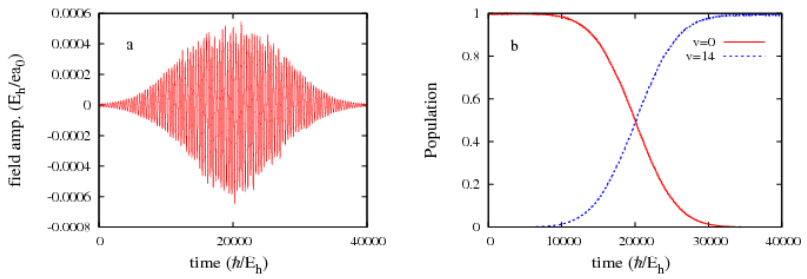
Optimal control theory (OCT) [1] has emerged as a comprehensive tool for designing laser pulses to achieve prescribed dynamical goals. Use of OCT to control biological molecules is difficult because of their inherently complex dynamical properties. Studies on the control of vibrational quantum dynamics of hydrogen bonds in biomolecules using optimally designed lasers will provide greater insights into their dynamical behavior. Use of lasers to control photodissociation of ternary aniline cluster has been carried out, utilizing the strong interaction between N-H stretching vibration and adjacent hydrogen bond [2]. Time dependent interaction among DNA base pairs have been used as basis for control studies on hydrogen transfer[3].

We have used OCT to design infrared laser pulses for the selective vibrational excitation of amino N-H bond present in two different molecular environments, one in the free adenine molecule and second in the hydrogen bonded state, present in A-T base pair (N-H...O). The interaction with the laser field is treated within the dipole approximation. Density functional theory is used to obtain the potential energy and dipole moment functions for both systems. Plot a shows the optimized field and plot b shows the variation of various states involved in the v=0 to v=14 transition in N-H...O. Our results show that optimized laser fields are obtained which give virtually 100% excitation probability to the preselected vibrational levels.



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Molecular pharmacology of arsenic trioxide and the cure of acute promeylocytic leukemia

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Acute promyelocytic leukemia (APL) is a blood cancer characterized by a rapid accumulation of abnormal white blood cells in the bone marrow and blood resulting in anemia, susceptibility to infections, bleeding, and hemorrhage. Recent clinical studies have demonstrated that Trisenox or arsenic trioxide is effective in providing for a complete remission in APL patients, especially those who have relapsed from conventional all-trans retinoid acid and anthracycline-based chemotherapy. It has been reported that ATO causes degradation of the fusion protein PML-RAR alpha, morphological changes, and DNA fragmentation characteristic of apoptosis in APL patients. However, the molecular mechanisms of its pharmacological action are not well elucidated. In this research, we hypothesize that ATO treatment of APL cancer is mediated through oxidative stress leading to p53 activation, cell cycle modulation, genotoxicity and apoptosis in leukemia cells. To test this hypothesis, we performed a number of molecular pharmacology and toxicology assays on human leukemia cells exposed to various doses of ATO.

Data from the MTT assay indicated a strong dose-response relationship with regard to the cytotoxic and therapeutic properties of ATO. Upon 24 h of exposure, the dose required to kill 50be about 6 ug/ml. Western Blot analysis also demonstrated a strong dose- response relationship with regard to the expression of p53, tumor suppressor protein. Similarly, strong dose-response relationships were found in connection to ATO-induction of malandialdehyde formation and DNA damage. ATO-induced apoptosis was characterized by a significant increase in the percentages of annexin-5 and caspase-3 positive cells, and an increase in DNA fragmentation.

Our direct in-vitro findings indicate that the pharmacology of ATO as an effective anti-cancer agent is associated with its cytotoxic effects in leukemia cells. This cytotoxicity is found to be mediated by oxidative stress, up-regulation of the p53 tumor suppressor protein, DNA damage, biochemical changes leading to phosphatidylserine externalization and caspase-3 activation, and apoptosis leading to morphological changes.

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Identification of novel scaffolds leading to small molecule DNA polymerase-β inhibitors with potential in neurodegenerative and oncology disorders

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The common analogy of drug action is that of a lock and key, with a drug acting as a selective 'key' that fits into the 'lock' of a specific drug target. However, a growing body of post-genomic biology is revealing a far more complex picture of drug action with many keys for each lock, single keys to fit multiple locks and drug targets, as DNA polymerase-β (DNA pol- β), which are often involved with multiple diseases. All the above phenomena fall within poly-pharmacology.

The full-length DNA pol-β consists of an amino-terminal lyase domain (8 kDa, 90 residues), connected via a short protease-sensitive segment to a carboxyl-terminal polymerase domain (31 kDa, 250 residues). The 31-kDa carboxyl-terminal polymerase domain has little or no affinity for single- strand DNA (ssDNA); it binds double-strand (dsDNA) and possesses active- site residues necessary for the nucleotidyl transferase activity. The 8-kDa domain binds strongly to ssDNA, but weakly to dsDNA; in addition, it has dRP lyase activity.

DNA repair in mammalian cells is a multi-pathway process that protects the integrity of DNA in the presence of DNA damaging agents. Many currently used anticancer therapeutic agents rely on the ability to create DNA lesions, leading to cancer cell death. The ability of cancer cells to repair such DNA damage is a major cause of resistance to these clinically used antitumor agents. One strategy to address this issue involves targeting proteins involved in DNA repair in cancer cells, thereby overcoming resistance to DNA damaging agents employed for anticancer therapy.

The aberrant expression of cell cycle proteins -"the cell cycle hypothesis of Alzheimer's disease (AD)"-, and the presence of de novo DNA-polβ- mediated DNA replication in neurons have been described as deleterious to neurons, which undergo death rather than complete the cell cycle. Although our understanding of the neuronal cell cycle is not complete, experimental evidence suggests that compounds able of arresting the aberrant cell cycle will yield neuroprotection. The search for efficient and specific DNA pol-β inhibitors is particularly relevant in light of the possibility to test the effects of these compounds in animal models of AD.

As opposed to classical cytostatic drugs, selective DNA pol-β inhibitors might represent a "polypharmacological" key to neuronal-specific cell cycle inhibition and means for sensitizing cells to therapeutically relevant chemotherapeutic agents. A synergistic approach combining Ligand-Based Drug Design, purchasable databases screening and docking (Structure-Based Drug Design) to find candidate inhibitors for in vitro and animal models assays will be presented. Porting of the softwares to a GRID infrastructure and their improved performance will be also discussed.

The hierarchical QSAR technology for virtual screening and drug design

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In the given work the Hierarchical QSAR Technology (HiT QSAR) on the base of Simplex Representation of Molecular Structure (SiRMS) and its application for different QSAR/QSAPR tasks have been considered. The essence of this technology is a sequential solution (with the usage of the information obtained from the previous steps) of QSAR problem by the series of enhanced models. Actually, it's a system of permanently improved solutions.

The unique and principle feature of the HiT QSAR consists in multiple- aspects hierarchical strategy that related to: models of molecular structure description (1D → 2D → 3D → 4D); models of atoms description in molecular simplexes (descriptor → physical-chemical → field); structural descriptors (local → integral); scales of activity estimation (binary → nominal → ordinal → continual); mathematical methods of analysis the structure-activity relationship (pattern recognition → rank correlation → multivariate regression → PLS); final aims of QSAR research (prediction → interpretation → structure optimization → molecular design).

The set of different QSAR models that supplement each other is a result of applying HiT QSAR. These models, together (consensus modeling) solve the problems of virtual screening, evaluation of the influence of structural factors on activity, modification of known molecular structures and design of new high-performance potential antiviral agents.

Innovative aspect and main advantages of HiT QSAR are: Simplex representation of molecular structure, that is providing universality, diversity and flexibility of description of compounds related to different structural types; HiT that depending on the concrete aims of research allows to construct the optimal strategy of QSAR models generation, avoiding at the same time the superfluous complication that doesn't results in the adequacy increase; HiT QSAR does not have the restrictions of such well-known and widely used approaches as CoMFA, CoMSIA, and HASL, usage of the lasts is limited in the structurally homogeneous set of molecules and only one conformer; HiT QSAR hasn't the lacks of HQSAR which are related to the ambiguity of descriptors system formation. On the every stage of the usage of HiT QSAR one can determine the features of molecular structure which are important from the point of view of investigated activity, and, respectively, exclude the rest. It shows unambiguously the limits of expedient QSAR models complication and allows not to waste superfluous resources for needless calculations.

HiT QSAR efficiency was demonstrated by it comparison with the most popular modern QSAR approaches on two representative examination sets. The examples of HiT QSAR successful application for various QSAR/QSPR investigations at the different levels (1D-4D) of molecular structure description are also highlighted. Reliability of developed QSAR models as the predictive virtual screening tools and their ability to serve as the base of directed drug design was validated by subsequent synthetic, biological, etc. experiments.

Electronic properties and reaction mechanisms of selected anticancer metallodrugs

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The anticancer activity (IC50) of the derivatives of cisplatin (diammine- dichloro-platinum(II) complex) was compared with an aquation reaction, which can be considered as an activation of these metallodrugs. In this process the chloro-ligards is replaced by one or two water molecules. The energetic (thermodynamic) parameters together with rate constants were determined for this reaction. It can be shown that rate constants partially correlate with the cancer indexes, at least if the same biological impact can be expected.

Detailed mechanism of the adduct formation of diaqua-tetrakis-μ- acetatodirhodium to purine DNA bases is examined using ammonia as a model for interacting species (nucleobase), which attacks the Rh-O(acetyl) or Rh- O(aqua) coordination bonds. Several different mechanisms were explored modeling different environment of the complex. Thermodynamic affinity and as well as kinetic data for the ammonia interaction with Rh-complex demonstrate presence of an enhanced reaction mechanism in acidic environment.

Replacement of the chloro-ligand in [Ruthenium(II)(Arene)(en)Cl]+ by water is studied in connection with the complex activation, in analogy to cisplatin activity. The influence of the different arene ligands on aquation reaction was examined. Also transition states for process of the water replacement (substitution) by purine nucleobases was searched in gas phase as well as water solution using polarizable continuum model. Thermodynamic and kinetic data were found for aquation and substitution reactions confirmed experimental conclusion on preference of the guanine- adduct formation in real samples.

Computer-aided design of inhibitors of amino acid biosynthesis

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Enzymes involved in biosynthesis of amino acid — crucial metabolites of living organisms are highly interesting targets for potential drugs and agrochemicals. Two examples of application of such a strategy in design of biologically active compounds will be discussed, namely glutamine synthetase and pyrrolidine 5-carboxylate reductase.

Glutamine synthetase (E.C. 6.3.1.2, GS), the enzyme which catalyses the synthesis of glutamine from glutamate and ammonium ion, is of high importance for nitrogen metabolism. Inhibitors of glutamine synthetase exhibit interesting applications both in medicine and agriculture. It was proven that they could be efficient antituberculosis drugs by inhibiting the growth of the pathogen — Mycobacterium tuberculosis. Preliminary data suggest also that inhibitors of GS could be useful in cancer therapy. On the other side, one of the most potent inhibitors of GS — phosphinothricin (1) is commercially available total herbicide. The inhibition of GS in plant causes accumulation of toxic ammonia. Thus discovery of novel, potent and selective GS inhibitors is of high interest.

Rational discovery of novel inhibitors should be based on the knowledge on the structure of active site, mechanism of the reaction and interactions between substrates, products and inhibitors with protein. Thus, we have docked known inhibitors of GS to its active site and analyzed important structural and electronic features of these compounds [1]. Then, using LUDI program, several new inhibitors were designed. After evaluation of their synthetic accessibility, we have chosen five structures and synthesized them in enantiomerically pure form. Kinetic measurements showed that obtained inhibitors rank between most active GS inhibitors (K_i = 0.59 mM was found for compound (2)) [2,3].

δ1-Pyrroline-5-carboxylate reductase (P5CR) is the enzyme that catalyses the last step of proline biosynthesis by reduction of δ1-pyrroline-5-carboxylate (P5C) to proline. It is the common step in several pathways leading to this amino acid. Its inhibitors could be potential highly active and safe herbicides. It was found that derivatives of aminomethylenebisphosphonic acids are effective inhibitors of this enzyme [4]. Molecular modeling studies suggested strongly that these compound docks in the NADPH binding site. The synthesis and evaluation of several derivatives allowed also building 3D QSAR model of their activity [5].

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Reaction of cisplatin aquation products with cysteine and methionine at constant pH

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The effect of pH on the thermodynamics of interaction of cisplatin hydration products with amino acids cysteine and methionine is explored. In the first step the most suitable procedure for calculation of solvation Gibbs free energies is searched based on the comparison with experimental pK_{as} of amino acids and simple platinum complexes. The resulting procedure combines the DFT/B3LYP density functional with D-PCM implicit solvation model and charge-consistent UAHF cavities developed under this study. In the procedure of cavity formation, formal partial charges used in the original UAHF formulation were found inappropriate for platinum complexes. Our modification of the model is based on replacing of the formal (semi-)integer charge for scaling the vdW radii by the NBO partial charge. This modification works surprisingly well - root mean square error of calculated pK_{as} is 0.74.

In the next step we applied this methodology on calculation of acid dissociation constants of all complexes arising from interaction of cisplatin with amino acids. We calculated thermodynamic potentials for substitution reactions at constant T, p and pH using Legendre transformation

$$G' = G - n_c\mu(H^+) \tag{1}$$

where n_c is the total amount of hydrogen component [1].

At pH 7, the transformed Gibbs free energies differ up to 15 kcal/mol from constant charge approach we used previously. Regarding reaction with cysteine calculations confirmed the strong thermodynamic preference for sulfur coordination followed by nitrogen and oxygen. As for reaction with methionine the most stable structure depends on reacting complex. In case of diammine-aqua-chloro-platinum, the nitrogen coordination is thermodynamically preferred but in case of diammine-aqua-hydroxo-platinum, the sulfur coordination is the most favorable. Interestingly this preference is reversed in favor of nitrogen at pH 9.7. The same effect was observed experimentally on chemically related system by Lempers et al. [2].

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Consensus prediction of aqueous solubility of military compounds

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The objectives of this study are: 1) development of new QSPR equations which will accurately predict aqueous solubility for compounds of US Army interest (explosives and their metabolites) using Simplex Representation of Molecular Structure approach; 2) subsequent validation of obtained results using broad spectrum of available experimentally determined data.

The series of the different QSPR models that supplement each other excludes the application of additive schemes and all together solve the problems of virtual screening, evaluation of influence of the structural factors on solubility, etc were developed and used by Consensus principles of Hierarchical QSAR Technology.

We applied the 2D level of representation of molecular structure obtain the set of well-fitted, robust and predictive (internally and externally) QSPR models (R^2 = 0.90 – 0.95; Q^2 = 0.85 – 0.91; R^2_{test}=0.78 – 0.87). External validation using five different test sets also reflects high level of predictability (R2test1 = 0.7 – 0.87; R^2_{test2} = 0.82 – 0.88; R^2_{test3} = 0.66 – 0.76; R^2_{test4} = 0.86 – 0.91; R^2_{test5} = 0.71 – 0.73). Training set consists of 135 compounds and test set totally includes 181 compounds. Two different approaches (Ellipsoid DA and Williams Plot) were used for estimation of Domain Applicability (DA) of obtained models.

Comparison of predicted values for test set compounds by our QSPR results and EPI SuiteTM technique indicates that both DoD and Environmental Protection Agency will have considerable advantage using developed by us SiRMS models.

Acknowledgements: This study has been performed in the framework of basic science research projected of the US Army, ERDC # 08-41 "Development of New QSAR Equations for Accurate Prediction of Solubility and Octanol-Water Partition Coefficients for Military Compounds".

Normal vibrations and music harmony

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The connection between chemistry and music is mostly referred to famous Russian composer Alexander Borodin (1833-1887) who also had several achievements in organic chemistry. Apart from such personal connections, it is interesting to check, if some natural relations between these two, so much different disciplines, exist. The lecture will focus on essential property of any kind of chemical molecules – on their normal vibrations. Any molecule has well defined number of such vibrations and each vibration has fixed frequency. These frequencies can be recalculated into the acoustic range and used to produce different music sounds. As the normal vibrations of the molecule are simultaneous, the corresponding sounds should be played together, forming specific chord, which one may hear as a consonance or dissonance. In classical music, selected chords have complex relationships to each other, forming the well known system of traditional music harmony. It was found, that normal vibrations of some small molecules can be related to particular harmonic chords, which will be demonstrated during the lecture.

