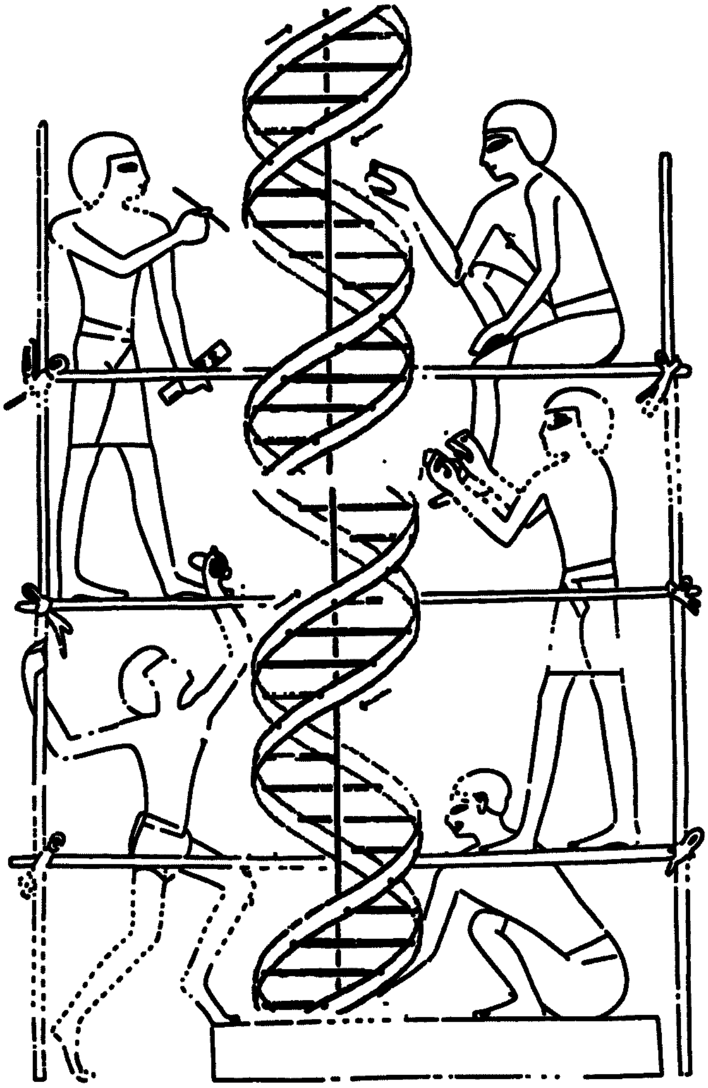
Modeling & Design of Molecular Materials 2010

Wrocław, Poland – July 4-8, 2010



Conference information & abstracts

Modeling & Design of Molecular Materials 2010

a meeting organized by

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

NSF Interdisciplinary Center for Nanotoxicity
Jackson State University, Jackson, MS, USA

Charles University in Prague, Czech Republic

Wrocław Center for Supercomputing and Networking (WCSS)

Conference website: www.mdmm.pl/2010

an event sponsored in part by

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Jackson State University, Jackson, MS, USA

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Wrocław University of Technology (WUT), Wrocław, Poland

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Conference program

July 4, 2010 (Sunday)

14:00-21:00	Registration - lobby of D-20 building, ul.Janiszewskiego 8

July 5, 2010 (Monday)

8:00-9:00	Registration (ctd.)
9:00-9:10	Conference opening
Session 1	**Modeling molecular materials for hydrogen storage** (chair: J. Murray)
9:10-9:40	**L1:** H. Cheng (Singapore) *Mechanistic study of hydrogen spillover in carbon based materials*
9:40-10:10	**L2:** A. Tachibana (Kyoto, Japan) *Energy density concept: a stress tensor concept*
10:10-10:40	**L3:** I. Cukrowski (Pretoria, South Africa) *Intramolecular steric H-H clashes or stabilising H-H bonds in transition metal complexes?*
10:40-11:00	**L4:** B. Nemeth (Budapest, Hungary) *Amine- and phosphine-boranes*
11:00-11:15	coffee break
Session 2	**Modeling molecular materials for nanotechnology** (chair: H. Cheng)
11:15-11:45	**L5:** M. Samoć (Wrocław, Poland) *Third-order nonlinear optical materials: practical issues and theoretical challenges*
11:45-12:15	**L6:** W. Grochala (Warsaw, Poland) *Quantum modeling in suport of chemical intuition - case studies in inorganic chemistry*
12:15-12:35	**L7:** D. Thompson (Cork, Ireland) *Harnessing molecular motion for materials design*
12:35-14:30	Lunch break

Session 3	**Advances in computational methods** (chair: Z. Latajka)
14:30-15:00	**L8:** B. Lesyng (Warsaw, Poland) *Causality analysis of proton transfer processes in molecular systems - a novel methodological approach*
15:00-15:20	**L9:** D. Rohr (Łódź, Poland) *Efficient calculation of isotope effects for large molecules*
15:20-15:40	**L10:** M.P. Mitoraj (Kraków, Poland) *A combined charge and energy decomposition scheme for analysis of chemical bonds and reaction paths*
15:40-16:00	**L11:** P. Szarek (Wrocław, Poland) *The self-capacitance density of atoms and molecules based on electron cloud deformation analysis*
16:00-16:15	Cofee break
Session 4	**Modeling biomolecules** (chair: V. Moliner)
16:15-16:45	**L12:** S. Filipek (Warsaw, Poland) *Modeling of G-Protein coupled receptors and shared mechanisms of their activation*
16:45-17:15	**L13:** P. Cysewski (Bydgoszcz, Poland) *Environmental influences on the aromaticies of nucleobases and aminoacids*
17:15-19:00	Poster session A (P1-P33)

July 6, 2010 (Tuesday)

Session 5	**Drug design** (chair: S. Filipek)
9:00-9:30	**L14:** A. Lodola (Parma, Italy) *Understanding structure-activity relationship of FAAH inhibitors by QM/MM mechanistic modelling*
9:30-10.00	**L15:** J. Grembecka (Ann Arbor , USA) *Development of small molecules targeting menin-MLL interaction in leukemia*
10:00-10:30	**L16:** T. Cierpicki (Ann Arbor, USA) *NMR in rational drug design for protein-protein interactions*
10:30-10:50	**L17:** D. Plewczyński (Warsaw, Poland) *VoteDock: the consensus docking metod for prediction of protein ligand-interactions*
10:50-11:05	coffee break

Session 6 **Modeling chemical reactions** (chair: P. Politzer)

11:05-11:35 **L18:** J. Murray (Cleveland, USA)
Reaction force analyses of energetic molecule decomposition
11:35-12:05 **L19:** J. Burda (Prague, Czech Republic)
The thermodynamic and kinetic description of reactions of the organometallic complexes
12:05-12:35 **L20:** Z. Latajka (Wrocław, Poland)
Proton transfer dynamics in strong hydrogen bonded systems

12:35-14:30 Lunch break

Session 7 **Modeling interactions in molecular materials** (chair: K. Ghio)

14:30-15:00 **L21:** P. Politzer (New Orleans, USA)
Some applications of molecular volumes in materials science
15:00-15:30 **L22:** O. Shishkin (Kharkov, Ukraine)
Structural properties of nucleic acid bases in polar environment
15:30-16.00 **L23:** S. Roszak (Wrocław, Poland)
Resonance Raman spectra in detecting nerve agents
16:00-16:20 **L24:** V. Andruschenko (Praha, Czech Republic)
Simulations of nucleic acid vibrational spectra

16:20-16:35 Coffee break

16:35-18:30 Poster session B (P34-P66)

July 7, 2010 (Wednesday)

Session 8 **Progress in predicting biomolecular structure** (chair: O. Shishkin)

9:00-9:45 **L25:** M. Neumann (France)
Crystal structure prediction of molecular compounds - beyond proof of concept
9:45-10.15 **L26:** J. Bujnicki (Warsaw, Poland)
RNA 3D structure prediction: from comparative to de novo modeling
10.15-10:45 **L27:** D. Gront (Seattle, USA)
Protein structure determination based on fragmentary experimental measurements

10:45-11:00 Coffee break

Session 9 **Modeling reaction mechanisms** (chair: T. Brinck)

11:00-11:30 **L28:** K. Ghio (Pisa, Italy)
Theoretical prediction of selectivities in nonreversible and reversible hydroformylation reactions catalyzed by unmodified Rh-carbonyls
11:30-12:00 **L29:** P. Kozłowski (Louisville,KY, USA)
How the Co-C Bond is cleaved in coenzyme B12-dependent mutases
12:00-12.30 **L30:** P. Paneth (Łódź, Poland)
Isotopic fractionation calculations of reactions between environment pollutants and permanganate
12:30-12:50 **L31:** T. Borowski (Kraków, Poland)
DFT studies on the reaction mechanizm of intra- and estradiol dioxygenases

14:30-16:30 Wrocław sightseeing

16:30-17:00 Panorama art gallery show

17:30-18:30 Boat trip along Odra river

19:00 Conference dinner

July 8, 2010 (Thursday)

Session 10 **Catalyst and biocatalyst design** (chair: P. Paneth)

9:00-9.30 **L32:** K. Yoshizawa (Fukuoka, Japan)
Computational mutation of enzymatic reaction: QM/MM studies
9:30:-10:00 **L33:** T. Brinck (Stockholm, Sweden)
Promoting carbon-carbon formation - the Holy Grail in the design of enzymes and organocatalysts
10:00-10.30 **L34:** V. Moliner (Castellóe la Plana, Spain)
Theoretical design of new biological catalysts
10:30-11:00 **L35:** A. Michalak (Kraków, Poland)
Theoretical studies on the ethylene polymerization catalyzed by half-metalocene Ti(IV) complexes with arylo ligands

11.00-11:15 Coffee break

Session 12 Modeling biomolecules II (chair: J. Burda)

11:15-11:35	**L36:** A. Sikorski (Warsaw, Poland) *Properties of two-dimensional polymer-solvent systems. A Monte Carlo study*
11:35-11:55	**L37:** T.S. Barata (London, United Kingdom) *Structural studies on glycosylated gen. 3.5 PAMAM dendrimers*
11:55-12:15	**L38:** K. Mikulska (Torun, Poland) *Steered MD simulations of adhesive protein contactin*
12:15-12:35	**L39:** M. Łaźniewski (Warsaw, Poland) *Squalene epoxidase as target for new hypocholesterolemic drugs*
12:35-12:55	**L40:** M. Długosz (Warsaw, Poland) *Brownian dynamics study of the association between the 70S ribosome and elongation factor G*
13:00	Conference closing

Conference posters

No.	Presenting authors	Title
P1/A	Mateusz Banach	*Identification of protein-protein complexation area*
P2/A	Teresa S. Barata	*Method development for glycosylated PAMAM dendrimer 3D structure generation*
P3/A	Mohammad R. Bayati	*The influence of current type on photocatalytic performance of MAO-derived nano/micro-structured titania films*
P4/A	Karol M. Langner W. Andrzej Sokalski Wiktor Beker	*Accuracy of molecular properties estimated from cumulative atomic multipole moment expansions*
P5/A	Aneta Buczek	*Estimation of anharmonic amide modes in the Kohn-Sham limit using the polarization consistent basis sets*
P6/A	Maria Jaworska Piotr Lodowski Aleksandra Chmielowska	*Geometry and electronic structure of the A-cluster in acetyl-CoA synthase.*
P7/A	Henryk Chojnacki	*Non-empirical quantum chemical studies on electron transfer reactions in platinum (II) complexes*
P8/A	Ewa Chudyk	*Developing Monte Carlo methods for modelling reaction mechanisms*
P9/A	Piotr Cysewski	*Recognition of 8-oxoguanine, isoguanine and 8-oxoadenine via proteins direct readout*
P10/A	Żaneta Czyżnikowska	*A computational study of Cu(II)–ßXaaHisGlyHis complexes*
P11/A	Żaneta Czyżnikowska	*Influence of oxidative damage of purines on the nature of stacking interactions. A post-HF and DFT-SAPT study*
P12/A	Wojciech Grochala Mariana Derzsi	*Electronic structure and magnetism of* $AgSO_4$*, an unusual 1D antiferromagnet – insights from DFT*
P13/A	Przemysław Dopieralski	*Mechanochemistry, metadynamics, QM/MM*
P14/A	W. Andrzej Sokalski Agnieszka Dzielendziak	*Analysis of the catalytic role of water molecules*
P15/A	Andrzej J. Gorączko	*Modeling of spectrum of the dodecacarbonylo-triangulo-triosmium*

P16/A	Andrzej J. Gorączko	*Effects of interaction of the spectrum resolution and the peak location accuracy in the isotopomeric cluster*
P17/A	Dominik Gront	*BioShell - a universal utility library for structural bioinformatics*
P18/A	Marcin Hoffmann Marcin Nowosielski	*Designing of new inhibitors of Saccharomyces cerevisiae squalene epoxidase*
P19/A	Piotr Cysewski Marcin Jakubiak	*Structural and energetic heterogeneities of oligonucleotides containing 2-OH-A*
P20/A	Adrian Jasiński	*Fluorescent probes PRODAN and ALADAN inside a protein cavity – molecular dynamics simulations at different electronic states*
P21/A	Maciej Długosz Maciej Jasiński	*Insights into solution structure of peptide nucleic acids. Molecular dynamics simulations*
P22/A	Tadeusz Andruniów Paweł M. Kozłowski Maria Jaworska Piotr Lodowski	*Photophysical properties of B12 cofactors: inside from quantum chemical calculations*
P23/A	Jerzy T. Jodkowski	*Mechanism of the gas-phase decomposition of trifluoro-, trichloro-, and tribromomethanols in the presence of hydrogen halides*
P24/A	Jerzy T. Jodkowski	*Hydroxyurea and hydroxythiourea methyl derivatives as effective drugs for the treatment of sickle-cell anemia. A DFT and MP2 computational study*
P25/A	Jerzy T. Jodkowski	*Derivatives of N-hydroxyurea and N-hydroxythiourea as potential drugs for the treatment of sickle-cell anemia. A DFT and MP2 computational study on aliphatic cyclic and acyclic mono N(OH)-substituted species II*
P26/A	Paweł Kadłubański Szczepan Roszak	*The evolution of bonding and thermodynamics properties of boron doped small carbon clusters – an ab initio study*
P27/A	Grzegorz Krasiński	*Modeling of ring-opening copolymerization of L,L-lactide and ε-caprolactone by DFT methods*
P28/A	Grzegorz Krasiński	*Molecular modeling of enzyme-catalyzed transestrification and hydrolysis reactions*
P29/A	Katarzyna Kulczycka	*Quantum mechanical studies of lincosamides*
P30/A	Katarzyna Kulińska Tadeusz Kuliński	*Insights into structure, dynamics and hydration of DNA/DNA and DNA/RNA duplexes with pyridylphosphonate internucleotide bonds from molecular dynamics simulations*
P31/A	Żaneta Czyżnikowska Justyna Kurzawa Wojciech Bartkowiak	*On the reliability of ab initio methods in prediction of electric dipole (hyper)polarizabilities of betaine and merocyanine dyes. A critical study*
P32/A	Maria Jaworska Piotr Lodowski	*Mechanism of methyl transfer from CH3Co(dmgBF2)2Py to phosphine nickel complex: DFT study*

P33/A	Robert W. Góra Michał Maj	*Verification of the resonance-assisted hydrogen bond model within spin-coupled valence bond theory*
P34/B	Mateusz Mariański	*Explicit water hydration of alpha-helices in the gas phase and in a continuous solvent. A density functional theory study*
P35/B	Paweł Kędzierski Dorota Matelska	*Homology modeling of a potential methyl-histone binding module of human SGF29*
P36/B	Karolina Mikulska	*Nanomechanics of Ig-like domains of human contactin (BIG-2)*
P37/B	Michaela Nekardová Jaroslav V. Burda	*Exploration of cisplatin interactions with glycine; a DFT study*
P38/B	Marcin Hoffmann Marcin Nowosielski	*How do substituent effects affect conformational freedom of squalene in cholesterol biosynthesis*
P39/B	Anna Pabiś Katarzyna Świderek	*FEP/MD study on binding ibuprofen to human serum albumin*
P40/B	Peter Palencar	*Folding of long-chain polyalanine in the cavity*
P41/B	Mariusz P. Mitoraj Monika Parafiniuk	*Activation of B-H bond in ammonia borane catalyzed by [Ir(dppm)$_2$]OTf – an analysis based on the combined charge and energy decomposition scheme*
P42/B	Łukasz Piękoś Artur Michalak	*Molecular dynamics modeling of half-metallocene titanium(IV) ethylene polymerization catalysts*
P43/B	Dariusz Plewczyński Michał Łaźniewski	*Prediction of three dimensional structure of protein complexes*
P44/B	Tomás Peña Ruiz	*TD-DFT study of the bandgap in a series of poly(arylethynylene)s*
P45/B	Mariusz Radoń	*DFT and ab initio modeling of bioinorganic iron complexes with noninnocent ligands*
P46/B	Sheikh Shilbe Rahman	*Complex formation between antibacterial drugs and escort molecules in the combat against multidrug resistance in bacteria*
P47/B	Rafał Roszak Szczepan Roszak	*Potential energy surfaces for hydrogen adsorption on beryllium doped graphite*
P48/B	Dorota Rutkowska-Zbik	*Theoretical investigation of structural and electronic effects in the metalation of tetrapyrroles*
P49/B	Joanna Sarzyńska	*Structural basis of the uniform binding of different tRNAs by a ribosome*
P50/B	Tadeusz Kuliński Joanna Sarzyńska	*Origins of enhanced thermodynamic stability of 2'-O-methyl RNA/RNA duplexes with single LNA-2-thiouridine residue studied by molecular dynamics and free energy simulations*
P51/B	Jakub Šebera	*Computational study and analysis of infrared spectra of uridinemonophosphate*
P52/B	Jakub Šebera	*First – principle analysis of formation and reactivity of oxametallacycle intermediate on Au and Pt clusters*

P53/B	Oleg V. Shishkin Svitlana V. Shishkina	*Competition between π-π conjugation and n-σ^* hyperconjugation in heteroatomic analogues of butadiene*
P54/B	Marek Skoršepa	*Theoretical study of interactions between VEGFR2 and newly-designed inhibitors*
P55/B	Tadeusz Andruniów Dorota Ślepieńczuk	*DFT calculations of cobalamin-DNA and cobalamin-RNA interactons in B12-retro-riboswitches*
P56/B	Anna Stachowicz	*Electronegativity equalization method in force field atoms resolution*
P57/B	Robert W. Góra Rafał Szabla	*Theoretical studies of the mechanism of nucleotides formation in prebiotically plausible conditions*
P58/B	Piotr Paneth Katarzyna Świderek	*Binding isotope effects on M_4 and H_4 isoforms of L-lactate dehydrogenase*
P59/B	Paweł Szarek	*Modeling the electronic density kernels*
P60/B	Damien Thompson	*Rational design of linked gold nanocrystals for electronics*
P61/B	Zuzana Vokáčová	*Does nonplanarity of nucleic acid bases affect NMR parameters?*
P62/B	Tadeusz Andruniów Elżbieta Walczak	*Molecular dynamics silulations of Zoanthus yellow fluorescent protein in vacuo and condensed phase*
P63/B	Tomasz Borowski Anna Wójcik	*The mechanism of the reaction of intradiol dioxygenase with hydroperoxy probe. A DFT study*
P64/B	Łukasz Wolański Tadeusz Andruniów	*CASPT2//CASSCF and CASPT2//DFT(BLYP) calculations for the zFP538 protein chromophore – structure and spectral properties in vacuo*
P65/B	Zbigniew Zawada	*Reaction of pyridine and acridine derivatives the with hydrogensulfide anion - a model of quinacrine action on prion protein*
P66/B	Agnieszka Zawada Wojciech Bartkowiak	*(Hyper)polarizability density analysis of molecular model systems*

Lecture abstracts

in chronological order

Mechanistic study of hydrogen spillover in carbon-based materials

Hansong Cheng

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3 Science Drive 3, Singapore 117543

Recent studies on hydrogen storage have shown significant storage capacities in several carbon-based materials, including graphite nanofibers, carbon nanotubes and some metal-organic framework compounds. The unusually large hydrogen uptake in these materials, reportedly up to 5.5wt.%, was attributed to the so-called "hydrogen spillover" phenomena, in which dihydrogen molecules first undergo dissociative chemisorption upon interacting with platinum catalysts and subsequently hydrogen atoms are spilled over onto the carbon substrates via an adsorption process. To achieve the reported high storage capacity, it is essential that the adsorbed hydrogen atoms be nearly free to move to other adsorption sites far from where the catalysts reside. Using density functional theory under the generalized gradient approximation, we systematically investigated the possible hydrogen spillover mechanisms. We first calculated the sequential H desorption energies in a selected Pt cluster and identified the threshold energy required for H atoms to desorb from the catalyst. Subsequently, we evaluated the thermochemical energies and barriers of "spillover" process at the catalyst-substrate interface. The substrates selected in the present study include MoO_3 solid, which is a well-known hydrogen reservoir upon hydrogen spillover, and several carbon-based materials. Detailed H-diffusion pathways in the lattices were examined. We will show that hydrogen spillover at ambient conditions in MoO_3 is energetically feasible. However, spillover in carbon-based materials could only occur via a physisorption mechanism. The implications to hydrogen storage will be discussed.

Energy density: a stress tensor concept

Akitomo Tachibana

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Conceptual insights from the density functional theory have been enormously powerful in the fields of physics, chemistry and biology. A natural outcome is the concept of "energy density" as has been developed recently: electronic drop region, spindle structure, interaction energy density. Under external source of electromagnetic fields, charged particles can be accelerated by Lorentz force. Dissipative force can make the state of the charged particles stationary. In quantum mechanics, the energy eigenstate is another rule of the stationary state. Tension density of quantum field theory has been formulated in such a way that it can compensate the Lorentz force density at any point of space-time. This formulation can give mechanical description of local equilibrium leading to the quantum mechanical stationary state. The tension density is given by the divergence of stress tensor density. Electronic spin can be accelerated by torque density derived from the stress tensor density. The spin torque density can be compensated by a force density, called zeta force density, which is the intrinsic mechanism describing the stationary state of the spinning motion of electron.

[1] A. Tachibana, *Journal of Molecular Structure: THEOCHEM* **2010**, *943*, 138-151.

Intramolecular steric H-H clashes or stabilising H–H bonds in transition metal complexes?

Ignacy Cukrowski

Department of Chemistry, Faculty of Agricultural and Natural Sciences,
University of Pretoria, Lynnwood Road, Pretorias 0002, South Africa

Zinc(II) complexes with nitrilotriacetic acid (NTA) and nitrilotri-3-propanoic acid (NTPA) were studied at the B3LYP/6-311++G(d,p) level of theory in solvent, CPCM/UAKS. The topological data (AIM theory of Bader) explained the observed difference in stability of the ZnNTA and ZnNTPA complexes. All ZnNTPA conformers have two intramolecular H–H bonds, such as CH34–H31C and CH27–H28C in Fig 1. From energies of H-atoms in a -CH_2- fragment of 6-member chelating rings in ZnNTPA it was found that these two H–H bonds provide, on average, stabilizing contribution of 10.8 ± 1.9 kcal mol^{-1}.

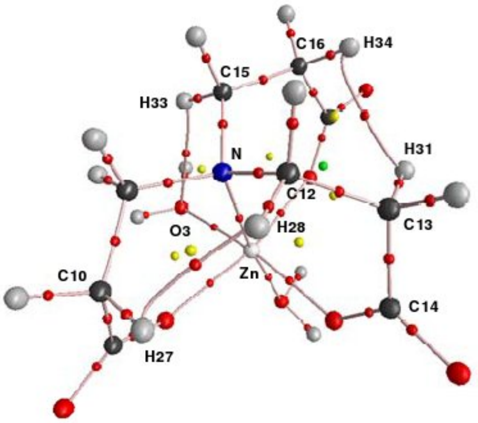

Fig. 1: Molecular graph of ZnNTPA.

The H-H bonding interactions were confirmed by comparing the atomic energies of the H-atoms when they were and were not involved in the bonding interaction. On average, the decrease in the atomic energy of atoms involved in H-H bonding is 4.5 kcal mol^{-1}. H-H bonding found in ZnNTPA shows typical characteristics of a chemical bond, e.g. a decrease in the QTAIM-defined delocalization index DI(H,H) with an increase in the bond length (Fig. 2).

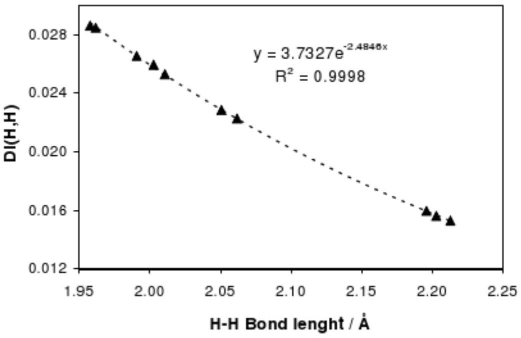

Fig. 2: Correlation between DI(H,H) and the internuclear separation of H-atoms involved in bonding.

The departure of the bond path angles (BPA) from the geometrical bond angles (GBA) was used to map the strain energy distribution within the 6-member rings. The largest strain energy is associated with the bonds of the C-O-Zn ring fragment, but the smallest strain energy is related to the bonds of the bite angle O-Zn-N, which classically has been used to evaluate stability of a complex.

The overall energy of ZnNTPA would be larger by about 11 kcal mol^{-1} in the absence of H–H bonding and this would decrease stability of the complex by ca. 8 log K units. It is reasonable to assume that, since log K(ZnNTPA) = 5.3, this complex is formed only due to the intramolecular H-H bonds which decreased the strain energy in the as-in-complex ligand. Since in the energy-optimised equilibrium structure the net repulsion or attraction forces are not present (they must cancel of) the argument of effective repulsion destabilizing forces due to steric hindrance between two H-atoms cannot hold.

Amine- and phosphine-boranes

Balázs Németh[1,2], Brahim Khater[1], Tamás Veszprémi[2], Jean-Claude Guillemin[1]

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Avenue du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France
[2] Budapest University of Technology and Economics, Department of Inorganic and Analytical
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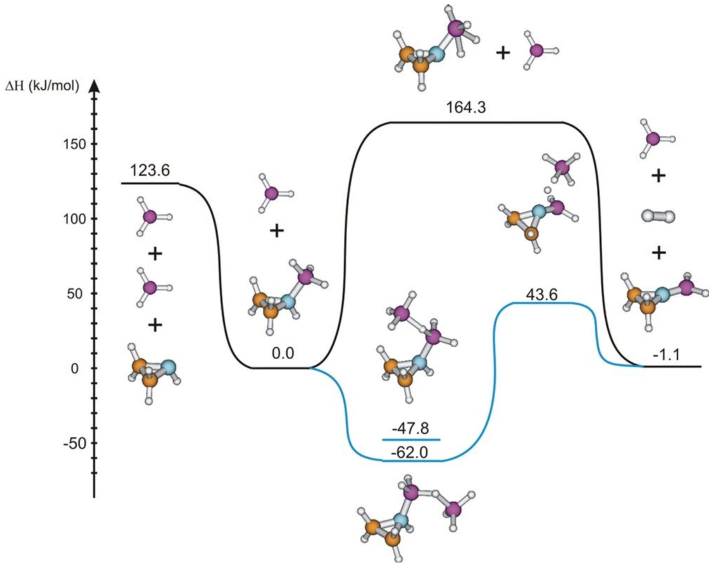

Fig. 1: Enthalpy profile showing the hydrogen release and the dissociation of aziridine-borane at B3LYP/aug-cc-pVTZ level.

A series of amine- and phosphine-boranes was synthesized. ^{1}H, ^{13}C, ^{15}N or ^{31}P NMR, photoelectron and mass spectra were recorded to study the differences between the complexation of amine and phosphine group with borane. Quantum chemical calculations were performed to gain an extensive insight to the borane complexation of the lone electron pair of these amines and phosphines and to have a greater knowledge of the properties of these new complexes. The photoelectron spectra can be described in case of α,β-unsaturated compounds by the change of the direct conjugation between the lone electron pair and the π-bond in the free phosphines to hyperconjugation of the $\sigma_{\text{P-B}}$ bond with the unsaturated moiety in the corresponding complexed derivatives. In the case of β,γ-unsaturated derivatives the observed hyperconjugation in phosphines disappears with the complexation. The observed ionization potentials, the flash vacuum thermolysis as well as the results of the complexation energy calculations denote that the dative $\sigma_{\text{N-B}}$ bond is more stable than the $\sigma_{\text{P-B}}$ bond. The most conspicuous geometry difference is that the P-C bond shortens while the N-C bond elongates during the complexation, which is in line with the changes of the atomic charges: the difference increases between P and C but decreases between N and C.

