Modeling & Design of Molecular Materials 2018

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Meeting programme

Sunday, 24.06.2018

14:00–19:00 Registration
19:00–22:00 Grill

Monday, 25.06.2018

9:00–9:15 Opening ceremony: prof. W. Bartkowiak – Vice Dean for Research of WUST Department of Chemistry

Advances in computational methods (chair: J. Leszczynski)

9:15–9:50 K. Szalewicz (Newark, DE, USA)
New generation of physics-based force fields with nearly exact long-range behavior

9:50–10:25 T. Clark (Erlangen, Germany)
Feynmann dispersion correction

10:25–11:00 T. Wesolowski (Geneva, Switzerland)
Multi-levels simulations based on Frozen-Density Embedding Theory

11:00–11:15 Coffee break

Modelling biomolecules (chair: B. Lesyng)

11:15–11:50 R. Wade (Heidelberg, Germany)
Computational approaches to protein target dynamics for drug discovery

11:50–12:25 N. Gresh (Paris, France)
Development, validations and applications of a polarizable ab initio molecular mechanics/dynamics potential

12:25–13:00 J. Korchowiec (Krakow, Poland)
Modeling lung surfactant interactions with benzo[a]pyrene

13:00–13:05 Conference photo

13:05–15:00 Lunch

Modelling electronic structure (chair: M. Hoffmann)

15:00–15:30 Z. Latajka (Wroclaw, Poland)
Noble gas compounds – theoretical studies of structure and nature of bonding

15:30–16:00 L. Komorowski (Wroclaw, Poland)
Imaging the bond reorganization by the reaction fragility spectrum

16:00–16:30 K. Strasburger (Wroclaw, Poland)
Accurate nonrelativistic wavefunctions and energies of the ground state and first excited state of the boron atom
16:30–17:00 J. Fanfrlik (Prague, Czech Republic)
Sigma-hole interactions of boron clusters
17:00–19:00 Poster session A (P1A – P26A)
19:00–21:00 Dinner

Tuesday, 26.06.2018

Modelling molecular materials (chair: T. Clark)

9:00–9:40 T. Head-Gordon (Berkeley, CA, USA)
Methods and models for condensed phase simulations
9:40–10:20 T.Brinck (Stockholm, Sweden)
Local surface properties in the design of nanostructured catalysts: regium bonds and beyond
10:20–11:00 W. Grochala (Warsaw, Poland)
How theory guided experiment in quest for analogs of magnetic precursors of oxocuprate superconductors
11:00–11:15 Coffee break

Modelling chemical reactions (chair: T. Brinck)

11:15–11:50 A. Mulholland (Bristol, UK)
Multiscale modelling for chemical biology
11:50–12:25 J. Burda (Prague, Czech Republic)
The thermodynamic and kinetic description of the reactions in solutions with constant pH
12:25–13:00 L. Gorb (Kiev, Ukraine)
Semi-empirical computational approach to analyze multistep biological and chemical reactions
13:00–15:00 Lunch

Modelling reactions, catalysts and biomolecules (chair: T. Borowski)

15:00–15:30 S. Shishkina (Kharkiv, Ukraine)
Study of intermolecular interactions in polymorphic modifications of biologically active compounds
15:30–16:00 W. Beker (Warsaw, Poland)
Bottom-up approach to biocatalyst design
16:00–16:30 M-B. Sarosi (Leipzig, Germany)
Closo-carborane derivatives of indomethacin methyl ester
16:30–17:00 R. Szabla (Warsaw, Poland)
Mechanistic insights into selective UV-induced self-repair of DNA lessions

17:00–19:00 Poster session B (P27B – P53B)
19:00–21:00 Dinner

Wednesday, 27.06.2018

Modelling molecular materials (chair: W. Grochala)

9:00–9:40 M. Head-Gordon (Berkeley, CA, USA)
Some advances in energy decomposition analysis
9:40–10:20 O. Prezhdo (Los Angeles, CA, USA)
Excited state dynamics at nanoscale interfaces for solar energy harvesting: time-domain ab initio studies
10:20–11:00 C. Czaplewski (Gdansk, Poland)
Molecular dynamics study ionic liquids: temperature dependence of ionic conductivity
11:00–11:15 Coffee break

Modelling biomolecules (chair: N. Gresh)

11:15–11:50 V. Moliner (Castellon, Spain)
DAD's not in charge of Me
11:50–12:25 A. Lodola (Parma, Italy)
Rational design of covalent inhibitorsi through QM/MM mechanistic modeling
12:25–13:00 A. Sikorski (Warsaw, Poland)
Motion in a crowded environment: the influence of obstacles mobility, size and model of transport
13:00–15:00 Lunch
14:30–19:00 Excursions
20:00–22:00 Conference dinner

Thursday, 28.06.2018

Modelling & design by alumni of Wroclaw universities (chair: Z. Latajka)