Accurate interaction energies of building blocks of biomacromolecules: quantum chemical study

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Structures and stabilization energies of noncovalently bound molecular clusters playing a role in biodisciplines are investigated. Specifically, we consider H-bonded and stacked structures of DNA base pairs and amino acid pairs in a gas phase as well as in an environment. Structure of pairs is either optimized or is taken from experiment. Benchmark stabilization energies of complexes studied are determined as the Complete Basis Set (CBS) limit of the CCSD(T) calculations and various constructions of these energies are discussed. The role of CCSDT and CCSD(TQ) levels is also considered. Resulting stabilization energies of H-bonded and stacked pairs are very large, much larger than considered before. This is especially true about stacked DNA base pairs and amino acid pairs. It is expected that these energies are highly accurate and differ from the real numbers by less than 0.5 kcal/mol. Stabilization energy of stacked structures originates exclusively in London dispersion energy and only high-level wave function and density functional theories can be applied. Electrostatic energy is responsible for the orientation of the cluster and bringing subsystems closer together. The partitioning of the total interaction energy to the components is performed by using the DFT-SAPT method and the role of electrostatic and dispersion energies in stabilizing staked and H- bonded structures is discussed. The use of density functional theories including the recently introduced hybrid meta GGA functionals is briefly considered and successes and failures of these procedures is mentioned. It is shown that stability of DNA double helix is mainly due to stacking interactions of nucleic acid bases while H-bonding is playing the role in molecular recognition. The unique role of dispersion energy is stressed.

Single strand breaks in DNA induced by low energy electrons - possible mechanisms

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Several mechanistic proposals concerning DNA damage induced by low energy electrons are considered. The mechanisms, based on computational data, comprise the σ C-O or P-O bond cleavage proceeding via: π-shape resonances of pyrimidines, a π^* resonance localized to the P=O group of the phosphate unit, adiabatically stable valence anions of pyrimidines, a consecutive attachment of two electrons to pyrimidine nucleotides and, finally, a sequence of proton/hydrogen atom transfers within a stable valence anion of a nucleotide. Strengthens and weaknesses of these proposals are discussed against existing experimental data.

Acknowledgements: This work was partially supported by the Polish State Committe for Scientific Research Grant No. DS/8221-4-0140-8. The calculations were performed at the Academic Computer Center in Gdańsk (TASK).

RNA base pairing and RNA building blocks

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Due to an unprecedented advance of hardware and software in the last 10-15 years, computational studies can be used as a useful complement to experimental techniques. Specifically, the task of computations is not to merely reproduce experimental data, but mainly to provide qualitative additional insights into areas not directly accessible by experimental methods. However, computational studies also have major limitations, and when used in an inexpert way, lack any biochemical relevance and bias the literature substantially. This talk summarizes advances, limitations and the areas of application of computational methods in studies of RNA.

Ab initio quantum chemistry can provide an accurate description of the intrinsic forces in nucleic acids, such as base stacking or the highly versatile RNA base pairing. Such physically complete calculations serve as a reference for the parametrization and verification of other methods. There are no experimental methods that show such direct structure – energy relations, and recent calculations reach close to an ultimate accuracy. The main and rarely properly tackled problem of these calculations is proper extrapolation from model calculations to real systems.

MD simulations capture the qualitative differences of the intrinsic flexibilities of rRNA building blocks, which possess contrasting intrinsic flexibility signatures. Simulations can visualize stochastic fluctuations that are of the upmost importance for biomolecular machines that are stochastic in nature. Fluctuations are only poorly captured by experimental techniques, which provide mostly static averaged structural snapshots. For example, Kink-turns show profound elbow-like intrinsic flexibility. K-turn oscillatory dynamics typically pivot at the A- minor interaction mediating the contact between *C- and NC-stems*, associated with dynamical water insertion, and the motion is anharmonic. Such structural elements are well suited to passively mediate large-scale motions in ribosomes. Consecutive RNA building blocks can further create architectures with complex patterns of preferred low-energy motions, as in the Helix 42-44 portion of the 23S rRNA (GTPase-associated center rRNA). Overall, the Helix 42-44 rRNA is constructed of a sophisticated intrinsically flexible anisotropic molecular double-elbow stochastic nanoarm. The main advantage of simulations is the unprecedented detailed 3D dynamical description of all aspects of the simulated structures. This picture, however, is limited by force field approximations, which will also be discussed. Simulations can be very efficiently combined with bioinformatics, for example, by relating the impact of selected base mutations in RNA motifs with phylogenetic data.

Fast development of hybrid quantum chemical/molecular mechanical methods brings some hopes to directly describe chemical reactions in RNA enzymes.

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The post-SCF complete basis set quantum chemistry characteristics of the energetic heterogeneity of stacking interactions in crystallographic DNA

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Contemporary X-ray crystallography and NMR experiments provide detailed structural information at atomic resolution. Although the direct use of such coordinates is not recommended [1], base pair and base pair step parameters available in nucleic acid databases [2] are a source of detailed conformations of stacked complexes. The post-SCF quantum chemistry method at the DF-MP2/aDZ level are thought to be a reliable tool [1,3,4] for predicting stacking energies. Interestingly, H-bonded pairs observed in high resolution crystal structures of DNA oligomers correspond to minima on the potential surfaces of isolated monomers.

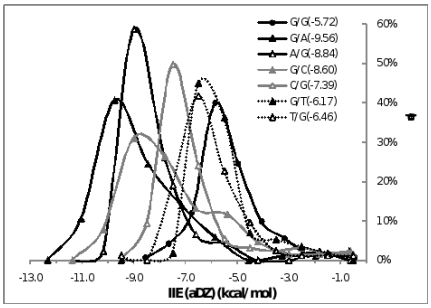

Fig. 1: Fig.1. The IIE distributions of pairs formed by guanine with all four nucleobases in stacked arrangements that match to ones found in crystallographic B-DNA.

Hence, the intrinsic features of such pairs may be easily described by simple models "outside" of the DNA environment. This fortunate circumstance allows for precise analysis of HB complexes on state-of-art levels of theory. On the contrary the stacked configurations found in DNA crystals exhibit great variability and usually do not correspond to most favorable arrangements of isolated monomers in stacked conformations [3]. Consequently, the essential base-base stacking interactions are significantly affected by DNA polymorphism and it is well known that these interactions reach up to 65-75% of the maximum possible stabilization energies.

Thus, knowledge of the distribution of intermolecular interaction energies (IIE) corresponding to base pairs found in natural arrangements of DNA seems to be important. This aspect, along with detailed structural variability of all possible pairs comprising canonical purines and pyrimidines are the subject of current investigations. Many interesting properties were revealed by analysing histograms characterizing the distributions of IIE, base pair and base step parameters. For example, significant context dependence of IIE may be noticed and the strongest stacking interactions are expected between adenine and guanine in the 5'-G/A-3' sequence.

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Probing the structure and dynamics of the RNA dinucleoside monophosphates (ApA, ApC, CpA, CpC) with NMR spectroscopy

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Functional diversity of nucleic acids (NAs) makes their study crucial for deeper understanding of many essential biological processes. Basic structural parameters used for the description of NAs are shown in Figure 1: the backbone torsion angles (α, β, γ, δ, ϵ, ζ), the sugar pucker (C2'-endo and C3'-endo), and the glycosidic torsion angle (χ).

In our previous study we correlated the theoretical NMR indirect spin-spin coupling constants calculated using the DFT method with the backbone structural classes found by X-ray in ribosomal RNA [1]. Each structural pattern of RNA backbone corresponds to the specific values of the scalar couplings [1]. In the present study we attempted to correlate the scalar coupling constants in the dinucleoside monophosphates with the NMR experiment [1].

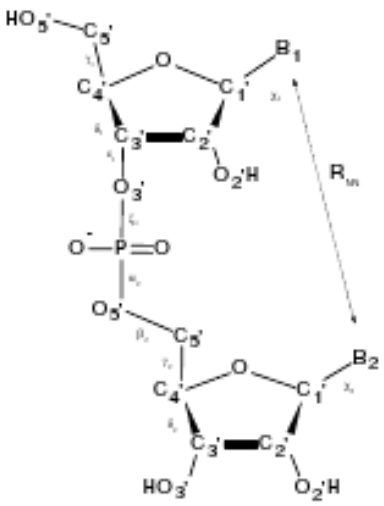

Fig. 1: Fig.1. Scheme of dinucleoside monophosphate.

The calculated scalar couplings were confronted with the empirical Karplus relations [2,3]. Since the RNA dinucleoside monophosphates are flexible the molecular dynamics was used for modeling their dynamical behavior. Time evolution of all torsion angles and other selected geometry descriptor and and the stacking interactions were studied in the dependence on sequence of the dinucleoside monophosphate containing Adenine and Cytosine bases; ApA, ApC, CpA and CpC.

Acknowledgements: This work was supported by the Grant Agency of the Czech Academy of Sciences, IAA400550701. This study was further supported by Grants HFSP and by Grant Agency of Charles University in Prague.

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Common convenient misconceptions: theory versus experiment

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It has been well established that:

1. High level ab initio calculations provide data that are as accurate as precise experiments

2. Experimentalists either do not value theoretical predictions or consider them to be ultimate answers

3. A number of high level theoretical predictions do not match experimental findings

The talk will reveal some of the reasons that items 1 and 3 contradict each other. Intrinsic limitations of the applied computational methods as well as common misconceptions will be discussed. A number of examples will be provided.

Acknowledgements: This research was supported by the CMCM grant from the ERDC (Vicksburg, MS) and the Army High Performance Computational Research Center (University of Minnesota).

Poster abstracts

in alphabetical order of the leading author's last name

Poster session A - June 24 (Tuesday)
Posters: P1-P26

Poster session B - June 26 (Thursday)
Posters: P27-P53

Structural motifs and H-bonding patterns of homo-oligopeptides consisting of Ala and Gln residues

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Polyalanine and polyglutamine are homo-oligopeptides (HOPs) composed of the same amino acids, namely alanine (Ala) and glutamine (Gln) residues, respectively. These two HOPs play a relevant role in the formation of several neurodegenerative diseases, and they are well-known to cause various human illnesses. Therefore, the aim of our study was to examine the structural motifs and intramolecular H-bonding patterns of the aforementioned HOPs.

The conformational analysis of poly-$(Ala)_n$ and poly-$(Gln)_n$ peptides with different lengths (n = 7, 10, 14, 20) was performed by simulated annealing calculations [1]. The molecules were modeled either with charged N-terminal amino and C-terminal carboxyl groups, or with the N- and C-termini blocked by acetyl and N-methyl amide groups, respectively.

In the case of poly-(Ala) and poly-(Gln) peptides, various secondary structures (i.e. type I and III β-turns, α-helix, 3_{10}-helix and antiparallel β-strand) were identified. The β-turns were observed along the entire sequence of both HOPs, additionally, numerous conformers were detected, which possess two or more β-turns, either consecutively or separately. For the periodic secondary structures, segments with various lengths were found, which were characterized α-helical, 3_{10}-helical or antiparallel β-strand structural elements. Moreover, our results revealed the existence of local poly-proline II conformations for all individual Ala and Gln residues. Beside the above-mentioned secondary structures, a variety of other non-conventional structural motifs evolved in the tripeptide units was identified. According to the presence of β-turns, 310- and α-helical segments, typical H-bonding patterns were observed in the conformers of poly-(Ala) and poly-(Gln) peptides. For both HOPs, mostly i←i+3 and i←i+4 H-bonds appearing between the backbone CO and NH groups were determined. Nevertheless, in the case of poly-(Gln) peptides, additional intramolecular H-bonds were detected, in which the CO and NH groups of Gln side-chains participated as acceptors and donors, respectively.

The results of our conformational study performed on poly-(Ala) and poly-(Gln) peptides pointed out that both HOPs exist as an ensemble of conformational states characterized by a variety of secondary structural elements and intramolecular H-bonding patterns.

Acknowledgements: This work was supported by grants GVOP-3.1.1-2004-05-0492/3.0 and RET 08/2004.

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Structure of chiral peptide nucleic acids (cPNAs)

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Peptide nucleic acids (PNAs) are compounds which have natural or modified nucleic bases on the side chain with a great variety of backbone structure. These structures . on the basis of experimental results can provide the formation of PNA-PNA and PNA-DNA duplexes. PNAs backbones are chemically more stable and insensitive than that of the DNA. This property supports their possible application in medicine.

The conformations of the backbone and the bases (A, C, T, G and U) connected to the Cγ-atom of the side chain of L- or D-chiral peptide backbone of peptide nucleic acid (L- or D-cPNA(A,C,G,T,U)) were studied by molecular mechanics (SP4 force field) with random conformational search. The best structures were optimized by semiempirical quantum chemical methods PM3 and PM6 in gas phase and with implicit solvation model COSMO. The best structures obtained were refined by ab initio quantum chemical method and dispersion corrected density functional (DFT) methods. The best conformations of L- or D-cPNA(A,C,G,T,U)6 were also calculated by molecular mechanics with random conformational search and Boltzmann jump. The secondary structures (torsion angles, H-bonds) were analyzed in order to find any rules in the formation of stable conformers. The interactions between the bases and the backbone atoms further backbone atoms with each other were also analyzed.

Acknowledgements: This work was supported by the Hungarian Research Fund (OTKA K61577). Calculations were performed at the HPC Group of the University of Szeged.

Quantum chemistry calculations in pharmacology

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Medicine and pharmacology in particular are expected to be ready for individual therapy. The set of drugs used for particular disease shall be specifically designed for particular individual patient. The single nucleotide polymorphism (SNP) discovered in the entirely sequenced human genome makes us individual phenotypes recognized as the specificity of each person. It turned out, that the common disease appeared also to be of individual character for each patient. Thus the therapy (including drug applied) shall be of individual character.

Bioinformatics makes possible to design the drugs [1] for each patient developing the tools to simulate the chemical processes between ligands and proteins and to predict the possible reaction of the individual organism to particular chemical compound. Quantum chemistry is expected to produce the parameters for huge number of different molecules, which may act as ligands interacting with target proteins and modify their biological activity according to our therapeutic expectations.

Large number of new drugs is generated using the de novo design system, however many of new compounds of pharmaceutical use can be generated as the result of aim-oriented chemical modification of ligands interacting naturally with proteins.

The natural ligands data base [2] containing the complete set of parameters necessary to simulate the interaction with proteins (parametrization compatible with protein-oriented force field) has been generated and developed including currently about 170 molecules. The parameters available are: equilibrium molecular geometry, partial charges (calculated according to several quantum mechanics methods e.g. Mulliken populations, Hirshfeld charge analysis, Voronoi charges and point charges fitted to the electrostatic potential), van der Waals (vdW) parameters and force constants for torsional potential. The ligands data base with the set of parameters (ready for simulation of interaction with proteins) is available [3].

The folic acid which modified into methotrexate (MTX) is widely applied in the cancer therapy will be shown as the example of pharmacological use on one hand and as the example of quantum chemistry-based parametrization on the second.

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"The Origins Project": a closer look at formamide dimers

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How did life on Earth begin? This question has intrigued scientist for years. Many groups with many different approaches have investigated this question. The ideal of being able to retrodict the past has caused prebiotic chemistry to emerge as a special area of synthetic organic chemistry [1].

Using nucleic acids as the focus point as the building blocks of life, formamide dimers play an important role in the investigation of hydrogen bonds in peptides and proteins.

This present work uses Coupled-Cluster with Singles and Doubles at the 631++G (d, p) level of theory to fully optimize structures and find all harmonic frequencies of five different singly and doubly hydrogen bonded formamide dimers. The goal is to proceed with Coupled-Cluster with Singles, Doubles and Pertubative Triple excitations using the aug-cc-p5VZ and map the anisotropic surface.

Acknowledgements: :Support from Jackson State University High Performance Computational Design of Novel Materials grant. All calculations were done using The Mississippi Center for Supercomputing Research (MCSR).