The energy of the investigated hydrogen elimination reactions exhibits a wide range from strongly exothermic to endothermic. The hydrogen elimination of aziridine-borane is however close to thermoneutral (Figure 1). Moreover, it is a stable and easily handled compound, thus it has a huge potentiality of being convenient hydrogen storage material.

[1] Németh, B.; Khater, B.; Veszpémi, T.; Guillemin, J-C. *Dalton Trans.* **2009**, 3526-3335.
[2] Németh, B.; Khater, B.; Guillemin, J-C.; Veszpémi, T. *Inorg. Chem.* **2010**, 4854-4864.

Third-order nonlinear optical materials: practical issues and theoretical challenges

Marek Samoć

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

The advent of the self-mode-locked femtosecond-pulse Ti-sapphire lasers and of efficient optical parametric amplifiers has led to relatively easy availability of high power tunable sources of light, suitable for the investigations of nonlinear optical properties of materials within wide wavelength ranges. Such studies, are however, relatively rare. One of the reasons is the tediousness of the process of obtaining such data.

The author of this contribution has been active in the field of experimental studies of cubic nonlinear optical properties of molecules and materials for over two decades and has been concentrating, among others, on providing data on dispersion of cubic hyperpolarizabilities of molecules (especially organometallic molecules). The introduction to this presentation will include remarks on the practical goals in investigations of the cubic nonlinearity. They are many reasons for the practical interest in this property. The imaginary part of the cubic nonlinear susceptibility (and the imaginary part of the cubic hyperpolarizability on a molecular scale) leads to nonlinear absorption while the real part is related to nonlinear refraction. Both effects have potentially many applications, however, the Holy Grail of modern photonics: all-optical switching of telecommunication signals, remains elusive due to the difficulties of obtaining nonlinear materials with the right values of suitable merit factors.

Systematic studies of the complex cubic hyperpolarizability carried out using the Z-scan technique with high-power low repetition rate femtosecond laser pulses have led to the determination of the dispersion curves for a number of interesting structures. However, the understanding of the obtained relationships remains far from satisfactory. Since both the real and imaginary part of the hyperpolarizability are determined, it is tempting to treat them in terms of the Kramers-Kronig relation, but this leads to a number of conceptual and practical difficulties.

Even for relatively simple molecules like ones considered in a recent paper [1], the use of quantum chemistry approaches has not been easy and the results are not complete. While it is possible to compute the spectra of the two-photon absorption, full hyperpolarizability dispersion curves remain a hitherto unachieved target of theoretical approaches.

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Quantum modelling in support of chemical intuition – case studies in inorganic chemistry

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In this account we describe three cases where quantum modelling substantially supports chemical intuition, and is used to predict the structure (crystal or molecular) and selected properties of as-yet unknown $AgSO_{4(s)}$ and $AuF_{(s)}$ (in the solid state) and $CsFHeO_{(g)}$ (molecular entity), while encouraging experimentalists to synthesize these species.

$AgSO_4$ is an example of a compound with a d–block element in an unusual oxidation state (+2), where substantial delocalization of an unpaired electron is expected over the sulfate ligands [1a]. The DFT-screening of various hypothetical crystal structures [1b] suggests that $AgSO_4$ should adopt a structure which exhibits: (i) magnetically isolated Ag(II) centers (with no direct Ag–O–Ag bridges), (ii) Ag centers coordinated by O atoms at *ca.* 2.1–2.2 Å in a square-planar fashion (iii) no terminal O atoms on sulfate anions. The formulation as $Ag(I)_2S_2O_8$ or $Ag(I)[Ag(III)(SO_4)_2]$ may safely be excluded and $AgSO_4$ should be a genuine paramagnetic sulfate of Ag(II). These predictions will be confronted with the recent experimental findings [2].

AuF, despite its seemingly simple chemical formula, the presence of an accessible (+1) oxidation state of gold and its similarity to the known AgF, has never been synthesized. It is an example of a compound with a nominally closed d–shell, where relativistic effects leading to d-s mixing are expected to greatly influence energetics and properties. Our calculations, based on a 'follow the imaginary phonon' algorithm, predict that synthesis of AuF should be possible from $Au + \frac{1}{2}\ AuF_3$ precursors at pressures above 23 GPa [3a], and will be made more facile by addition of elemental xenon (formation of a XeAuF intermediate [3b]).

CsFHeO is yet another fascinating story [4]. This molecule is formally an adduct of CsF with the unstable HeO molecule or a cesium salt of the previously theorized $OHeF^-$ anion; our CCSD(T) calculations predict a very short 1.162 Å He–O bond length indicating covalent bonding. CsFHeO should be protected from more stable decomposition products by sizeable barriers, with the smallest barrier (towards He and CsOF) comparable to the energy of the F–He–O bending fundamental. Metastability should lead to an experimentally measurable lifetime, rendering CsFHeO as the first candidate for a neutral molecule containing a chemically bound He.

Following successful preparation of $AgSO_{4(s)}$, now $AuF_{(s)}$ and $CsFHeO_{(g)}$ await synthesis.

Acknowledgements: Calculations were performed at the ICM Supercomputer Center.

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Harnessing molecular motion for materials design

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I will describe recent applications of High Performance Computing for the design of materials for electronics and health. The focus is on atom-scale simulations that reveal the underlying mechanisms for molecular recognition and self-assembly in "bottom up" nanofabrication.

Atom-scale molecular dynamics and free energy calculations were used [1] to describe the discriminating capacity of the "molecular printboard" soft-lithography technology for patterning molecules with nano-scale resolution. Discrimination is obtained via a combination of single-site binding free energy differences, multiple (multivalent) binding events and conformational penalties, rationalising the observed patterning. A combination of atom-, meso- and macro-scale modelling was used [2] in combination with spectroscopic experiments to describe the kinetics of molecular motion along multivalent surfaces.

A related technology, microcontact printing, relies on the deposition of sharp self-assembled monolayer (SAM) patterns on gold using alkanethiol "ink" molecules. Simulations on the order of one million atoms [3] reveal that naturally-occurring SAM domain boundaries impede the diffusion of excess ink molecules and can, in some cases, permanently trap excess inks. There is competition between ink spreading and ink trapping, with the ink/SAM interaction strongly dependent on both the ink concentration and the SAM orientation at domain boundaries. SAM defects thus provide potential diffusion barriers for the control of excess ink spreading, and simulations also illustrate atom-scale mechanisms for the repair of damaged areas of the SAM via self-healing. Trapping is discussed in relation to experimental efforts to reduce molecular spreading on SAMs for the creation of ultrahigh resolution nanopatterns.

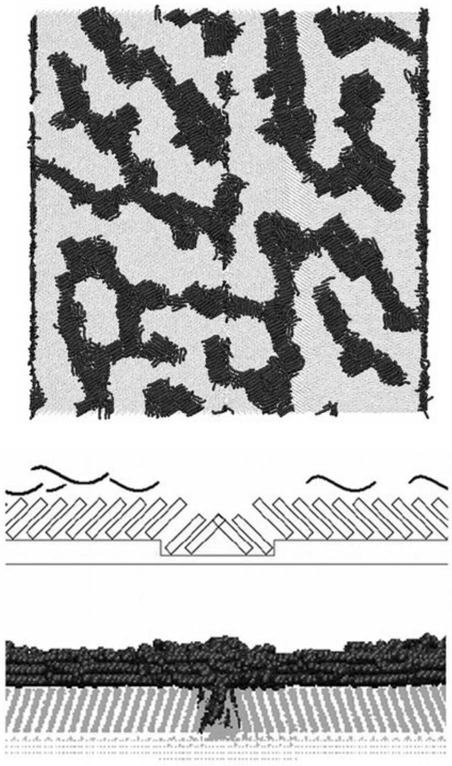

Fig. 1: Million-atom simulation of excess molecules diffusing on a defect self-assembled monolayer surface.

Acknowledgements: Travel support from Enterprise Ireland (EI) project ORD3D is acknowledged, together with research funding from EU projects FP6 NaPa and FP7 FunMol. Calculations were performed using Science Foundation Ireland (SFI)-supported computing resources at Tyndall National Institute and at the Irish Centre for High-End Computing (ICHEC).

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Causality analysis of proton transfer processes in molecular systems - a novel methodological approach

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Detecting causal relations in structural changes of (bio)molecular systems from MD, QD or QCMD simulation data is of crucial importance for the description of molecular mechanisms and understanding the logic of their functioning (see e.g. [1,2]). Time-dependent atomic positions, momenta, forces or their functions are treated as signals. Quantum degrees of freedom can also be incorporated in the analyses. In larger systems selection or construction of most important information channels to be analyzed is a nontrivial mathematical and computational problem.

A computational platform, *CausalMD*, for the time-series analysis extracted from MD simulations was designed using *Mathematica 7*. Three different methodologies were implemented: a conventional Granger causality method, a Multi-Variate Autoregressive Model (MVAR) with a Directed Transfer Function (DTF) method, and a nonparametric wavelet approach. Development and validation of the mentioned above methodologies to proton transfer process in malonaldehyde will be presented. Also, a Car-Parrinello and Born-Oppenheimer molecular dynamics studies of the intramolecular vibrational mode-sensitive double proton-transfer mechanisms in porphycene [3] will be discussed.

Acknowledgements: Studies supported by MNiSW - grant N519 384736. Calculations were carried out in CoE BioExploratorium, ICM and Juelich Supercomputing Centre.

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Efficient calculation of isotope effects for large molecules

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The calculation of isotope effects requires the knowledge of the vibrational frequencies of the system under study. To obtain the frequencies, the Hessian is calculated, which is a time consuming task. This is almost impossible for large systems. When QM/MM methods are applied this can only be done by the finite difference method, since analytical second derivatives are not available.

In our new approach we make use of the Teller-Redlich rules [1]. The isotope effect is calculated as a product of ratios of the frequencies from the two isotopomers. We exploit the fact that many of these factors are 1, because the frequency does not change with the isotopomers.

Applying an eigenvector following method [2] we selectively calculate those frequencies that yield a factor not equal to 1. This results in a considerable reduction of computational cost. Depending on the number of contributing frequencies we reduce the computational cost by a factor of 2 to 10.

An important part of our new method is the identification of the frequencies that contribute to the isotope effect. To this end we analyze the frequencies calculated with a low-level method, typically MM. The identified normal modes are then used as an input for the eigenvector following method.

Our new method has two advantages over the state-of-the-art method of the partial hessian. Firstly, we obtain correct frequencies. Secondly, our method is able to reproduce even the frequencies of delocalized normal modes.

Acknowledgements: Daniel Rohr gratefully acknowledges financial support from the German Research Foundation (DFG) under grant number 3894/1-1

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A combined charge and energy decomposition scheme for analysis of chemical bonds and reaction paths

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In the present work we have introduced a new scheme for the electronic structure analysis by combining the Extended Transition State (ETS) method [1] with the Natural Orbitals for Chemical Valence (NOCV) [2]. The ETS-NOCV [3] charge and energy decomposition scheme makes it not only possible to decompose the deformation density, $\Delta\varrho$, into the different components (such as σ, π, δ, etc.) of the chemical bond, but it also provides the corresponding energy contributions to the total bond energy. Thus, the ETS-NOCV scheme offers a *compact*, qualitative and quantitative, picture of the chemical bond formation within one common theoretical framework. The applicability of the ETS-NOCV scheme is demonstrated for various types of covalent and donor-acceptor bonds. We also included the applications involving inter- and intra-molecular (agostic) hydrogen bonding (see Figure below). Finally, we will show that ETS-NOCV can be used not only to analyze the stationary points on PES, but its is also able to describe the changes in electronic structure along the reaction paths. Decomposition of energetic reaction barrier into the stabilizing (electronic and electrostatic) and destabilizing (Pauli repulsion and geometry reorganization) components will be discussed in a detailed way for the examples of reactions of industrial importance.

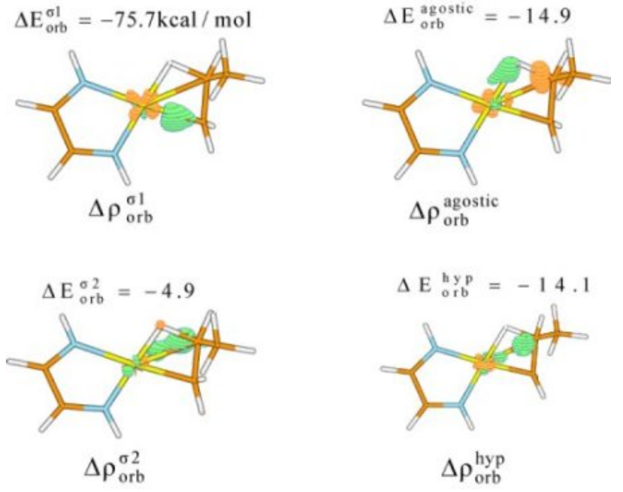

Fig. 1: The contours of relevant deformation density contributions, $\Delta\varrho_{orb}^{\sigma 1}$ and $\Delta\varrho_{orb}^{agostic}$, describing the bonding between the cationic nickel based fragment and the n-propyl group together with the corresponding energies obtained from ETS-NOCV scheme [3].

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The self-capacitance density of atoms and molecules based on electronic cloud deformation analysis

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The electronic stress tensor has proven to be a useful tool for analysis of electronic structures and properties of atoms, molecules and nano-size systems. Since it can be estimated at every point in space it is very convenient for characterization of local electronic environment. It is shown here that self-capacitance at atomic scale can be derived from electronic stress tensor. The capacitance C of a charged system determines the specific amount of work per unit charge required to bring a fixed amount of charge from the vacuum level to the system in question. The regional chemical potential expressed in terms of energy density, resulting from internal stresses of electronic charge is used to calculate the capacitance density in the system. The regional electronic chemical potential represents the effective potential experienced by associated electron density. The chemical potential also measures the tendency of particles to diffuse (a function of spatial location). The capacitance of nanoscale systems depends on the amount of charge in the system. Thus, the self-capacitance can be rewritten as a function of the local energy density and electron density. The calculated capacitance reproduces very well the relative global hardness of atoms and molecules.

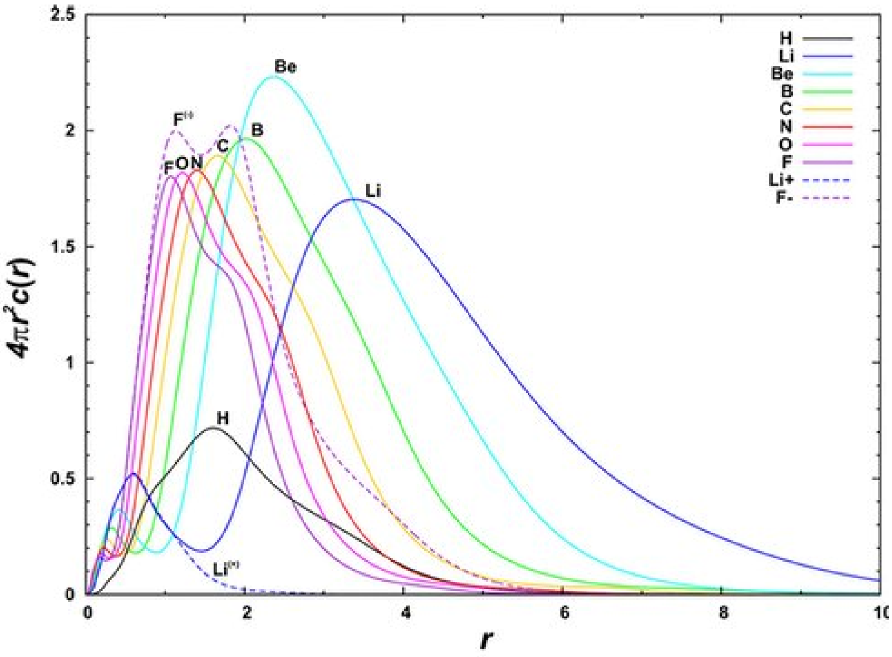

Fig. 1: Radial distribution of spherically averaged capacitance density for main group elements (in a.u.).

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

Modeling of G-protein coupled receptors and shared mechanisms of their activation

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To explore how a subtle alteration of the ligand structure influences the receptor destiny we investigated two concurrent processes: the final steps of ligand binding in the receptor binding site and the initial steps of receptor activation. To trace such early activation steps the membranous part of the receptor was built on an inactive receptor template while the extracellular loops were built using the *ab initio* CABS method. We used the simulated annealing procedure for ligand docking and all-atom molecular dynamics simulations for finding the immediate changes in the structure of the ligand-receptor complex. Binding of an agonist, contrary to antagonist, induced breaking of the 3-7 lock (a hydrogen bond D3.32-Y7.43) between helices TM3 and TM7 (Fig. 1). We also observed an action of the extended rotamer toggle switch which can suggest interdependence between those two switches.

Sensing mechanisms proposed so far estimated activation effects on the basis of still structures of complexes of receptors with docked ligands. Here, based on molecular dynamics (MD) simulations of complexes of the tightly related pair of compounds, we provide further support for our earlier proposition [1, 2] of a sensing/activation mechanism for opioid receptors DOR, KOR, and MOR. For the first time, using MD simulations, it was possible to explain different properties of a structurally similar pair of ligands: 5'-GTNI is a potent antagonist of kappa opioid receptor (KOR) while 6'-GNTI is a potent agonist of the same receptor [3].

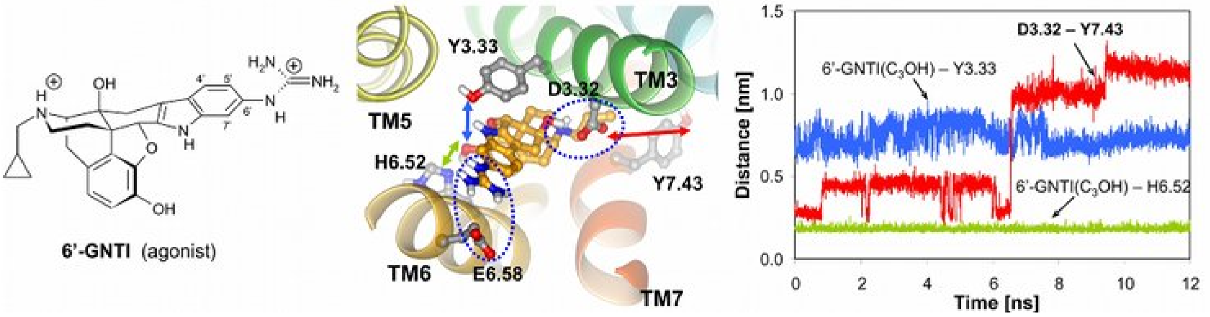

Fig. 1: The early activation step, breaking of 3-7 lock, in KOR by an agonist 6'-GNTI.

Acknowledgements: Support from Polish Ministry of Science and Higher Education grant no. N N301 2038 33 is acknowledged.

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Environmental influences on the aromaticicies of nucleobases and amino acids

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Environment influence on aromaticities of canonical nucleobases and aromatic amino AIDS were quantified in terms of geometric (HOMA) and magnetic (NICS) indices. Different surroundings were taken into account as polarity of the environment, protolytic equilibriums, explicit interactions with solvent molecules in micro-, oligo- and poly-hydrated conditions as well as direct interactions via hydrogen boding and stacking contacts. Besides native protein and B-DNA interiors were analysed in details by means of quenching MD and hybrid QM/MM methods. Not only significant environment influences on aromaticities were noticed but also heterogeneities of aromaticity indices were found as consequences of direct interactions with molecular neighbourhood. Polar environment usually increases aromatic character of both pyrimidine and imidazole rings. Protolytic equilibriums are also important especially in cases where exocyclic groups are involved. Furthermore, environment effects of protein and DNA are non-negligible sources of aromaticity changes imposed on aromatic rings of nucleobases and amino acids residues. Base-base stacking interactions usually increase aromatic character of nucleobases in analysed conformations, while hydrogen boding reduces aromaticities with respect of isolated monomers. Cooperativity of hydrogen-bonding and stacking interactions on aromaticities are also discussed. According to obtained results these two effects are additive and can be separated each from other.

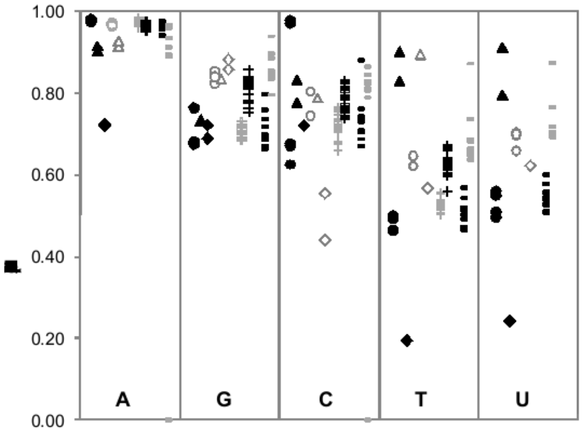

Fig. 1: Values of structural index of aromaticity (HOMA) estimated for pyrimidine rings of neutral (circles), protonated (triangles) and deprotonated (diamonds) forms of nucleobases, nucleosides and model nucleosides. Series marked with dash stands for HOMA values influenced by direct interactions of nucleobases with small molecule as water, ammonia, HCl and HF. Black symbols represent gas phase geometries, while gray symbols denote structures obtained after full gradient geometry optimization in the presence of water field (CPCM). Series denoted by plus signs represent values estimated based on QM/MM method for explicit water (gray) and B-DNA (black) environments, respectively.

Acknowledgements: Results were obtained the part of computational grant no 39 of Poznań Supercomputing and Networking Center (Poznań, Poland). The allocation of computational facilities are greatly appreciated.

Understanding structure-activity relationship of FAAH inhibitors by QM/MM mechanistic modelling

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Fatty acid amide hydrolase (FAAH) is a member of the amidase signature family that inactivates signaling lipid amides, including the endocannabinoid anandamide [1]. Alkyl carbamic acid biphenyl-3-yl esters, including the reference inhibitor URB597, irreversibly inhibit FAAH by carbamoylation of the active serine (S241) with concurrent expulsion of a biphenol [2,3]. Carbamate reactivity can affect compound pharmacokinetics and its propensity to react with off-targets. The introduction of an electron-donating group on the biphenyl scaffold can increase electron density around the carbamate carbon, thus reducing its propensity to react with nucleophiles. In fact, the introduction of a 4-hydroxyl group on the proximal phenyl ring of cyclohexylcarbamic acid biphenyl-3-yl ester increases carbamate stability, both in alkaline buffer and in rat plasma, and it significantly reduces rat liver carboxylesterase inhibition [4].

On the other hand, the same substitution does not affect FAAH inhibition, thus leading to a new inhibitor (URB694) with improved *in vivo* potency and selectivity *vs.* putative off-targets.[4] The reason why FAAH shows limited sensitivity to modulation of carbamate electronic density is investigated by combined quantum mechanics/molecular mechanics (QM/MM) approach, modeling the carbamoylation of FAAH by URB694 and its related analogues at B3LYP/6-31G+(d)//PM3-CHARMM level.

Results of the simulations and their agreement with experimental data will be presented and discussed.

Acknowledgements: Calculations were performed at the Centre of Computational Chemistry, University of Bristol.

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Development of small molecules targeting menin-MLL interaction in leukemia

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The interaction of menin with MLL fusion proteins has been validated as a new therapeutic target for leukemias with MLL translocations. Using both the fragment-based screening and High Throughput Screening (HTS) we identified several classes of lead compounds which interact with menin and inhibit menin interaction with MLL fusion proteins both *in vitro* and in human leukemia cell lines. These compounds represent the first small molecule inhibitors of the menin-MLL protein-protein interaction. In addition to the high therapeutic value, our studies demonstrate how a combination of different approaches: biophysical, biochemical, medicinal chemistry and cell biology can result in successful lead identification and lead development for protein-protein interactions in the absence of structural data for the protein target. Medicinal chemistry efforts are currently underway to convert these compounds into new potential drug candidates for leukemia treatment. These efforts are supported with rational design using computational ligand-based drug design methods. The step-by-step procedure of lead identification and lead development process for a new protein-protein interaction will be demonstrated. We believe that a similar methodology can be successfully applied to develop novel lead candidates targeting other protein-protein interactions of therapeutic value.

Acknowledgements: Support from the Leukemia and Lymphoma Society (LLS TRP 6070-09), NIH (R03 MH084875), and the Department of Pathology, University of Michigan, is acknowledged.

NMR in rational drug design for protein-protein interactions

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Development of small molecule inhibitors of protein-protein interactions requires multidisciplinary approaches and combination of experimental and computational methods. NMR spectroscopy is one of the most versatile techniques used for ligand development. We will present several NMR-based approaches to support targeting protein complexes in leukemia. Rigorous biochemical studies revealed that interaction of menin with LEDGF and MLL fusions represents an essential step in development of leukemias with translocations of MLL gene. To target LEDGF interactions with menin and MLL we employed fragment based screening using both, computational and NMR experimental screening. Subsequently, to identify the binding modes for experimentally determined ligands we carried out docking using the crystal structure of LEDGF and NMR chemical shift perturbations. Analysis of the experimental and computational docking will be compared. We will also demonstrate the application of NMR techniques to identify inhibitors of the menin-MLL interaction where the crystal structure is not available. The applications range from verification of hits from HTS, epitope mapping for the active compounds, and the design of bidentate analogs. Altogether, we will demonstrate that involvement of NMR into the multidisciplinary drug discovery projects is essential to develop compounds with potent biological activities.

VoteDock: the consensus docking method for prediction of protein-ligand interactions

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Molecular recognition plays a fundamental role in all biological processes, which is why great efforts have been made to understand and predict protein-ligand interactions. Finding a molecule that can potentially bind to a target protein is particularly essential in drug discovery, although experimental techniques are still expensive and time-consuming. Thus, in silico tools are frequently used to screen molecular libraries in order to identify new lead compounds [1]. If information about protein structure is known, various protein-ligand docking programs can also be used [2,3].

The aim of docking procedure is to predict correct poses of ligand in the binding site of the protein, as well as to score them according to the strength of interaction in a reasonable time frame. The purpose of our studies was to present the novel consensus approach to predict both protein-ligand complex structure and its binding affinity. Our method, called VoteDock, uses as the input the results from seven docking programs (Surflex, LigandFit, Glide, GOLD, FlexX, eHiTS and AutoDock) that are widely used by community, as most of them are part of popular modeling software packages like Sybyl, Discovery Studio or Maestro. Those programs were evaluated on the extensive dataset of 1300 protein-ligands pairs from refined set of PDBbind database[4], for which the structural and binding affinity data are available. We compared independently ability of proper scoring by calculating Pearson correlation between docking score and experimental binding affinities, and posing by measuring RMSD of obtained conformations with native structure. That procedure allows us to compare performance of individual programs with that of VoteDock.

In most cases our consensus-based method was able to dock properly about 20% of pairs more than docking methods in average, and more than 10 % of pairs more than single best program. Also drop in RMSD of top scored conformation can be observed, with value 0.5Å lower than that of best individual program, namely GOLD. Similar increase in overall docking accuracy can be also observed for subsets created based on PDBbind, that explore various physico-chemical properties of ligands, their size or hydrophobic potential. Finally, we are able to boost the Pearson correlation of the predicted binding affinity in comparison to the experimental value up to 0.5, although scoring functions used as an input could not exceed 0.4 value.

Acknowledgements: Calculations were performed at the Interdisciplinary Center for Mathematical and Computational Modelling. This work was supported by Polish Ministry of Science and Higher Education N301 159735 grant.

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Reaction force analyses of energetic molecule decomposition

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The concept of the reaction force provides a rigorous basis for analyzing the course of a chemical process [1,2]. This presentation will apply the reaction force to five possible decomposition processes.

Three of these will be the nitro/*aci* tautomerizations of picric acid (2,4,6-trinitrophenol), trinitromethane and trinitromethanol [3]. The other two will be internal rearrangements of pentaerythritol tetranitrate (PETN) and its remarkedly sensitive silicon analogue Si-PETN [4].

Acknowledgements: We gratefully acknowledge the support of this work by the Defense Threat Reduction Agency, through Contract No. HDTRA-07-1-0002, Project Officer Dr. William Wilson.

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The thermodynamic and kinetic description of the reactions of the organometallic complexes

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The interaction of the derivatives of cisplatin (diammine-dichloro-platinum(II) complex) with amino acids were explored in various environment. Similarly, the hydration process of cisplatin was re-considered compared with an aquation reaction, which can be considered as an activation of these metallodrugs.

Detailed mechanism of the adduct formation of diaqua-tetrakis-μ-acetatodirhodium to purine DNA bases is examined using ammonia and guanine 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 as well as kinetic data for the ammonia interaction with Rh-complex demonstrate presence of a enhanced reaction mechanism in acidic environment.

Comparison of different ruthenium complexes in the process of activation was performed. Replacement of the chloro-ligand in $[Ru(II)(Arene)(en)Cl]^+$ and $Ru(II)(Arene)(PTA)Cl_2$ was examined together with cisplatin “reference” complex. Obtained results clearly demonstrate correlation between bond strength of the Ru-Cl coordination and reaction barrier of the metallocomplex.