9:00–9:40 D. Leszczynska (Jackson, MS, USA)
Development of nanosensors based on graphene
9:40–10:20 J. Leszczynski (Jackson, MS, USA)
Towards improvement of solar cell efficiency – computational approach
10:20–10:40 B. Blasiak (Wroclaw, Poland)
Effective one-electron potentials – route for condensed phase quantum chemistry
10:40–11:00 M. Janicki (Wroclaw, Poland)
Photochemical properties of oxazoline prebiotic precursors of RNA nucleotides
11:00–11:15 Coffee break

Modelling molecular materials (chair: J. Burda)

11:15–11:35	M. P. Ciemny (Warsaw, Poland) *A simulation environment for efficient modeling of proteins and their peptide complexes: CABS-flex and CABS-dock*
11:35–11:55	M. Ingr (Zlin, Czech Republic) *Interactions of hyaladhedrins with hyaluronan and its neutral analog*
11:55–12:15	K. Bojarski (Gdansk, Poland) *Microsecond scale MD study of a protein-heparin complex*
12:15–12:35	S. Zaczek (Lodz, Poland) *Ligand-driven conformational dynamics influences selectivity of UbiX*
12:35–12:55	M. Szczepanska (Katowice, Poland) *Theoretical perspective on photochemical properties of hydroxocobalamin and aquacobalamin*
12:55–13:00	Meeting conclusion
13:00–14:30	Lunch

Lectures

New generation of physics-based force fields with nearly exact long-range behavior

Krzysztof Szalewicz

Department of Physics and Astronomy, University of Delaware, Newark, Delaware 19716, USA

Simulations of condensed phases and biomolecular systems, as well as material design have become mainstream methods in science and engineering and are expected to become even more important as computers pass the exaflop performance threshold. All such calculations require values of potential energies and forces. Currently, these are mostly either taken from empirical potential energy surfaces (PESs) or computed on-the-fly using density-functional theory (DFT) methods. An alternative to these two approaches are physics-based PESs fitted to *ab initio* calculations (APES) for dimers and trimers. In particular, symmetry-adapted perturbation theory (SAPT) is well suited for such calculations due to its seamless connection to asymptotic interaction energies. APESs predict interaction energies that are much more accurate than either those from empirical PESs or from DFT calculations. At the same time, the resources needed for molecular dynamics simulations with APES are only a few times larger than in the case of empirical PESs. The APES approach has been used less frequently than the other two mainly since the generation of APESs used to be very human-time consuming.

To bring APES to the forefront of the field, a new methodology was developed in our group. It includes the following modules: (a) *ab initio* calculations of interaction energies using SAPT [1] (any other suficiently accurate electronic structure method can be used as well); (b) SAPT-based calculations of asymptotic interaction energies [2] which provides an accurate description of a large subspace of the configuration space at essentially no costs; (c) automatic fitting of PESs (autoPES) [2]; (d) interface to molecular dynamics codes. All these steps are performed by running a single software package with input consisting just of monomer geometries.

AutoPES is capable of computing very accurate PESs for small dimers, sufficiently accurate to allow calculations of dimer spectra with accuracy challenging experiments. On the other end, PESs can be developed for monomers containing dozens of atoms. Since the form of such PESs is not much more complicated than that of typical empirical PESs, it should be possible to use them in simulations for systems with close to a million of atoms for millisecond times. As an example of such an application, crystal structure predictions will be presented for a set of cocrystals of organic molecules built of about 20 atoms each. This work, performed in collaboration with experimental groups, is aimed at design of cocrystals, i.e., the cocrystals of these substances have not yet been grown and ongoing attempts at growing them use theoretical guidance.

The current work in our group is aimed at implementations to still larger systems. This will be achieved by both standard means like splitting of large molecules into fragments and by making our APES approach even more related to monomer properties (currently, all long-range terms are obtained in this way, but short-range ones are not). The new generation forces fields will differ from the existing ones that they will not be just given by a fixed set of parameters. To obtain a force field for a system, autoPES will first perform {\em ab initio} calculations for monomers or fragments, construct a force field, and then perform a limited number of close-range SAPT calculation to check the quality of this force field.

[1] Szalewicz K.; *Wiley Interdisc. Rev.-Comp. Mol. Sci* **2012**, *2*, 254.
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A Feynman Dispersion Correction

Maximilian Kriebel, Constantin Weber and Timothy Clark

Computer-Chemie-Centrum, Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany

It is well known that self-consistent field and density functional theories do not reproduce the dispersion interaction. The solution has mostly been to add two-center potentials to the quantum mechanical Hamiltonian in order to represent the dispersion interaction. Although such corrections are computationally economical and apparently quite effective, they are not self-consistent and do not take possible multi-center interactions into account. We have investigated an alternative to these techniques.