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The structural aromaticity alteration of para substituted benzene analogues imposed by solvent: implicit versus explicit models

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The molecular geometries may be significantly affected by presence of the solvent. Such relaxation of gas phase geometry may be expressed directly either as the difference in total energies or via elegant ways as the alteration of the structural index of aromaticity (HOMA). However, there are often contradictory predictions if alternative solvation methods are applied. Here, the water solution is modeled either as polarized continuum field approximation (PCM) or hybrid quantum chemistry combined with molecular mechanics method (QM/MM). Significant structural changes imposed by the solvent were noticed for many molecules. There were 127 para benzene derivatives analyzed in details. The difference between HOMA values corresponding to gas phase and water solution reached up to 25% for some aromatic compounds. The rationale of this fact was provided based on the frontier orbital analysis. The incoherent predictions of the applied models of solutions are discussed and methodology based on chemical intuition is proposed. The main conclusion is that in some cases the applied PCM method artificially exaggerate the geometry relaxation in solution what is not observed if explicit solvent molecules are taken into account.

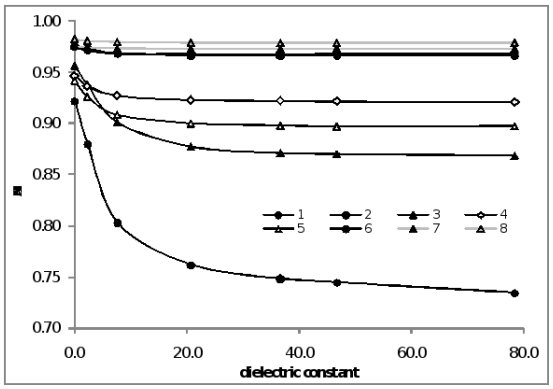

Fig. 1: Fig.1.The alteration of the HOMA values imposed by presence of solvent modelled in PCM approximation. The following compounds are characterized: aniline (1), p-NO-aniline (2), p-NO_2-aniline (3), p-CN-aniline (4), p-CHO- aniline (5), p-CH_3-aniline (6), p-OCH_3-aniline (7) and p-OH-aniline (8).

The post-SCF complete basis set quantum chemistry characteristics of the energetic heterogeneity of stacking interactions in crystallographic DNA

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Telomers play a crucial role in preserving genomic stability. It has been shown, however, that GGG fragments are very susceptible to oxidizing agents and the presence of 8-oxo-guanine lesions in telomeric sequence have disordering impact on the binding process [1]. Reasons of much lower affinity of TRF1 to oxidized telomers may be related to structural, energetic and electrostatic alteration of modified chain [2].

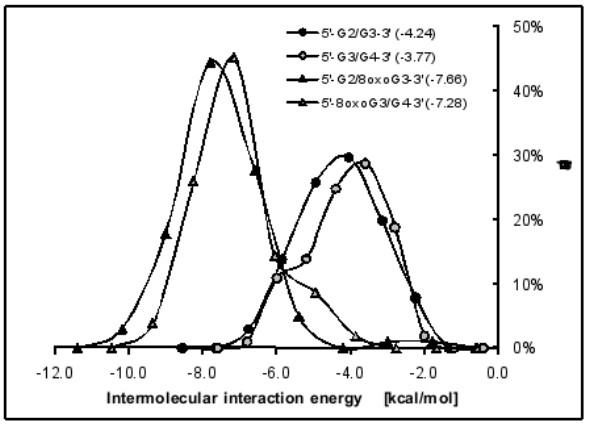

Fig. 1: Fig.1.The stacking energy of G/G and 8oxoG/G pairs found in central triad of telomeric 5'-ACTTA1G2X3G4T5T6AGGG-3' B-DNA fragment (X=G or 8oxoG).

In the present work we have applied quenching molecular dynamics (MD) methods combined with DF-MP2/aug-cc-pvdz single point energy calculations for gaining insight into the stacking interactions of central 5'-G2X3G4-3' telomeric triad (X=G or 8oxoG). The MD method was used for generation of 2000 snapshots characterizing the time evolution of native and oxidized model telomeric 14-mer. These data were used for structural diversity characteristics[3]. Besides, the values of intermolecular interaction energy (IIE) were estimated based on DF-MP2/aug-cc-pvdz level for every 20ps snapshot. Significant impact of 8-oxo-guanine presence on structural and energetic properties of stacked dimers were observed. Particularly, as it was presented in Fig.1, the stacking interactions of 8oxoG with guanine are much stronger then between two standard guanine molecules. In fig.1 the smoothed histograms characterize populations of IIE for pairs found in non- modified and oxidized telomeric fragments and the most probable values were presented in parenthesis.

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Nucleic acid bases complexes: elucidation of the physical origins of their stability

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The stacking interactions of aromatic complexes are one of key factors responsible for stabilization of many important biological complexes. It is now well recognized that the stabilization energy of stacked nucleic acid bases strongly depends on their mutual alignment. The local conformational space of biomacromolecules such as DNA and RNA determines drugs binding and intercalation processes. Moreover, the nucleic acids are exposed to endo– and egzogenic mutagenic factors. The result of interaction of hydroxyl radical with DNA and RNA is the formation of modified purines, pirymidines and dehydratation of deoxyribose. The damage of nucleotides can lead to a series of mutations. Until recently, little was known about the nature of intermolecular interactions of nucleic acid bases. In particular, the complexes of modified nucleic acid bases have scarcely been studied. In the present contribution, we report on the results of our recent investigations within this field. The analysis of the origins of stabilization of nucleic acid bases dimers for over 140 different conformations of dimers of purines and pirymidines appearing in B–DNA crystals shall be presented and discussed.

DFT modeling of the structure and vibrational spectra of 4-hydroxybenzoic acid hydrazide

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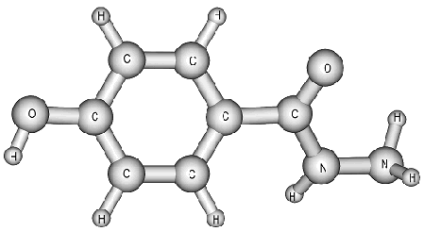
Hydrazides, a class of compounds of general formula $RCONHNH_2$, show various important properties useful in analytical chemistry, agriculture and medicine. In the last area, the most famous compound is isoniazid (4- pyridinecarboxylic acid hydrazide), which is widely used as an anti- tuberculosis drug [1]. Intense work is carried out with substituted hydrazides as anti-cancer agents [2] or intermediates in their syntheses [3]. Hydrazide group is also present in complex drugs, such as nitrofurans, that are used to inhibit bacterial growth [4].



The compound studied in present work, 4-hydroksybenzoic acid hydrazide (4-HBAH) has also been tested for biological activity. It has been observed that 4-HBAH is able to induce resistance to tomato wilt disease [5]. In the present work, the molecular structure and normal vibrations of 4- HBAH were modeled at the DFT level using the B3LYP functional and the 6-311++G(d,p) basis set.

Despite many hydrogen bonds which bind the 4-HBAH molecule in the crystal lattice, its structure is close to that predicted by calculations in gaseous state and shown in Figure. The skeletal atoms of hydrazide group form a plane twisted from the aromatic ring plane by 24.9° which is very well comparable with DFT optimized value of 21.6°.

Calculations also revealed that another conformer with the OH group rotated by 180° is also stable and its energy is about 0.0003AU lower. The optimized structure was used for computation of frequencies, IR intensities and Raman activities of 51 normal vibrations, further described in potential energy distribution terms. The computed normal vibrations were correlated with observed IR and Raman bands. In order to trace the hydrogen bonding influence on vibrational frequencies, the spectra of the O,N- deuterated compound were measured and reproduced in DFT calculations. Observed and computed band shifts were very helpful in their mutual correlation. It was also found that deuteration may cause substantial changes in some vibrations not directly related to deuterated groups of atoms.

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To tunnel or not to tunnel? Methylmalonyl-CoA mutase story, part II

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B12-dependent methylmalonyl-CoA mutase (MMCM) catalyzes the rearrangement of methylmalonyl-CoA (MCoA) to succinyl-CoA. There are two hydrogen atom transfer reactions in the overall catalytic cycle of MMCM. The first one from the substrate (methylmalonyl-CoA) to the 5'-deoxyadenosyl radical (dAdo) initiates the isomerization reaction in the enzyme and was found to exhibit an anomalously large KIE, in particular 50 at 5°C which was confirmed by EA-VTST/MT calculations carried out employing a combined quantum mechanical and molecular mechanical (QM/MM) potential-energy surface with unrestricted AM1 method [1].

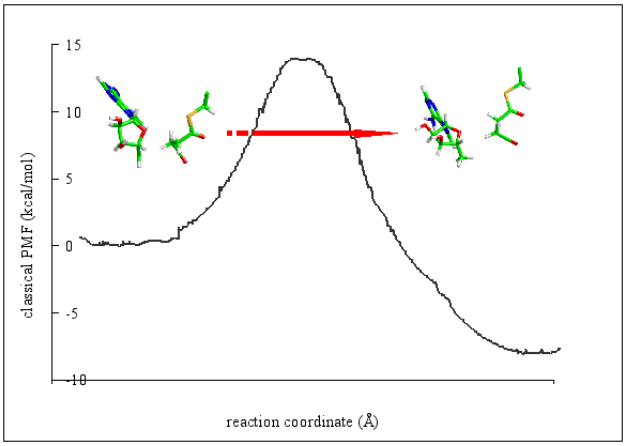

Fig. 1: Computed classical mechanical PMF at 5°C for hydrogen transfer reaction between the 5'- deoxyadenosyl radical and succinyl-CoA.

The product (succinyl-CoA) is formed during the reabstraction of the hydrogen atom. This second H atom transfer unexplored experimentally was modeled using the same computational procedure [1] and the results suggest significant lowering of free energy of activation (14.0 kcal/mol vs 21.3 kcal/mol in the presence of methylmalonyl-CoA) (Figure 1) and reduction of KIE (8 vs. 50, respectively).

Acknowledgements: Calculations were performed at the Minnesota Supercomputing Institute (Minneapolis, MN, USA).

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Phosphotriesterase-catalyzed hydrolysis of sarin: modeling of the enzyme-substrate complex

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Biodegradation of hazardous organophosphorus pesticides and related chemical warfare agents is currently a matter of the utmost interest. Among the enzymes identified as capable of enhancing such a reaction, phosphotriesterase (PTE) has been recognized as a prime candidate due to wide substrate acceptance and high turnover number [1]. Despite the abundance of experimental data regarding PTE properties, the molecular basis of its action has not yet been unequivocally established [2, 3]. This research has been aimed at computational evaluation of the way PTE achieves its enormous rate enhancement. The knowledge of factors affecting substrate specificity and/or catalytic efficiency would allow for rational engineering of PTE mutants designed specifically to suit broad range of purposes.

Well–founded model of the enzyme–substrate complex is an essential prerequisite necessary for a reliable modeling of an enzyme-catalyzed reaction. Since no experimental structures of the latter are available in case of phosphotriesterase, the consecutive steps employed in building and validation of PTE–sarin system will be the subject of this contribution. Apart from classical molecular dynamics simulation, hybrid quantum mechanical and molecular mechanical (QM/MM) methodology will be employed to reveal molecular details of enzyme-substrate recognition along with its implication for PTE catalytic properties.

Acknowledgements: Funding from ERDC grant #W912MZ0420002 is acknowledged.

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Topological analysis of the electron density in model compounds containing nitrogen-nitrogen bonds

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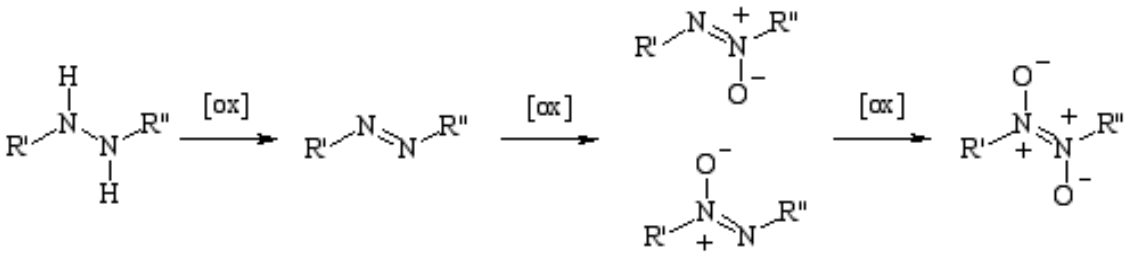
The N–N bond is encountered in several open-chain nitrogen compounds in very variable environment. The electronic structure of the hydrazo-, azo- , azoxy- and azodioxy- groups has recently been a subject of comprehensive revision and evaluation [1]. The nature and properties of this bond can be demonstrated on a simple series of model compounds:



R = H, Me, Ph

The purpose of this report is to analyze the relation between the level of oxidation of the nitrogen-nitrogen bond and its electronic properties, especially focused on the topological analysis of electron density on the basis of 'Atoms in Molecules' (AIM) quantum theory proposed by Bader [2]. Molecular geometries of the studied compounds were optimized using standard density functional theory (DFT) [3] and Möller-Plesset second order perturbation theory (MP2) [4] with 6-311++G** level of theory. The Bond Critical Points (BCP) were localized and their properties were calculated using MORPHY program [5].

Acknowledgements: Interdisciplinary Centre for Mathematical and Computational Modelling (University of Warsaw) is acknowledged for computational facilities.

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Towards the design of asymmetric organocatalysts

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Due to the rapid development of computer technology and scientific software it is now possible to study chemical reactions more accurately than ever before. Stereoselective organocatalysis, which have attracted the attention of experimentalists for the last couple of years, now became a matter of interest to computational chemists.

Our efforts are directed towards the computational exploration of aldol reactions catalyzed by proline. Despite the broad and comprehensive experimental studies, the molecular basis of these type of reactions still remain limited. Houk et al. performed successful calculations of different model systems and determined product ratios that are highly consistent with the experiments [1]. In our study, the aldol reaction involving cyclohexanone enamine with isobutyraldehyde generating four diastereoisomeric products is considered.

We attempt to deduce the general characteristics of the molecular environment resulting in optimal stereoselectivity from catalytic fields [2], which recently appeared to be a useful tool for studying enzymatic systems, aiding design of better catalysts [3-4]. The innovative approach of this project is an application of catalytic fields to nonenzymatic asymmetric reactions, catalyzed by small organic compounds like proline and its derivatives. Since the 3D or slice-like representations of catalytic fields are suitable for studying enzymes, here we utilize the local differential electrostatic potential calculated at the discreet points in the vicinity of the reacting system. Determining the most favorable catalytic environment is an essential step in the predictions of various substituents as factors modifying proline stereoselectivity.

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Conformational studies of organophosphorus pesticides towards the discernment of their esterase inhibition

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In the modern age the exposure of humans to harmful organophosphorus (OP) agents has been shown to be exponentially increasing. Due to the steady rise in deleterious health incidences more must be understood about the physico-chemical properties mediating such events in compromised mammalian systems. Towards the elucidation of such events in neural networks, we have carried out ab initio conformational analysis on a certain class of OP agents which are manifest as pesticides i.e. parathion (PA), paraoxon (PO), and chloropyrifos (CP).

All three of these OP pesticides act through the same mode of biological activity. Wherein an influx of the pesticide into the synaptic cleft or motor endplate arrests the binding event of acetylcholine to the enzyme Acetylcholinesterase (AchE). Similar competitive inhibitions have been shown in the X-ray crystallography studies of OP pesticides complexed with the AchE-similar enzymes Phosphotriesterase and Plant Carboxylesterase main active sites. To this end, we have compared the low-energy conformers of PA, PO, and CP to the existing analogous inhibitors embedded within their respective holoenzymes.

We have carried out a rigorous partial-geometry leading to full-geometry optimization approach for achievement of the low-energy conformers for PA , PO, and CP which showed six, six, and four conformers respectively. For the discernment of electrostatic charge distribution we have mapped molecular electrostatic potentials (MEPs) on the isodensity surfaces of all low-energy conformers. The MEP comparisons between our low-energy conformers and that of the analogous inhibitors show not only geometrical homology between structures, but electronic structural homology as well.

Thermochemical analysis was conducted at the DFT and MP2 levels of theory within a 6-31G(d,p) and more diffuse 6-31++G(d,p) basis set (same parameters for the geometrical analysis). These calculations reveal that all low-energy conformers are connected through certain bond-rotational transition states calculated by the second quadratic synchronous transit (QST2) method. Such transition states and low-energy conformers were verified through harmonic vibrational frequency analysis. Upon thermal correction populations of these rotamers were even more achievable than at 0 K, making such states thermally allowed.

Lastly, the effects of water solvation on the low-energy conformational space were calculated using the CPCM polarized continuum model. Dipole moment magnitudes, relative solvation free energies, and relative free energies show that PA, PO, and CP each have preferred low-energy conformations that are consistent with conformations of analogous inhibitors in applicable Phosphotriesterase and Plant Carboxyesterase crystal structures.