Proton transfer dynamics in strong hydrogen bonded systems

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

The rapid development of computer power with efficient codes as well as theoretical models 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 molecular mechanics (Force Fields) is not able to take into account large electron distribution 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. In contrary to the classical molecular dynamics the CPMD calculations do not require an a priori determined model interaction potential because the internuclear forces for each configuration of nuclei are calculated from the first principle – the model Hamiltonian is defined in the density functional theory formalism. The quantum behavior of proton from a hydrogen bridge as well as remaining heavy atoms can be taken be means of the path integration molecular dynamics (PIMD).

The chemical systems with strong single or double O-H. . . O hydrogen bonds are very common in many chemical and biological systems. In the lecture results of CPMD and PIMD calculations will be presented for model systems with the O-H. . . O bonds like dimers in the gas phase, small clusters and crystals of mono- and dicarboxylic acids. Moreover, the examples of proton transfer in strong intramolecular O-H...O and N-H...N will be presented. The classical and quantum nature of bridged proton will be discussed.

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Some applications of molecular volumes in materials science

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Molecular volume is not a physical observable, but nevertheless is a very useful property [1]. Since it does not have a rigorous basis, it can be defined functionally, as appropriate for a particular application. Two such applications, both very important in the design of energetic materials, are in predicting (a) both molecular and ionic crystal densities [2,3], and (b) sensitivities toward impact [4]. The definition and use of molecular volume for these purposes will be described.

Acknowledgements: We gratefully acknowledge the support of this work by the Defense Threat Reduction Agency, through Contract No. HDTRA-07-1-0002, Project Officer Dr. William Wilson.

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Structural properties of nucleic acid bases in polar environment

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Nucleic acid bases uracil, thymine, cytosine, guanine and adenine represent one of the main constituents of nucleic acids. They play very important role in structure and functioning of this vital type of biopolymers. Therefore structure and properties of bases are the focus of experimental and theoretical studies for many years.

Isolated molecules were investigated by almost all available modern quantum-chemical methods. It was established that in equilibrium geometry it is observed clear localization of endocyclic double bonds in uracil, thymine, cytosine and guanine reflecting tetra- and dihydroaromatic character of pyrimidine ring. Adenine contains aromatic conjugated π-system leading to delocalization of the electron density. However, appearance of polar environment, for example, water surroundings, results in significant polarization of bases leading to redistribution of the electron density and change of geometrical parameters. Degree of such polarization depends on number and location of bonded water molecules. Formation of complete water shell around nucleobases results in significant contribution of zwitter-ionic resonant forms into total structure of all molecules except adenine. This leads to shift of structure of pyrimidine ring to aromatic in uracil and thymine, and 1,4-dihydroaromatic for cytosine and guanine accompanied be enolization of carbonyl groups.

Significant polarization of nucleic acid bases by polar environment causes considerable changes of structural properties of molecules. It was demonstrated that pyrimidine rings in all nucleobases possesses high conformational flexibility, Change of value of relevant endocyclic torsion by $\pm 20^{\circ}$ results in energy increase less than 1 kcal/mol for uracil, thymine and cytosine, 1.5 kcal/mol for guanine and 2 kcal/mol for adenine. Polarization of nucleobases by water surroundings leads to considerable decrease of conformational flexibility of pyrimidine ring in all molecules except adenine due to significant contribution of less flexible aromatic or dihydroaromatic resonant forms of ring. In the case of adenine it is observed some increase of flexibility.

It should be noted that modeling of polarizing environment of nucleobases by closed chain of water molecules leads to similar results as it is obtained from Car-Parrinello molecular dynamics simulation. Application of polarized continuum model of solvent results in the same trend of nucleobase polarization but with considerably weaker manifestations.

Resonance Raman spectra in detecting nerve agents

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A detailed theoretical investigation has been carried out at the density functional level of theories to investigate the nature of Raman intensities of the –P=O stretching mode of a model nerve agent DFP (diisopropylfluorophosphate) when bound to different gold (Au_8, Au_{20}) and oxide-supported gold ($MgO\ldots Au_4$, $CaO\ldots Au_4$, $TiO_2\ldots Au_4$, $Al_2O_3\ldots Au_4$, $M_{16}O_{16}\ldots Au_8$, and $[M_{16}O_{15}\ldots Au_8]^{2+}$, M = Ca, Mg) clusters. All of these clusters and the DFP bound clusters are fully optimized and the computed energetics shows that DFP attaches itself weakly to these clusters. The normal Raman spectra calculations on these clusters show that there is substantial enhancement of the –P=O stretching mode of DFP compared to the isolated species. This enhancement has been found to be due to the polarization of the –P=O bond of DFP when bound to the clusters. Significant enhancement in intensity has been observed in the case of $Au_n\ldots DFP$ (n =8, 20), $M_{16}O_{16}\ldots Au_8\ldots DFP$, and $[M_{16}O_{15}\ldots Au_8]^{2+}\ldots DFP$ (M = Ca, Mg) clusters. The resonance Raman calculations on the $Au_n\ldots DFP$ (n =8, 20) reveals that this enhancement could be made quite large and selective – a feature which is unique to the nerve-agents and could be used as a property for detecting them.

Simulations of nucleic acid vibrational spectra

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Vibrational spectra of nucleic acids contain rich information on their structure and conformations. Furthermore, due to a wide availability and relatively fast acquisition time vibrational spectroscopy becomes especially useful for structural studies of biomacromolecules. However, it is not trivial to extract the structural information from the spectra due to their complexity, large bandwidth, many overlapping bands and coupling of vibrations. Therefore, interpretation of spectra and establishing a reliable spectra-structure connection can be a tedious task resulting in ambiguous results.

We have developed a method allowing reliable simulation of vibrational spectra of relatively large nucleic acid fragments as well as other biomolecules.[1] Such simulations can not only streamline the interpretation of the spectra, but often clarify the ambiguity in assigning a particular spectrum to a particular structure as well as provide a vast information on the energetics of different conformers and interaction with the ligands, obtained from the first principles.

A brief explanation of the methodology will be presented along with several examples of its application for simulations of the infrared (IR) and vibrational circular dichroism (VCD) spectra of various nucleic acid structural forms.

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Crystal structure prediction of molecular compounds – beyond proof of concept

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Crystal structure prediction is a challenge of significant industrial importance that provides a stringent test for a diverse set of modelling techniques, ranging from high-level ab initio calculations over force fields to global search algorithms.

Many properties of crystalline molecular materials, such as solubility, dissolution rate, density or colour depend not only on the molecular geometry but also on the crystal packing. The ability of one and the same molecule to crystallize in different crystal packings, known as polymorphism, provides an opportunity for fine tuning properties, but also presents a threat when it comes to producing materials with well-defined characteristics. The early identification of the thermodynamically most stable crystal form is of particular importance in the pharmaceuticals industry.

At the last blind test on crystal structure prediction[1,2] held in 2007, for the first time a single method, implemented in the GRACE program, correctly predicted the crystal structures of all 4 test compounds. Using the method, first a tailor-made force field[3] (TMFF) is generated for every molecule to be considered by fitting all force field parameters consistently to a balanced set of reference data generated by dispersion-corrected density functional theory calculations[4] (d-DFT). Combining the TMFF with a Monte Carlo parallel tempering algorithm, crystal structures are generated, minimized and ranked according to their lattice energy. The best candidate structures are ranked again with higher accuracy at the d-DFT level.

Various aspects of the computational approach will be discussed, and extensive validation material will be presented, including past blind tests, paracetamol, work only confidential pharmaceutical compounds and work in progress on molecular salts.

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RNA 3D structure prediction: from comparative to de novo modeling

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RNA is a large group of functionally important biomacromolecules. In striking analogy to proteins, the function of RNA depends on its structure and dynamics, which in turn is encoded in the linear sequence. There are numerous methods for computational prediction of protein 3D structure from sequence, with comparative modeling being the most reliable approach if a structure of a related molecule is available. However, there are very few such methods for RNA. We have developed tools for 3D modeling of RNA structure: ModeRNA for comparative modeling and SimRNA for de novo modeling.

As an input, ModeRNA requires a 3D structure of a template RNA molecule, and a sequence alignment between the target to be modeled and the template. ModeRNA can model post-transcriptional modifications, a functionally important feature analogous to post-translational modifications in proteins. ModeRNA can also model DNA structures or use them as templates. It is equipped with many functions for merging fragments of different nucleic acid structures into a single model and analyzing its geometry, and can build models of very big molecules, such as ribosomal RNAs (>1000 nucleotides). The program is available free of charge at http://iimcb.genesilico.pl.

SimRNA is a coarse-grained method for simulating RNA folding. It employs a reduced representation (3 atoms per nucleotide), a statistical potential derived from a database of known structures as an energy function, and a Monte Carlo searching scheme. It can model RNA structures based solely on sequence information, but the simulation can be also restricted by user-defined restraints. SimRNA-generated structures of low energy are often very similar to the native structure. These tools will be useful for studying sequence-function relationships in RNA molecules.

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Protein structure determination based on fragmentary experimental measurements

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Conventional methods for protein structure determination require collecting huge amounts of high-quality experimental data. For a successful NMR experiment a vast number of experimental restraints, both for backbone and side chain atoms must be measured. In our work we combined Rosetta simulation protocol with data resulting from different types of experiments focusing on yet unexplored techniques such as Solid State NMR. In the first phase Rosetta builds low resolution models using Monte Carlo fragment assembly and a coarse grained energy function. In a subsequent step these models are refined using a combinatorial side-chain optimization and gradient-based minimization of all torsional degrees of freedom in an all-atom force field. Combination of this protocol with several different kinds of experimental data, such as RDC, NOE and Chemical Shifts (CS) has already proven to be very successful [1].

Here we focus on the very initial step of the protocol: preparation of the fragment database. The new algorithm allows one use experimental data to guide the fragment search process. We also focused on novel types of experiments: Solid-State NMR, disulphide bond location, Electron Microscopy and H/D exchange. The resulting short peptides (from 3-mers to 15-mers) whose conformation agrees with the experimental data are subsequently used by the Rosetta protocol to build protein models. The data is also used in the modeling step to guide the Monte Carlo search.

In our work we provide an initial demonstration that local backbone information acquired in solid-state NMR experiments may be used to obtain protein structures without the need for measuring interatomic distances. Additional experimental data, such as H/D exchange may be used for further refinement.

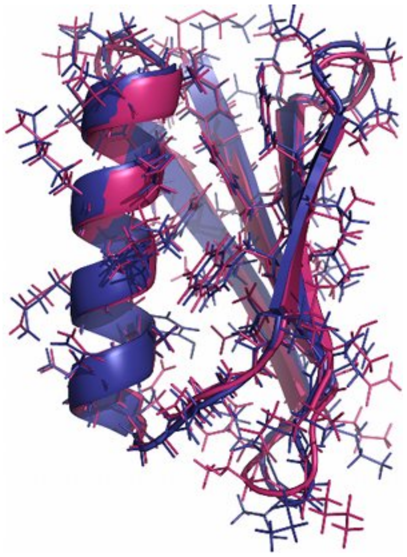

Fig. 1: Lowest energy model (blue) of the GB1 protein, solved solely with backbone-only information (CS + TEDOR data), deviates only 0.8Å from the native structure (red)

Acknowledgements: Support from Marie Curie fellowship (FP7-people-IOF) is greatly acknowledged.

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Theoretical prediction of selectivities in nonreversible and reversible hydroformylation reactions catalyzed by unmodified Rh-carbonyls

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Under Rh-catalyzed hydroformylation conditions, the alkene insertion into the Rh–H bond, which gives rise to alkyl-metal intermediates, can be a reversible or nonreversible step, depending primarily on the temperature and the substrate nature. At 100 °C β-hydride elimination occurs for various substrates, such as ethyl vinyl ether, 1-hexene, allylethylether, styrene and other aromatic substrates. While for aliphatic vinyl and allyl alkenes the β-elimination involves both alkyl intermediates, for aromatic substrates mainly concerns the branched ones [1].

Experimental results, obtained for regio- and diastereoselectivities in Rh-catalyzed hydroformylations and deuterioformylations of a variety of unsaturated substrates using unmodified Rh catalysts, are compared with values computed in the density functional theory (DFT) framework at the B3P86/6-31G* level, employing effective core potentials for Rh in the LanL2DZ valence basis set.When the isomeric alkyl metal intermediate formation is nonreversible; the selectivity for alkyls reflects the selectivity for the aldehydes: the differential stability of all the relevant alkyl rhodium transition states (TS) determined with computational methods turns out to be in good agreement with the experimental data obtained under mild reaction conditions. A significant split between theory and experiment is conversely obtained for hydroformylations of vinylidenic olefins, such as 1,1-diphenylethene, carried out at high temperature, where β-hydride elimination can take place rendering reactions reversible. The investigation of further steps of the reaction mechanism was thus necessary, as well as the inclusion of zero point and thermal corrections. The calculations, performed on 1,1-diphenylethene that yields almost exclusively linear aldehydes, allowed us to put forward a novel explanation for that behavior [2]. The approach of the fourth CO group to the tricarbonyl intermediate to produce the tetracarbonyl one, a step usually overlooked in the literature because of the tetracarbonyl Rh intermediate remarkable stability, proceeds with a barrier in the branched isomer, but not in the linear one.

A similar behavior, observed for a number of other substrates, is also reported and discussed.

Acknowledgements: Calculations were performed at the MML of the IPCF-CNR.

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How the Co-C Bond is cleaved in coenzyme B_{12}-dependent mutases

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Detailed theoretical and X-ray based structural analysis has been carried out in order to unmask the role of the tyrosine residue (Y) in the activation of the Co-C bond in AdoCbl-dependent mutases. In particular, methylmalonyl-CoA mutase (MCM) and glutamate mutase (GLM) enzymes have been studied; in the case of MCM, the significance of the Y89 residue has been analyzed extensively. Three different theoretical platforms encompassing the DFT, CASSCF/QDPT2, and QM/MM frameworks have been employed to elucidate the energetics of the AdoCbl-Y^- complex while taking into account a varied degree of structural complexity. The diradical state, $[\mathrm{AdoCbl}]^{\bullet -}$-$Y^{\bullet}$, has been found to be the lowest electronic state of the AdoCbl-Y^- complex, providing strong evidence that electron transfer from the Y89 residue to the cofactor is feasible. Crystallographic analysis of the active sites of MCM and GLM enzymes reveals that substrate binding can play a critical role in displacing the hydroxyl proton of Y residue (Y89 in the case of MCM enzyme and Y181 in the case of GLM enzyme) that will facilitate the electron transfer (ET), hence making the activation process a case of proton-coupled electron transfer (PCET). PCET-inspired enzymatic catalysis implies that the cleavage of the Co-C bond takes place in a one-electron reduced form of the AdoCbl cofactor (i.e. $[\mathrm{AdoCbl}]^{\bullet -}$), rather than neutral analogue, thus providing an efficient mode of cleavage that can help in understanding the origin of the catalytic effect in such enzymes.

Isotopic fractionation calculations of reactions between environment pollutants and permanganate

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Due to its low cost and high activity, permanganate is frequently used in remediation of spots polluted with organic pollutants such as VOC, VOC-Cl, PCB, and many others. However, details of reactions between these pollutants and permanganate are not fully understood. We have therefore modeled several of these reactions in order to characterize their mechanisms as well as expected isotopic fractionation. The results of these calculations will be presented and discussed.

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DFT studies on the reaction mechanisms of intra- and extradiol dioxygenases

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The catalytic reaction mechanisms of several different ring-cleaving dioxygenases, catalyzing intra- and extradiol type cleavage, have been studied with the hybrid density functional method B3LYP. The studied biocatalysts include: Fe(III)-dependent protocatechuate dioxygenase (PCD), Fe(II)-dependent 2,3-homoprotocatechuate dioxygenase (HPCD), Fe(II)-dependent homogentisate dioxygenase (HGD), and Mn(II)-binding homoprotocatechuate 2,3-dioxygenase (MndD). In addition, a functional Fe(III) model complex for intradiol-cleaving dioxygenases has been studied with the same computational methods.

The selected systems perform oxidative ring fission by which both atoms of dioxygen are incorporated into the acyclic products, i.e. an important step in the metabolism of aromatic compounds. Models of active sites in enzyme-substrate complexes, with up to 90 atoms, have been used to characterize the structures and energetics of stationary points along the reaction paths. Synthesis and comparison of the available results, which is provided in this contribution, yields valuable insights into the catalytic strategies utilized by these enzymes, e.g. revealing the factors controlling the type of the cleavage reaction, i.e. intra- or extradiol.

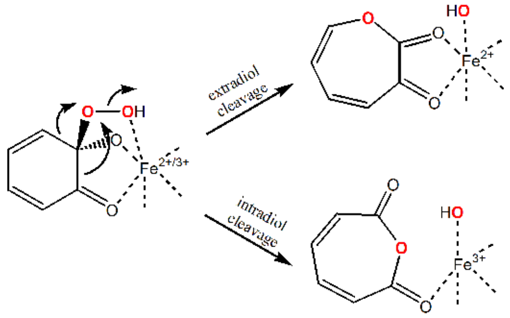

Fig. 1: Intra- and extradiol cleavage reactions catalyzed by catachol dioxygenases.

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Computational mutation of enzymatic reactions: QM/MM studies

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Large-scale quantum chemical calculations for more than ten thousands atomic systems are now possible with the QM/MM method. Our studies on metalloenzymes such as methane monooxygenase, cytochrome P450, heme oxygenase, dopamine β-monooxygenase, and tyrosinase are presented. These metalloenzymes involve metal-oxo species in their active intermediates in most cases. The reactivity of the metal-oxo intermediates can be predicted from the oxygenation activity of the bare transition metal-oxo species such as FeO^+ and CuO^+ [1,2]. In this talk our recent a mutation analysis using QM/MM computations of coenzyme B_{12}-dependent diol dehydratase is presented [3-5]. Mutants His143Ala, Glu170Gln, Glu170Ala, and Glu170Ala/Glu221Ala are considered to estimate the impacts of the mutations of His143 and Glu170. The results are in good agreement with a real mutation analysis based on biochemical techniques, which encourages us to theoretically design a man-made enzyme that has high performance compared to a natural enzyme.

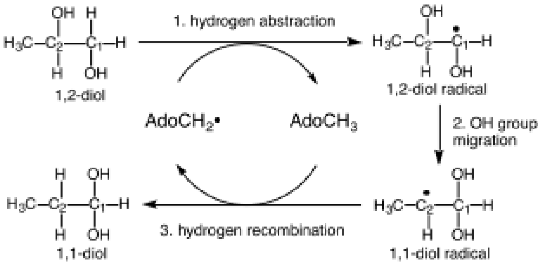

Fig. 1: Proposed catalytic action of diol dehydratase.

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Promoting carbon-carbon formation - the holy grail in the design of enzymes and organocatalysts

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The selective formation of carbon-carbon bonds is of fundamental importance in organic synthesis. Over the last decades there has been a continuous development of metal-based catalyst for this purpose. In recent years the focus has shifted from catalysts based on palladium and nickel to less expensive and more environmentally benign metals, such as copper and iron. However, the development of effective metal-free organic catalysts and biocatalysts for the same purpose could further reduce the cost and environmental impact of producing synthetic building blocks for the chemical industry.

The Diels-Alder reaction is probably the most important reaction for producing ring and cage structures via carbon-carbon bond formation. Despite the reaction's great versatility and extraordinary stereoselectivity, it rarely appears in nature. However, recent studies have shown that it can be catalyzed by organic hydrogen bond donors. We have utilized high-level quantum chemical and density functional theory methods to investigate how the electronic and steric properties of organic catalysts can be fine-tuned to optimize their catalytic efficiencies. Using this information we have attempted to redesign a lipase for efficient catalysis of the Diels-Alder reaction. On the basis of a combination of quantum chemical calculations in model systems and full protein molecular dynamic simulations, we have found that a redesigned enzyme can provide transition state stabilization of similar magnitude as the best organic hydrogen bond donors. Still the enthalpic stabilization is limited to 4-5 kcal/mol and is easily overshadowed by the entropic cost of bringing the reactants together at the catalytic site. Our kinetic analysis clearly shows that optimization of substrate binding and the choice of solvent is crucial for effective catalysis. We demonstrate that a double mutant of the Candida antarctica lipase B is capable of producing catalytic rate enhancements of 10^3, which are two orders of magnitude higher than the best organic catalyst.

We also present recent results that a lipase can catalyze formation and breaking of carbon-carbon bonds via a lyase mechanism in substrates with a nitrile moiety. Interestingly both experiments and computations show that catalysis requires a nonpolar solvent. Molecular dynamics simulations demonstrate that solvents of low polarity induce structural changes in the active site geometry that result in substrate binding and activation. Subsequent quantum chemical calculations based on the MD structures reveal the details of the catalytic mechanism. The computational results together with experimental findings indicate that the entire catalytic machinery of the lipase, including both the catalytic triad and the oxyanion hole, participates in the catalysis of the promiscuous reaction.

Theoretical design of new biological catalysts

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The methods and techniques of Computational Chemistry have become a promising complementary tool to design biological catalysts. An alternative computational protocol is presented in this communication and, although containing some limitations, it sorts out the difficulties present in previous strategies. This is based on Molecular Dynamic simulations that, combining quantum mechanics and molecular mechanics (QM/MM) methods, allows obtaining the TS of the chemical reaction in the presence of a completely flexible protein environment. All the specific substrate-protein interactions that are established in the active site of the enzyme can be analyzed, both at the Michaelis complex and at the real TS, which is not necessary equal to the TSA structure obtained by X-ray diffraction. The knowledge of this pattern of interactions will provide clues to decide which residues of the active site of a protein should be replaced to better stabilize the TS relative to the Michaelis complex, which would presumably enhance the rate constant of the chemical step of a full catalytic process. Nevertheless, as all these peaces are part of a complex puzzle, it is not possible to predict that a single mutation was going to produce a rate enhancement of the chemical reaction without side part effects. In this regard the free energy profile can be traced from reactants to products, via the corresponding TS, rending theoretical predicted barriers comparable with experimental data and allowing testing directed mutations. This theoretical strategy can be considered as a numerical experiment helping experimentalists in active-site redesign by means of a few mutations. Some efforts in this direction will be presented.

The starting point of our protocol is the X-ray structures of a protein scaffold that presented a threshold value of catalytic activity for a certain chemical reaction. In particular, we are using Catalytic Antibodies, that are able to catalyze chemical reaction by their presumably affinity for the TS [1, 2] or enzymes capable of catalyzing secondary reactions [3, 4]. Since the catalytic efficiency of both kind of proteins are still far behind primary reactions catalyzed by natural enzymes, the target will be to obtain novel enzymes with new catalytic functions.

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Theoretical studies on the ethylene polymerization catalyzed by half-metallocene Ti(IV) complexes with aryloxo ligands

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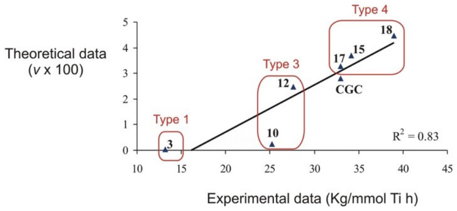
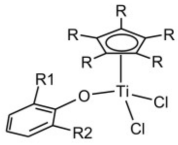
Density functional theory based computational methods have been applied in the mechanistic studies of the ethylene polymerization processes catalyzed by the half-metallocene titanium (IV) complexes with different ligands. In particular, a special attention has been paid to the catalysts with aryloxo ligands due to their activity in the high-temperature polymerization and co-polymerization experiments.

The main goal was to rationalize the changes in activity for the systems with different substituents on the phenoxo ligand. For comparison, a well-known constrained-geometry-catalyst (CGC) was also included in the investigated set of complexes. The results reproduce the experimental trends: it has been found that the activity of systems with a single substituent in the ortho position of the phenyl ring (*asymmetric systems*) is comparable to that of CGC, while the complexes with two substituents at both ortho-carbon atoms (*symmetric systems)* are substantially less active. Further, it has been shown that an unique feature of the asymmetric complexes is an energetic preference of the back-side pathway of the ethylene insertion. In contrast, a preference of front side insertion is observed for the symmetric complexes as well as for CGC. The origin of this preferences was investigated using the ETS-NOCV method applied for the respective transition states. It was found that the final preference of the backside or front-side transition state comes as a balance between the electronic preference of the former, and the steric preference of the latter. Thus, the unique energetic preference of the backside insertion observed for asymmetric catalysts appears as a result of reduced steric crowding. The openness near the metal center and the conformational flexibility leads to enhanced catalytic activity of those systems. It was further shown that at the *free-energy* level, due to *entropic* destabilization of the backside transition state, the front side insertion becomes viable.

It has also been demonstrated that a rotation of the aryloxo ligand around the Ti-O-C bonds is feasible; it allows for easy transformation between the non-reactive and reactive isomers/pathways. Results of static DFT calculations were supported by Molecular Dynamics (MD) simulations, performed at the semiempirical (MSINDO) and the *ab initio* (CP-MD) level.





R	R1	R2	Complex	
H	Pr^i		**3**	Type 1
Me	H		**10**	Type 3
	Pr^i		**12**	
Me	H	Me	**15**	Type 4
	H	Pr^i	**16**	
	H	Bu^t	**17**	
	H	Ph	**18**	

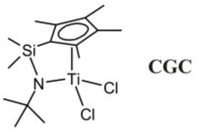


Fig. 1: Theoretical vs. experimental activity of the complexes studied in the present work.

Properties of two-dimensional polymer-solvent systems. A Monte Carlo study

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In this work we investigated the percolation in two-dimensional systems containing long flexible polymer chains with explicit solvent molecules. The polymer chains were represented by linear sequences of lattice points restricted to a two-dimensional triangular lattice. The Monte Carlo simulations were performed applying the cooperative motion algorithm (CMA) [1]. The percolation thresholds and the critical exponents of chains and solvent molecules were determined and the influence of the chain length on the percolation was discussed. It was shown that the percolation threshold deceased strongly with the chain length what is closely connected with changes of chains' structure with the decreasing polymer concentration [1,2]. The critical exponents for all chains under consideration and for solvent molecules were found almost constant and close to the theoretical values [3]. The structure of percolating clusters was also determined.

Acknowledgements: This work was supported by the Polish Ministry of Science and Education grant N N507 326536.

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Structural studies on glycosylated gen. 3.5 PAMAM dendrimers

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Dendrimers are macromolecules that are considered as potential medicines that display polyvalency but also share properties with low molecular molecules (e.g. low viscosity). Monosaccharide modified polyamidoamine (PAMAM) dendrimers have been reported to have immunomodulatory activity which can prevent the progress of LPS triggered inflammatory responses [1]. It is thought that this activity is due to the interactions of the dendrimer with the cell membrane TLR4-MD2 complex. The divergent synthetic strategy used in the conjugation of the saccharide molecules allows the loading of these dendrimers to be chemically determined, but their exact position on the dendrimer cannot be determined. Therefore, we have developed a method that allows the *in silico* generation of initial 3D models of the modified dendrimers.

The electronic properties of these molecules were studied and the Frontier Molecular Orbital theory was used to understand the saccharide loading and distribution on the modified dendrimer's surface. Conformational flexibility and the potential availability of the sugars for possible interactions with the protein target were studied by the molecular dynamics of fully solvated molecules. Molecular properties were estimated for all generated structures. The representative conformations of flexible glycosylated dendrimers were used in rigid docking studies with MD2, a component of the LPS recognition system. Since dendrimers are not proteins, several software packages were used to understand the basis of their biological activity.

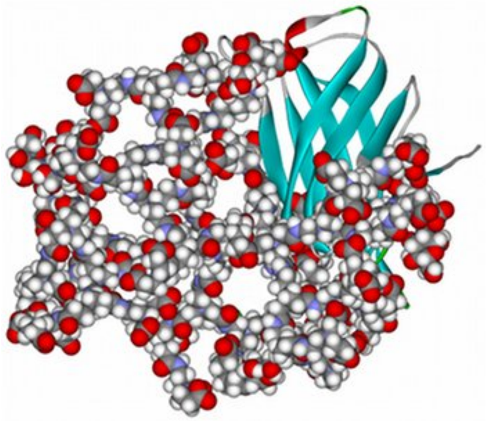

Fig. 1: Tentative model of MD2 and Dendrimer with 8 glucosamine molecules. Docking study performed with PatchDock1.0 and visualised with DS Visualiser2.5.

These studies are beginning to provide a better understanding of the mechanism of action of saccharide modified PAMAM dendrimers, and will aid the design and synthesis of new more potent dendrimers with improved molecular properties.