Acknowledgements: This work was facilitated by the support of NSF CREST grant no. HRD-0318519 and NSF EPSCOR grant no. 440900 362427-02. We would like to thank the Mississippi Center for Supercomputing Research for a generous allotment of computer time.

Computational study of Ru(II) ligands interacting with DNA

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Ruthenium(II) complexes have similar behavior in biological systems like well known anti-cancer drug cisplatin. However, cisplatin has a lot of drawbacks so other complexes has to be examined in order to improve the treatment. Ru(II) complexes are quite promising compounds. They have interesting structure with so called "piano-stool" shape where is π-coordinated to central Ru atom and another three ligands build tripod.

In our study the [(η-benzene)RuII(en)Cl] complex is explored and compared with experimental data [1,2]. In water solution with low concentration of free chloride ions, the coordinated Cl in complex is substituted by water. Consequently the aqua-complex interacts with bio-organic environment such as amino acids or nucleic bases. We mainly concentrated on the interaction with guanine since cisplatin interacts with DNA in similar way. We assume that Ru(II) complex is bonded to N7 position of guanine, which is thermodynamically the most preferable. Consequently intrastrand bounding between two guanines can be formed similarly in case of cisplatin.

Our model consists of six-pair DNA oligomer which is neutralized by natrium cations. In the middle of this double helix model two guanines are localized and together with Ru(II) complex they form a central (QM) part of the system. Remaining DNA bases as well as sugar-phosphate backbone and water molecules are keeping in MM region. The QM/MM scheme is realized by a system of scripts called Comqum [3,4] where QM computations are performed by Turbomole (RI-DFT method) and MM simulations by Amber with FF96 force field.

Acknowledgements: Support from GAUK grant No. 2470 is acknowledged. Calculations were performed at the Computational Cluster at Charles University in Prague.

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Prediction of double-charge ion pattern by modeling of the high- and low-resolution isotopomeric forms

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The double-charged ions can be observed down than M/2 in the spectrum. It is assumed, the structure of their isotopomeric patterns can be originated from the high-resolution forms of the considered single-charged ion of the same formula. The solution applied the modeling of low-resolution mass ion cluster which was presented last MDMM conference [1].

The starting point of the prediction is mass defects values and summary formula of the ion charged ±1. The first step procedure generates an accurate mass isotopomeric pattern of „high-mass" ion. The next modeling predicts the form of double-charged ion located in low-mass range of the spectrum. The real problem considers the purity of the experimental cluster of the double-charged cluster.

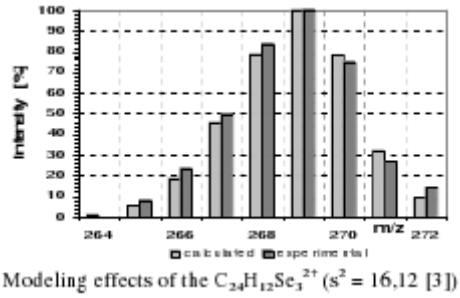
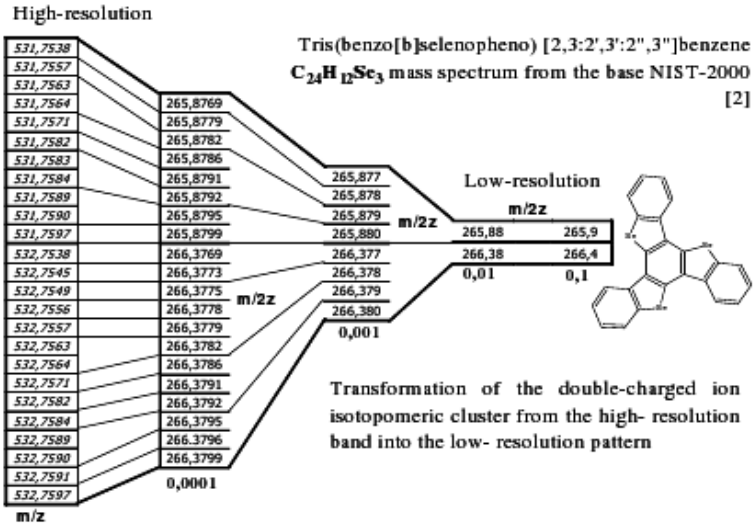


Fig. 1: Modeling the effects of $C_{24}H_{12}Se_3^{2+}$ (s^2 = 16,12 [3])



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Detection of symmetrical decomposition of the molecules - isotopomeric analysis of the M/2 clusters

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The occurrence of poly-isotopic elements in a molecule or ion can result in complex isotopomeric cluster of the ion. This fact creates new interesting possibilities in spectra interpretation. Separately the ms-clusters located at M/2 m/z values or in the range lower than M/2 are very difficult to interpret. In this area (0 – M/2) there can be observed many disturbances, much more as in M/2 – M area. The source of the problem can be: a coincidence of different fragmentation pathways, an existence of multiply- charged ions, a background level, etc.

The present study is an attempt at answering the following question: can be applied the isotopomeric structure of the pattern for investigations of the genesis of the cluster and for the detection of the double-charged ions occurrence in the spectrum as well as the identification of the products of symmetrical destruction of a molecule.

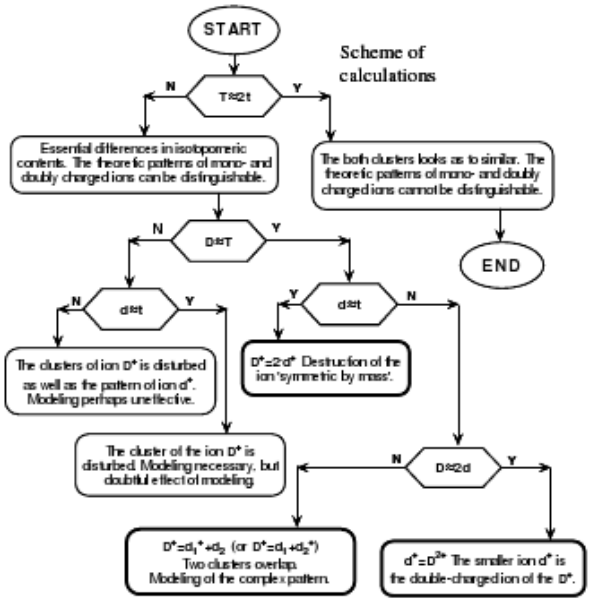

Fig. 1: Scheme of the method used.

*the transformation considers the signal locations m/z

The method is based on the relations between natural ion clusters (high- and low-mass marked by **D** and **d**, and the predicted ones **T** and **t**) and transformed patterns ('divided' **D/2** and **T/2**, and 'doubled' ones **2d** and **2t**) as presented in the scheme in Fig.1.

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In search of potential peptidomimetic HCV protease inhibitors

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[2]Quantum Chemistry Group, Adam Mickiewicz University, Poznań, Poland

Hepatitis C virus (HCV) is one of the major health problems affecting approximately 200 million people worldwide [1]. The limited efficacy of current therapies and the substantial side effects leading to the discontinuation of therapy in some patient groups clearly highlight the need for new and more effective therapeutic alternatives. Recently, the virally encoded HCV non-structural proteins (NS2 and NS3) have emerged as a particularly attractive targets for antiviral treatment [2]. Several potent inhibitors of HCV NS3 serine protease have been identified to date, with VX-950 and BILN-2061 to be the most promising [3].

In the presented work, we take the advantage of the recently designed tool MIMIC [4] for an automated generation of peptidomimetic compounds that are less prone to the hydrolysis and exhibit a controlled degree of flexibility. The initial selection of native peptides was based on a careful survey of all protein–ligand complexes deposited in the Protein Data Bank database possessing structural similarity to the target protein. The resultant set of compounds was ranked by docking scores using an Electronic High-Throughput Screening flexible docking procedure to select the most promising molecules.

The set of best performing compounds is synthesized in our lab and subjected to further analyses.

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The importance of molecular polarization for crystal structure prediction of multicomponent crystals

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The ability to predict the most stable form of multicomponent organic crystals is of great interest in academic research and in pharmaceutical industries. Understanding the properties and molecular interactions within a crystal, and the packing preferences of potential drug molecules is particularly important in the development of a dosage form. The aim of our work is to explore the most accurate methods to predict crystal structures of multicomponent crystals. Prediction of multicomponent systems is a challenge, due to the much larger search space compared to systems with one independent molecule in the asymmetric unit.

Three systems of lutidine with fumaric acid: a salt, a salt with a guest molecule and a cocrystal, which are similar in terms of starting components, but differ in final products, were chosen as representative systems to study the effect of various models for prediction by lattice energy minimization. Normally simulations are based on building crystals from molecules, for which electrostatic interactions are based on isolated molecule charge densities. This simplified model does not consider the environment around molecules in the crystal, which leads to polarization of the molecular charge density. We report on an inexpensive computational approach, to estimate polarization effects in lattice energy calculations, where the environment of the molecule is modeled as a polarizable continuum and the dielectric constant is a measure of the polarity of the environment. Our results demonstrate, that polarization of the molecular charge density has an important effect on lattice energy ranking of predicted crystal structures and must be considered for salt structure prediction.

Chameleonic ligand in self-assembly of grid-type copper(I) and zinc(II) complexes

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The reactions of a chameleonic ligand L, comprising NNO donor atoms units, with appropriate metal ions lead to different structural motifs of resulting compounds depending on the kind of metal ions used in coordination. [1,2] These results are a consequence of preferred metal coordination geometry and their electronic properties. Here we examined the self-organization process occurring between the chameleonic ligand and isoelectronic cation centers Zn(II) leading to tetranuclear grid-type complex with Zn center coordinated octahedrally while Cu(I) center coordinated tetrahedrally generates [2x2] grids. Quantum mechanical calculations provided insight into recognition process and the electronic structure of Zn(II) and Cu(I) complexes.

Acknowledgements: M.H. thanks the Foundation for Polish Science for support via FOCUS fellowship. Calculations were performed at the Poznan Supercomputing and Networking Center.

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Controlling micelle structures by included molecules

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[1]Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen, Germany
[2]Interdisciplinary Center for Molecular Materials (ICMM), FAU Erlangen, Germany
[3]Forschungszentrum für Elektronenmikroskopie, Freie Universität Berlin,Germany
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Long time-scale molecular-dynamics simulations have been used to investigate the structure and dynamics of structurally persistent micelles that consist of seven or twelve specifically designed T-shaped amphiphilic calix[4]arene derivatives [1].

Experimental investigations by NMR and cryo-TEM techniques with subsequent 3D-reconstruction [2] confirmed a highly developed topological arrangement of the micelles in water. However, other experiments such as ultrasonification of the micelles together with hexane and water led to micelles with a different topology and that consist of twelve monomers.

The results presented allow the cryo-TEM 3D-reconstructions of the micelles to be interpreted in detail and several fascinating details of the structure of the solvent around the micelles and of the factors that affect the structure of the micelles. Moreover, we predict that the presence of hexane molecules in the center of the dodecameric micelles determines the structure of the micelles and favors the formation of larger structures than without hexane.

Our predictions made on the basis of the simulations have been tested and verified experimentally and further simulations and experiments will cast light on the influence of other encapsulated lipophilic molecules. These simulations and experiments help us to understand and guide the forces responsible for the defined structures of these persistent micelles and will be used to help us develop structured micelles for nanotechnological applications, such as the development of high-performance drug-delivery capsules.

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Conformational study of cyclic disulphide-bridged nonapeptides, Arg- and Lys-conopressins

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Arg-conopressin-S (H-CIIRNCPRG-NH_2) and Lys-conopressin-G (H-CFIRNCPKG-NH_2) were isolated from the venom of marine cone snails, *Conus striatus* and *Conus geographus*, respectively [1]. These two conopeptides consist of a 20-membered ring formed by a disulphide-bridge between the Cys^1 and Cys^6 amino acids, as well as of a C-terminal amidated tripeptide tail. Although, the physiological properties and biological effects of conopressins have been studied in detail, data derived either by experimental or by theoretical investigation have not been supplied in the literature so far, regarding the three-dimensional structure of these peptides. Therefore, our aim was to carry out a comprehensive conformational analysis and structural characterization of both Arg- and Lys-conopressins.

To explore the conformational spaces of two conopeptides, molecular dynamics simulated annealing calculations were performed. Since both peptides possess Pro amino acid in the seventh position, thus the *cis* and *trans* isomers of conopressins were modeled, respectively, applying the appropriate torsional restraints for the Cys^6-Pro^7 peptide bond.

In order to characterize the structural and conformational features of conopeptides, various examinations were carried out on the conformers obtained from the simulated annealing calculations. To describe the F-Y conformational spaces in detail, Ramachandran and pseudo-Ramachandran plots were constructed using the F and Y torsion angles of amino acids. Based on these plots, the preferred conformational regions were identified, and conformational similarity indices ($CS_{XX'}$) were calculated. Applying the above-mentioned plots and $CS_{XX'}$ indices, the conformational distributions were compared to each other. For the side chain of amino acids, the proportions of *g(+)*, *g(-)* and trans rotamer populations were determined. In the conformers of conopressins, the occurring characteristic secondary structural elements were identified, including different types of b-turns as well as inverse g-turn. The majority of these turn structures were found to be stabilized by typical intramolecular H-bonds. Nevertheless, additional H-bonds were also detected, which could play an important role in the formation and stabilization of various conformational states of these conopeptides. In the case of conformer populations, cluster analyses were performed, in order to identify the conformationally related subfamilies and to determine their representative conformations.

To the best of our knowledge, our conformational analysis is the first structural investigation performed on Arg- and Lys-conopressins, which supply a detailed characterization of different structural and conformational properties of these conopeptides, nevertheless, our results might lead to better understanding of the bioactivity of conopressins.

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Non-empirical quantum chemical studies on platinum(II) – cysteine systems

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The differences in therapeutic ability of antitumor drug cisplatin (cis- diamminedichloroplatinum(II)) and its trans-isomer, are still intriguing for investigators who would like to learn in more detail about the molecular bases of such behavior [1]. It is well documented that cisplatin has high antitumor activity and strong toxicity, especially towards kidneys, whereas the trans isomer is therapeutically inefficient and non nephrotoxic.

However, the studies on mechanisms of biological activity of both isomers, performed so far, were focused on interaction of platinum(II) complexes with DNA as critical target molecule. The problems of cisplatin and its congeners toxicity, though clinically very important, were far less studied [1]. Similar preferences can be observed in theoretical approaches [2].

Contrary to this tendency, our interest has been concentrated on the toxicity of cisplatin in comparison with non-toxicity of its trans isomer. Therefore we evaluated the reactions responsible for harmful biological effects, and consequently, the impact of platinum(II) complexes on molecules containing sulfur donors became the object of the presented study.

Our approach relied on applying quantum chemical in silico methodology for the evaluation of "platinum(II) – cysteine" and its model systems. There were investigated the following systems: (1) a/cisplatin (b/transplatin) with CH_3SH; (2) a/cisplatin (b-transplatin) with cysteine.

The electronic structure for molecular systems have been studied at non-empirical all-electron level by using density functional (DFT) or Moeller-Plesset (MP2) methods within the correlation consistent cc-pVTZ [3] basis set. In the case of platinum the widest Huzinaga basis set with polarization functions has been used. In order to avoid the long optimization process, at the first stage, the optimization was performed at the all-valence MOPAC-PM6 method [4] following the B3LYP density functional or MP2 formalism [5] in the next step. The B3LYP [6] density functional was applied using GAUSSIAN-03 program package [7].

Our results and obtained by other authors [8] working on similar systems were discussed.

Acknowledgements: The numerical calculations have been performed in part at Wroclaw Networking and Supercomputing Center. Wroclaw University of Technology.

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Theoretical models of nitrile hydration

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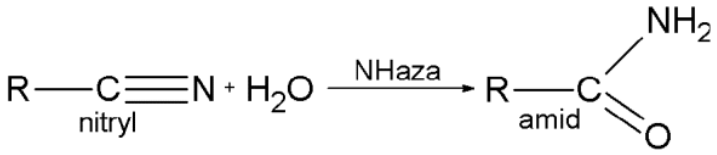
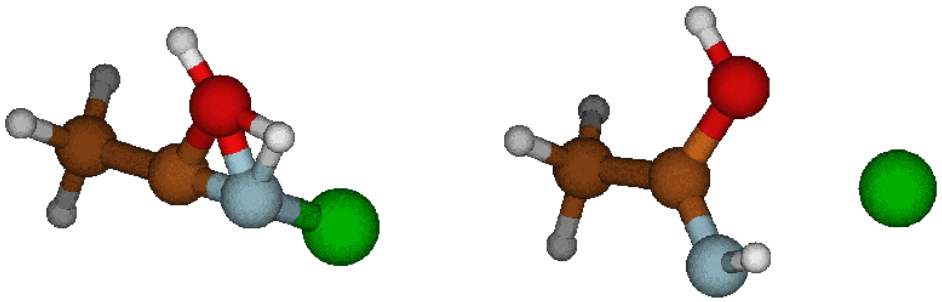
Hydration of nitriles and formation of corresponding amides is important reaction in industry. This reaction commonly is carried out using strong acid or base. Recently the enzyme from bacteria (nitrile hydratase, NHase) is used for green production of acrylamides [1].The mechanism of this reaction has not been explained, yet:



In order to understand better hydration of amides we used quantum chemical modeling of water nucleofilic attack on acrylonitryle. Calculations were performed using the DFT/B3LYP/6-311G* level of theory implemented in the Gaussian03 suite. Some preliminary scans of potential energy surfaces were done using the PM3 method (ArgusLab). The reaction with the hydroxide ion was investigated as well. We have found that, in contrast to the OH- ion, water molecule alone is too week nucleofile to perform uncatalysed hydration of acrylonitrile. However, when model metal ions are present (Ca^{2+} or Co^{3+}) the hydration is possible. Some spatial arrangements leading to the nitrile hydration were identified:



Results of this calculations will be critically compared to proposed NHase reaction mechanism presented in the literature [2,3].

Acknowledgements: Support from MEiN grant No. 2P04A07229 is acknowledged. Calculations were performed at UCI UMK.

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Accurate gas phase basicities of hydroxyl radical modified pyrimidines estimated by advanced quantum chemistry methods

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The susceptibility to protonation or deprotonation affects such phenomena as pairing via hydrogen bonds, aromatic stacking or interactions with metal ions. One of the spectacular consequence of nucleobases protonation is potential mutagenic mispairing of complementary bases [1]. For example cytosine protonated at the O2-oxygen is expected to be responsible for the stabilization of the adenine-cytosine mispair that was observed in single crystals of oligonucleotide duplexes [2]. Furthermore, protonation is the first stage of the process of the N-glycosidic bond hydrolysis conditioning the stability of the standard and modified nucleoside [3].

The gas phase basicities of 16 hydroxyl radical derived analogues of model pyrimidine nucleosides were analyzed on B3LYP/aug-cc-pvdz and G3MP2B3 levels of theory. The macro-basicity is defined as the change of Gibbs free energy of protonation reaction (GPB). All possible tautomeric equilibriums were taken into account of neutral and protonated forms of model cytosine, thymine and uridine analogues. The micro-basicities understood as the measure of the susceptibilities to protonation of individual proton- acceptor centers. Both measures of basicities were significantly affected by pyrimidine oxidation. For most studied analogues, reduction of basic character is observed. There are, however, few exceptions. Such derivatives as 5-hydroxycytidine (CA) and 5,6-dihydroxycytidine (CC) are more basic then model cytidine if both macro- and microscopic measures of basicities are used for comparison. Besides, 6-hydroxy-5,6-dihydrocytidine is characterized by more basic character of N3 atom compared to most basic O2 center of cytidine, despite the GPB value of this lesion is lower compared to GPB of cytidine. Although the B3LYP/aug-cc-pvdz approach seems to be accurate and robust method for GPB estimation, the microscopic protonation properties are much more sensitive to applied method since the difference in energies between some tautomers are often less than 1.0 kcal/mol with method dependent succession. In cases where B3LYP/aug-cc-pvdz and G3MP2B3 methods lead to contradictory predictions of order of neutral or protonated tautomers, the latter is suggested, to be used in the interpretation of microscopic protonation properties. Nevertheless, if only macroscopic property is necessary the B3LYP/aug-cc-pvdz level is sufficient since it provides GPB values within 1.0 kcal/mol of experimental data for DNA bases [4].

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Comparison of interaction energy decomposition schemes for small dimers, revisited

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Partitioning of the intermolecular interaction energy into well-defined components yields valuable data allowing to validate or derive approximate methods used in modeling and designing molecular materials. However, various available decomposition schemes differ either in accuracy or numerical efficiency.

In this report we analyze the performance of several available methods against accurate benchmark results obtained for model dimers using saturated even-tempered basis sets and complete basis set extrapolation of correlation consistent basis sets. Herein we use a hybrid variation-perturbation approach [1] implemented in GAMESS at the MP2 level [2] and Symmetry-Adapted Perturbation Theory (SAPT) [3] to test various variational schemes derived from the original Morokuma scheme.

In the hybrid variation-perturbation approach [1] the interaction energy is partitioned into the following terms:

$$\Delta E_{MP2} = \underbrace{\underbrace{\underbrace{\underbrace{\Delta E^{(1)}_{el,mtp} + \Delta E^{(1)}_{el,pen} + \Delta E^{(1)}_{ex}}_{\Delta E^{(1)}_{el}} + \Delta E^{(R)}_{del}}_{\Delta E^{(R)}_{SCF}}}_{\Delta E^{(1)}} + \overbrace{\Delta E^{(2)}_{disp} + \Delta E^{(2)}_{corr,intra}}^{\Delta E^{(2)}_{corr}} \qquad (1)$$

and defines a sequence of interaction energies at various levels of theory simultaneously ordered by rising computational cost – $\Delta E^{(1)}_{el} > \Delta E^{(1)} > \Delta E^{(R)}_{SCF} > \Delta E_{MP2}$.

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Theoretical and experimental study of UV-Vis spectra of functionalized carbazole-azo dyes

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Novel carbazole-azo dyes have been synthesized with an eye towards their potential usefulness as photonic materials. Due to their unique properties, the carbazole-azo dyes and their derivatives have been widely employed as effective charge-transfer components of photorefractive media [1,2,], hole-transport layers in electroluminescent devices [3] and photoconductors in xerography [4], just to mention only a few of possible applications. Recently the carbazole-azo dyes have attracted much attention because they constitute a large group of species exhibiting absorption in a wide spectral range what makes them interesting systems for various optoelectronic applications.

The UV-Vis spectra of carbazole-azo derivatives exhibit a strong band associated with $\pi - \pi^*$ transition. The intensity and the location of this band strongly depends on the charge-transfer character of the substituents and the polarity of environment [5].

In the present study we report on the comparison of theoretical and experimental excitation spectra of six trans carbazole-azo derivatives of various charge-transfer character of the $\pi - \pi^*$ transition. Excitation energies and polarity of the (π, π^*) excited states were calculated using a Time-Dependent Density Functional Theory (TD-DFT) with inclusion of solvent effects. These calculations have been performed with the standard hybrid functionals B3LYP and PBE0. Because of the incorrect treatment of the long-range exchange the standard DFT functionals are not able to reproduce the position of the charge-transfer bands with satisfactory accuracy. Therefore the gas phase spectra calculations were repeated with the use of CAM-B3LYP functional [6,7].

Acknowledgements: The authors gratefully acknowledge the support of the Poznan Supercomputing and Networking Center (PCSS), Wroclaw Centre for Networking and Supercomputing (WCSS) and Academic Computer Centre CYFRONET AGH

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Quantum chemical studies on substitution effects in the reaction of the silylative coupling of olefins

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Silylative coupling of olefins is an effective method for obtaining substituted vinylsilanes, which are important substrates in stereocontrolled organic syntheses (Fig. 1).

The main goal of this report will be the presentation of theoretical findings, based on Density Functional Theory (DFT) calculations. The substitution effects in the reaction of the silylative coupling of olefins are discussed. Bulky tert-butyl group, electron donating and smaller methyl moiety as well as highly electronegative fluorine atom has been chosen as model substituents for vinyl hydrogen atom. The effect of methoxy group replacing all methyl groups in silyl moiety has been studied too. In all cases the rate determining step is the insertion of an alkene into the Ru-Si bond coupled with the silyl moiety migration from Ru to C atoms (Fig. 2). The activation barriers for the examined reaction range from 13 kcal/mol to 18 kcal/mol, so all of the examined replacements are decreasing energetic barrier of the rate determining step of the reaction (20 kcal/mol for model non-substituted vinylsilane [1]).

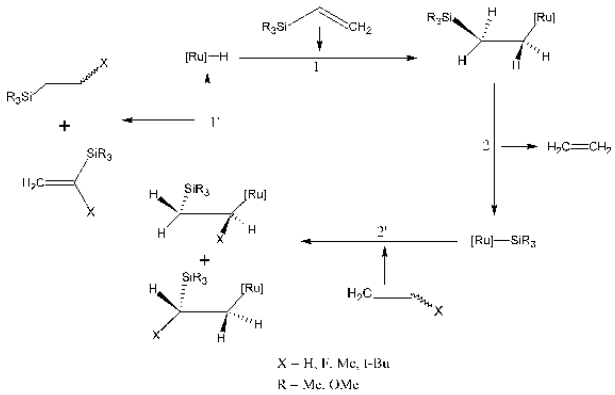

Fig. 1: Catalytic cycle of silylative coupling of olefins.

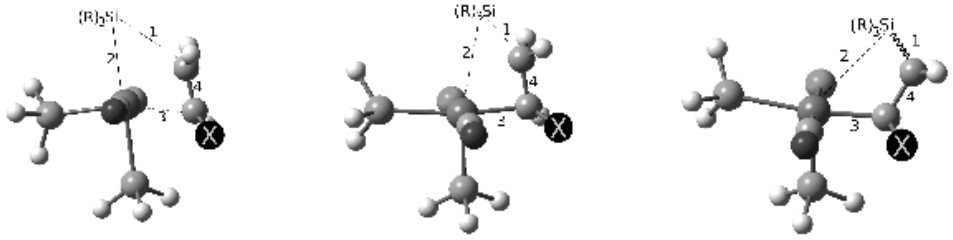

Fig. 2: Silyl moiety migration as a rate determining step of the examined reaction –X = H, F, Me, t-Bu; R = Me, OMe

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Modeling phosphorus oxide immobilization on the silica surface

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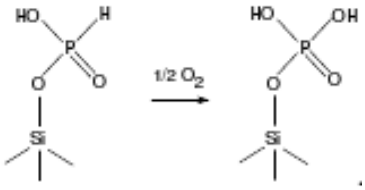

The quantum-chemical ab initio calculations in the 6-311* G basis set have been provided for research of increasing inhibiting properties of phosphorus containing substances by means immobilization on the silica surface. The research of chemical reactions with disperse oxides particles connected with study of interaction particularity of the modifying reagents with active centers at the adsorption or chemisorptions on the surface. During chemical modification the new active centers have been forming and their quality determines the nature and structure of obtained modifying layer. The subject of research was choused phosphorus oxides that substantially influent on the hydrogen flame as inhibitors [1]. As was shown in our previous paper [2], the immobilization active inhibiting components on the silica surface can increase the inhibition effect. The solid matrix influents on the phosphorus containing functional groups and reactivity of such groups depends from the nearest surroundings and spatial reach for other chemical partners. For the element-oxygen bonds in the groups Si-O-Si and Si-O-P, that can be channel for electronic density flow by the dp -pp - coupling (difference from -CH_2- groups), the influence of solid substrate nature at the phosphorus containing reaction centers more essentially.

The effect of changing of oxidation extent on the fire extinguishing properties of phosphorus containing substances has been research too. During additive thermo treatment of samples of fire extinguishing powders the P^{3+}phosphorus atom converts in P^{5+} th the formation of surface derivatives of phosphorus acid.

So, samples of fire extinguishing powders have been obtained due to following the results of quantum chemical calculations on reactivity of phosphorus-containing compounds and radicals (both gas phase and grafted to silica surface). Their activity has been checked in extinguishing oxygen-hydrogen flame.The greater extinguishing activity of phosphorus containing samples as compared with that of the standard P2-APM powder has been shown to be connected with both decrease in bond dissociation energy for surface compounds on modified silica and ultra disperse state of phosphorus-containing silica.

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New antisense/antigene agents with pirydylphosphonate internucleotide bonds: ab initio characterisation

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Targeting mRNA (antisense approach) or double-stranded DNA (antigene approach) to modulate gene expression as a routine medical treatment still encounters severe problems though its principle is simple and of general applicability. Recent advances in development of oligonucleotides analogs solved some of the fundamental problems of antisense and antigene techniques (*e.g.* susceptibility of oligonucleotides to enzymatic degradation in vivo), but at the same time generated numerous new issues (*e.g.* chirality at phosphorous center, lower stability of the formed complexes, lack of the Rnase H induction ability).

Nucleoside pirydylphosphonates offer a novel type of nonionic nucleic acids analogues. A pyridine ring is found in many natural products, and constitutes an indispensable structural element of various drugs. Pyridylphosphonates as a new type of modification of a phosphorus center in biologically important DNA phosphate esters combine several structural features that can be essential for tuning chemical and biological properties of potential antisense / antigene agents: a chirality of the phosphorus center permits to control the orientation of the pyridyl ring in double-stranded complexes (major versus minor groove) and the presence of a nitrogen atom potentially can modulate stability of double- or triple- stranded complexes via formation of hydrogen bonds or coordination of metal ions. It offers also a possibility of introducing additional functionalities to a pyridyl ring like quaternization of the nitrogen atom, or substitutions in the pyridyl ring, that can further modify chemical, biological, and therapeutic properties of drugs bearing a pyridylphosphonate moiety.

To characterize physicochemical properties of this new type of the oligonucleotide analogs with modification center, estimate and verify the prediction of their ability of binding to biological targets we are applying computational chemistry methods, molecular modeling, molecular dynamics and free energy calculations combined with spectroscopy and crystallography.

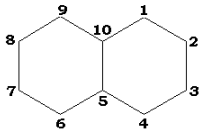
In this communication we present the results of *ab initio* studies of the models of 2-, 3-, and 4- pyridylphosphonate and pyridyltiophosphonate analogs.

Acknowledgements: Support from grant No. PBZ-MNiSW-07/1/2007 is acknowledged. Calculations were performed at the Poznań Supercomputing and Networking Centre

Estimation of equivalence of molecular graph vertexes on the basis of topological model of the informational field

Lyudmila N. Ognichenko, Victor E. Kuz'min, Anatoly G. Artemenko

A.V. Bogatsky Physical-Chemical Institute National Academy of Sciences of Ukraine, Odessa, Ukraine

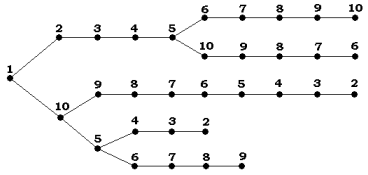


In the framework of the information field model [1] every atom "feels" an influence of all other atoms of given molecule. Character of such influencing depends on atom properties used during the procedure of construction of informational field and mutual position of atoms in molecule. The topological informational field model is used for the molecular structure representation at 2D level. In the framework of such model the molecule is represented as molecular graph. Each vertex of molecular graph is a source of information. It should be noted that all possible paths between every atom pair are taken into account. Analogically to the calculation of 2D informational potential (IP) [1] the topological IP of i-th atom can be represented as:

$$IP_i = w_i \cdot \sum_{j=1}^{n} \frac{\sum_m lb\left(\frac{r}{2R_{ij}+1}\right)}{m} \tag{1}$$

where m – the number of all possible paths between every atom pair, n – the number of atoms in the given molecule, R_{ij} – the number of bonds between the i-th and j-th atoms (path length), w_i - weighed parameters describing any property (p) of the atoms, r - a tuning parameter of the model, $lb = log_2$.

We start by defining a path, i.e. a self-avoiding walk in a molecular graph as a sequence of adjacent edges such that no vertex is visited more than once in the sequence. Search trees are constructed for all vertices in the graph. As example on figure depicts the search tree for the vertex at position 1 in naphthalene.