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Steered MD simulations of adhesive protein contactin

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Contactins are axonall cell adhesion molecules belonging to the immunoglobulin superfamily (Ig-CAMs). These proteins, present in various regions of the brain, are closely connected with the functioning of the nervous system. Contactins are characterized by the presence of six Ig-like domains (Fig. 1), four fibronectin type III-like repeats, and a glycosylphosphatidylinositol (GPI)-anchoring domain. Contactin 4 (CNTN4, BIG-2) is one of the six members of the contactin family. It has been shown that it is crucial for the formation and maintenance of functional odor map in the olfactory bulb [1]. The human CNTN4 was also identified as a candidate gene responsible for 3p deletion syndrome [2]. Moreover, it seems that mutations affecting CNTN4 function may be relevant to Autism Spectrum Disorder pathogenesis [3].

We are using the Steered Molecular Dynamics (SMD implemented in NAMD code) method in order to understand better nanomechanical properties of this modular protein. In SMD external forces are applied to the simulated biopolymer to probe its mechanical strength as well as to accelerate processes that are otherwise too slow to be observed. These simulations mimic single molecule experiments such as Atomic Force Microscopy or Optical Tweezers.

Results of over 220 nanosecond simulations of both FNIII and IgC2 domains will be presented and discussed (Fig. 2). In particular we are trying to correlate observed mechanical unfolding pathways of individual domains with their amino acid sequences.

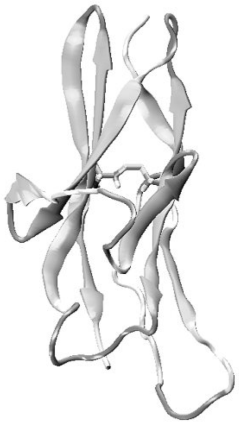

Fig. 1: Domain IgC2$_1$ CNTN4.

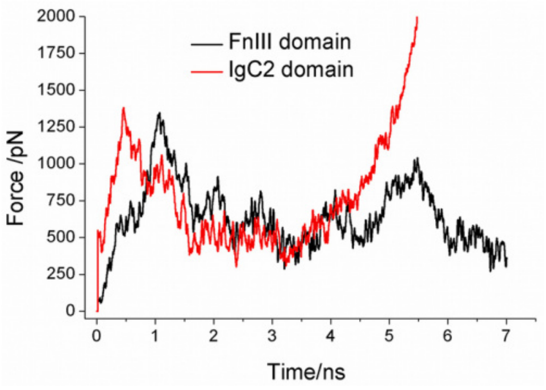

Fig. 2: Force vs. time plots of two different types of CNTN4 domains.

Acknowledgements: Support from Polish Funds for Science (grant No. N202 262038 and nationwide license for Accelerys software) is acknowledged. Calculations were performed at the Computational Center TASK in Gdańsk.

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Squalene epoxidase as target for new hypocholesterolemic drugs

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Increased concentration of cholesterol in blood is one of the most important risk factors for development of arthrosclerosis It can can cause many others severe problems, like myocardial infarction, hypertension, or ischemic stroke, and therefore may further lead to patient's death. Educational campaigns addressing that problem to public are often repeated, yet the number of people with obesity (Body Mass Index over 30) is staidly increasing every year. According to the prognosis of WHO more than 800 million obese people is estimated in 2015. Therefore, the high interest is now paid on development new drugs that inhibit endogenous production of cholesterol.

Squalene monooxygenase (epoxidase) is one of the crucial enzymes taking part during cholesterol synthesis. The enzyme is responsible for adding oxygen atom to squalene creating epoxide between the second and the third carbon atoms of substrate. The activity of enzyme is down-regulated by the cholesterol concentration in cell. Cholesterol molecule binds to allosteric site of the enzyme, blocking the squalene to bind to the active site, therefore stopping the entire reaction. Because the structure of epoxidase is not known, neither in human, nor mammal, thus the detailed mechanism of the reaction is not yet confirmed on molecular level. Moreover, the lack of three dimensional structure makes it impossible to utilize ligand docking techniques in order to select further candidates for new inhibitors.

The purpose of our work was to first build the high quality three dimensional model of human squalene epoxidase by homologue modeling techniques. Template identification was done using 3DJury MetaServer [1], than protein model was prepared using Modeller software. The four carbon cores were proposed based on visual inspection of the active site, then using LEGION a combinatorial library was built for each of them. Two docking programs, namely Surflex and GOLD, were used for the virtual screening procedure. In addition, the consensus based scoring approach improved our initial results allowing for selection of the most promising drug candidates. The scores of new inhibitors were compared with those obtained by docking dodecyl gallate, which is known to have activity toward rat epoxidase [2]. The consensus scoring using rank-by-rank approach the set of promising inhibitors for human squalene epoxidase is proposed.

Acknowledgements: Calculations were performed at the Interdisciplinary Center for Mathematical and Computational Modelling. The authors would like to thank Kamil Steczkiewicz and Łukasz Kniżewski for help during the preparation of this work, which was supported by OxyGreen (KBBE-2007-212281) 6FP projects and the Polish Ministry of Science and Higher Education N301 159735 grant.

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Brownian dynamics study of the association between the 70S ribosome and elongation factor G

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Ribosomes are massive supramolecular assemblies ($\sim$ 200Å in diameter) of proteins and RNA. Bacterial ribosomes (Fig. 1) consist of three RNA chains and over 50 different proteins constituting two subunits, named 30S and 50S, according to their sedimentation coefficients.

The role of the ribosome is to translate the genetic information stored in the mRNA into a polypeptide chain of specific sequence. mRNA comprises a series of codons that dictate to the ribosome the sequence of amino acids in the synthesized polypeptide chain. Using the mRNA as a template, the ribosome traverses each codon of the mRNA, pairing it with the amino acid provided by the tRNA. There are three specific RNA binding sites located on the ribosome (Fig. 1). The A site binds an aminoacyl-tRNA, the P site binds a peptidyl-tRNA and the E site binds a free tRNA before it exists the ribosome. Protein synthesis on the ribosome involves a number of protein factors that bind at its functional sites. One example is the elongation factor G (EF-G) (Fig. 1) that promotes the translocation of the newly formed peptidyl-tRNA from the A site to the P site, together with its associated mRNA.

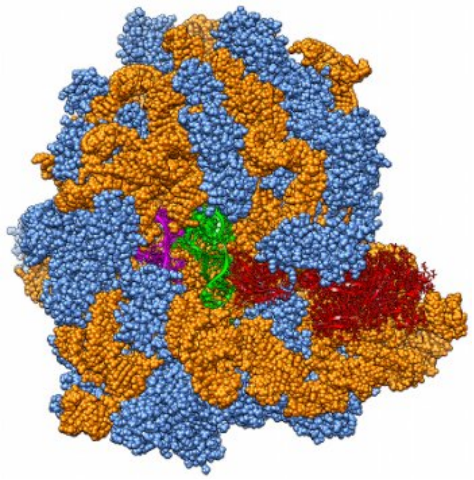

Fig. 1: An atomic model of the bacterial (70S) ribosome. Ribosomal proteins are shown in blue; ribosomal RNAs are shown in orange. The tRNA molecules occupying the ribosomal A and P sites are shown in green and magenta, respectively. The EF-G protein is shown in red.

We apply Brownian dynamics to study the mechanism and kinetics of association of EF-G with the bacterial (70S) ribosome. Our simulations use full-atom description of rigid molecules and mesoscopic solvent characterized with the Poisson-Boltzmann model. A number of still unanswered questions are the EF-G/ribosome recognition and the EF-G association pathway, especially due to high negative charge of associating molecules (the overall charge of the ribosome is $\sim$–3800e with a significant surface density of negative charges; the overall charge of the EF-G is $\sim$–22e). The size of the studied system (the ribosome alone consists of over 250'000 atoms) poses a great challenge for modeling studies not only regarding the computer time and resources, but also analysis.

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Poster abstracts

in alphabetical order of the leading author's last name

Poster session A - July 5 (Monday)
Posters: P1-P33

Poster session B - July 6 (Tuesday)
Posters: P34-P66

Identification of protein-protein complexation area

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The technique to recognize the protein-protein interaction in complex creation based on the hydrophobicity distribution is presented. The homodimers available in PDB were selected to analyse the residues responsible for complexation.

The distribution of the hydrophobicity density ($\tilde{H}o_j$) in the protein molecule is expressed by the function presented by Levitt [1]:

$$\tilde{H}o_j = \frac{1}{\tilde{H}o_{sum}} \sum_{i=1}^{n} \left(H_i^r + H_j^r\right) \begin{cases} \left[1 - \frac{1}{2}\left(7\left(\frac{r_{ij}}{c}\right)^2 - 9\left(\frac{r_{ij}}{c}\right)^4 + 5\left(\frac{r_{ij}}{c}\right)^6 - \left(\frac{r_{ij}}{c}\right)^8\right)\right] & \text{for } r_{i,j} \le c \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

where H_i^r expresses the hydrophobicity of i-th residue the and r_{ij} denotes the distance between effective atoms of i-th and j-th residue.

The theoretical hydrophobicity distribution is expressed by the three-dimensional Gauss function generating the “fuzzy oil drop” [2]:

$$\tilde{H}t_j = \frac{1}{\tilde{H}t_{sum}} \exp\left(\frac{-(x_j - \bar{x})^2}{2\sigma_x^2}\right) \exp\left(\frac{-(y_j - \bar{y})^2}{2\sigma_y^2}\right) \exp\left(\frac{-(z_j - \bar{z})^2}{2\sigma_z^2}\right) \tag{2}$$

where $\tilde{H}t_j$ expresses the theoretical hydrophobicity in the (x_j, y_j, z_j) point and $(\sigma_x, \sigma_y, \sigma_z)$ expresses the standard deviations for the directions x, y and z respectively, what measures the size of drop.

The ”fuzzy oil drop” is defined in analogy to the ”oil drop” model expressing the hydrophobic core responsible for tertiary structure of proteins [3].

Both hydrophobicity values: observed and expected are normalized. The discrepancies between these two dispersions identifies the specificity of particular protein:

$$\Delta\tilde{H}_j = \tilde{H}t_j - \tilde{H}o_j \tag{3}$$

The irregularities ($\Delta\tilde{H}_j$) expressed by the hydrophobicity deficiency are interpreted as the potential ligand binding area ($\Delta\tilde{H}_j > 0$). The residues representing the excess of hydrophobicity ($\Delta\tilde{H}_j < 0$) - particularly localized on the protein surface are interpreted as the potential area for protein-protein interaction.

The sensibility and specificity of the method was verified using the ROC curves for the homodimers database derived form PDB. The examples of homodimers of high and low accordance with model will be presented.

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Method development for glycosylated PAMAM dendrimer 3D structure generation

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Mono-saccharide modified polyamidoamine (PAMAM) dendrimers have been reported to have immuno-modulatory and anti-angiogenic activity that can prevent the progress of inflammatory responses [1]. It is thought that dendrimer interactions with the LPS recognition system may be responsible for its activity. End-group conjugation of the saccharide to the dendrimer can to be estimated, but the position of the saccharide moieties cannot be determined since only a fraction of the end groups are derivatised with the saccharide. To aid in the efforts to determine structure activity relationships (SAR), computational methods have been developed to generate defined 3D models of the saccharide modified dendrimers.

The hyper-branched structure of PAMAM dendrimers is derived from a diaminobutane core. Repetitive units form branches that are capped at the surface with carboxylates. The morphology of the dendrimer structure can be seen as a sequence of interconnected monomers.

The geometry and electronic properties of the monomers within the dendrimer are not known due to the absence of experimental structural data. A set of *ab initio* and molecular mechanics calculations was conducted to evaluate the geometric parameters of a 3-D structure. Topology and parameter files were written and the 3-D structures were generated with XPLOR-NIH (Figure 1).

The 3-D structures of the glucosamine modified PAMAM dendrimers are providing insight about the structural properties of these molecules. These computational efforts are designed to enable us to understand the possible interactions of our dendrimers with the cell membrane TLR4-MD2 complex. This method can be used to build other types of hyper-branched dendrimers to provide a basis to help predict the interactions of different hyper-branched macromolecules through the sequential assembly of their building blocks.

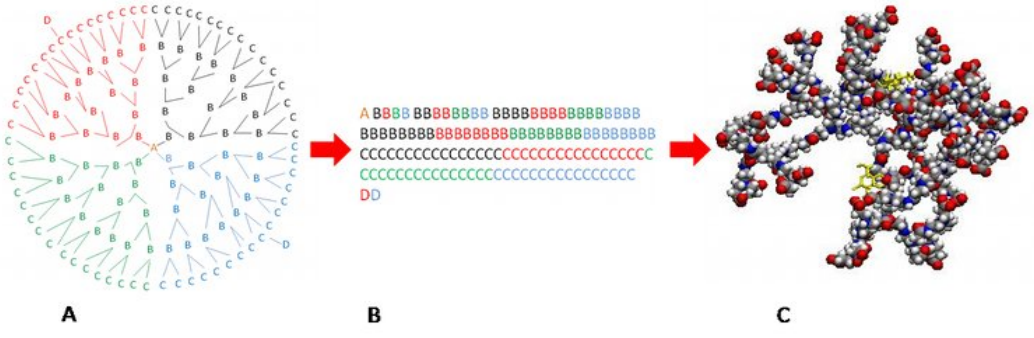

Fig. 1: Schematic representation of the method to generate 3D structures of the glucosamine dendrimers. A – Hyperbranched structure represented with the one letter code subunits; B – Corresponding sequence introduced in Xplor-NIH; C – 3D structure generated by Xplor-NIH.

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The influence of current type on photocatalytic performance of MAO-derived nano/micro-structured titania films

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In this research, porous TiO_2 layers were grown on the titanium substrates via micro arc oxidation (MAO) process under direct and pulse currents. Three sodium phosphate solution with a concentration of 10 g.l^{-1} was utilized as electrolyte. Scanning electron microscopy (SEM) was employed to investigate surface microstructure of the fabricated samples. It was revealed that the pore size increased with the applied voltage; moreover, the layers synthesized under pulse current consisted of finer pores, and applying higher frequencies and/or lower duty cycles resulted in decreasing the pores size. Phase structure of the layers was studied by X-ray diffraction (XRD) technique. The TiO_2 layers consisted of anatase and rutile phases fraction of which was observed to vary with the electrical parameters. The highest anatase/rutile relative content was obtained in the layers which were grown under pulse currents, especially those synthesized at the frequency of 500 Hz, duty cycle of 5%. This parameter, which determines the photocatalytic activity of the layers, increased with the applied voltage, reached its maximum value at intermediate voltages, and, then, decreased at high voltages. Finally, photocatalytic performance of the layers was studied by measuring the degradation rate of methylene blue on their surface under UV illumination. The layers grown with applying pulse current exhibited higher photoactivity due to their higher effective surface area and anatase relative content when compared to the layers synthesized under direct current.

Accuracy of molecular properties estimated from atomic multipole expansions

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Intermolecular interaction energies can be partitioned into several parts, among which electrostatic component is most frequently the major one. In addition, the electrostatic term can be approximated using multipole expansions. However, *molecular* multipole moments describe reasonably various properties such as electrostatic potentials or interaction energies only at large distances.

This problem can be solved by partitioning the electron density into smaller, for example *atomic* segments, enabling reliable results at shorter intermolecular distances of chemical interest. Previously reported results have usually been obtained in limited basis sets and for short multipole expansions, however, which sometimes does not fully represent the complex topology of molecular charge distributions, requiring the use of higher order polarization functions and multipole expansions of sufficient length.

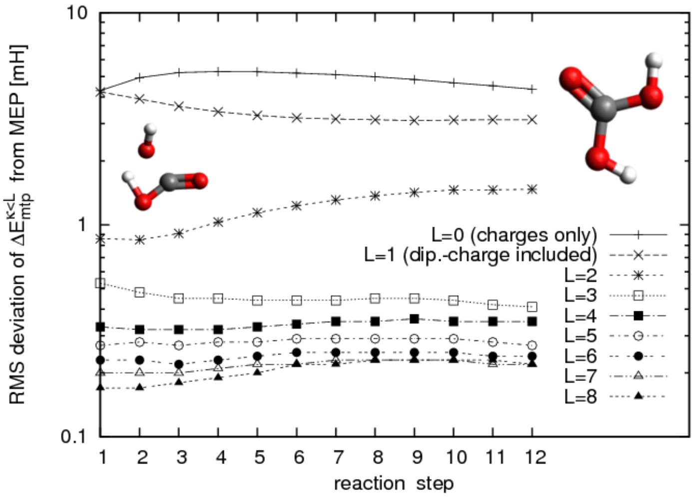

Fig. 1: Deviation of the multipole-derived electrostatic potential $\Delta E_{\mathrm{mtp}}^{\kappa<\mathrm{L}}$ compared to its ab initio value on the Connolly surface [3] along the reaction path of carbon dioxide hydration. Here L denotes the order at which the multipole expansion was truncated.

The aim of the present study is the systematic analysis of errors resulting from the choice of basis set and from the truncation of higher order atomic multipole moments. Calculations have been performed using recently developed software [1] that utilizes cumulative atomic multipole moments (CAMM) up to an order of 16 [2]. Our preliminary tests involved the molecular electrostatic potential (MEP) of water and hydrogen sulfide molecules. Fig.1 on the other hand demonstrates the order of error to be expected when approximating the MEP in this way along a reaction path.

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Estimation of anharmonic amide modes in the Kohn-Sham limit using the polarization consistent basis sets

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Organic chemists often use computational chemistry to predict and support IR spectral analysis. The accuracy of theoretical prediction depends critically on the used method and completeness of the basis set. Hence, calibration of the theoretical methods is crucial and depends on reliable experimental parameters of small molecules, preferably in the gas phase or in inert solvents. Although scaling of harmonic frequencies computed even at the Hartree-Fock level gives reasonable results, the developments of hardware and software are allowing the *a priori* prediction of anharmonic wavenumbers. Obviously, in more accurate theoretical studies the effect of solvent should be included.

Second-order vibrational perturbation theory (PT2) [1] combined with density functional theory (B3LYP) was used to estimate anharmonic amide I, II, III and A modes of formamide and *trans* *N*-methyl acetamide (*trans*-NMA) in the Kohn-Sham (KS) complete basis set limit (CBS). Polarization consistent pc-n ($n = 0, 1, 2, 3, 4$) basis sets were used [2, 3], and the results fitted with simple mathematical formula. Calculated vibrational frequencies (wavenumbers) were compared with those obtained using Pople's basis sets up to 6-311++G(3df,2pd) and experimental values (Figure 1).

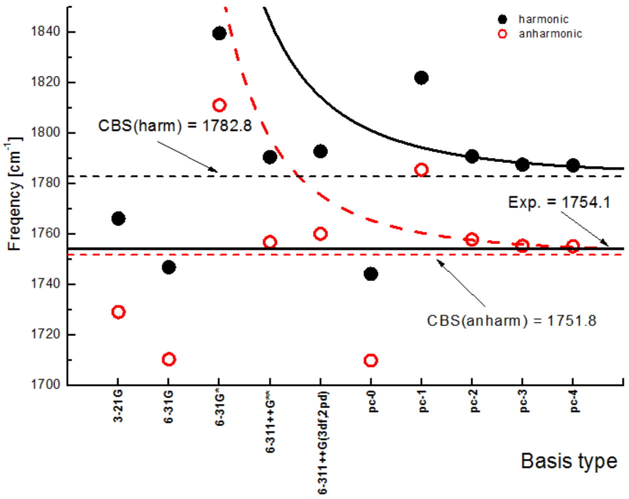

Fig. 1: Convergence of harmonic and anharmonic AI mode in formamide.

The results confirm a very good performance of pc-n basis sets in computing anharmonic amide modes. The obtained frequencies both in the gas phase and in solvents (chloroform and water) show very good agreement with the experimental data. The convergence of harmonic and anharmonic frequencies with respect to basis set size shows that pc-n basis sets consistently performs better than other alternatives.

Acknowledgements: Aneta Buczek is a recipient of a Ph.D. fellowship from a project funded by the European Social Fund. Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

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Geometry and electronic structure of the A-cluster in acetyl-CoA synthase

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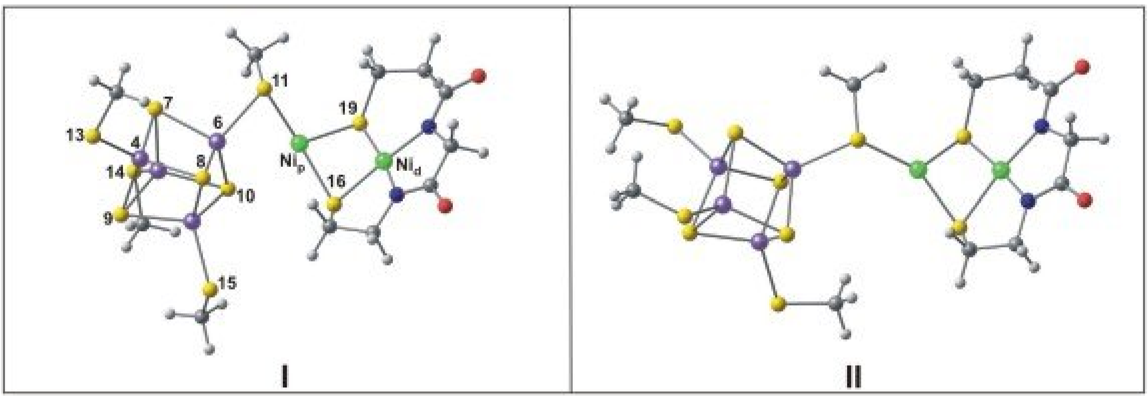
Acetyl-CoA synthase catalyses the synthesis of Acetyl-CoA from CoA, CO and methyl group. Methyl group comes from $CH_3CoFeSP$, which contains methyl-cobalt-corrinoid unit. A-Cluster consists of Fe_4S_4 cubane linked to dinuclear nickel complex: Fe_4S_4 - Ni_pNi_d, where Ni_p amd Ni_d denote nickel atoms proximal and distal to the cubane, respectively.

The geometry of the A-Cluster was optimized with the use of DFT/OLYP method. Two main structural conformations were found, closed (I) and open (II). The effect of polar environment on the geometry was studied with the use of PCM solvation model. Geometry of A-Cluster with ligands bound to Ni_p was also optimized for ligands: CH_3, H, CO and H_2O. Atomic charges and spin densities of A-Cluster in different oxidation states were analyzed.



Non-empirical quantum chemical studies on electron transfer mechanism in platinum(II) anticancer complexes

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In this work we searched for theoretical confirmation of new hypothesis proposed by Lu et al. [1,2] that cisplatin biological activity could be determined by processes based on dissociative electron transfer (ET) mechanism. Authors challenged the paradigm that initial bioactivation step rely on hydration reactions going according to associative SN2 ligand exchange. Instead, they postulated that the crucial for cisplatin activity are electron-induced reactions leading to transition products with unpaired electron (radical) as it was given by equation (1), where ep^- is a prehydrated electron:

$$\begin{aligned} ep^- + \mathrm{Pt(NH_3)_2Cl_2} &\rightarrow [\mathrm{Pt(NH_3)_2Cl_2}]*^- \rightarrow \mathrm{Pt(NH_3)}^{\cdot} + \mathrm{Cl}^- \\ ep^- + \mathrm{Pt(NH_3)_2Cl} &\rightarrow [\mathrm{Pt(NH_3)_2Cl}]*^- \rightarrow \mathrm{Pt(NH_3)}^{\cdot} + \mathrm{Cl}^- \end{aligned} \tag{1}$$

The above mode of reactions of trans- and cisplatin with free (ep-) as well as with hydrated electrons (e^-aq), were the subject of our QM calculations. The electronic structure for molecular systems has been studied at non-empirical level by using density functional (DFT) or Moeller-Plesset (MP2) methods within the correlation consistent cc-pVTZ [3] basis set and GAUSSIAN-09 program package [3].

As a result, it was shown that cisplatin vs. transplatin behaviour differs significantly when both compounds react with aquated electron. The noticed differences might be related to disparities in biological action of cis/trans isomers if ET mechanism was accepted.

Acknowledgements: The numerical calculations have been performed in part at Wrocław Networking and Supercomputing Center.

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Developing Monte Carlo methods for modelling reaction mechanisms

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Multiscale quantum mechanics / molecular mechanics (QM/MM) simulations provide a useful tool for the investigation of the mechanism of enzyme-catalysed reactions [1]. Sampling of the configurational space of the system is typically performed using molecular dynamics simulations. However, these simulations are constrained by the high computational cost of evaluating the QM forces on the atoms. This limits the timescale of the simulations, typically to no more than a few nanoseconds even with approximate QM/MM methods.

Monte Carlo (MC) methods could provide a route to increasing the amount of sampling performed during a QM/MM simulation [2]. Recently we developed a QM/MM MC method [3] and free energy calculations for the perturbation of water into methane in explicit water, and of relative hydration free energies of organic solutes, have given promising results. These calculations were based on a multi-level MC move which used an MM potential to guide sampling of a QM/MM Hamiltonian [3]. In this work we have developed the algorithm of QM/MM MC simulation for reacting systems.

An archetypal enzyme-catalysed reaction is the Claisen rearrangement of chorismate to prephenate, which is catalysed by the enzyme chorismate mutase. This reaction occurs as part of the Shikimate pathway in fungi, bacteria and higher plants. This relatively simple, single-step reaction, proceeding in the same way in both gas-phase and solution, has been investigated in detail using QM/MM MD simulations [4].

We have applied our QM/MM MC method to the reaction of chorismate to prephenate. We have compared MC sampling against MD sampling for both gas-phase and explicit water simulations. The novel method of sampling using different z-matrix templates along the reaction coordinate reproduces MD geometries for both of these environments. This demonstrates that MC methods can be used to sample phase space of the reaction. The results are promising in indicating that high-level QM/MM MC methods can provide effective methods for computational enzymology.

Acknowledgements: We thank the EPSRC for funding this work and the Centre for Computational Chemistry at the University of Bristol for providing computer resources.

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Recognition of 8-oxoguanine, isoguanine and 8-oxoadenine via proteins direct readout

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Protein–DNA recognition plays an essential role in many vital processes as for example DNA replication, repair, regulation of gene expression, protein folding and other activities of cellular machinery. Regulatory proteins are known to possess remarkable recognition specificities originating both from direct protein-DNA contacts and indirectly through the conformational properties of the DNA strands. Specific interactions between protein and DNA are called direct readout. The most significant contributions come from electrostatic interactions between charged groups, hydrogen bonding, stacking, van der Waals and hydrophobic interactions.

The aim of this project is energetic and structural quantification of recognition patters of selected oxidized purines in their most abundant tautomeric forms. Modified nucleobases mentioned in the title occur spontaneously in cellular DNA under circumstances promoting oxidative stress. Thus recognition and repair is crucial for cells survival. The astonishingly high fidelity of repair system is the main motivation of this study, which aim is to characterize energetic and structural origins of direct interactions of amino acids with canonical and oxidized analogues of adenine and guanine. The pairs stabilized both by hydrogen bonds and stacking interactions were studied on different levels of theory. The Protein Brookhaven Database was search for characteristic patterns found by quantum chemistry computations providing direct link between applied models and observed direct readouts in variety of protein-DNA complexes.

Many examples of distinct interactions were founds providing direct rationale on the molecular level of the discrimination origins of canonical and oxidized nucleobases. Even such non-specific interactions as aromatic π-π stacking can help in recognition of modified nucleobases. As an example of this fact the intermolecular contour maps are presented in Fig.1 for pairs comprising canonical and oxidized guanine stacked with histidine moieties.

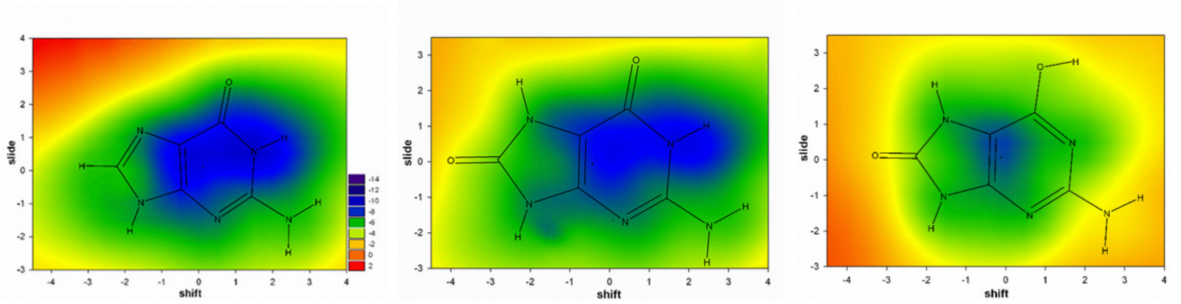

Fig. 1: Intermolecular interaction energies (MP2/aug-cc-pvDZ) level of guanine (G), 8-oxogunaine (GA1) and 6-enol-8-keto-8-oxoguanine (A2) stacking with histidine ring as a function of parallel displacements of monomers.