Analyzing this tree, we can easily calculate lengths of all possible paths from a vertex 1 to the other graph vertexes. On the basis of these values, we can calculate value of IP in a vertex 1. Repeating similar procedure for all atoms of naphthalene, it is possible to get value of IP for every atom. It is noteworthy that the amount of all possible paths between atoms exponentially increases with multiplying the amount of cycles in a molecule that results in impossibility of complete calculation for the structures containing plenty of cycles. (for example, fullerenes with the amount of atoms more than 32). For the analysis of such structures it is necessary to take into account all possible not paths between atoms, but only those which less critical (L_{CRIT}). $L_{CRIT} = D + n, n \in N$ where D is the diameter of the corresponding molecular graph. The efficacy of developed approach has been demonstrated on the set of fullerenes.

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Analysis of interaction energies for molecular systems of unprecedented size

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The design of large functional molecular systems (drugs, catalysts, sensors) requires approximate descriptions of intermolecular interactions by force fields, which sometimes leads to artifact structures that influence other results [1]. Knowledge of well-defined interaction energy components from the first principles of quantum mechanics can help verify questionable results and systematically derive or validate simplified methods. Established procedures such as SAPT (Symmetry-Adapted Perturbation Theory) are limited to medium–sized complexes, whereas a hybrid variation-perturbation approach [2] implemented with direct-SCF [3] and parallelization capabilities at the MP2 level [4] allows much larger problems to be tackled.

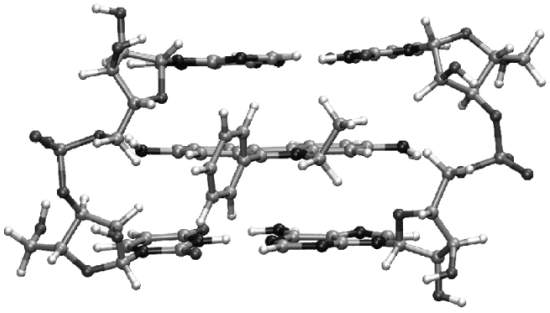

Fig. 1: Test bench: ethidium molecule intercalated between UA/AU base pairs, RNA side chains included [6].

Stacked complexes, nucleic acid bases included, are especially challenging for computational chemistry in this regard due to the large magnitude of the expensive dispersion term [5]. Here we present fresh results for a few chosen systems of unprecedented size that belong to this class.

Resources needed to analyze the interaction energy of an ethidium molecule intercalated between UA/AU base pairs – RNA side chains included as shown in Fig.1 with 168 atoms and over 1760 molecular orbitals – amounted to 6400h of CPU time and 1.4TB of dynamic memory; the calculation lasted 8.5h on 752 CPUs. On the other hand, the same procedure for a cytosine dimer using the aug-cc-pV5Z basis set (over 2200 molecular orbitals) required more than 7000h of CPU time and 800GB of memory, lasting 14 hours on 500 processors. While these benchmarks probe the current upper limit of such methods, somewhat less problematic chemical problems can be treated very systematically [7].

Acknowledgements: These calculations were possible at the Wrocław Centrer for Networking and Supercomputing Center (WCSS). The authors are especially indebted to Dr. Paweł Dziekoński for his help and technical supervision.

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Application of QSAR technique to prediction of properties and activities of selected nanomaterials

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Nanomaterials are structures with one or more components that have at least one dimension in the range of 1 to 100 nm and include nanoparticles, nanofibres and nanotubes, composite materials and nano-structured surfaces. Nanoscale materials find use in variety of different areas, such as electronics, magnetic and optoelectronics, biomedical, pharmaceutical, cosmetics, energy, environmental, catalytic, and materials applications. Use of nanomaterials (e.g., fullerenes, carbon nanotubes, metal nanoparticles and metal oxides) in various industries is projected to increase dramatically in the near future and therefore, the environmental contamination by these materials is expected to closely follow their production and applications.

Nanomaterials exhibit unique physical/chemical properties and impart enhancements to engineered materials, including better magnetic properties, improved electrical activities, and increased optical properties. In addition to the dose and the elemental composition of the nanoparticles, factors such as their surface area, the characteristics of the surface, tendency to aggregate, solubility, the form of the particles and their surface charge all play decisive roles in their distribution through the environment, ecosystem and particularly, through live organisms, including human body, and such exposure may cause different toxic effects. There is clear need for short-term testing of their hazard in order to gain information towards risk assessment of nanoparticles. However, the large variety of nanoparticles and their diverse characteristics (including sizes and coatings) indicate that the only rational approach that avoids testing every single nanoparticle is to relate the physicochemical characteristics of nanoparticle to its toxicity in a QSAR (Quantitative Structure Activity Relationship) model. If such a model was to be developed then, ideally, an untested nanoparticle could have its toxicity predicted on the basis of its physico-chemistry.

This presentation provides summary of our recent investigations on characteristics of various nanomaterials. We have developed a new approach to characterize the metal oxide nanomaterials for predicting Young modulus (modulus of elasticity) values by correlation weighting of nanomaterials codes. Taking into account that solubility of nanoparticles plays important roles in toxicity exhibition, we performed a number of studies regarding structure-solubility relationship for the fullerene in various solvents. For the characterization of carbon nanotubes solubility we suggested to use the chiral vector components and this approach was tested on a set of single-walled carbon nanotubes. We also constructed the predictive model for thermal conductivity of nanomaterials by using the correlation weighting of the technological attributes codes.

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Aromaticity and tautomeric equilibrium study of hydroxyphenyl and naphthalene Schiff bases

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Hydroxyaryl Schiff bases present an interesting object of study due to their wide potential application as liquid crystals, nonlinear-optical materials, anti-corrosive materials and anti-cancer medicines. Hydroxyaryl Schiff bases contain quasi-aromatic hydrogen bonding widely discussed in the literature. The advantage of these compounds is their rather efficient change of acid-base equilibrium by substitution in the phenol moiety, the nitrogen atom as well as the carbon atom of the imine fragment. The options of substitutes, and particularly the steric effect of a bulky substitute, can bring about shortening of the hydrogen bridge up to extra-short ones.

We accomplished an analysis of aromaticity with the assistance of the HOMA and HOSE aromaticity indices of the phenyl and naphthalene derivatives of the hydroxyaryl Schiff bases. Moreover, it was found that the aromatic system strongly coupled with the chelate formation plays an important role in describing tautomeric equilibrium. The aromaticity balance was studied: the increase in $^{\pi}$-electron delocalization in the chelate chain during the decrease in $^{\pi}$-electron delocalization in the adjacent aromatic ring and the increase in $^{\pi}$-electron delocalization in the distant aromatic ring under the shift of tautomeric equilibrium into the direction of the proton transfer form. This results present a comparison of experimental data[1], DFT and ab initio study of intramolecular hydrogen bonding[2,3] and topological parameters obtained with the application of AIM theory[4].

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Proton transfer and intramolecular hydrogen bonding in o-hydroxyaryl ketimines

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The process of intramolecular proton transfer in o-hydroxyaryl ketimine was investigated in detail using DFT calculations. The non-adiabatic potential shape for the proton-transfer process was calculated including full optimization of all the parameters of a molecule, while gradually changing the hydroxyl bond length in the range of 0.8 – 2 Å. Shortening and linearization of the hydrogen bridge increased until the transition state. From this point on, the trend was reversed. In the transition state we observed the shortest hydrogen bridge (d(ON) = 2.4071 Å); however, there is no symmetrical potential there. A symmetric potential was found at d(ON) equal to 2.4195 Å, where the proton was located at the center of the hydrogen bridge. The adiabatic potential for proton vibrations was also calculated along the reaction pathway.

The influence of solvent on the potential shape was studied within the SCRF model. For the molecular tautomer the increase in electric permittivity led to larger anharmonicity of the proton vibrations and to a lowering of the energy for the local minimum. The opposite effect was found for the proton-transfer tautomer. The calculations performed for 2(N-methyl-^{O}-iminoethyl)-phenol, 5-fluoro-2(N-methyl-^{O}-iminoethyl)-phenol and 4,6-dichloro-2(N-methyl-^{O}-iminoethyl)-phenol showed that increased acidity of the phenolic part of the intramolecular hydrogen bond leads to potential changes in the same direction as the polarity of the environment. The hydrogen bond energies were determined by comparison of the intramolecularly hydrogen bonded case with a reference state without hydrogen bridge.

Quantum-chemical and molecular dynamics study of Cu^{2+} and Mn^{2+} complexes with a neurotoxic fragment (106-126) of human PrPC protein

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Transmissible spongiform encephalophathies (prion diseases) are a group of fatal neurodegenerative disorders, and their development is associated with accumulation of misfolded prion proteins, oxidative damage to the brain, and neuronal cell death. The function(s) of prion proteins has not been fully described but metals such as copper, manganese, zinc and iron could play a role in this. The prion protein has a neurotoxic domain (Fig. 1) composed of eight amino acids (KTNMKHMA) which can bind ions [1]. Complexes of this fragment with Cu^{2+} and Mn^{2+} were computed by the density functional theory (DFT) method and the ZINDO method as implemented in the CACHe code [2]. The effects of DFT functionals were checked by performing calculations using B88-LYP, B88-PW91 and D-VWN approximations. The DFT/6- 31G** data were used to develop a special set of CHARMM27 force field compatible parameters. Molecular dynamics trajectories of 106-126 fragment of human prion with and without ions were investigated and relative flexibilities of various forms of prion fragments were determined.

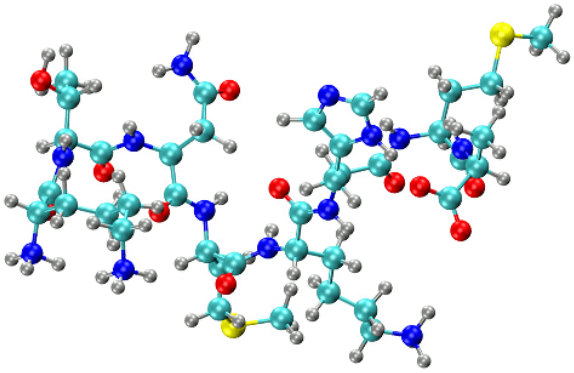

Fig. 1: Structure of neurotoxic prion protein fragment.

Cimetidine (CIME, Fig. 2) is one of the most potent H(2) receptor antagonists for inhibiting excessive histamine-induced acid secretion and is currently used worldwide to treat peptic ulcers. Recently it has been found that CIME can form complexes with both Cu(I) and Cu(II), and has super oxide dismutase-like activity, so it may be a good candidate for anti- prion drug [3]. Therefore the electronic structures of Cu-CIME complexes were also investigated using the DFT approach and these structures were compared with Cu-PrP neurotoxic fragments.

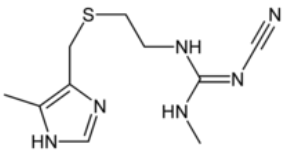

Fig. 2: Cimetidine.

Acknowledgements: ML acknowledges support from UMK 428-F grant.

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2D QSAR analysis of toxicity of nitroaromatics against rats, *tetrahymena pyriformis* and *vibrio fischeri*

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Problems of toxicity pertaining to widely used nitroaromatic explosives, pesticides, etc. and of damage to living organisms and the environment still remain crucial. Therefore, the aims of present study are: (i) the application of the Hierarchical Technology for Quantitative Structure - Activity Relationships (HiT QSAR) for the evaluation of the influence of such well known pollutants as nitroaromatic compounds on their toxicity against rats, Tetrahymena pyriformis and Vibrio fischeri, (ii) prediction of toxicity values for new nitroaromatic derivatives, (iii) analysis of the characteristics of the substituents in nitroaromatic compounds influence on their toxicity. The 50% lethal dose concentration for rats (LD_{50}), 50inhibition growth concentration (CIG_{50}) for Tetrahymena pyriformis and 50effective concentration (EC_{50}) of reduction on bioluminesce of bacteria Vibrio fischeri have been used to develop QSAR models based on simplex representation of molecular structure. Obtained 2D QSAR PLS models are quite satisfactory (R^2=0.86–0.98; Q^2=0.71–0.95). The predictive ability of QSAR models was confirmed by usage of three different test sets (maximal and minimal similarity with training set and also random choice, taking into account toxicity range only) for any developed model (R^2test=0.54–0.97). Since obtained 2D QSAR PLS models are predictive, the prediction of toxicity for new nitroaromatic derivatives (virtual screening), and the revelation of molecular fragments that promote and interfere with toxicity have been performed. The comprehensive analysis of substituent effect on toxicity and contributions of electrostatic, hydrophobic and van der Waals interactions of toxicants with the biological target was carried out. It was concluded, that non-additive substituents interference in benzene ring plays the determining role for their toxicity. The results show that all new (poly)nitroaromatics explosives and their metabolites including HMX, RDX, CL-20, etc. are highly toxic pollutants. Obtained QSAR models applicability domain has been estimated using DA ellipsoid and leverage approaches. Only molecules which belong to domain applicability have been predicted.

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Folding kinetics of implicitly solvated alanine oligomers

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According to the widely accepted "framework model" [1], the first phase of protein folding is the formation of secondary structural elements. In the second phase, proteins go through a hydrophobic collapse and form a molten globule [2], which is an intermediate state on the way to the native structure. Alternatively, the partially folded proteins can aggregate and form an amyloid-like structures. Several factors influence this pathway. Among others all those changes, which hinder the formation of secondary structural elements, may force the system in the direction of aggregation. The extension of homo-polypeptide regions of a protein can be one of these factors. This happens in the case of Oculopharyngeal Muscular Dystrophy and the Huntington's disease, where poly-(Ala) and poly-(Glu) sequences appear, respectively.

In our study, the folding of Ace-$(Ala)_n$-NMe (n = 7, 10, 12, 14, 16, 18, 20) was investigated using an ensemble molecular dynamics simulation with an implicit solvent model. One hundred independent, 10 ns long simulations started from extended structures with random initial velocities were carried out at 300 K. The average helicities of poly-(Ala) chains were calculated during the simulation period. From these results two processes with different speed (characteristic time) were identified. The characteristic times of the slower processes were used to estimate the chain length dependence of the folding time of poly-(Ala). For the investigated systems, a one-unit elongation of poly-(Ala) chain resulted in 17% increase of folding time.

The detailed analysis of main chain-main chain H-bonds showed that the folding starts with a very fast process, where the linear extent of the system decreased and unordered structures were formed, which were stabilized by different number of H-bonds. If these H-bonds are not formed between the $(i+n)^{th}$ and i_{th} (n = 2, 3, 4), but between any other residues (non-helix-like H-bonds), they will hinder the folding process. Following the method of Bertsch et al [3], it was also pointed out that the folding time depends exponentially on the maximum number of these non-helix-like H-bonds. The average activation free energy related to these H-bonds was also calculated.

Acknowledgements: This work was supported by grants GVOP-3.1.1-2004-05-0492/3.0 and RET 08/2004. Calculations were performed at the HPC Group of the University of Szeged.

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3- and 5-methyl-6-aminouracils with natural DNA bases: a computational study

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Because of their potential role in regulating gene expression, the design of new, artificial nucleobases is one of the premier tasks in nucleic acid research. From the beginning of the 1990s, the increasing computer capacities and the more sophisticated program codes provide new possibilities to narrow down suitable (classes of) candidate molecules, in advance of the costly experimental explorations. Although the computational model systems are often strongly simplified compared to the species used in experiments, it turned out that in certain cases they are really well applicable.

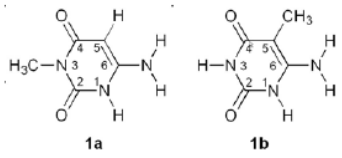

Fig. 1: 3- and 5-methyl-6-aminouracils, respectively

In the present study we have theoretically analyzed the hydrogen bonding of two artificial nucleobases (3- and 5-methyl-6-aminouracils, Figure 1a and 1b, respectively) with the natural DNA bases using BP86/TZ2P level of theory with the ADF program package [1]. The molecular orbital analysis of the monomers provides the possibility to distinguish different active parts of the molecules and the interactions energy with natural nucleobases are determined by the extended transition state method [2,3]. The bonding energy of the two artificial nucleobases with one of the natural DNA bases amounts mostly to values around the Adenine-Thymine pair with a few exceptions which are close to the Guanine-Cytosine pair. For a possible incorporation in the natural DNA, a pair of an artificial base with a natural DNA base must also fit into the Watson-Crick geometry.

Acknowledgements: This work was done in the framework of project HPC-EUROPA (RII3-CT-2003-506079)) and the EU6 project (Grant TRIoH, LSHB-CT-2003-503480). It was also supported by the grant OTKA No K61577. We also thank the National Research School Combination Catalysis (NRSC-C) and the Netherlands Organization for Scientific Research (NWO-CW and NWO-NCF) for financial support.