A computational study of Cu(II)–*β*XaaHisGlyHis complexes

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Copper(II)-histidine species have been extensively investigated for over past four decades with an eye towards understanding the role of Cu(II) in the cell metabolism. Among a plethora of experimental studies concerning Cu(II)-polypeptide complexes theoretical studies are relatively rare, although molecular modeling techniques may provide complementary pieces of data, just to mention structural and energetical properties of the complexes in solution. In the present study, we analyze the binding of copper (II) to the tetrapeptides in water solutions at several levels of theoretical approximation. The methods used to study the energetical and structural properties of the complexes in question include semiempirical Hamiltonians, density functional theory as well as ab initio approaches including electron correlation effects. In order to shed light on the nature of interactions between Cu(II) and peptides, the decomposition of interaction energy into physically meaningful components is applied. Moreover, the UV-Vis spectra are computed using time-dependent density functional theory and compared with available experimental data.

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

Influence of oxidative damage of purines on the nature of stacking interactions. A post–HF and DFT–SAPT study

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It is of paramount importance to understand the biological consequences of oxidative damages to nucleic acids. For this reason, various aspects of modification of nucleic acid bases have been the subject of numerous experimental studies. In order to support experimental findings with reliable theoretical guidance, it is crucial to employ accurate force fields in molecular simulations. This requires development of accurate *ab initio* results of intermolecular interaction energy components. Unfortunately, the data concerning the nature of interactions in oxidized complexes are scarcely available. Thus, in the present study we investigate the stacking interactions in complexes composed of purines modified by hydroxyl radical at the post–Hartree–Fock level of theory and with the aid of the density functional theory. In particular, we aim at description of the impact of nucleic acid base modification on the total intermolecular interaction energy and its physically meaningful contributions. The analysis is performed for seven complexes in various conformations. For the intermolecular interaction energy partitioning we use the variational–perturbational scheme and the SAPT–DFT approach. In most cases, the oxidation of adenine and guanine leads to increase of interaction energy which has it roots in significantly larger electrostatic interaction.

Acknowledgements: Calculations were performed at the Wroclaw Centre for Networking and Supercomputing. Work in the USA was supported by the NSF CREST Grant No. 9805465.

Electronic structure and magnetism of $AgSO_4$, an unusual 1D antiferromagnet – insights from DFT

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$AgSO_4$ in the solid state is an example of a compound with a d–block element in a rare oxidation state (+2), where substantial delocalization is expected of an unpaired 4d electron over the sulfate ligands, just like for the $AgSO_4$ molecule [1]. The theoretical DFT-screening of various hypothetical crystal structures [2] suggested that $AgSO_4$ should adopt a structure which exhibits: (i) magnetically isolated Ag(II) centers (with no direct Ag–O–Ag bridges), (ii) Ag centers coordinated by O atoms at *ca.* 2.1–2.2 Å in a square-planar fashion (iii) no terminal O atoms on sulfate anions. The formulations as $Ag(I)_2S_2O_8$ or $Ag(I)[Ag(III)(SO_4)_2]$ could safely be excluded and $AgSO_4$ should be a genuine paramagnetic sulfate of Ag(II). These predictions have been fully confirmed by recent experiments [3]. Unusually strong 1D antiferromagnetism, which persists up to thermal decomposition of the compound at ∼100 °C, has been reproduced by LSDA+U calculations, with the small predicted electronic bandgap of 0.83 eV. The LDA scheme proves superior to a more general GGA approach in reproducing density of $AgSO_4$ [4], which is of importance for understanding possible pressure–driven phase transitions.

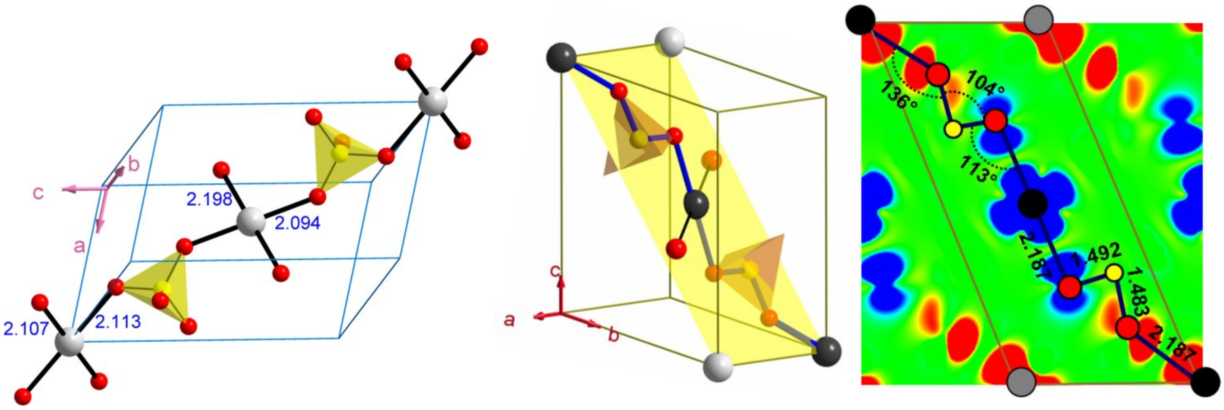

Fig. 1: Left: Experimental unit cell of $AgSO_4$ emphasizing propagation of 1D $[Ag(SO_4)]_\infty$ chains along the main cell diagonal and coordination spheres of Ag1 and Ag2. Right: Projection of spin density on the 011 plane (bottom) as calculated using spin–polarized GGA+U method.

Acknowledgements: Calculations were performed at the ICM Supercomputer Center.

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Mechanochemistry, metadynamics, QM/MM

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Mechanochemistry is a field with a long history going back to year 1892. In recent years the term mechanochemistry has also been used to describe mechanically induced chemistry as observed in single-molecule atomic force microscopy (AFM), force-clamp and sonochemical experiments. Latest theoretical framework was proposed by Ribas-Arino [1,2] and Martinez [3]. It allows to investigate most directly how Potential Energy Surface (PES) changes as a function of applied mechanical force F_0 in an exact, fully non-linear, and self-consistent approach. Now we are going one step further devising the framework based on Car-Parrinello Molecular Dynamics (CPMD) and force-transformed Free Energy Surface (FES), which is able to explore possible reaction pathways as a function of applied external constant force F_0 at desire temperature.

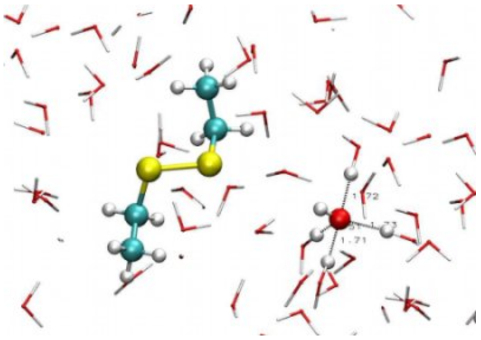

Fig. 1: Simple model system with disulfide bridge in water solution: CH_3-CH_2-S-S-CH_2-CH_3 + OH^-

Intriguing force-clamp spectroscopy experiment have been done last year by Fernandez et al. [4]. Authors have studied effect of mechanical force on the rate of a S_N2 reaction at which a protein disulfide bond is reduced by nucleophiles. Experiment have been performed on 27^{th} immunoglobulin-like domain of cardic titin. The results demonstrated that the rate of the reduction reaction exhibits an abrupt change at a force of 500 pN.

There are few possible explanations proposed by the authors, nevertheless there is no theoretical evidence what kind of mechanism is involved. Based on our new approach we are trying to explain the experimentally observed phenomenon. Presented in Fig. 1 model system have been chosen, as well as full 27^{th} immunoglobulin-like domain of cardic titin - Fig. 2.

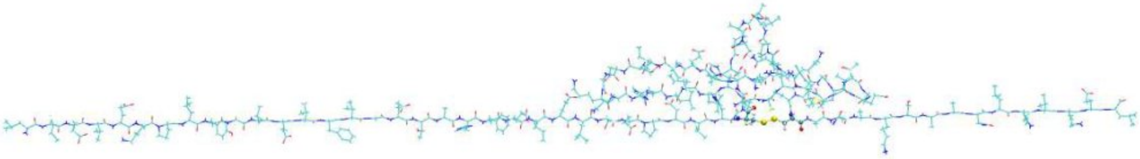

Fig. 2: Stretched 27^{th} immunoglobulin-like domain of cardic titin up to the point of S-S bond - QM/MM with 29000 of water molecules, by courtesy of Padmesh Anjukandi.

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Analysis of the catalytic role of water molecules

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Most of water molecules surrounding reacting biological systems in enzyme active sites or DNA bases pairs undergoing chemical reactions may be treated as passive elements of molecular environment. However, some waters are directly involved in the reaction mechanism and have to be included in QM part of the entire system treated within QMMM approach. To our knowledge there is no clear recipe how to distinguish both kinds of water molecules. The hypothesis put forward by Ken Houk implies that in the enzymes displaying highest catalytic activity transition states are covalently bound to active site [1]. The aim of this work is to determine the specific properties of water molecule indicating covalent character of its interactions with reacting system. As the simple model where the catalytic role of molecular environment can be analyzed we selected 4 water molecules consisting first hydration shell of guanine-cytosine base pair undergoing double proton transfer [2]. The role of water molecules in reacting complexes of β-Lactams [3] has been investigated too. The covalent nature of above mentioned systems has been analyzed using variation-perturbation partitioning of interaction energy and AIM tested previously for series of hydrogen bonded complexes [4].

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

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Modeling of spectrum of the dodecacarbonylo-triangulo-triosmium

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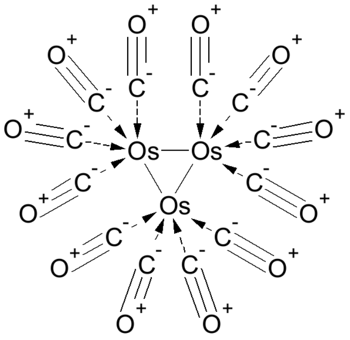
The peaks locations in the mass spectrum of dodecacarbonylo-triangulo-tri-osmium indicates the presence of 12 clusters of singly charged ions (molecular ion and 11 the fragmentation ones) and 12 peaks corresponding to doubly-charged ions. The used calculations are combination of the MMIP method [1] in single charged ions area. For predictions of the double charged ions was applied method presented in the recent MMDM conference [2].



The calculations allow detecting the substantial error of peaks locations. In base data the locations of peaks are shifted 2 Da down and the value is equal for all data relevant to the doubly charged ions. In the singly-charged ions area the differences are the same and amounts to 4 Da. The incorrect values are not corresponding with the average masses as well as the nominal ones. The compensation by hydrogen atoms quantity can not be applied. The fact can be solely the result of errors in spectrometer calibration. The modeling of isotopomeric clusters can detect discrepancies arising between location of dominated peaks and the ion's weight.

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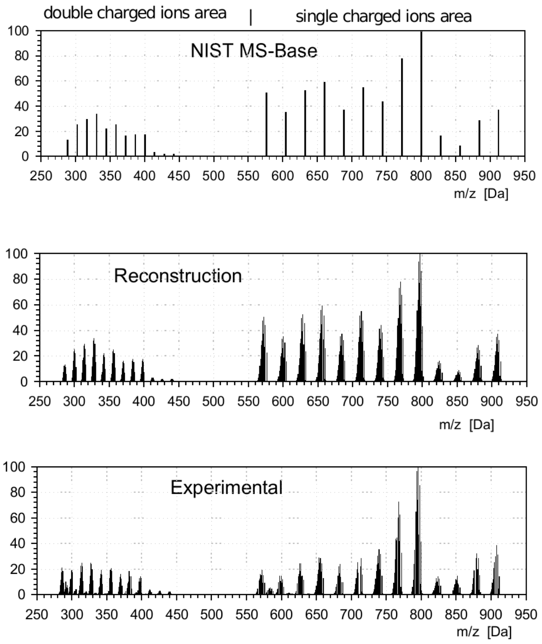

Fig. 1: The mass spectra of dodecacarbonylo-triangulo-triosmium: a – spectrum from MS-Database NIST-2000 [3]; b – spectrum model predicted from a; c – experimental spectrum

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[0] IChOPAN - AMD-402 (Intectra, Germany), EI – 70eV 0,5mA, 200°C

Effects of interaction of the spectrum resolution and the peak location accuracy in the isotopomeric cluster

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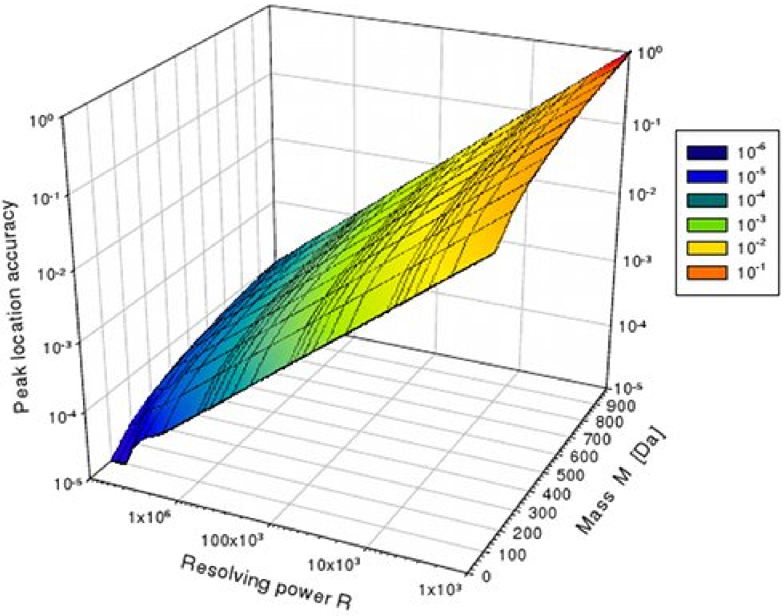

Fig. 1: Modeling of relation of mass spectral resolution, resolving power and peak matching (the lower, blue part of the surface concerns the high resolution MS and 0,0001 Da mass accuracy.

The resolving power of a mass spectrometer is defined as $\boldsymbol{R=M/\Delta m}$, where $\boldsymbol{M}$ is the lower value m/z of two adjacent mass spectral peaks location. $\boldsymbol{\Delta m}$ (oftly incorrect called resolution) is the difference between $\boldsymbol{M}$ and the value of the next highest peak (m/z) value. The term is used to define the ability of a mass spectrometer to separate ions of two different m/z values. Instruments are operated at $\boldsymbol{R \geq 10000}$ (high resolution spectrometers), $\boldsymbol{10000 \geq R \geq 5000}$ (medium resolution) or $\boldsymbol{\Delta m = 1}$ (low resolution equipment). The resolution $\boldsymbol{\Delta m}$ can be calculated from these two peaks if will have a 10% valley and represents the smallest differences in m/z that can be separated. A common mistake made in referring to instruments in the high-resolution mode is that they automatically produce measured accurate mass data. This term is used when reporting the mass to some numbers of decimal places, and the measured mass should be reported with a precision of measurement. All spectrometers are capable of yielding measured accurate mass data regardless of their resolving power capability through the use of peak matching.

Is possible relation of resolution and resolving power and peak matching $\boldsymbol{\Delta m = f(R,M)}$? In which area the accurate mass can be estimated high resolution ? This work tries to explain this problem.

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BioShell - a universal utility library for structural bioinformatics

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[2]University of Warsaw, Warsaw, Poland

BioShell project has been started in 2005 as a set of stand-alone programs to simplify typical bioinformatics tasks. It has since then evolved to become a fully featured scripting language for biomolecular modeling and structural bioinformatics. The package is addressed to a wide audience of users. It can be used in three ways:

- by calling **command-line programs** to do simple tasks as statistical data analysis, file parsing, sequence and structure alignment and RMS calculations
- as a library of **modules for scripting languages** running on JVM, such as Python (interpreted by jython) or Ruby (interpreted by jRuby)
- as an **Application Programming Interface (API)** to simplify bioinformatics software development using Java

BioShell has been already used during several scientific projects e.g. for bioinformatics data analysis and processing trajectories from molecular simulations. Other typical application comprises various calculations on biomolecular structures. The newest features include clustering of protein structures, optimal structure alignment and advanced estimation tools such as kernel-based methods.

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Designing of new inhibitors of *Saccharomyces cerevisiae* squalene epoxidase

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Squalene epoxidase (SE) catalyses the stereo-specific epoxidation of squalene to 2,3-(S)-oxidosqualene including mammalians [1] and fungi [2]. This reaction is the key step in ergosterol and cholesterol biosyntheses, what makes it an attractive potential target for drugs used to inhibit the growth of pathogenic fungi or lower cholesterol blood level in humans. First success trials with squalene epoxidase inhibitors active against several fungi were reported in 1985. Allylamines Naftifine and Terbinafine were found to block ergosterol biosynthesis inter alia in S. cerevisiae and dermatophytes like *C. ablicans.* Under different commercial names such as Lamisil, Corbinal or Naftin terbinafine and naftifine are still being sold and are currently topical or systemic antifungal drugs. However, there are reports of increasing fungi resistance on these allylamine squalene epoxidase inhibitor agents [3]. Clinical case studies show another threat. It has been demonstrated that *Saccharomyces cerevisiae,* well-known yeast used in the food industry, can cause different forms of invasive infection even after administration as a probiotic [4]. In described clinical cases of such infections mortality rates very high 20%. So far there is a lack of information about therapy of these invasions. It is doubtful if active compounds available on the market will guarantee effective treatment.

Due to threat of increasing fungi resistance to currently used drugs and limited information on infections caused by *S. cerevisiae*, there is a need to consider developing of new SE inhibitors, particularly the specific ones. Consequently structures of four new *S. cerevisiae* squalene epoxidase inhibitors were proposed and set of docking simulations along with MM/QM study were performed to examine their binding affinity to the enzyme. Obtained results suggest that at least one of proposed new structures may inhibit growth of fungi more effectively than currently used antifungal active agents.

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

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Structural and energetic heterogeneities of oligonucleotides containing 2-OH-A

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It is widely accepted that 2-hydroxyadenine (also know as iso-guanine) is one of many product of nucleobases degradation under oxidative stress. It can form hydrogen bonding pairs with cytosine and guanine [1, 2] apart from canonical thymine. However, structural and energetic properties of B-DNA comprising this lesion are not known to date. This work intend to fill this gap. Thus, long time scale trajectories generated via molecular dynamics simulations are the source of structural heterogeneities of 13-oligomers. The initial structure has context coincidental to B-DNA sequence of Molluscum contagiosum virus type 1 [3]. The rest of analyzed oligomers were constructed for analysis of different sequences and contexts of intermolecular interactions of 2-hydroxyadenine. Based on the most representative structures intermolecular interactions energies were estimated on DF-MP2/aDZ level. Structure to energy relationships are discussed in details.

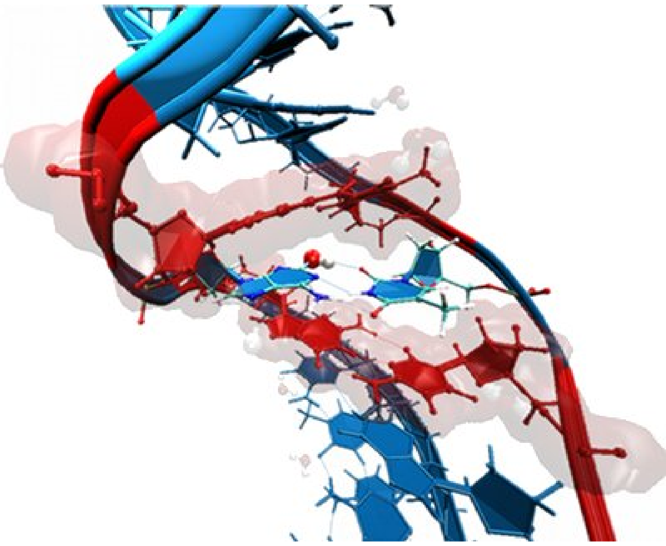

Fig. 1: Conformations of d(XpisoG) and d(isoGpX) dinucleotide steps in B-DNA form (where X denotes one of four canonical nucleobases and isoG represents 2-OH-adenine (isogunaine)) were collected in 20ns molecular dynamics runs.

Acknowledgements: Results were supported in part by computational grant No. 39 of Poznań Supercomputing and Networking Center (Poznań, Poland). The allocation of computational facilities are greatly appreciated.

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Fluorescent probes PRODAN and ALADAN inside a protein cavity – molecular dynamics simulations at different electronic states

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Fluorescent sensors have become increasingly important in the study of biological materials. We used PRODAN (*6-propionyl-2-(dimethylamino)naphthalene*) and ALADAN (*(2S)-2-amino-4-(6-dimethylaminonaphthalen-2-yl)-4-oxobutanoic acid*) (Fig. 1), both similar fluorescent probes, and incorporated them into a model protein. PRODAN was introduced by Weber & Farris (1979) [1], it is one of the best studied environment-sensitive fluorophores. Its derivative ALADAN was synthesized by Cohen et al. in 2002 [2]. ALADAN is a fluorescent synthetic amino acid exceptionally sensitive to the polarity of its surrounding. ALADAN may be incorporated site-selectively at buried and exposed sites, in both soluble and membrane proteins. Peptides including this residue show great potential for sensing protein/protein interactions. However, the effect of a sudden change of the electronic state of the probe upon excitation by light on a protein structure has not been studied yet.

We have developed CHARMM27 force field "compatible" parameters for both molecules in various electronic states. Probes were inserted into the heme cavity of a model protein: apomyoglobin variant 1DUO. We used AUTODOCK 4.2 to localize fluorophores in the protein. The nanosecond scale molecular dynamics of PRODAN and ALADAN located inside the protein cavity were investigated, including time evolution of their ground and two electronic excited states (GS, Locally Excited and the hypothetical Twisted Intramolecular Charge Transfer states). We used the program NAMD 2.6. The effects of post-translational modifications of 1DUO were studied, especially an influence of the changing electronic states of fluorophores on mechanical and structural properties of the model protein.

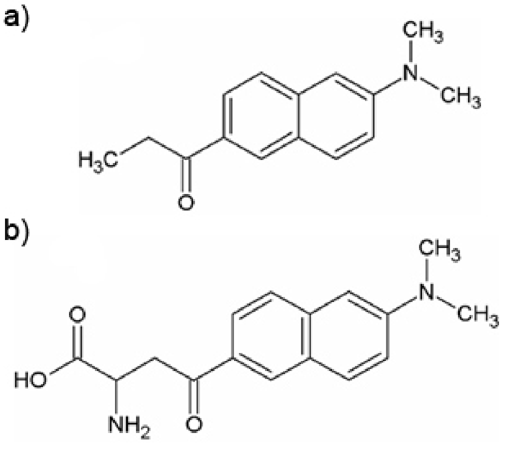

Fig. 1: Fluorescent probes: a) PRODAN, b) ALADAN

Acknowledgements: Support of MNiSZ for Accerys software.

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Insights into solution structure of peptide nucleic acids. Molecular dynamics simulations

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Peptide nucleic acid (PNA) is a DNA mimic with an uncharged pseudo-peptide backbone. The ability of PNA to form stable complexes with complementary strands of RNA and DNA and their resistance to enzyme degradation makes them particularly useful in the antigene and antisense therapy. PNAs can be thus designed to specifically inhibit gene expression and microbial cell growth. The long-term aim of our research is to design specific PNA-based compounds that will target the ribosomal RNA with high specificity, inhibiting bacterial translation, and will effectively penetrate the cell wall. Here we report the results of atomistic molecular dynamics simulations in explicit solvent of three different, single-stranded PNA decamers. PNA sequences were designed to target the proximity of the A-tRNA binding site located centrally between the platform and the head of the small ribosomal subunit. Solution structures of the studied PNA oligomers will be described and compared. We will discuss the role of sequential and non-sequential stacking and hydrophobic interactions in stabilizing the PNA structure. The presented work is the initial step to modeling and constructing PNA-derivatives with a therapeutic potential. Our findings regarding PNAs' structural properties in solution will be further used in designing such derivatives.

Photophysical properties of B_{12} cofactors: inside from quantum chemical calculations

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Adenosylcobalamin (AdoCbl or coenzyme B_{12}) is the cofactor of several enzymes, which catalyze the intramolecular 1, 2 shift of a hydrogen atom with a functional group such as alkyl, OH, or NH_2. During the enzymatic catalysis, the Co–C bond of AdoCbl is cleaved homolytically, with formation of the Ado radical and cob(II)alamin. Over the past few years transient absorption spectroscopy has been applied by Sension and co-workers [1] to investigate nature of electronically excited states and photochemistry of alkylcobalamins. While these recent spectroscopic studies provided a new insight into the electronic structure of B12 cofactors, the nature of their excited states remains largely unexplained. The analysis of the electronic structure of adenosylcobalamin has been performed by means of time-dependent density functional theory. Calculations were carried out using the gradient corrected Becke–Perdew (BP86) functional together with the TZVPP basis set and COSMO solvent model. In calculations simplified cobalamin model was used, in which all the corrin side chains were replaced by hydrogen atoms and the 5,6-dimethylbenzimidazole *trans* axial base was replaced by an imidazole. The calculations were carried out with the use of TURBOMOLE program.

Full geometry optimization was performed for the ground state (S_0) and the first singlet excited state (S_1). The S_1 excited state is characterized as a MLCT type and is derived from the $d/\pi \to \pi^*$ excitation, where π and π^* orbitals are localized on the corrin ring. For the ground and excited S_1 state, potential energy curves were determined as a function of Co-C_{Ado} bond length. The Co-C_{Ado} bond was repeatedly stretched with the step size of 0.05 [1FA?], and the geometries of S_0 and S_1 states were reoptimized at every point. At each optimized point the manifold of singlet and triplet states were calculated using the TDDFT/BP86/TZVPP level theory. The obtained results were compared with the corresponding calculations for methylcobalamin [2].

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Mechanism of the gas-phase decomposition of trifluoro-, trichloro-, and tribromomethanols in the presence of hydrogen halides

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Ab initio calculations at the G2 level were used in a theoretical analysis of the kinetics of the decomposition of trifluoro-, trichloro-, and tribromomethanols. The high-pressure limiting rate constants $k_{\mathrm{diss},\infty}$ for the thermal dissociation of CF_3OH, CCl_3OH, and CBr_3OH were calculated using the conventional transition state theory. In the temperature range of 200-3000 K the calculated rate constants can be expressed as:

$$
\begin{array}{rll}
k_{\mathrm{diss},\infty}(CF_3OH) = & 2.3\times10^{13}\times(T/300)^{0.52}\times\exp(-18550/T) & s^{-1} \\
k_{\mathrm{diss},\infty}(CCl_3OH) = & 9.5\times10^{13}\times(T/300)^{0.27}\times\exp(-16860/T) & s^{-1} \\
k_{\mathrm{diss},\infty}(CBr_3OH) = & 9.2\times10^{13}\times(T/300)^{0.20}\times\exp(-15680/T) & s^{-1}
\end{array}
$$

The results of potential surface calculations show that in the presence of the hydrogen halides HX (X = F, Cl, and Br), considerably lower energy pathways are accessible for the decomposition of CF_3OH, CCl_3OH, and CBr_3OH. The mechanism of the reactions appears to be complex and consists of three consecutive elementary processes with the formation of pre- and post-reaction adducts. The presence of hydrogen halides considerably decreases the energy barrier for the bimolecular decomposition of the alcohols CF_3OH, CCl_3OH, and CBr_3OH. The derived temperature dependence of the rate constants for the HX-catalyzed decomposition of the perhalogenated methanols is given by the equations:

$$
\begin{array}{rll}
k^{(2)}(CF_3OH + HF) = & 4.6\times10^{-14}\times(T/300)^{2.50}\times\exp(-6970/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CF_3OH + HCl) = & 1.4\times10^{-14}\times(T/300)^{2.34}\times\exp(-10410/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CF_3OH + HBr) = & 1.3\times10^{-14}\times(T/300)^{2.30}\times\exp(-10340/T) & cm^3 molecule^{-1} s^{-1}
\end{array}
$$

$$
\begin{array}{rll}
k^{(2)}(CCl_3OH + HF) = & 6.3\times10^{-14}\times(T/300)^{2.13}\times\exp(-6800/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CCl_3OH + HCl) = & 8.1\times10^{-14}\times(T/300)^{2.72}\times\exp(-8025/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CCl_3OH + HBr) = & 4.2\times10^{-14}\times(T/300)^{2.69}\times\exp(-6990/T) & cm^3 molecule^{-1} s^{-1}
\end{array}
$$

$$
\begin{array}{rll}
k^{(2)}(CBr_3OH + HF) = & 8.2\times10^{-14}\times(T/300)^{2.28}\times\exp(-6045/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CBr_3OH + HCl) = & 5.0\times10^{-14}\times(T/300)^{2.74}\times\exp(-7490/T) & cm^3 molecule^{-1} s^{-1} \\
k^{(2)}(CBr_3OH + HBr) = & 2.8\times10^{-14}\times(T/300)^{2.72}\times\exp(-7430/T) & cm^3 molecule^{-1} s^{-1}
\end{array}
$$

Results of this study indicate that hydrogen halides can considerably accelerate the homogeneous decomposition of perhalogenated methanols when they are present in the reaction area at sufficiently high concentrations. However, the atmospheric concentrations of hydrogen halides are too small for efficient removal of atmospheric CF_3OH, CCl_3OH, and CBr_3OH.

Acknowledgements: This research was supported by Wroclaw Medical University under grant no. ST-263. The Wroclaw Center of Networking and Supercomputing is acknowledged for the generous allotment of computer time.

Hydroxyurea and hydroxythiourea methyl derivatives as effective drugs for the treatment of sickle-cell anemia. A DFT and MP2 computational study

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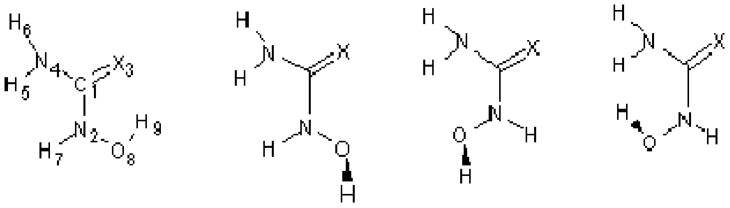

N-hydroxyurea (Hu) and its derivatives have attracted more attention since Hu has become an efficient drug for sickle cell anemia treatment[1,2]. At molecular level its interaction with hemoglobin followed by sequence of oxidation reactions results in formation of N-hydroxyurea nitroxide radical. The N- hydroxyurea nitroxide then decomposes to nitric oxide. Unfortunately, the above reactions occur at relatively moderate rates so a large excess of hydroxyurea is required. Huang et al., demonstrated experimentally for several N-hydroxyurea derivatives that they can form NO-producing radicals more quickly than Hu itself. Rohrman and Mazziotti [3] observed that hydroxyurea's hydrogen atom abstraction from the hydroxide group to form the corresponding nitroxide radical is a rate-limiting step in overall NO radical generation process. Further, they assessed the relative effectiveness of Hu and/or its derivatives to form nitroxide radicals to the energy gap defined as E(HuNO·) - E(HuNOH). It was assumed that lowering energy gap should cause an increase of corresponding nitroxide radical formation rate constant. In our study amidolic forms of N-hydroxyurea and N-hydroxythiourea, and their mono methyl derivatives with the DFT(B3LYP) and MP2 quantum chemical schemes. Predicted energy gap values for Hu methyl derivatives are generally smaller than their unsubstituted parent systems. Also, data obtained for corresponding thio analogs suggest their better efficiency than reference N-hydroxyureic species.

Acknowledgements: We wish to thank to the Wroclaw Center for Networking and Supercomputing for generous allotment of computer time.

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Derivatives of N-hydroxyurea and N-hydroxythiourea as potential drugs for the treatment of sickle-cell anemia. A DFT and MP2 computational study on aliphatic cyclic and acyclic mono N(OH)-substituted species II

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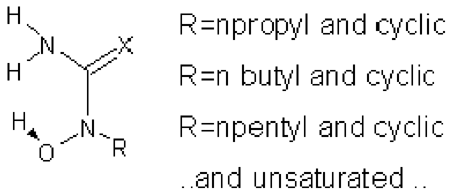
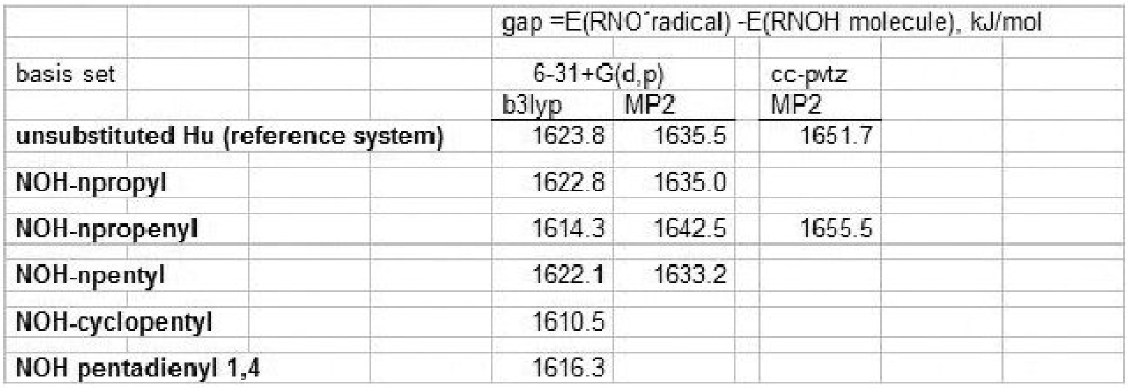
A simple N-hydroxyurea (Hu) C3-C5 aliphatic derivatives were investigated using the DFT(B3LYP) and MP2 quantum chemical methods. Actually, the energy gap defined as E's(R-HuNOC) - E(R- HuNOH) difference was analyzed due to the simple Rohrman and Mazziotti's [1] model. According to this model the smaller gap should indicate a better therapeutical activity of the species. We were analyzing C3-C5 aliphatic N(OH)-substituted Hu's for it's the most stable conformer, i.e., e-form, (see graph). The conformation is related to C=X (X=O, S) and CNOH traditionally recognized as trans orientation. Some preliminary results are collected in the table listed below. Preliminary data indicate that some of N(OH)-substituted derivatives should act better than its parent unsubstituted Hu.





	gap =E(RNO˙radical) -E(RNOH molecule), kJ/mol		
basis set	6-31+G(d,p)		cc-pvtz
	b3lyp	MP2	MP2
unsubstituted Hu (reference system)	1623.8	1635.5	1651.7
NOH-npropyl	1622.8	1635.0	
NOH-npropenyl	1614.3	1642.5	1655.5
NOH-npentyl	1622.1	1633.2	
NOH-cyclopentyl	1610.5		
NOH pentadienyl 1,4	1616.3		

Acknowledgements: We wish to thank to the Wroclaw Center for Networking and Supercomputing for generous allotment of computer time.

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[3] Rohrman, B. A.; Mazziotti, D.A. *J. Phys. Chem. B* **2005**, *109*, 13392.

The evolution of bonding and thermodynamic properties of boron doped small carbon clusters — an *ab initio* study

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Theoretical studies of the BC_n (n=2-6) clusters have been performed using the state of the art calculations. Several alternative structures of these clusters were studied to locate the lowest-energy isomers and to determine the path for structural evolution of BC_n (figure). Using theoretically determined partition function, thermodynamic data are computed and experimental enthalpies are enhanced. The *ab initio* atomization energies of boron carbides compare well with corrected experimental functions.

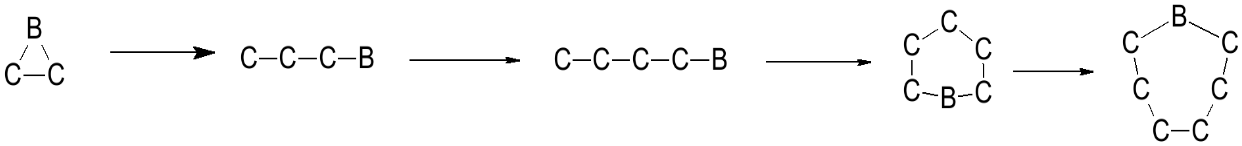

Fig. 1: The energetic optimal path for structure evolution of BC_n.

Modeling of the ring-opening copolymerization of L,L-lactide and ε-caprolactone by DFT methods

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Poly(L,L-lactide) (PLA) and poly(ε-caprolactone) (PCL) (cf. structures c and d in Fig. 1) have drawn much attention due to their special properties like biocompability and biodegradability, making them an interesting target for biomedical and environmental applications [1]. Both polymers are obtained almost exclusively employing a ring-opening polymerization (ROP) of the corresponding cyclic monomers (cf. structures a and b in Fig. 1). ROP of LA and CL monomers is usually initiated by a variety of metal alkoxides, among which the aluminum alkoxides are the most versatile and provide highly selective and controlled polymerizations [2].

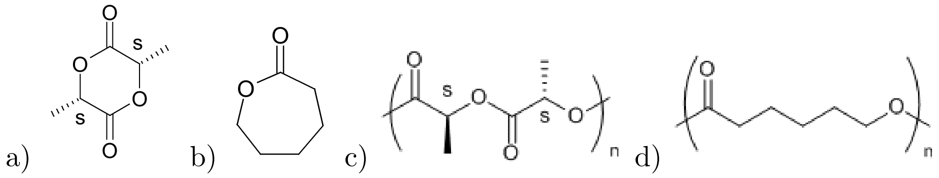

Fig. 1: a) L,L-lactide (LA); b) ε-caprolactone (CL); c) PLA; d) PCL.

The ratio of the absolute rate constants of propagation ($k_{p(CL)}/k_{p(LA)}$) initiated by Al(O*i*-Pr)$_3$ can be as high as $6.7\cdot10^3$ (THF, 20 °C) [3]. Surprisingly, in the CL/LA copolymerization, the LA comonomer is consumed first, yielding block, or gradient copolymers [4a, 4b]. However random copolymers can be also formed, depending on the reaction conditions [4c]. So far this interesting phenomenon hasn't been explained on the molecular level. We addressed this problem by theoretical chemistry means. The density functional theory (DFT) was applied to study the initiation and propagation of homopolymerization and copolymerization of L,L-lactide and ε-caprolactone. The energy profiles of these processes were developed at the B3LYP/6-311+G(2d,p)//B3LYP/6-31+G* level. In order to get more reliable thermodynamic data the Self-Consistent Reaction Field (SCRF) scheme was applied in our computations. The theoretical results explain fairly well the experimental behavior of the copolymerization of LA and CL.

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Molecular modeling of the enzyme-catalyzed transesterification and hydrolysis reactions

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The application of chiral organophosphorus compounds containing stereogenic centre on phosphorus atom in asymmetric organic synthesis, biochemistry and catalysis, grows rapidly. The enzymatic resolution of the racemate of **1** and P-borane derivative **2** (Fig. 1) is a suitable method towards such enantiopure compounds.

Among many different lipases tested by us [1, 2], enzyme CAL B from *Candida Antarctica* showed unexpectable stereoselectivity, when applied to compounds **1** and **2** (Fig. 1).

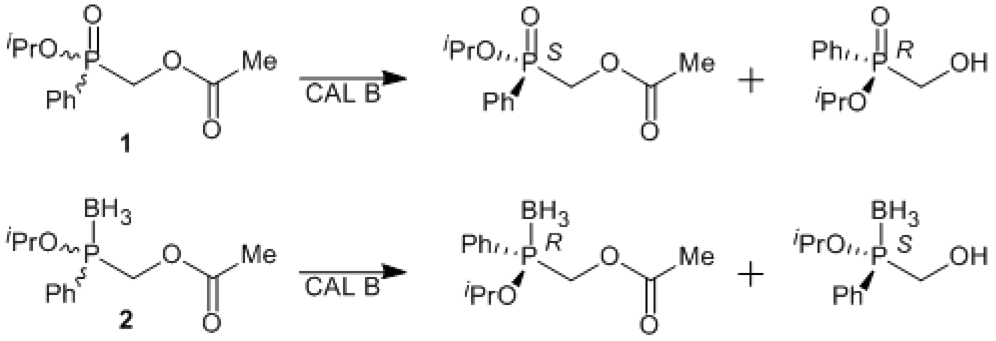

Fig. 1: Enzyme-aided kinetic resolution of racemate **1** and **2**.

The mechanism of the ester hydrolysis catalyzed by lipases like CAL B, containing catalytic triad (serine activated by histidine and aspartic acid) is well described in the literature [3]. In order to explain the stereoselectivity of CAL B, we investigated the transesterification and hydrolysis reactions of the model compounds using quantum mechanical methods. We examined the influence of environment, hydrogen bonds and of the role of hydrolytic agent on the hydrolysis process. These initial investigations are only an introduction to more advanced QM/MM modeling of the stereospecific enzyme-aided hydrolysis of **1** and **2**.

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Quantum mechanical studies of lincosamides

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Antibiotics are drugs used to treat diseases caused by microorganisms but also to boost the decreased levels of immunity. One of the important groups of antibacterial agents are lincosamides, consisting of three compounds: lincomycin, clindamycin and pirlimycin. Lincosamides interact with the bacterial large (50S) ribosomal subunit and inhibit the process of protein synthesis. Lincosamides are effective against Gram-positive bacteria as well as against some protozoal diseases. The expanded use of these antibiotics has been accompanied by the increase of resistance in many strains of bacteria. Acquired bacterial resistance is the main reason to search for better compounds.

Currently, there are two available structures of clindamycin in the complex with the 50S[1,2] ribosomal subunit (Protein Data Bank). The conformations of the antibiotics in these complexes are significantly different. In our work, we investigated the geometry and the physicochemical properties of these known structures of clindamycin using quantum-chemical methods (MP2 and DFT). Based on the structures of clindamycin we built the models of other lincosamides and studied their properties as well. We compared the internal flexibility of lincosamides in these two ribosome binding geometries.

Acknowledgements: The authors acknowledge support from ICM University of Warsaw (BST1450/2009, G31-4 and G18-4), Polish Ministry of Science and Higher Education (N N301 245236) and Foundation for Polish Science (Focus program). The research for this poster was partially supported by the EU through the European Social Fund, contract number UDA-POKL.04.01.01-00-072/09-00.

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Insights into structure, dynamics and hydration of DNA/DNA and DNA/RNA duplexes with pyridylphosphonate internucleotide bonds from molecular dynamics simulations

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Pyridylphosphonates as a new type of modification of a phosphorus centre 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 centre 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 quaternisation 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 at the atomic level the structure, dynamics and hydration of DNA/DNA and DNA/RNA duplexes containing oligothymidylate strands with stereodefined 2-, 3-, and 4- pyridylphosphonate or pyridyltiophosphonate moieties we applied computational chemistry methods, molecular modeling and molecular dynamics simulations. The replacement of the native phosphodiester bond by the P-chiral 2-, 3- or 4-pyridylphosphonodiester bond in oligodeoxyribonucleotides does not introduce significant geometric alterations to the structure of duplexes. The modification has, however, remarkable influence on the internal bonding network and hydration.

We discuss our results in relation to experimental studies indicating that the sense of chirality at the phosphorus centre and the position of the nitrogen atom in the pyridyl ring of a pyridylphosphonate moiety are important factors governing stability of double- and triple-stranded complexes formed by these oligonucleotide analogs.

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

On the reliability of *ab initio* methods in prediction of electric dipole (hyper)polarizabilities of betaine and merocyanine dyes. A critical study

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In order to achieve satisfactory agreement with experimental data, numerous factors must be taken into account in the case of modeling of nonlinear optical properties of molecules in liquid or solid state. Reliable predictions of electric dipole (hyper)polarizabilities is still challenging task even for systems in the gas phase. Betaine and merocyanine dyes might serve as an excellent example in this context [1,2]. This study is primarily concerned with the influence of the electron correlation effects on the molecular (hyper)polarizabilities in the zero-frequency limit for the two groups of dyes. For this purpose, we analyze the properties in question using wide range of *ab initio* methods, including SCF, CASSCF, MP2 and a hierarchy of coupled-cluster theories (CC2, CCSD, CCSD(T), CC3). The highly accurate *ab initio* results are then used as a reference to assess the performance of recently proposed long-range corrected exchange-correlation potentials employed within the density functional theory framework [3].

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Mechanism of methyl transfer from $CH_3Co(dmgBF_2)_2Py$ to phosphine nickel complex: DFT study

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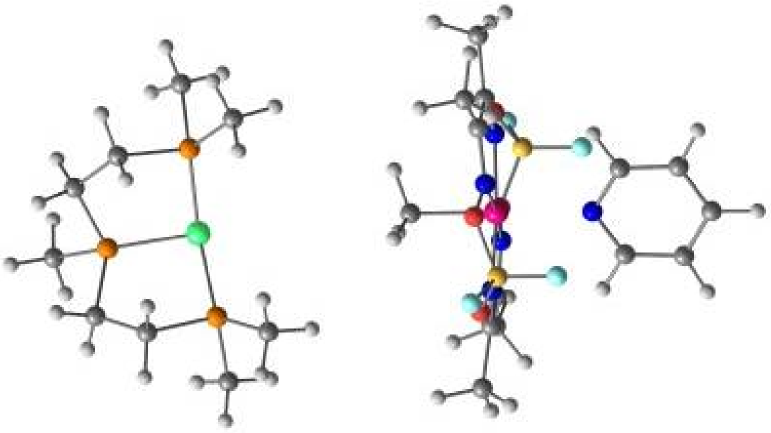
Methylation reactions of nickel complexes are studied in relation to catalytic mechanism of ACS/CODH enzyme. The enzymatic process involves methylation of nickel on 0 or +1 oxidation state by methyl cobinamide.

DFT/OLYP calculations were performed for the reaction of phosphine nickel(0) complex with $CH_3Co(dmgBF_2)_2Py$. The energy of reactants was calculated as function of nickel – methyl distance. Two reacting systems were considered, one with $CH_3Co(dmgBF_2)_2Py$ and second with $CH_3Co(dmgBF_2)_2$ without pyridine. The influence of solvent on the reaction was taken into account by the PCM model. The mechanism of methylation is discussed.



Verification of the resonance–assisted hydrogen bond model within spin-coupled valence bond theory

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Resonance–assisted hydrogen bond model was first introduced by G. Gilli *et al.* in order to characterize short–strong hydrogen bonds formed in enol forms of beta-diketones in which proton–donor and acceptor are linked through π–conjugated bonds [1]. In fact it was more a qualitative argument used by Gilli to explain observed bond length alterations characteristic for the so–called resonance effect.

Recently, we observed that in the case of intermolecular double–hydrogen bonds, like those formed in dimers of carboxylic acids or formamide, the dominant contribution from the charge delocalization energy seems to be a distinguished feature of such interactions [2]. Since our conclusions were based on the results of interaction energy partitioning scheme performed using a moderate basis sets, we second these calculations with analysis of the basis set extension effects.

Furthermore, we report the results of fully variational complete active space valence bond (CASVB) calculations of doubly hydrogen-bonded carboxylic acids, amides and their derivatives, including the established resonance energies. Our preliminary results indicate, that the determined resonance effects are in fact quite small and the actual origins of the observed cooperativity of interactions are the charge delocalization effects.

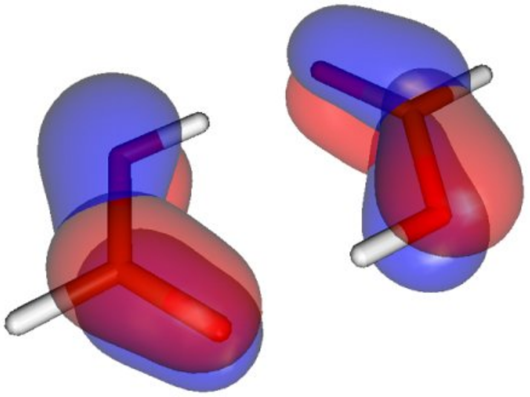

Fig. 1: Four singly–occupied, highly delocalized CASVB orbitals of centrosymmetric formic acid dimer.

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Explicit water hydration of alpha-helices in the gas phase and in a continuous solvent. A density functional theory study

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The set of Ac(Ala)nNHMe (for n=12-18) alpha-helices was optimized using few popular density functionals (B3LYP, X3LYP, M06, MPWB1K with d95** basis set) in a gas phase and in a water solution using conductor-like polarizable continuous model (CPCM) . Different regions of hydration were recognized – C-end hydration, N-end hydration and side-hydration, while each region possesses few distinct possible hydration sites (3 and 4 at C-end and 2 and 3 at N-end respectively in gas and solution calculations using B3LYP). The stability of hydration follows pattern: C-end > N-end > Side both in a gas and a solution but the stability of different sites inside one region varies. The explicit water affects the helices structures by both lengthening and shortening backbone's hydrogen bonds. The calculations of the infrared spectra were performed too. The peak of the amide I vibration redshifts upon going from gas phase to solution. Further redshift is observed upon adding explicit water in CPCM. Thus, the CPCM model does not saturate the solvation effects as explicit water changes the properties of the system. The first solvation shell is found to be important in a description of helices in continuous model calculations.

Homology modeling of a potential methyl-histone binding module of human SGF29

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Remodeling of chromatin structure by protein complexes possessing enzymatic activity is one of epigenetic mechanisms which control gene expression. Histones are subjects for several types of covalent modifications forming an interface for various binding domains. Components of SAGA (Spt-Ada-Gcn5 acetyltransferase) and ATAC (Ada 2A-containing) complexes carry out acetylation of histones which is commonly linked to transcriptional activation. SGF29 (SAGA-associated factor 29 kDa) has been characterized as a subunit of these complexes in human, rat, *Drosophila melanogaster* and yeast. Both molecular function and structure of SGF29 have not been defined so far, however its presence has been shown to regulate carcinogenis in tumor cells [1].

We applied state-of-the-art homology modeling methodology in order to further investigation of possible molecular function of SGF29. It consists of two functional domains – an N-terminal coiled-coil domain and a C-terminal Tudor domain. Detailed analysis revealed the presence of an aromatic pocket within the Tudor domain, characteristic for domains binding methylated residues (shown in the figure). Hence, we hope that the model presented in this work will serve as a helpful guide for experiments and indicate the direction of bioinformatic selection of epigenetic effector modules.

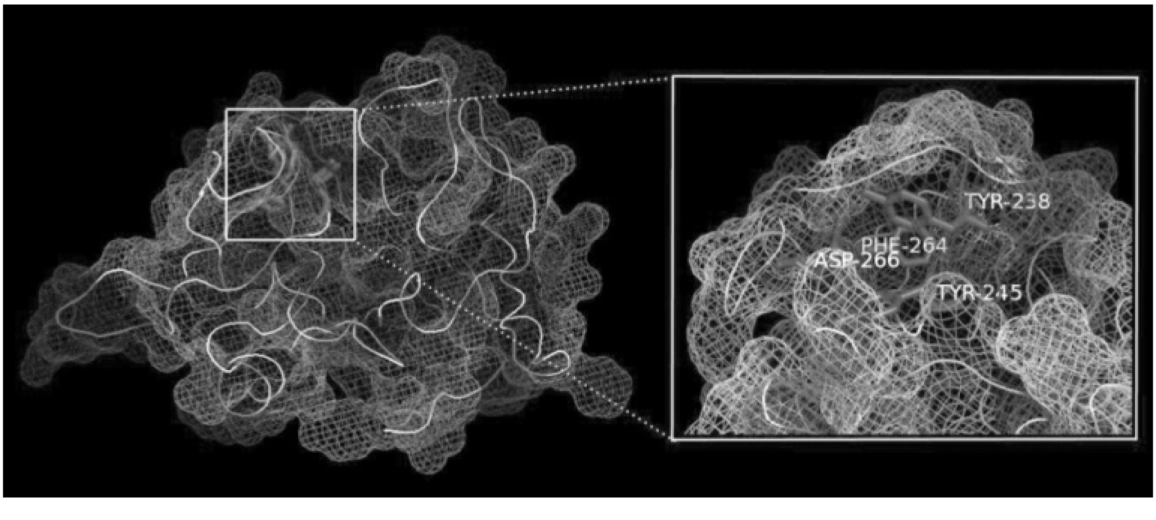

Fig. 1: Schematic model of the Tudor domain of human SGF29. Residues forming a predicted aromatic pocket are presented in a rectangle as sticks.

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Nanomechanics of Ig-like domains of human contactin (BIG-2)

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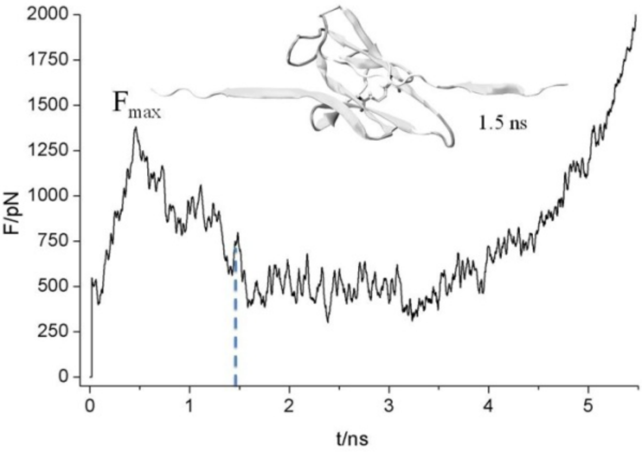

Fig. 1: Force vs. time plot and the structure of $IgC2_1$ domain. The results of F_{max} in different simulations of $IgC2_1$: 1380.6, 1375.6, 1301.4, 1278.5, 1177.0, 1437.5 pN.

Contactins are a subgroup of molecules belonging to the immunoglobulin superfamily. These proteins, present in various regions of the brain, are closely connected with the functioning of the nervous system. Contactins are characterized by the presence of six Ig-like domains C2 type (IgC2) with the presence of disulfide bonds, four fibronectin type III-like repeats (FnIII), and a glycosylphosphatidylinositol (GPI)-anchoring domain (Fig. 1) [1]. Contactins family consists of six members. One of them is Contactin 4 (CNTN4, BIG-2), which is crucial for the formation and maintenance of functional odor map in the olfactory bulb. This protein was also identified as a candidate gene responsible for 3p deletion syndrome [2]. It seems that mutations affecting CNTN4 function may be also relevant to Autism Spectrum Disorder (ASD) pathogenesis [3].

In this work we compare sequences, three-dimentional structures and mechanical resistances of individual Ig-like domains of CNTN4. In this way we try to find some characteristic, highly conserved motifs to understand the mechanical properties of single IgC2 domains of CNTN4 – a material crucial for the nervous system functioning. We obtained results from Steered Molecular Dynamics simulations. Maximum forces (Fig. 2) that are needed to stretch each Ig-like domain have been calculated.

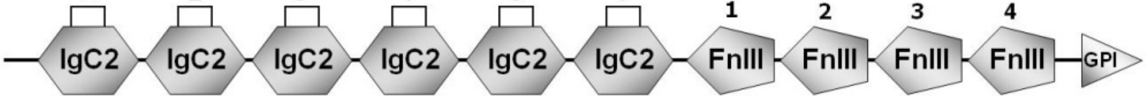

Fig. 2: Domain structure of Contactins.

Acknowledgements: Support from Polish Funds for Science (grant No. N202 262038 and nationwide license for Accelerys software) is acknowledged. Calculations were performed at the Computational Center TASK in Gdańsk.

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Exploration of cisplatin interactions with glycine; a DFT study

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Interactions of hydrated cisplatin complexes with glycine were explored using density functional theory (DFT) with B3LYP functional. Both thermodynamic and kinetic characteristics of these interactions were determined. The square-planar cis-$[Pt(NH_3)_2(Cl)(H_2O)]^+$, cis-$[Pt(NH_3)_2(OH)(H_2O)]^+$, cis-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ complexes were chosen. All the structures were optimized in polarisable continuum model (IEFPCM) and gas phase where vibration frequencies and thermodynamic corrections were estimated. The reaction and bonding energies were determined in gas phase and implicit solvent models in approach of isolated molecules as well as in supermolecular approach. First step of the reaction is a substitution of the aqua ligand by carboxyl or amine active site of glycine. In the second step, another cisplatin ligand (Cl, OH or aqua) is eliminated forming a chelate complex. First step of the reaction is exothermic for all tested structures in all approaches. In the second step as well as the whole reaction is exothermic only for dehydrated form of reactants. The strongest coordination of cisplatin to glycin was found in cis-$[Pt(NH_3)_2(H_2O)(Gly\text{-}N)]^{2+}$ (-89.4 kcal/mol). The pK_a of were estimated for the possibility to determined the dependence of Gibbs free energy on pH of solution.

How do substituent effects affect conformational freedom of squalene in cholesterol biosynthesis

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It is known that the shape of a flexible multi-substituted molecule is resultant of steric interactions between its substituents themselves as well as the main chain and effects of sterically demanding end-groups [1]. This dependency gives chemists a great spectrum of possibilities. Unfortunately, controlling conformation of open chain molecules by the type and location of its substituents occurs to be highly demanding task and is not often possible. Nevertheless, nature succeeded in developing of molecules with a preference to adopt the conformation which is optimal for the function it may serve. The spatial arrangement and the distance between the functional groups often define the activity of biologically active compounds by making them to accept "active conformation". Probably substituent effects affect particular biological reactions in different ways.

One of these reactions is polycyclization of 2,3-(S)-oxidosqualene to lanosterol. Product specificity and high stereoselectivity are believed to be achieved by several factors such as forcing the substrate to occupy a prefolded conformation, progression of the reaction through rigidly held, partly cyclized carbocationic intermediates, and stabilization of the intermediate carbocations by cation–π interactions [2].

Although listed factors can explain selectivity of squalene cyclization process, there is at least one more, peculiar and rather neglected factor, that is substituent effect affecting polycyclization path leading to lanosterol. Therefore we utilized DFT and *ab inito* methods for squalene epoxide and its analogues with different substituent groups [3] to compute potential energy surfaces for rotations leading to ring closure. PES analyses provided insight into such sophisticated mechanism, based on the effects exerted by substituents attached to squalene, which results in significant lowering of activation barrier for the proper prearrangement of the native substrate and the course of the reaction. Described effect is not only intellectually absorbing but may be very useful in understanding other biochemical cyclization reaction and designing in vivo activated prodrugs.