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Computational model of the interaction of small peptides and its modifications with an amyloid fibril

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is characterized neuropathologically by amyloid fibrils formed mainly by the β-amyloid peptides Aβ1–40 and Aβ1–42. In several studies Aβ1–42 has been used as a therapeutic target for drug design and one of these approaches led to the discovery of peptide-like inhibitors of Aβ1–42 aggregation [1].

In our present work, we combined the well-known docking technique with molecular dynamics (MD) calculations. As a first step we prepared the model of the Aβ1–42 fibril for the docking calculations, where eight Aβ1–42 monomers were placed next to each other according to the result of experimental measurements [2]. This octamer were relaxed by a 1 ns explicit water type MD simulation, where the α-carbon atoms were kept fixed.

Next we docked the small ligands with the autodock4 [3] program and the results of the docking calculations were used as the starting geometries in the MD calculations. Then, we performed again a 1 ns explicit water type MD simulation for the docked systems, and using the trajectory of the complexes we calculated the average binding energy of the ligands with the help of the MMGBSA method.

This procedure lets us to distinguish the binding ligands from the non-binding ones. It turned out that we have to suppose different mechanism of action for certain ligands that have biological effect but they did not bind to the fibril.

Acknowledgements: Excellent service by the HPC centre at the University of Szeged is gratefully acknowledged.

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The structure of polymer systems in a confinement - a Monte Carlo study

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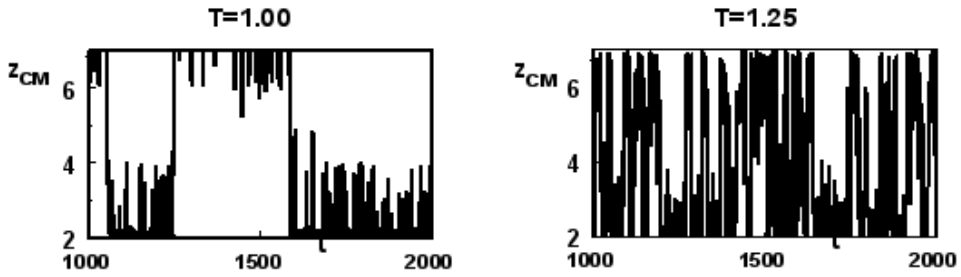
The properties of confined polymer chains have been recently investigated in many experimental and theoretical works. This was caused by great importance of polymers at interfaces, like size-exclusion chromatography, polymer adhesion, lubrication and wetting [1]. Up to date most of the theoretical works were devoted to slits with purely repulsive surfaces confining linear polymer chains [2]. Therefore, we decided to study the more complicated confinement potentials and chains with different internal architectures.

A coarse-grained model of polymer chains confined in a slit was studied [3]. The slit was formed by two parallel impenetrable surfaces, which were attractive for polymer beads. The polymer chains were represented by flexible homopolymers and heteropolymers composed of united atoms whose positions in space were restricted to vertices of a simple cubic lattice. The architectures of macromolecules used in the simulations were different: linear, regular star polymers consisted of *f=3,4* branches of equal length and rings. The chains were modeled in good solvent conditions and, thus, there were no long-range specific interactions between polymer beads – only the excluded volume was present. Monte Carlo simulations were carried out using the algorithm based on a chain's local changes of conformation. The influence of the chain length, the number of chains, the distances between the confining surfaces and the strength of the adsorption on the properties of polymers was studied. It was shown that the universal behavior found previously for the size of chains was not valid for some dynamic properties. The strongly adsorbed chains could jump between both surfaces with the frequency depending on the size of the slit and on the temperature only (see Figure below).



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Theoretical investigations of mono- and biradical forms of 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine

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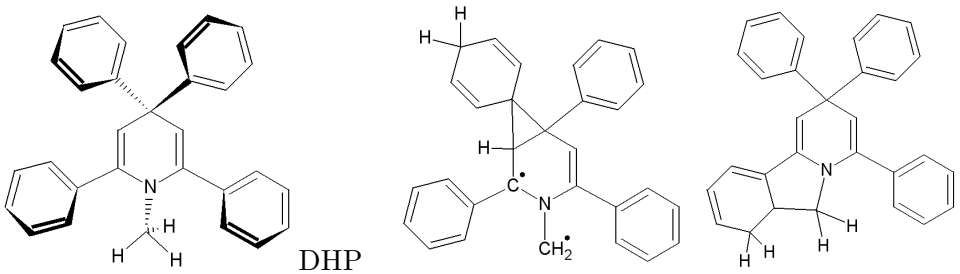
The 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine (DHP) belongs to the class of photochromic materials [1–3]. In normal conditions the sample of DHP is transparent in the visible range. Material after irradiation by the UV absorption changes color. This phenomenon was observed in the solid state as well as in solution. The colored form of DHP is very stable. The explanation of the above observation is based on biradical forms of DHP. Theoretical investigation of geometry of DHP stable form, possible intermediates, as well as final products (generally, non-radical in nature) were performed before using semiempirical MNDO and GRINDOL approaches [2]. The aim of the present paper are theoretical studies on mono- and biradical forms of DPH at the B3LYP level.



The stable form of 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine (DHP), and tree and five ring intermediate products determined at B3LYP/6-311G(d,p) approach.

Acknowledgements: Calculations were performed at the Poznan Supercomputing Networking Center (PCSS), Wroclaw Centre for Networking and Supercomputing (WCSS), and Academic Computer Centre in Gdansk (CI TASK).

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On the basis set superposition error in supramolecular calculations of interaction-induced electric properties – many-body components

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In the present work we report an analysis of BSSE removal methods from many-body components of interaction-induced electric properties - molecular dipole moments, polarizabilities and hyperpolarizabilities. Valiron-Mayer Function Counterpoise (VMFC) [1], Site-Site Function Counterpoise (SSFC) [2] and TB [3] methods have been employed in order to obtain incremental optical components for linear hydrogen fluoride clusters – $(HF)_n$, where $n \in 2, 3, 4$. Following Mierzwicki and Latajka [3], who have performed similar calculations for interaction energies, we compare these three methods of eliminating BSSE using several of Dunning's correlation consistent basis sets.

Answers to the following questions are presented:

· How large is the BSSE in many-body components of interaction-induced electric properties for the analyzed cluster, especially in the case of hyperpolarizability?

· How do results obtained with various methods differ?

· Are the conclusions about these methods in interaction-induced electric property calculations similar to those for interaction energy?

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Theoretical description of bonding in the Co, Rh, Ir complexes with NHC ligands

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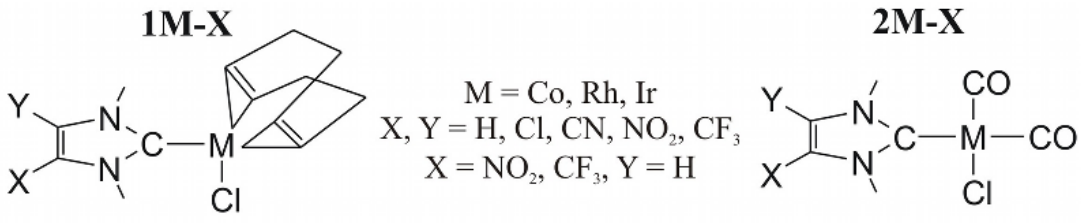
An increasing importance of N-heterocyclic carbenes (NHC) used as catalysts, nucleophilic reagents, and ligands for metals has led to a growing interest in understanding of the metal-NHC bonding. Based on a great number of experimental and theoretical research, it is generally assumed that NHC ligands are strong σ-donors, comparable with trialkylophosphines, with negligible π-acceptor properties. However, it has been recently demonstrated on the basis of crystallographic as well as spectroscopic (^{1}H-NMR and IR) analysis of various NHC-rhodium(I) complexes that acceptor abilities of NHC ligands are "not only negligible, but tunable" in the context of the change in the π-acidity of the substituents on the N-heterocyclic carbenes [1].

The main goal of this study was a theoretical examination of the bond formed between N-heterocyclic carbenes and the transition metal in the NHC-M(I) complexes, M = Co, Rh and Ir, with particular emphasis on the back-bonding. Thus, donor/acceptor character of the NHC-metal bond in two groups of square-planar complexes with chloride and olefin/CO (Figure 1): (NHC)MCl(cod) (1M-X) and (NHC)MCl(CO)^2 (2M-X) with substituted imidazol-2-ylidene ligands (X = H, Cl, NO^2, CN, CF^3) was described with use of the Natural Orbitals for Chemical Valence and the Ziegler-Rauk bond energy decomposition. A mutual influence of the NHC ligand and the ligand in the trans position (an olefin or CO) was also investigated.

The results obtained for 1Rh-X and 2Rh-X show that indeed the NHC-metal bond consists of the components originating from donation and back-donation of comparable importance. The ligand trans to NHC strongly affects the back-bonding component; for the complexes 1Rh-X, the back-donation is substantially enhanced compared to 2Rh-X. The back-bonding component increases with an increase in the π-withdrawing ability of X for both, 1Rh-X and 2Rh-X. However, this effect is relatively small. Back-bonding components of the two bonds involving metal are strongly coupled; an increase in NHC-Rh leads to a decrease in Rh-olefin/CO(trans). The changes in back-bonding are too small to be followed by the trends in bond-energies that are finally determined by the steric term. The same analysis for Co- and Ir-based NHC complexes, allows one to discuss the influence of the metal.



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Theoretical study on the copolymerization of ethylene with polar monomers: bonding of the monomer by the catalyst's metal center

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Department of Theoretical Chemistry, Faculty of Chemistry, Jagiellonian University, Kraków, Poland

The Ziegler-Natta coordination-insertion mechanism of the controlled copolymerization of α-olefins with polar monomers using the late-transition-metal-based complexes as catalysts involves in the initial steps a competition between comonomers. For successful incorporation of polar monomer into a polymer chain, it must be bound to the metal center by its double C=C bond (π-complex) rather than by the donor atom of the polar group (σ-complex). Thus, the preferred binding mode of the nitrogen/oxygen-containing monomers seems to be crucial for the activity of the catalyst.

The main goal of present study was to explore the factors influencing the polar monomer binding mode in the complexes with organometallic ethylene polymerization catalysts. Considered systems involved cationic Ni-/Pd-based and neutral Ni-based catalysts with Brookhart and anilinotropone ligands respectively, and a series of neutral as well as N-/O-containing polar monomers (Figure 1). On the basis of the Ziegler-Rauk bond energy decomposition and the Natural Orbitals for Chemical Valence analysis, the role of the electronic and steric factors together with the donor/acceptor properties of a series of monomers for all considered catalysts in both type of coordination mode (π and σ-complexes) was discussed.

The results demonstrate a significant influence of metal-based fragments on the σ/π relative stability. The increase in preference of π-binding mode going in the sequence: NN̂-Ni(H)+ → NN̂-Pd(H)+ → NÔ-Ni(H). For all considered models of the catalyst, the monomer binding in the π-complexes is more effectively stabilized by orbital interaction terms due to higher values of the NOCV total electron charge transfer. The orders of σ-donor and π-acceptor properties of monomers in the π-complexes are nearly the same for all catalysts. The absolute values of V_d/V_{bd} are shifted up/down in the sequence of metal-based fragments: NÔ-Ni(H) → NN̂ Ni(H)+ → NN̂-Pd(H)+. The same is observed for the σ-binding mode.

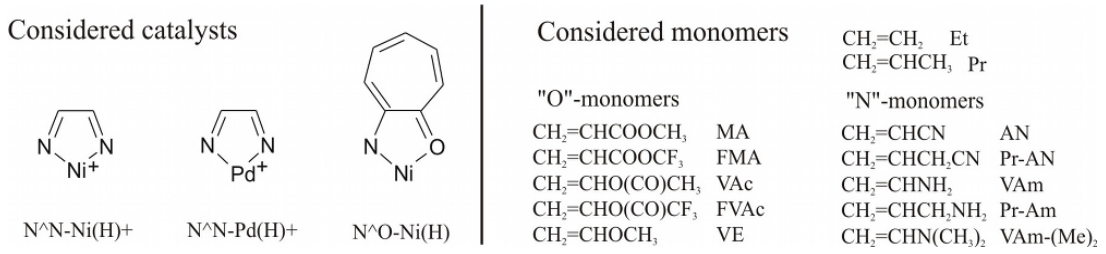

Fig. 1: Species studied in the present work.

Molecular modeling of the $\boldsymbol{\delta}$ and $\boldsymbol{\mu}$ opioid receptor interactions with cyclic deltorphin analogues containing urea bridges

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Opioid receptors are members of the large superfamily of G protein-coupled receptors (GPCRs). They are responsible for pain perception being activated both by endogenous opioid peptides and by exogenous opiates, such as morphine. The deltorphins (Tyr-*D*-Ala-Phe-Asp/Glu-Val-Val-Gly-NH_2), isolated from the skin of the frog *Phyllomedusa bicolor*, are the most selective naturally occurring opioid agonists for δ-opioid receptors.

In this study, the interaction of δ and μ opioid receptor with ten cyclic deltorphin analogues containing the urea bridges between residues 2 and 4 have been investigated.

The starting conformations of all peptides have been generated using the experimental data (NMR). Three-dimensional models of the opioid receptors were constructed by combining the multiple sequence alignment and the bovine rhodopsin crystal structure as a template. The ligands have been docked into the receptors using the AutoDock program. The relaxation of the receptor-ligand complexes using energy minimization, followed by the constrained simulated annealing protocols (CSA), has been performed in the all-atom AMBER 2003 force field in AMBER 9 package.

The receptor-bound conformations of the investigated analogues have been proposed. The residues responsible for ligands binding to opioid receptors have been identified and the differences in hepta- *versus* tetrapeptide deltorphin analogues binding have been discussed.

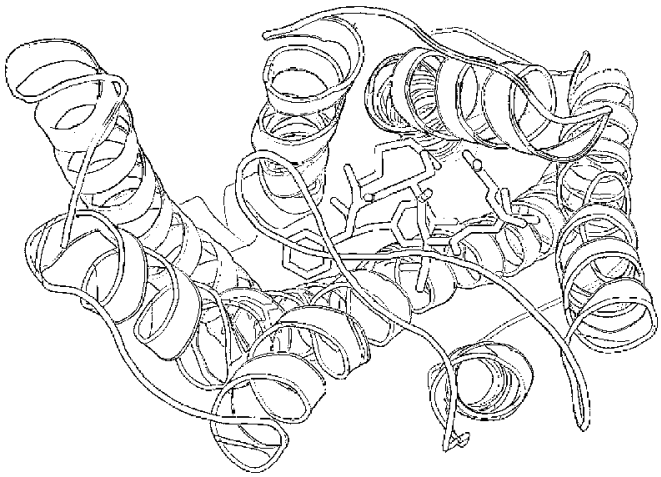

Figure 1: Heptapeptide deltorphin analogue docked into δ-opioid receptor cavity.

Acknowledgements: Supported by University of Gdańsk grant no. BW/8000-5-0140-8. Magdalena J. Ślusarz is supported by the Foundation for Polish Science (stipend for young researchers). The computational time in CI TASK Gdańsk is acknowledged.

Molecular dynamics of vancomycin and representative peptidoglycan fragment

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Vancomycin is glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. It acts by inhibiting proper cell wall synthesis in this bacteria, specifically, vancomycin prevents incorporation of N-acetylmuramic acid and N-acetylglucosamine peptide subunits into the peptidoglycan matrix, which forms the major structural component of Gram-positive cell walls [1, 2, 3].

In this work we are trying to elucidate the best vancomycin and C-terminal peptidoglycan fragment (representation of bacterial cell wall) conformations obtained from molecular dynamics simulations, which could subsequently help in constructing new vancomycin analogs active against Gram-positive vancomycin-resistant organisms. We have used four different pentapeptides: Ala-D-Glu-Lys-D-Ala-D-Ala, Ala-D-Glu-Lys-D-Ala-Ala, Ala-D-Glu-Lys-Ala-D-Ala, Ala-D-Glu-Lys-Ala-Ala.

The molecular dynamics (in three different environment models: in vacuo and both explicit and implicit (continuum) solvent models; Amber 9.0) results show that proposed, modified peptidoglycan fragments bind to vancomycin with less strength than native (unmodified) fragment. Points of interactions are identified and discussed. The expected vancomycin modifications could be proposed on the basis of missing vancomycin-peptidoglycan fragment interactions.

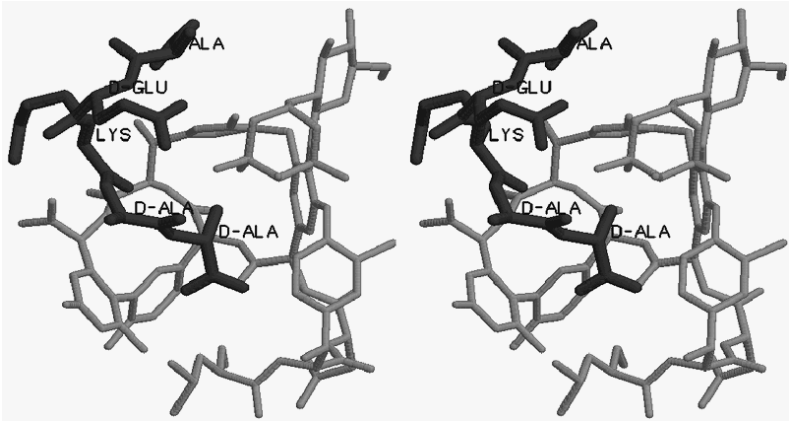

Fig. 1: Stereoview of an example vancomycin-peptidoglycan interactions: Ala-D-Glu-Lys-D-Ala-D-Ala peptide (black) embeded into vancomycin structure (gray).

Acknowledgements: The computational time in the Academic Computer Center in Gdansk CI TASK, Poland is acknowledged.

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Modeling properties of iridium complexes

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We present calculations of structural and spectroscopic properties of highly phosphorescent Ir complexes. These complexes have two cyclometalated ligands and a single bidentate, monoanionic ancillary ligand, making the complexes neutral. They have been used as emitters (dispersed in a charge transporting organic matrix), and are known to emit efficiently in the red, green, and blue part of the spectrum. The emission color from the complex dependents on the choice of the cyclometalating ligand. It is believed that luminescent iridium(III) polypyridine complexes are promising candidates for various bioanalytical applications. It is also anticipated that these complexes can offer additional advantages over traditional organic fluorophores in biological labeling because of their long-lived and intense luminescence, large Stokes' shifts and high photostability. Among many kinds of metal complexes, iridium complexes are the most effective and show intense phosphorescence at room temperature so they are also very good candidates to be use as phosphorescent dyes in full-color flat panel displays based on OLEDs technology.

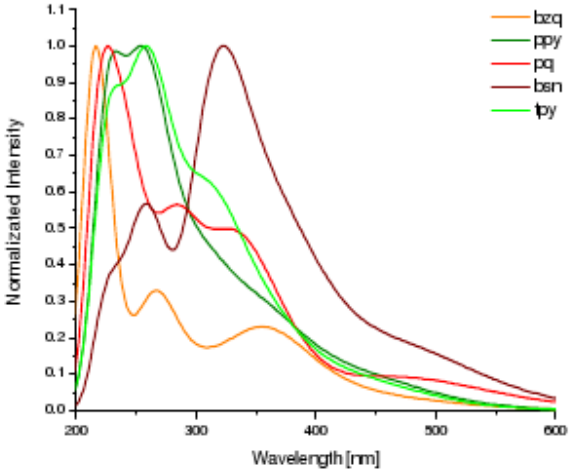

Fig. 1: Calculated absorption spectra of iridium complexes using B3LYP functional.

We have used comparison with the experimental geometries of (bis(2- phenylene pyridine) acrylate iridium, $(ppy)_2Ir(acac)$, and bis(2-(p- tolyl)pyridine) acrylate iridium, $(tpy)_2Ir(acac)$ to select the theory level. Then we have examined excited states properties obtained from the time-dependent density functional theory (TD-DFT) and from the configuration interactions with single excitations (CIS). We have compared experimental photophysical data with calculated absorbance and emission for five iridium complexes; $(ppy)_2Ir(acac)$, $(tpy)_2Ir(acac)$, $(bzq)_2Ir(acac)$, $(bsn)_2Ir(acac)$, $(pq)_2Ir(acac)$.

All geometries were fully optimized at the density functional theory level, using B3LYP, B3P86, M05, M06, and M06x2 functionals. LanL2DZ, LACV3P** and def-SV(P) were used. Vertical excitation energies were obtained from configuration interaction theory with single excitations (CIS) and from time-dependent density functional theory (TD-DFT) as implemented in Gaussian, using all functionals and LanL2DZ basis set. Implicit solvent model with conductor-like polarizable continuum model of electrostatics (CPCM) was used to account for solvent 2-Me-THF. On the basis of our studies it seems possible to predict emission spectra of Ir(III) complexes prior to their synthesis and to seek computationally complexes of the desired spectral properties.

Molecular dynamics of self-assembled monolayers of functionalized alkanethiols for protein adsorption

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Alkanethiols chemisorbed on the surface of a gold-covered electrode form mostly stable, uniform and compact self-assembled monolayers (SAMs). By chemical modification of the alkane chain, the properties of the surface and, consequently, the electrode can be changed. Such approach opens broad range of applications, including design of highly specific biosensors. Namely, functional groups, that bind in the active pocket of selected enzyme could be used [1] or the functionalized SAM can be further extended by deposition of enzymes or antibodies [2].

This work aims at understanding the role of the functional groups (methyl, carboxyl, amine) in binding of an enzyme to the surface of SAM. It applies molecular dynamics simulations and focuses on investigation of the properties of the system, like the tilt and precession angle, orientation, radius of gyration or eccentricity, which can be related to experimental measurements of the monolayer thickness, AFM images etc. Comparison of titrable terminal groups is particularly important, because exchanging the functional group between neutral, negatively or positively charged, may alter the fine balance between specificity of binding and deformation of the enzyme, leading to the loss of catalytic activity [3]. Results of the presented simulations may help to understand the experimental data and facilitate the design on new SAMs.

Acknowledgements: This work is supported by FCT grant No. SFRH/BPD/38809/2007.

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Search for inhibitors of aminoacyl-tRNA synthases by virtual click chemistry

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The increase of multidrug-resistant strains of bacteria to known classes of antibiotics present a severe challenge for modern medicine. The most promising strategy to combat pathogenic bacteria is to discover new drug targets, taking advantage of the information obtained from genomic and proteomic research. In this regard, aminoacyl-tRNA synthetases (AA-RS) are particularly well suited to develop novel drugs that show no cross-resistance to other classical antibiotics. [1] AA-RS are essential enzymes for protein biosynthesis. When one AA-RS is inhibited, the protein synthesis is inhibited, which, in turn, causes cell growth arrest. Consequently, each compound that inhibits any of the AA-RS is a potential antibacterial agent. Moreover, there are significant structural differences between the eucariotic (human) and procariotic (bacterial) enzymes that can be exploited in drug design. The clinical utility of AA-RS inhibitors is proven by the natural product Ile-RS inhibitor pseudomonic acid, which is currently marketed as an antibacterial agent for topical application. [2] Up to day various chemical structures that inhibit AA-RS have been identified. These inhibitors have either been isolated from natural sources or have been generated synthetically. The synthetic inhibitors are modifications of natural inhibitors, derivatives of the natural synthetase substrates and reaction intermediates, or have been identified by screening of compound libraries. Previously, we have created the database of various AA-RS inhibitors [3] and by the use of Ligand.Info approach [4] towards identification of similar compounds we proposed new inhibitors of Tyr-AA. [5]

In this report we present an interesting approach towards generating of Leu-RS inhibitors by virtual click chemistry. That is we identified key fragments for ligand binding within catalytic pocket of Leu-RS, generated the collection of similar fragments with the use of Ligand.Info, identified the fragments that are most strongly bound in different areas within the catalytic pocket, and finally with the use of virtual click chemistry we generated a set of molecules which are most likely to act as highly potent bacterial Leu-RS inhibitors.

Acknowledgements: Financial support from European Committee grant no. LSHG-CT-2003-503265 and Polish Ministry for Science is gratefully acknowledged. Authors thank the Foundation for Polish Science for a FOCUS fellowship.

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Theoretical modeling of the reaction mechanism of phosphonoacetaldehyde hydrolase

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Phosphonates, compounds containing P–C bonds, can enter the environment as pesticides, herbicides, chemical warfare agents or detergent additives. The ability to metabolize phosphonates as nutrient sources has been demonstrated only in bacteria. One of very few enzymes catalyzing P–C bond cleavage is phosphonoacetaldehyde hydrolase (trivial name – phosphonatase). The natural substrate of phosphonatase is 2- phosphonoacetaldehyde (PALD). The reaction catalyzed by the enzyme has been proposed to happen in two steps: the first step being formation of a Schiff base intermediate between the carbonyl group of the substrate and the terminal amino group of the neutral Lys53 [1]. The second step is the nucleophilic attack of Asp12 on PALD phosphorus, causing P–C bond cleavage. Afterwards hydrolysis occurs, releasing acetaldehyde and orthophosphate.

In this project, a different reaction mechanism, proposed by modelers [2], was studied. The chosen enzyme was phosphonatase from *Bacillus cereus* (PDB entry code 1RQL) [3]. The phosphonatase model used in calculations was build from the crystal structure of *Bacillus cereus* phosphonatase complexed with an inhibitor, vinyl sulfonate. The inhibitor was replaced with the structure of PALD which was previously optimized at the HF/6-31G(d) level. The system was investigated with the use of the combined quantum mechanical/molecular mechanical (QM/MM) technique. Molecular mechanics energy minimization and molecular dynamics simulations were also carried out.

QM/MM adiabatic mapping, using semi-empirical (AM1 and PM3) and DFT (B3LYP) methods, was performed to obtain potential energy profiles for each reaction step. Two different reaction coordinates were tested. Structures were fully optimized at each value of the chosen restrained reaction coordinate.

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Positron binding systems

Małgorzata Wołcyrz

Institute of Physical and Theoretical Chemistry, Wroclaw University of Technology, Poland

Modified adiabatic approximation, with the nucleus treated as light pseudonuclus and its charge included only partially in the electronic hamiltonian, has been applied to compute energies and anihilation rates of positronium hydride (PsH), lithium positride (LiPs), positronic beryllium (e^+Be) and positronic magnesium (e^+Mg). Three models of effective positron mass were introduced as nonadiabatic correction.

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Influence of the solvent on the interaction induced first-order hyperpolarizability of H-bonded HF dimers

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Institute of Physical and Theoretical Chemistry, Wroclaw University of Technology, Wrocław, Poland

Passing from the molecular to macroscopic optical response for molecular materials is not trivial [1]. It has been well established that the properties of bulk might differ considerably from those of isolated molecules [2, 3]. In this work the influence of the solvent on the interaction induced first-order hyperpolarizability of H-bonded HF dimers have been studied. In order to understand the role of the solvent effect on the nonlinear optical properties of the investigated complexes, the polarizable continuum model (PCM) has been employed to simulate the polar environment. The optimization of analyzed structures and calculations of components of static electric first-order hyperpolarizability have been executed at the MP2 level of theory. Various Dunning's correlation consistent basis sets (aug-cc-pVXZ, X=D, T, Q) have been tested. Moreover, the BSSE-free two-body components have been calculated in order to analyzed their influence on first-order hyperpolarizability. Significant influence of polar solvent on the interaction induced first-order hyperpolarizability of the H-bonded HF dimers has been found.

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Detection of symmetrical decomposition of molecules - isotopomeric analysis of M/2 clusters

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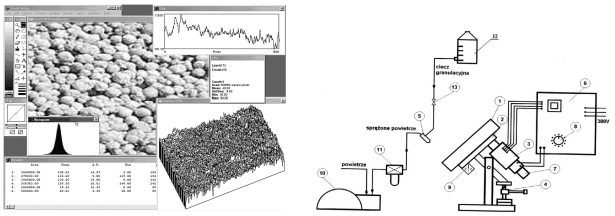
University of Technology and Life Sciences, Bydgoszcz, Poland

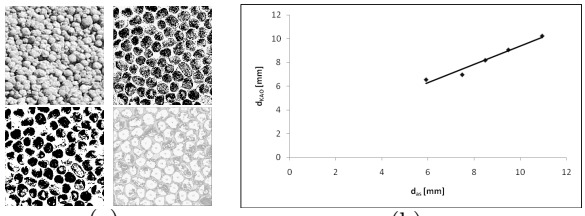
The process of non-pressure of agglomeration phosphorous fertilizer is widely used in the chemical industry. Fertilizers undergo the process of granulation are a dust materials at a very diverse physicochemical properties. A lot of experimental research on the characteristics of different agglomerated materials were realized. It is very important to define the parameters of the technological process of non-pressure of granulation because they have an impact on its performance and quality of obtained granules. Despite of a lot of research and development of the theoretical foundations of this process, in practice there are problems in obtaining adequate capacity and quality of granulated products. This is mainly due to changing characteristics of loose material undergoing granulation. It is difficult to achieve every time the same physical and chemical properties of these materials, because it is related to the impact of many external factors. Sometimes alters the supplier of granular material which also has an impact on the diversity of physicochemical properties.



(a) (b)

Fig. 1: (a) Image analysis program *Scion*. (b) Scheme of plate granulation.

To prevent such problems tried to preliminary research aimed at developing methods of computer modelling pelleting process. It has to be a method which will be continuously monitored the process of granulation and responds to changing the properties of granular materials as well as changing external conditions, such as change in temperature or humidity.



(a) (b)

Fig. 2: (a) The stages of preparation for the computerized image analysis: treshold, smooth, the number of pellets. (b) Chart according to the diameter designated by computer image analysis dKAO than the diameter designated by sieve analysis.

The paper presents the results of research of non-pressure pelleting process phosphorous using computerized image analysis. I present a theoretical base for the development of a model of non-pressure of agglomeration based on the latest scientific reports. The scope of the research included both experimental studies on granulation plate and theoretical considerations. Much of the work included the development of methods for computer image analysis, which is used in the analysis process of granularity.

Author index

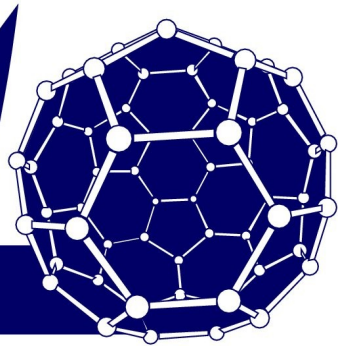
Keyword index

Wrocław University of Technology

MDMM

Modelling and Design of Molecular Materials

2008



Monday June 23			Registration	
Tuesday June 24	**Advances in computational methods** **L1:** T. Wesołowski **L2:** M. Meuwly	**Modeling zeolite materials** **L3:** R. van Santen **L4:** J. Sauer **L5:** P. Boulet **L6:** B. Szyja	**Interactions in molecular materials** **L7:** J. Murray **L8:** H. Cheng **L9:** O. Shishkin **L10:** S. Grabowski	**Poster Session A** **P1 – P26**
Wednesday June 25	**Modeling chemical reactions** **L11:** A. Toro-Labbe **L12:** P. Politzer **L13:** P. Paneth **L14:** Z Flisak	**Protein Dynamics** **L15:** T. Clark **L16:** A. Koliński **L17:** A. Sikorski	**Protein structure prediction** **L18:** A. Godzik **L19:** A. Liwo	**Properties of molecular materials** **L20:** R.A. Poirier **L21:** A.Tachibana **L22:** Z. Latajka **L23:** B. Kuchta **L24:** J.C. Wojdeł ***Grill***
Thursday June 26	***Excursions***		Workshop session Tools for computational chemistry	Poster Session B P27 – P52
Friday June 27	**Designed biomaterials** **L25:** M. Ramos **L26:** T. Brinck **L27:** J. Koca	**Modeling biomaterials** **L28:** P. Kozłowski **L29:** D. Plewczynski **L30**: P. Sharma **L31:** S. Sharma	**Drug design I** **L32:** P.Tchounwou **L33:** S. Guccione **L34:** V. Kuzmin	**Drug design II** **L35:** J. Burda **L36:** L. Berlicki **L37:** T. Zimmermann **L38:** E. Muratov **L39:** P.Drożdżewski ***Conference dinner***
Saturday June 28	**Nucleic acids I** **L40:** P. Hobza **L41:** J. Rak **L42:** J. Sponer	**Nucleic acids II** **L43:** P. Cysewski **L44:** Z. Vokacova **L45:** J. Leszczyński		