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

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FEP/MD study on binding ibuprofen to human serum albumin

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Human serum albumin (HSA) is the most abundant protein in blood plasma. This monomeric globular protein consists of three homologous α-helical domains (I-III), each divided into subdomain A and B. Having multiple binding sites, HSA is able to bind variety of ligands, mostly of acidic and lipophilic character, and some of the commonly known drugs, including warfarin, diazepam and ibuprofen. While high affinity of a drug towards HSA is increasing its solubility and facilitating distribution, it may also decrease its effective concentration, as only free (unbound) drug is pharmacologically active. Thus, precise knowledge of the drug binding affinity to human serum albumin is of primary interest in drug development studies.

Together with the experimental methods, variety of computational approaches have been proposed as tools for estimating the free energy of ligand-protein binding. Among them, free-energy perturbation (FEP) simulations are considered the most accurate ones. In FEP/MD method one computes the change in the free energy of the system as it evolves from state A to state B, according to the Zwanzig's equation:

$$\Delta G_{A \to B} = G_B - G_A = -\beta^{-1} ln \langle \exp\left(-\beta \Delta V\right) \rangle_A \tag{1}$$

where $\beta = 1/kT$, $\Delta V = V_B - V_A$ and V_A V_B are the potentials. $\langle\rangle_A$ denotes the ensemble average of ΔV over configurations sampled from the A state, generated in the molecular dynamics (MD) simulation. In practice, in order to provide a smooth and gradual transition between the two states, a family of intermediate potential energy functions, each of them being a combination of A and B, is introduced. Binding energy is then obtained on the basis of the free energy differences calculated from the independent simulations that run parallel at each of the intermediate steps.

Here we present the FEP/MD simulation on binding ibuprofen – widely used non-steroidal anti inflammatory drug - to one of the HSA active sites. In our calculations crystal structure of HSA complexed with ibuprofen (PDB code 2BXG) was placed in the water box and after initial minimization subjected to the FEP/MD simulation in the NVT ensemble at 300 K. In the simulation hybrid QM/MM scheme was used, in which ibuprofen was treated by the AM1 semiempirical method, whilst the solvent molecules and the protein were described by the OPLS force field. On the basis of the simulation results we calculated ibuprofen-HSA binding free energy and thus obtained the association constant K_A of the studied complex.

Acknowledgements: The authors thank Dr. Sergio Martí from Departament de Ciencies Experimentals, Universitat Jaume I, Castellon, Spain, for helpful discussions and suggestions concerning the FEP methodology.

Folding of long-chain polyalanine in the cavity

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The macromolecules have the ability to organize into specific structural forms. The mechanism of a folding is widely studied especially for proteins. Recently, protein folding in confined spaces mimicking a dense *in vivo* environment gained much interest [1]. Computationally, a convenient model of a confined protein is polyalanine (PA), well-known for its high propensity for the helical structures. Computational studies [1–4] revealed that the preference for the individual secondary structures of PA depends on the medium and chain length considered.

In the present study the behavior of a single long-chain PA molecule $(\mathrm{Ala})_{60}$ was simulated by all-atom molecular dynamics (MD) using Amber99φ force field in vacuum. The various confinement geometry (slit, cylinder, cube) and strength was considered. In case of free PA it was found [4] that a hairpin structure of two antiparallel α-helices was favored at T = 303 K. The "U" shaped double-leg structure (2-α) of free PA is depicted in Fig. 1. The organization of α-helices into parallel position in the hairpin was explained by attractive van der Waals interaction between helical legs, of about -2.5 kJ.mol^{-1} per Ala unit. The preference for hairpins was found to persist in $(\mathrm{Ala})_{60}$ also under confinement. The representative structures of PA in a cube (Fig. 1) clearly show a transition of the double-leg into multiple-leg hairpins (3-α, 4-α, 5-α) upon increasing the confinement. Under weak and moderate confinement the broken PA helices sustain the hairpin character of the structure. However, under strong confinement the helices melt considerably. The hairpin structure of PA found in the present simulations has a direct bearing on the helix-turn-helix structural motif well-established in membrane proteins [5].

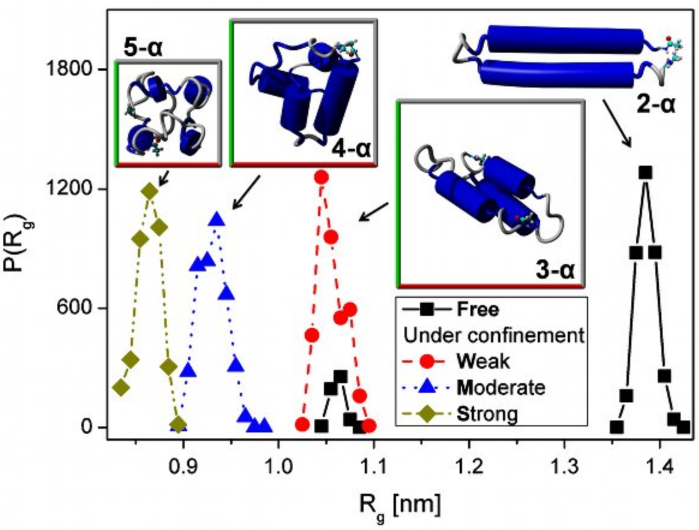

Fig. 1: Distribution functions of the radius of gyration of free and confined (given in the legend) long-chain PA at 303 K.

Acknowledgements: This work was supported by the project APVV-0607-07 and in part by the Centre of Excellence COMCHEM.

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Activation of B-H bond in ammonia borane catalyzed by $[Ir(dppm)_2]OTf$ – an analysis based on the combined charge and energy decomposition scheme

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Ammonia borane (AB) is a promising material in hydrogen storage technologies, mainly due to the high weight of its contents (19.4 Tues -%). This is important in terms of replacing "traditional" fuels (gasoline, oil, natural gas) by molecular hydrogen, which can reduce greenhouse effects by reducing CO_2 emissions. One of the method to produce molecular hydrogen is dehydrogenation of AB catalyzed by transition metal complexes. In these processes, the rate-determining step is the activation of X-H bonds (X = B, N). For this reason, understanding what determines an energetic barrier to activation is particularly important. Accordingly, the main goal of our investigation will be an ETS-NOCV based analysis of B-H activation reaction catalyzed by $[Ir(dppm)_2]OTf$ as recently proposed in the literature [1].

It turned out that the barrier to B-H activation is only $\Delta E = 3.8$ kcal/mol, what explains the relatively fast kinetics, even at a lower temperature. Decomposition of ΔE, into (i) the orbital interaction (ii) the electrostatic (iii) the Pauli repulsion and (iv) geometric distortion contributions lead to the conclusion that low values of ΔE is predominantly due to the changes in electrostatic contribution when going from substrate (1) to transition state TS(1-2). In addition orbital interaction term is not negligible in stabilization of TS(1-2). Furthermore, ETS-NOCV revealed that the existence of ΔE is mainly due to the change in Pauli repulsion contribution. The reorganization energy of the reactants contributes less significantly to the destabilization of TS(1-2). Finally, our results provided the information what types of catalyst could be used in the future to provide relatively low values of B-H activation barriers. Further investigation on other catalysts for dehydrogenation of AB are ongoing.

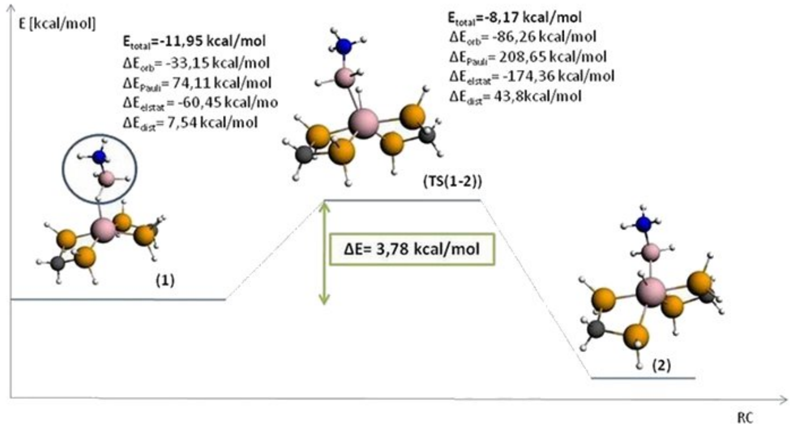

Fig. 1: Activation of B-H Bond in Ammonia Borane.

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Molecular dynamics modeling of half-metallocene titanium(IV) ethylene polymerization catalysts

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In the present work results of molecular dynamics simulations of half-metallocene titanium(IV) catalysts are presented. Molecular systems under consideration include non-bridged half-metallocene titanium complexes with aryloxo ligand acting as catalysts in ethylene polymerization process. Catalysts with various ligands and at various catalytic process stages are considered.

Methodology includes Car-Parinello molecular dynamics on the *ab initio* DFT level (CPMD software package) and Born-Oppenheimer molecular dynamics on the semiempirical level (MSINDO software package). Despite lower accuracy semiempirical approach is still useful due to ca. 3.5 orders of magnitude difference in performance comparing to DFT approach. Such performance allows for simulations on the timescale far beyond *ab initio* methods. Free molecular dynamics is used to study spontaneous transitions (including conformational changes and ethylene insertion reactions). Constrained molecular dynamics in slow-growth approach is used to obtain free energy profiles of ethylene insertion reaction.

Presented results include spontaneous conformational transitions affecting catalyst reactivity. Example where six stable conformations (including several transitions between them) can be observed on one simulation is also presented. Spontaneous insertion of ethylene is observed, followed by conformational changes which make catalytic cycle one simulation.

Projections of presented trajectories (i.e. plots of selected coordinates) as well as animated visualizations are presented.

Prediction of three dimensional structure of protein complexes

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Docking is one of the most commonly used techniques in drug design. It is employed for both identifying correct poses of a ligand in the binding site of a protein as well as for the estimation of the protein-ligand interaction strength. Since millions of compounds must be screened, before identifying suitable target for biological testing, all calculations should be done in a reasonable time frame. Thus all programs currently in use exploit empirically based algorithms, avoiding systematic search of the conformational space. Similarly, the scoring is done using simple equations, which allows speeding up the entire process [1]. Therefore docking results have to be verified by subsequent in vitro studies [2].

The purpose of our work was to evaluate seven popular docking programs (Surflex, LigandFit, Glide, GOLD, FlexX, eHiTS and AutoDock) on the extensive dataset composed of 1300 protein-ligands complexes from PDBbind 2007 database [3], where experimentally measured binding affinity values are also available. We compared independently the ability of proper posing (according to RMSD of predicted conformations versus the corresponding native one) and scoring (by calculating correlation between docking score and ligand binding strength). To our knowledge it is the first large-scale docking evaluation, with more than 1,000 protein-ligand pairs and covering the wide diversity of different protein families and inhibitor classes. Our results clearly show that using existing software ligand binding conformation could be identified in most cases, yet we still observe the lack of universal scoring function for all types of molecules and protein families.

Acknowledgements: Calculations were performed at the Interdisciplinary Center for Mathematical and Computational Modelling. This work was supported by Polish Ministry of Science and Higher Education N301 159735 grant.

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TD-DFT study of the bandgap in a series of poly(aryl-ethynylene)s

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In the last years, great efforts have been devoted to improve the electronic properties and solve the processability problems arising from the use of conjugated polymers. Different kinds of conjugated polymers and materials based on small organic molecules which show suitable properties for their use in optic and electronic applications such as organic light-emitting diodes (OLEDs), photovoltaic cells and field-effect transistors have already been synthesized [1]. Compounds in which heterocycles such as thiophene or thiadiazole and phenyl units are alternated have been widely studied due to their desirable chemical and electrical properties, i.e. narrow bandgap, low intramolecular reorganization energy in electron-hole transport processes, chemical and thermal stability, high persistence length or formation of liquid crystalline mesophases [2-4]. Furthermore, when those aromatic heterocycles and phenyl units are linked through acetylene groups, a π-system extended over the whole molecular structure, called poly(aryl-ethynylene) or PAE is obtained. As consequence of the axial symmetry of the triple bond, the conjugation of these molecular wires is maintained in different degrees between adjacent aryl groups at different relative orientations. In general, rotational barriers as small as 1 kcal mol^{-1} have been found for PAE systems. Hence, this kind of extended π-systems can have a wide variety of applications where efficient charge transport, fast energy transfer and good luminescence properties are required.

An interesting magnitude, as concerns polymer solar cells, is the optical bandgap. In general, the photocurrent in these devices is limited by the overlap between the absorption spectrum of the polymer and the spectrum of the sunlight which reaches the maximum photon flux at around 1.6–1.8 eV [12]. Hence, it would be useful to have appropriate theoretical methodologies to predict that property in order to rationalize the design of the future materials with improved features. Thus, the aim of this work is to test different time dependent (TD) DFT methods (TD-PBE0, TD-HSE06, and TD-M06-2X) to calculate the bandgap in a series of PAE oligomers and estimate the value of that property for the limit polymer through the oligomeric approximation. The estimated values will be compared with the reported experimental values in order to analyze the deviation of each method with respect to those values.

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DFT and *ab initio* modeling of bioinorganic iron complexes with non-innocent ligands

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Armed with multireference ab inito CASSCF/CASPT2 method in addition to, now standard, DFT calculations, we investigate the electronic structure of biologically relevant iron complexes with non-innocent ligands [1]. In this contribution we focus on iron(II)-nitrosyl ($FeNO^7$) complexes and high-valent iron-oxo complexes with organic macrocycles.

Our survey for the $FeNO^7$ complexes [2] includes both heme and non-heme species, in doublet ($S = 1/2$) and quartet ($S = 3/2$) electronic state, focusing on the electronic structure and NO binding energies. The CASSCF calculations clearly demonstrate a strong left-right correlation in the Fe-NO bond already at the equilibrium geometry. In order to translate this multireference description into a chemical language the CASSCF wavefunction is transformed to the basis of localized Fe 3d and NO π^* orbitals. This analysis points to a mixture of Fe^{II}-NO^0 and Fe^{III}-NO^- resonance structures in comparable contributions for various coordination environments and independently of the spin state. This is in a sharp contrast to the behaviour of spin densities, which dramatically change going from the doublet to the quartet state or in response to addition/removal of the sixth axial ligand. The spin densities are also very sensitive to the choice of the exchange functional in DFT calculations, with a striking difference between hybrid and non-hybrid functionals [3]. Our study shows that the spin densities from non-hybrid functionals most closely follow the CASSCF ones.

In the second part we discuss some new results for high-valent iron-oxo (FeO) complexes with porphyrin and other macrocyclic ligands. Here we focused on the problem whether the iron-oxo porphyrin complexes, usually described as iron(IV)-oxo cation radicals (Compound I species), may also have low-lying iron(V)-oxo electromers [1,4]. This poses the question whether the porphyrin ring could remain innocent in the presence of Fe(V) [1], which might be relevant to eventual role of the putative iron(V)-oxo electromer in the catalytic cycle of cytochrome P450 [4]. To this end, the DFT, CCSD(T), and CASSCF/CASPT2 relative energies of iron(IV)-oxo-(cation radical) vs iron(V)-oxo states will be presented for model complexes, with stress on DFT calibration against the ab initio results.

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Complex formation between substrates and escort molecules in the combat against multidrug resistance in bacteria

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Multidrug resistance (MDR) occurs mainly due to the presence of efflux pumps that can remove a broad-range of compounds from the bacterial cell. One way of combating MDR involves inhibition of efflux pumps using a variety of structurally unrelated molecules that come from various sources (natural products, drugs, synthetic analogues etc) [1]. This mechanism involves binding of the inhibitor to the hydrophobic regions of the efflux pump in a competitive or non-competitive manner or alternatively, the antibacterial drug might form a complex with an escort molecule which can bypass the efflux pumps responsible for MDR [2]. The current study investigates the latter mechanism.

The online database Super Drug was screened for molecules that might potentially complex with norfloxacin (NOR) and 89 drugs with the highest similarity (Tanimoto coefficients) to known efflux pump inhibitors were selected. The structures of these drugs were imported into VegaZZ and a 3000-step energy minimization applied using the SP4 force field. The minimised drug molecules were subjected to docking protocols with NOR as the target using the GLUE software package. It was found that the majority of selected drugs exhibited favourable binding energies with NOR.

The interactions present within the complex were inspected using VegaZZ and the molecular lipophilicity potential (MLP) surface calculated along with various other physical-chemical properties. Most dominant interactions between the drug and NOR molecules were aromatic face-to-face interactions. Evaluation of the various physical-chemical properties also pointed out that complexation would increase the lipophilicity of NOR allowing it to pass through the membrane with greater ease.

Minimum inhibitory concentration (MIC) assays and modulation assays were performed as described previously [2] to determine the antibacterial activity of ten chosen molecules against *Staphylococcus aureus* SA1199B. It was found that chlorpromazine and apomorphine exhibited weakly potentiating activity as the MIC of Nor was decreased 2-4-fold. NMR, UV and mass spectrometry data acquired confirmed the presence of interactions between NOR and the escort molecules.

This study therefore provides evidence of complex formation between efflux pump substrates (NOR) and escort molecules, and suggests that those molecules exhibiting good binding energies might also exhibit potentiating activity depending on the molecular properties of the complex between a drug and an antibiotic.

Acknowledgements: The authors would like to thank the Engineering and Physical Sciences Research Council (EPSRC) for providing studentship funding.

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Potential energy surfaces for hydrogen adsorption on beryllium doped graphite

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Carbon-based adsorbents are promising materials for hydrogen storage. However hydrogen adsorption energy for pure carbon material is to low for commercial applications. One of the methods which allow increase adsorption energy of carbon-material is doping by foreign atoms.

In this work a $C_{32}H_{14}$ graphene (figure below) was adopted as a graphite surface model. Structures of beryllium substituted graphene ($C_{31}BeH_{14}$) and series of di-substituted graphene ($C_{30}Be_2H_{14}$) with beryllium atoms separated by the C_0-C_4 linker were optimized using density functional theory. Potential energy surfaces for hydrogen adsorption on investigated materials were calculated applying the MP2 level of theory.

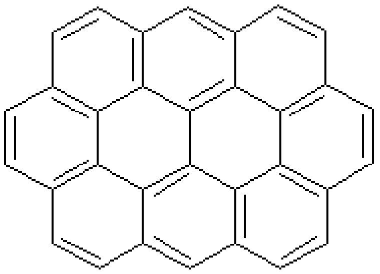

Fig. 1: $C_{32}H_{14}$ graphene

Theoretical investigation of structural and electronic effects in the metalation of tetrapyrroles

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The formation of tetrapyrrolic complexes (porphyrins, chlorins, bacteriochlorins) with different metal ions became very interesting due to their numerous applications in catalysis and medicine, e.g. in photodynamic therapy. On the other hand, transmetalation of chlorophylls readily takes place in plants grown on soils polluted with heavy metal salts.

It is known that the central metal ion strongly influences the photophysical and chemical properties of tetrapyrroles, therefore the investigation of mechanisms of central metal insertion and/or exchange as well as factors which govern these processes are of utmost importance for chemists and biochemists dealing with tetrapyrrolic compounds.

The aim of the present studies is to establish the structure-activity relationships in interactions of selected divalent meal ions with functionalized derivatives of porphyrins using theoretical and experimental methods.

A series of eight tetrapyrrolic ligands in which structural elements were systematically varied was synthetised and their reactivity with reactive Zn^{2+} and inert Pt^{2+} investigated using absorption spectroscopy. In parallel, quantum chemical calculations within density functional theory (functional Becke-Perdew, all electron basis sets of TZVP quality, Resolution – of – Identity approach with Turbomole v. 5.8) were performed for the same set of molecules to examine the influence of structural and electronic factors on the energies of frontier orbitals, the nucleophilicity/electronegativity of the macrocycle, its hardness and conformation. These static descriptors of chemical reactivity, relevant to metallation reactions, were verified against the results obtained in experimental studies.

In terms of chelator structure, the largest effects concern the size of the delocalized π-electron system and the presence of side groups. Both the DFT calculations and experimental results show the strong influence of the macrocycle rigidity and of peripheral groups on the chelating ability of porphyrinoids. In particular, the peripheral functionalization of the macrocycle system seems to drastically reduce its reactivity towards metal ions. The effect of peripheral groups is two-fold: (i) a lower electron density on the core nitrogens, and (ii) increased rigidity of the macrocycle. Moreover, the experimentally obtained kinetic data clearly show that the solvent has a crucial role in the activation of the incoming metal center.

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Structural basis of the uniform binding of different tRNAs by a ribosome

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To synthesize proteins a ribosome uses different tRNAs, which function equivalently. Measurements of tRNAs binding to the complementary anticodons on the ribosome show that several anticodons transplanted into $\mathrm{tRNA_2}^{\mathrm{Ala}}$ bind poorly as compared to the binding in its natural sequence [1]. Experiments indicate also that the 32-38 pair participates in adjusting tRNA affinity to the ribosome [2].

We have examined conformational dynamics of $\mathrm{tRNA_2}^{\mathrm{Ala}}$ anticodon loop, two chimeric loops combining $\mathrm{tRNA_2}^{\mathrm{Ala}}$ with $\mathrm{tRNA_2}^{\mathrm{Arg}}$ and $\mathrm{tRNA_2}^{\mathrm{Ala}}$ A32U mutant, using molecular modeling and molecular dynamics simulations. Chimeric $\mathrm{tRNA_2}^{\mathrm{Ala}}$ with the arginine anticodon, which shows poor binding to the ribosome, in our multiple MD simulations displayed convergence of the A32-U38 pair into Watson Crick geometry, not seen in the canonical form of tRNA. Other anticodon loops investigated in this study, which in experiment bind to the ribosome, formed non-canonical 32-38 pair.

Acknowledgements: J.S was supported by a scholarship from the Kosciusko Foundation.

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Origins of enhanced thermodynamic stability of 2'-O-methyl RNA/RNA duplexes with single LNA-2-thiouridine residue studied by molecular dynamics and free energy simulations

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Oligonucleotides have a wide range of applications in biotechnology and medicine. Properties of the oligonucleotides can by modulated by various chemical modifications.

2'O-methyl (2'O-Me) oligonucleotides are resistant to ribonucleases and form more stable hybrids with complementary RNA strands than equivalent RNA sequence. Locked nucleic acids (LNA), in which the ribose sugar is locked in C3'-endo conformation by a O2',C4'-methylene linkage, show exceptional thermodynamic stability when hybridized to complementary RNA. The 2-thiouridine (s^2U) modification enhances stability of A-s^2U base pair but not of G-s^2U base pair, thus increases selectivity of binding.

Experimental studies have indicated that LNA incorporated into the 2'O-Me-RNA strand enhances the stability of complementary duplexes formed with RNA. Additional improvement of binding and selectivity has been achieved by incorporation of LNA-2-thouoridine into LNA-2'OMe-RNA/RNA duplexes [1].

Extraordinary stabilization by LNA has been commonly explained by enhanced stacking interactions and helical preorganization of the single-stranded oligonucleotides [2]. However the origin of enhanced thermal stabilities of LNA-containing oligonucleotides is not fully understood.

We have performed molecular dynamics (MD) simulations of 2'-O-methyl RNA/RNA heptamers with single 2'O-Me-2-thiouridine or LNA-2-thiouridine for the sequences previously studied experimentally. MD simulations were curried out using CHARMM27 force field.

Analysis of the MD simulations shows that performed modifications did not influence on the structure of the studied duplexes but reduced their flexibility. Incorporated s^2U modifications enhanced the stacking interactions. The changes of duplex formation free energy associated with substitution of 2'O-Me-U by 2'O-Me-s^2U or LNA-s^2U were calculated by the free energy perturbation method. The calculated increase of the duplex stability is in good agreement with experimental thermodynamic data.

MD simulations revealed changes in the local hydration of the methylated strand upon s^2U and LNA modifications. Duplexes with LNA modification in the methylated strand show water bridges between O2' atom of LNA and O4' atom of the 3'-residue.

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Computational study and analysis of infrared spectra of uridinemonophosphate

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Calculations of IR spectra were performed using the DFT B3LYP method for the uridinemonophosphate with charge 0 (Ump), -1 (Ump-1) and -2 (Ump-2). In the future we plan to use these calculated IR spectra for assigning the experimental IR spectra of relevant model compounds, including the phosphate group in connection with our project on cleavage reactions in catalytic RNAs.

The conformational study was focused on the dependence of IR vibrations on torsion angles near the phosphate and on glycosidic torsion (Figure 1). The total energies of the Ump, Ump-1 and Ump-2 nucleosides with different sugar-to-base orientations differed by less than 10 kcal/mol. The IR spectra of the nucleosides depend noticeably on charge and conformation. For example, the peak at ~1100 cm^{-1} assigned to the CH_3-PO_4 stretch increases as the charge decreases: 1095 cm^{-1} for UmP, 1097 cm^{-1} for Ump-1 and 1101 cm^{-1} for Ump-2.

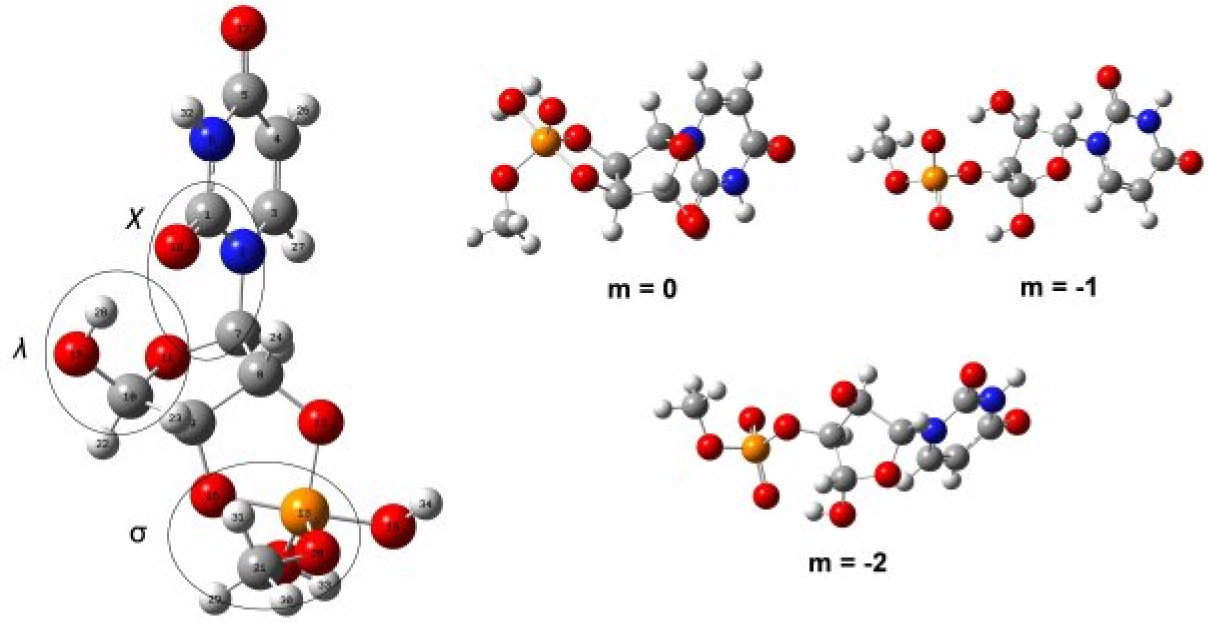

Fig. 1: The χ, λ and σ torsion angles in Ump nucleosides were varied (left). Sketch of the UmP, Ump-1 and Ump-2 nucleosides is depicted on the right.

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First–principles analysis of formation and reactivity of oxametallacycle intermediate on Au and Pt clusters

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There is a need to develop electrocatalytic materials appropriate for oxygen insertion reactions to double bonds. Specific reactivity could be achieved using metal nanostructured electrodes. In order to understand the mechanism of these reactions, the quantum chemical study of ethylene oxidation on Au and Pt clusters was carried out.

Prior to the modeling of ethylene oxidation, three-dimensional structures of Au_n and Pt_n ($n \leq 22$) clusters were optimized by the DFT/B3LYP without any symmetry constraints. In the case of Pt clusters different electronic configurations were examined. Optimized Au_{22} and Pt_{21} cluster structures were used in the following study of the process of ethylene oxidation by triplet or singlet oxygen. Figure 1 shows optimized structures of two possible stable surface oxametallacycle intermediates Au_{22}-C_2H_4O and Pt_{21}-C_2H_4O.

Optimized oxametallacycle intermediates were used for the search for transition states. Calculated energetic of the reaction paths including transition states enables us to better understand the individual elementary reaction steps and preferred products of reactions.

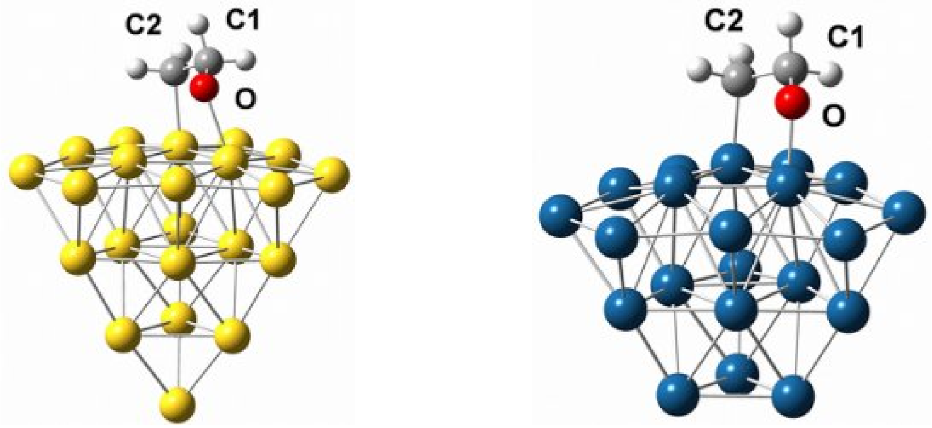

Fig. 1: Two possible oxametallacycle intermediates for the clusters Au_{22}-C_2H_4O (^1A) (left) and Pt_{21}-C_2H_4O (^9A) (right)

Acknowledgements: The access to the METACentrum supercomputing facilities is highly acknowledged.

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Competition between $\boldsymbol{\pi}-\boldsymbol{\pi}$ conjugation and n-$\boldsymbol{\sigma}^*$ hyperconjugation in heteroatomic analogues of butadiene

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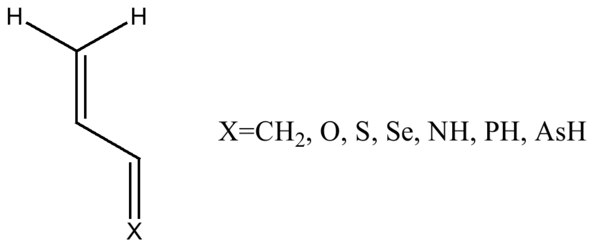

It is well recognized that structural properties of butadiene and its heteroatomic analogues are determined by π-π conjugation between double bonds. Usually it is postulated that replacement of terminal CH_2 group by heteroatom results in strengthening conjugation due to polarization of π-system of molecule. However, recent theoretical investigation of structure of derivatives of cyclohexene containing exocyclic double bond demonstrated disagreement with this common viewpoint [1]. Therefore, it was performed more detailed investigation of intramolecular interactions in butadiene and its heteroatomic analogues.

Increase of degree of conjugation between two double bonds should lead to shortening of central single C-C bond accompanying by increase of its order and other characteristics describing conjugation. However, results of calculations by MP2/aug-cc-pvtz method demonstrate that this bond in the oxygen- and nitrogen-containing molecules is longer as compared to butadiene. This indicates weakening of π-π conjugation between double bonds. Decrease of electronegativity of heteroatom results in shortening of single C-C bond and increase of conjugation in contradiction with common viewpoint.

Careful analysis of intramolecular interactions in molecules under consideration using NBO theory reveals existence of n-σ^* hyperconjugation between lone pair of heteroatom and antibonding orbital of single C-C bond. Energy of this interaction is the highest for the oxygen- and nitrogen-containing molecules and it becomes significantly smaller with decrease of electronegativity of heteroatom. Taking into account that this interaction results in some population of antibonding orbital of the C-C bond it should lead to weakening of this bond accompanying by its elongation.

Thus, geometry of heteroatomic analogues of butadiene is determined by two opposite interactions namely the π-π conjugation between double bonds leading to shortening of single C-C bond and the n-σ^* hyperconjugation causing weakening and elongation of this bond. In the case of the oxygen- and nitrogen-containing molecules strong hyperconjugation overpowers conjugation leading to elongation of single C-C bond. Protonation of heteroatom results in significant weakening (for X=O) or complete disappearance (for X=NH) of hyperconjugarion causing shortening and strengthening of this bond.

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Theoretical study of interactions between VEGFR2 and newly-designed inhibitors

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Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is considered a key component in initiation of new blood vessel creation [1]. Its importance in controlling the process of angiogenesis, particularly tumor angiogenesis, makes it a very attractive target of many recent studies focused on searching for its suitable inhibitors. Decreasing the activity of VEGFR2 by its inhibition is believed to be a possible way to treat cancer diseases [2, 3].

In our research a set of newly-designed structures with presumed inhibitory effect on VEGFR2 was proposed and theoretically tested. An idea of fragment-based ligand design was used to generate a family of structures by linking two fragments originating from known inhibitors with a flexible linker. New inhibitors were meant to accommodate better in the receptor binding site compared to the parent inhibitors. On the basis of this assumption a stronger interaction with receptor was expected.

Autodock Vina was used to perform molecular docking of the designed inhibitors in order to find their suitable positions fitting to the binding site [4]. Then the interaction energies for interaction region (a part of VEGFR2 representing the binding site and its close surroundings) and all newly-designed inhibitors were calculated using the PM3-D method. The results were compared to the interaction energies calculated for original inhibitors (and their fragments). Then the "best-evaluated" structures were interpreted. The Polarized Continuum Model (PCM) was used to include solvent effect into the calculations.

Acknowledgements: Support from UGA (Matej Bel University Grant Agency) grant No. I-09-00029 is acknowledged.

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DFT calculations of cobalamin-DNA and cobalamin-RNA interactions in B12-retro-riboswitches

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Cobalamins, active forms of vitamin B_{12}, may directly interact with nucleotide environment in covalent models and act as riboswitches [1]. Cobalt corrinoids are not only cofactors required to biologically activate B_{12} dependent enzymes, but also have abilities to control methyl group transfer process as molecular switches. Cobalamins can be switched between the „base-on" and the „base-off" forms by themselves, which could be a common occurrence in metabolite binding riboswitches called "Retro-switching" [2].

The density functional theory (DFT) calculations of complete cobalt corrinoids structures incorporated with thymine and guanine (Figure 1) were carried out. Cobalt corrinoids structural data along with calculations of the Co-C bond strength were obtained. Electronically excited states of cobalamin were calculated and then compared to experimental data. Obtained results help in finding out the properties and behavior of cobalt corrinoids interacting with nucleic acid moieties and in analyzing the influence of nucleic acids on cobalamins structures.

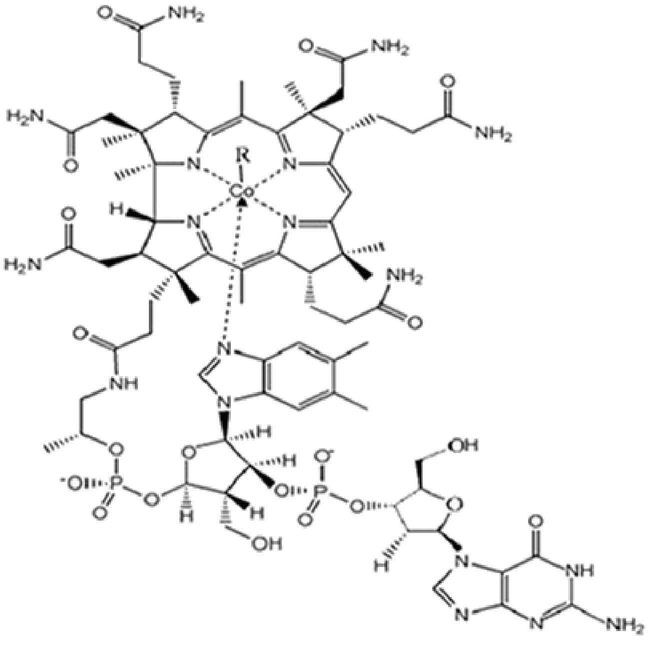

Fig. 1: Molecular structure of cobalamin incorporated with guanine.

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Electronegativity equalization method in force field atoms resolution

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Charge sensitivity analysis (CSA) was formulated in the nineties [1]. The formalism is rooted in density functional theory (DFT) and can be applied at different resolutions: local, molecular orbital, atoms-in-molecule (AIM), fragment and global. It refers to such concepts as electronegativity and hardness/softness data; all of them are rigorously defined within DFT. CSA provides a thermodynamic-like description of the system's equilibrium charge distribution and allows to describe its response to external potential and/or electron population perturbations. It has normally been used as a method complementary to *ab initio* calculations but it can likewise be treated as an independent semi-empirical method. One of the realizations of CSA is Electronegativity Equalization Method (EEM) for evaluating the charge distribution in a molecule at global equilibrium [2].

EEM is a very fast method and is usually adopted in AIM resolution in molecular mechanics/dynamics (MM/MD) software for computing initial charge distribution. It should be expected that by extending CSA to force field atom resolution the area of its application will be enlarged, e.g., to polarizable force fields. To enable this the atomic hardnesses and electronegativities have to be parametrized. This is the goal of our work. The AMBER force field has been employed here and the set of parameters for all standard atom types of the force field has been determined by fitting to the ab initio charge distribution of a set of test molecules. *Ab initio* charges were obtained via two methods, namely Mulliken population analysis (MPA) and charges derived from electrostatic potential fitting procedure. The optimization was performed with an evolutionary algorithm on a population of 50 entities.

The results obtained were satisfactory. The agreement between ab initio and EEM charges was good, especially for MPA charges. The correlation coefficient R^2=0.9699 was obtained, which is accurate enough to start applying EEM in the MM/MD calculations.

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Theoretical studies of the mechanism of nucleotides formation in prebiotically plausible conditions

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The question of the origins of life on Earth is perhaps one of the most fundamental and ancient, however, only recently the development of chemistry and biology allowed the scientists to examine the possible ways of formation of biological compounds from simple inorganic substrates. Perhaps one of the most widely recognized experiments in this field, related to the provenance of the earliest living organisms, was performed in 1950s by Miller and Urey. They demonstrated that the organic molecules (including amino acids) can be created in a fairly simple electrical discharge processes in a chamber containing inorganic compounds like ammonia, water, hydrogen, methane, carbon dioxide etc.

Unfortunately, the attempts of synthetic formation of ribonucleotides from nucleobases and a ribose sugar and phosphate for many years remained unsuccessful. Not until 2009 was the first RNA nucleotide synthesized in a prebiotically plausible conditions by Powner *et al.* [1]. The Authors proposed an entirely different pathway for pyrimidine ribonucleotide synthesis, in which the sugar and nucleobase emerge from a common precursor *i.e.* 2-aminooxazole (Fig. 1).

The main goal of the present study is an *ab initio* determination of the molecular mechanism of cytosine nucleotide synthesis, according to the reaction path suggested by Powner *et al.* In particular we investigate the first part of the multistage reaction – the formation of 2-aminooxazole from inorganic substrates.

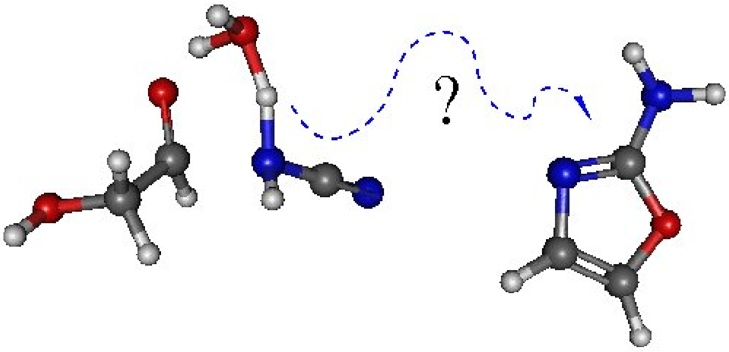

Fig. 1: Schematic drawing showing a preliminary transition state of the inorganic substrates: cyanamide, glycolaldehyde and water molecule and final product *i.e.* 2-aminioxazole

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

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Binding isotope effects on M_4 and H_4 isoforms of L-lactate dehydrogenase

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Lactate dehydrogenase (LDH) catalyses reversible conversion of pyruvate to lactate in the presence of its natural cofactor, nicotinamide adenine dinucleotide (NADH). Human serum normally consist 5 isoenzymes, which differ in electrophoretic mobility, and other properties. Each enzyme appears to be a tetramer composed of "H" and "M" polypeptide chains. Five combinations are possible: HHHH (H_4 or LDH-1), HHHM (H_3M or LDH-2), HHMM (H_2M_2 or LDH-3), HMMM (HM_3 or LDH-4), and MMMM (M_4 or LDH-5). Isoenzymes containing large proportions of H subunits tend to predominate in tissues with aerobic metabolism (e.g. heart) while isoenzymes containing mostly M subunits are found in tissues with considerable anaerobic metabolism (e.g. skeletal muscle and liver).

The mechanism and significance of the inhibition of LDH by high concentrations of pyruvate has been the subject of considerable experimental scrutiny and discussion. The H_4 isoenzyme is much more sensitive to this type of inhibition than is the M_4 isoenzyme and this has provoked us to study the interaction and binding isotope effects (BIEs) of ligands capable of binding in active sites of two different isoforms of human LDH-1and LDH-5.

In the present study we used two crystallographic structures; one of the human heart (PDB ID 1I0Z) and one of the human skeletal muscles (PDB ID 1I10). The examined ligands are: the natural substrates of LDH — pyruvate and L-lactate — and the natural inhibitors — oxamate and D-lactate.

Geometric optimization was performed using QM/MM methods as implemented in the QSite program. In our model, apart from oxamate, important residues such as Gln99/100, Arg105/106, Asn137/138, Leu164/165, Arg168/169, His192/193, Ala237/238 and Thr247/248 were also included in the QM region, which was described by the B3LYP functional expressed in the 6-31G++(d,p) basis functions. The rest of the protein and solvent water molecules were treated by the molecular mechanics OPLS-AA 2005 and TIP3P force fields. Finally, theoretical values of binding isotope effects (BIEs) were calculated using the ISOEFF program.

Acknowledgements: This work was supported by Grant NN204/1579/33 from the Ministry of Science and Higher Education, Warsaw, Poland. Access to Polish national computation facilities at Cyfronet, Cracow; PSSC, Poznan; and ICM, Warsaw, is acknowledged.

Modeling the electron density kernels

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Kernels are important non-local functions defined at the conceptual level of the DFT [1]. Little is known about the nature of kernels. There have been several trial function for the hardness kernel [2] also several models for softness kernel have been reviewed [3,4]; all have been based on the Vela and Gaquez proposal, which has been explored and proved useful in quantifying the Fukui functions. The formula is excellent inasmuch as it conforms to all known requirements for the softness kernel. However, this local approach entirely neglects the electron correlation effects within the softness kernel. More elaborate versions have also been proposed. They all contain the local term – the Dirac delta.

The aim of this study is to investigate properties of kernel quantities, by extending the approximation in the softness kernel beyond the Dirac delta, thus making it at least in some way non local. There are two possible ways of doing that:

- replacing the Dirac delta by its non-local counterpart, the normal Gauss function
- introducing a symmetrical role of both points connected by the softness kernel.

By applying this method, the softness kernel becomes continuous functions in space and may be used to calculate the linear response function of the electron density. For a given point of space, each of this functions can be visualized in 3D. The hardness kernel has been modelled separately by using the Mataga-Nishimoto approximation and the softness kernel.

Planar and 3D visualization of the softness kernel, linear response function and the hardness kernel have been presented for atoms.

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

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Rational design of linked gold nanocrystals for electronics

Damien Thompson, Michael Nolan, Aidan Quinn

Tyndall National Institute, University College Cork, Ireland

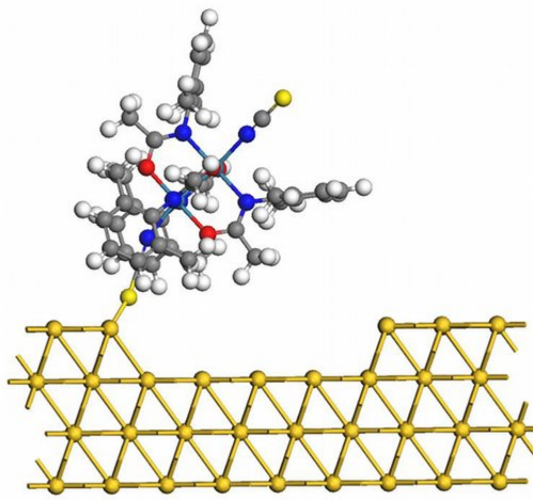

Fig. 1: Re-based linker molecule adsorbed on a nanoparticle surface “edge” site.

This poster describes how the design of functionalised nanoparticles for electronics and medical diagnostics applications [1] has been recently advanced by insights gleaned from multi-scale simulations [2]. The combination of molecular and periodic electronic structure calculations, together with classical simulations based on the derived molecule-surface potentials, provides a powerful means for understanding how molecules adsorb and assemble on the nanoparticle surface, and serves to explain some observed properties of aqueous multi-nanocrystal assemblies.

Adsorption of the functional linker molecule involves competitive replacement of citrate protecting groups on the nanoparticle surface. The citrate protecting group becomes less strongly bound as the relative population of coordinatively-undersaturated gold sites increases, i.e., as the nanoparticle radius becomes smaller. In contrast, the linker molecule becomes more strongly bound as the surface roughness increases. This has the combined effect of narrowing the gap in adsorption energy between the protecting group and the functional linker, increasing the likelihood of replacement of a protecting group by a functional linker molecule on the nanoparticle surface. Surface roughening penalises binding of the trivalent citrate with its three carboxylates, while favouring binding of the monovalent linker with its single thiocyanate anchor per nanoparticle.

Classical simulations were used to determine the degree of counterion stabilisation of the citrate protecting groups at the solvated nanoparticle surface and quantify the conformational space available to the second thiocyanate anchor when the linker is bound to one nanoparticle. Taken together the electronic structure and classical molecular dynamics data provide the atom-scale features of nanoparticle-linker-nanoparticle contact junctions.

Acknowledgements: Travel support from Enterprise Ireland (EI) project ORD3D is acknowledged, together with research funding from EU FP7 FunMol. Calculations were performed using Science Foundation Ireland (SFI)-supported computing resources at Tyndall National Institute and at the Irish Centre for High-End Computing (ICHEC).

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Does nonplanarity of nucleic acid bases affect NMR parameters?

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The glycosidic torsion angle χ is used as a measure of the nucleobase orientation with respect to sugar ribose in nucleosides and it is one of the major determinants of nucleic acid structure. The deformations from planar geometry arrangement in the deoxy-adenosine (dA), deoxy-cytidine (dC), deoxy-guanosine, and deoxy-thymidine (dT) nucleosides due to variation of the glycosidic bond orientation were investigated with the computational methods and the calculated trends were correlated with the X-ray data [1].

One of the methods often used for determination of the χ torsion is NMR spectroscopy. Correlation between value of ^{3}J-coupling and corresponding torsion angle is described by Karplus equation [2]. Our study showed that angular argument of Karplus equations for the ^{3}J(C8/6-H1') and ^{3}J(C4/2-H1') couplings assigned to the χ torsion, must reflect deformation from ideal tetrahedric and planar spatial arrangement of atoms around carbon C1' and/or nitrogen N9/1 involving in the χ torsion, respectively (conception of ideal tetrahedric and planar spatial arrangement consist in using of constant phase shift in Karplus equation [3]). Whereas, the calculated magnitude of the deformations revealed to be large at the side of the glycosidic nitrogen N9/1 (pyramidalization), the deformation of the arrangement around the carbon C1' (sugar side) was relatively smaller. The pyramidalization depends significantly on the χ torsion, namely the orientation of the pyramidalization (up and down). The magnitude of pyramidalization is also slightly different for molecules with different sugar conformation.

The deformation of the spatial arrangement of atoms around the carbon C1' and degree and orientation of the pyramidalization at the glycosidic nitrogen N9/1 affect mostly the phase factor in the Karplus equation for structural interpretation of the ^{3}J(C8/6-H1') coupling. The ^{3}J(C4/2-H1') coupling is effected slightly and only by deformation at the C1' arrangement.

The calculated dependence of pyramidalization on χ torsion for all deoxy-nucleosides shows similar behaviour, including the trends due to the sugar pucker.

Acknowledgements: This work was supported by the Grant Agency of the Czech Republic, grants no. P208/10/P398 and P205/10/0228.

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Molecular dynamics silulations of *Zoanthus* yellow fluorescent protein *in vacuo* and condensed phase

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The ability to localize, track and visualise organells and proteins in living cells is essential for understanding biological systems. It has become achievable by dint of fast development of fluorescent protein technology. The best known fluorescent protein is a green fluorescent protein GFP (PDB entry code 1EMB [1]) purified in 1962 from a jellyfish *Aequorea victoria.* More recently identified GFP-like protein is a yellow fuorescent protein zFP538 (PDB entry code 2OGR [2]) from coral *Zoanthus sp.* It is believed that due to the presence of additional 6-membered ring in the zFP538 chromophore, the absorption and emission maxima of yellow fuorescent protein is shifted to longer wave lengths in comparison to GFP chromophore.

zFP538 protein was investigated with the use of the molecular mechanical (MM) technique, using CHARMM27 [3] force field. MM energy minimisations and molecular dynamics (MD) simulations *in vacuo* and condensed phase were applied. In this work structural parameters of the chromophore, fluctuaction of the chromophore's atoms, energy and temperature deviations are discussed in terms of stability of the system.

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The mechanism of the reaction of intradiol dioxygenase with hydroperoxy probe. A DFT study

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Catechol 1,2 – dioxygenase (CatA) is a non-heme iron enzyme, found in soil bacteria, which takes part in aromatic degradation pathways. It binds dioxygen in a bridging fashion between iron (III) and catechol carbon. The catalytic cycle for CatA was investigated with computational methods using hybrid DFT with the B3LYP functional.

Different models of the first coordination sphere of iron were built and used in the search for intermediates and transition states defining the reaction path. 2-hydroperoxy-2-methylcyclohexanone was considered as substrate, since this compound is a probe reactant which was recently devised and tested by Xin and Bugg [1]. Based on chemical identity of the observed reaction products these Authors proposed a reaction mechanism where homolytic O-O bond cleavage leads to a reactive oxoferryl intermediate. This mechanistic proposal was tested with DFT calculations

The computational results suggest that protonation of the O-O group before O-O bond cleavage decreases an energy barrier for this step by about 10 kcal/mol and changes the chemical identity of the cleavage product, suggesting that the formation of the oxoferryl species is not strictly required, at least for this mechanistic probe. Indeed, the preferred mechanism of O-O cleavage does not involve oxoferryl species, since the homolytic dissociation of the O-OH bond is coupled to one electron oxidation of the phenol group of a tyrosine ligand. However, due to small energy difference between the barriers for two alternative reaction channels available for the reactive radical intermediate, the chemoselectivity of the reaction for this probe could not be unambiguously explained with the current models and methods.

In addition, theoretical studies were also performed for catechol, i.e. a native substrate, and they showed that O-O homolytic cleavage is the rate-limiting steps with an energy barrier of 34 kcal/mol in the ground state sextet spin state. Notably, this barrier is significantly lower on the quartet energy surface, with the calculated activation energy of only 18 kcal/mol. Since this barrier compares favorably with those previously found for alternative mechanisms of CatA [2], it suggests that the oxoferryl species is a likely intermediate in the reaction of CatA with the native substrate – catechol.

Acknowledgements: This project is a part of *Kraków Interdisciplinary PhD-Project in Nanoscience and Advanced Nanostructures* (MPD - Międzynarodowe Projekty Doktoranckie), financed by the European Union Innovative Economy Programme with the Foundation for Polish Science.

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CASPT2//CASSCF & CASPT2//DFT(BLYP) calculations for the *zFP538* protein chromophore – structure and spectral properties *in vacuo*

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Fluorescent proteins are very important group of proteins, that are very useful for labelling biological samples - cellular organelles, cells, tissues and whole multicellular organisms. These proteins are often used in a powerful technologies – i.e. in luminescence spectroscopy, as parts of biosensors and biodetectors or even to construct modern Organic Light-Emitting Diodes (OLED's).

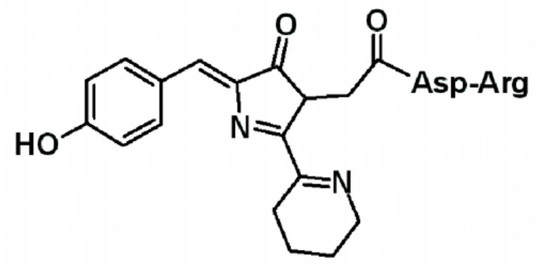

Fig. 1: Proposed structure of zFP538 chromophore [1].

As it was discovered, the chromophore of Yellow Fluorescent Protein from *Zoanthus sp.* (*zFP538*) contains three-ring structure [1]. It is important to note, that the other fluorescent proteins' chromophores usually contain only two-ring chromophores. The precise structure and properties of the *zFP538* protein chromophore are still not well known. A comparison of the structural and spectral properties for different types of chromophores can be possibly very useful to explain the dependencies between these two properties.

We used CASSCF and DFT(BLYP) computational methods to determine the structure of the chromophore in the ground state and fluorescent excited state. Moreover, we used CASPT2 methods to predict the basic spectral properties. We prepared two isomeric forms of the *zFP538* chromophore and took under consideration four different protonation states (cation, anion, neutral molecule and zwitterion). The comparison was made with theoretical and experimental data, when available. Additionally, the structural and spectral properties of *zFP538* and *GFP* chromophores were also compared.

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

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Reaction of pyridine and acridine derivatives with the hydrogensulphide anion – a model of quinacrine action on prion protein

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Conversion from the normal cellular form of prion protein (PrP^C) to a toxic one (PrP^{Sc}) is suspected to cause prion diseases. [1] This transformation can be prevented, at least in vitro, by quinacrine. [2] The acridine moiety of the quinacrine can undergo nucleophilic substitution with primary amines [3] and thiols [4] to afford acridine analogs, what was utilized in our laboratory during the study of acridinylation of free thiol groups of prion protein.

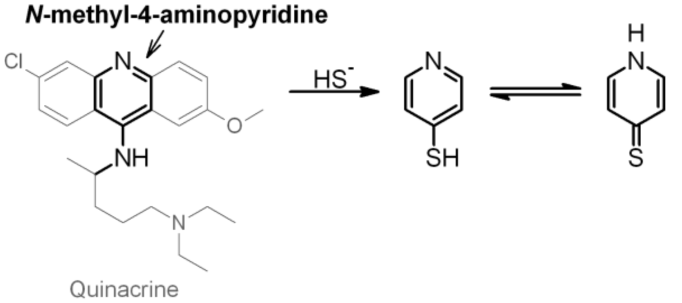

Fig. 1: Overall reaction of SH$^-$ anion, with *N*-methyl-4-aminopyridine in black.

To better understand the reaction, to improve reaction conditions and to rationally modify reactants, we modeled the acridinylation reaction theoretically, starting with simpler system: reaction of 4-chloropyridine with SH- anion. We found that the B3LYP functional with the 6-31+G** basis set and a dielectric solvent model provided realistic activation energies.

The calculated influence of different acridine substituents on activation energy of the reaction of 9-chloroacridines with SH- anion, as well as the facilitating effect of N-protonation on the reaction were consistent with experimental experience. A multi-step mechanism of the acridinylation reaction was suggested according to calculations of a model reaction of SH- anion with *N*-methyl-4-aminopyridine (Fig. 1).

Since the quinacrine is potential treatment for the Creutzfeldt-Jakob disease, which is believed to be caused by prion, we suggest that covalent bonding of acridine moiety to the prion protein free thiol groups may be crucial for quinacrine action in the disease treatment. The understanding of the acridinylation reaction mechanism thus might play an important role in the design of new acridine drugs.

Acknowledgements: This work was supported by the Czech Science Foundation (GA CR) grant no. 203/07/1517 and Research Project Z40550506.

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(Hyper)polarizability density analysis of molecular model systems

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Due to the potential applications of molecular materials in optoelectronics and photonics, quantities such as polarizability and hyperpolarizability, which describe interaction of matter with light at the molecular level, are intensively studied on purely theoretical basis with the aid of various quantum-chemical methods. Recently, great attention has been paid to the investigations of the interaction-induced electric properties. It has been well established that the properties of bulk might differ considerably from those of isolated molecules [1, 2]. One of the approaches to analyze the intermolecular interaction effects is the concept of the (hyper)polarizability density [2–4], which can provide information on the spatial contributions of electrons to (hyper)polarizability.

In this work the differential (hyper)polarizability density analysis has been performed for molecular model systems containing hydrogen bonds at the MP2 level of theory. Qualitative interpretation has been supported with numerical results obtained at the very same level of theory. It has been shown that visualization of (hyper)polarizability density makes a valuable supplement for data obtained from calculations of the interaction-induced properties.

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

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Wrocław University of Technology

MDMM

Modelling and Design of Molecular Materials

2010

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