The dispersion interaction is usually described within the London picture [1] as being due to instantaneous dipoles in the electron density that, in turn, induce dipoles in the electron density of an interacting species and thus results in a weak stabilization with an r^{-6} (dipole-induced dipole) distance dependence. An attractive alternative but equivalent [2] interpretation was presented by Feynman. [3] In the Feynman picture, dispersion is caused by a slight shift in electron density towards the nuclei and the internuclear regions of molecules. The figure shows the difference in Hartree-Fock (no dispersion) and MP2 (dispersion) electron densities for the argon dimer:

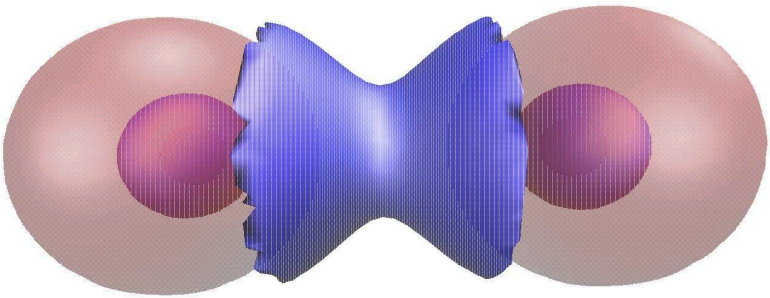

Figure: Ar_2 at its equilibrium distance (3.76 Å): Isodensity plots (ρ_{HF}-ρ_{MP2}/aug-cc-pVTZ). The isodensity levels are + (blue) and – (red) 9×10^{-5} a.u.

A simple nucleus-electron potential can be used to mimic this change in electron density to give a self-consistent and potentially multi-center dispersion correction. Results will be presented for the MNDO NDDO-based semiempirical Hamiltonian.

[1] *Über das Verhältnis der van der Waalsschen Kräfte zu den homöopolaren Bindungskräften*, R. Eisenschitz and F. London, *Zeitschr. F. Physik*, **1930**, *60*, 491-527.
[2] See, for instance, *Dispersion dipoles for coupled Drude oscillators*, T. T. Odbadrakh and K. D. Jordan, *J. Chem. Phys.*, **2016**, *144*, 034111.
[3] *Forces in Molecules*, R. P. Feynman, *Phys. Rev.*, **1939**, *56*, 340-343.

Multi-levels simulations based on Frozen-Density Embedding Theory

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Dépt. Chimie Physique, Université de Genève, Geneva, Switzerland

In Frozen-Density Embedding Theory (FDET) [1,2], two independent quantum-mechanical descriptors are used for the total system: the embedded N_A-electron wavefunction and the electron density $\rho_B(\mathbf{r})$ intergating to N_B. Various computer implementations of FDET have been developed by us and others. They differeing in a) method to generate $\rho_B(\mathbf{r})$, b) method to solve the N_A-electron problem, c) approximations for the density functionals for the non-electrostatic components of the energy and for the embedding potential (see Ref. [3] for review). Despite apparent similarity to QM/MM methods, the accuracy of the propertes calculated from FDET based methods is governed by its own rules. Except for the first-order electrostatic term in the intermolecular interaction energy, there is no one-to-one correspondence between the energy components in FDET and QM/MM. The present work reports a comprehensive benchmarking of FDET excitation energies which are compared to reference results from conventional supermolecule calculations (ADC(2)). The dataset includes up to ten lowest excitation energies in 50 intermolecular complexes. Each complex consists of a chromophore and one (or more) non-covalently bound molecule. The representative database makes it possible to relate the errors due to approximations made within FDET to various factors: both specific to FDET and the ones which are treated explicily in QM/MM.

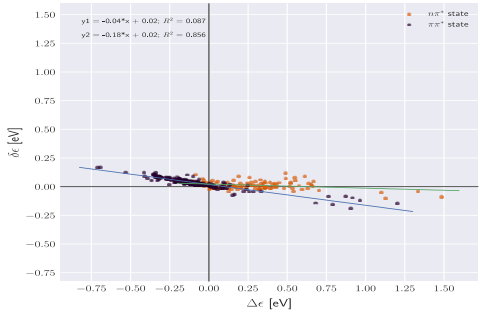

Figure: Errors in the LinFDET/ADC(2) excitation energies (δε) vs. reference (ADC(2) values of the complexaction induced shifts of the interaction energy (Δε).

Acknowledgements: This research was supported by grant from Swiss National Science Foundation (Grant No. 200021-152779).

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[3] Wesolowski, T.A.; Shedge, S.; Zhou, X. *Chem. Rev.* **2015**, *115*, 5891–5928.
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Computational Approaches to Protein Target Dynamics for Drug Discovery

Rebecca C. Wade

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The dynamic nature of protein structures provides challenges and opportunities for ligand design. We identify different types of protein binding pocket dynamics [1] and present TRAPP, a toolbox of computational approaches to identify TRAnsient Pockets in Proteins for ligand design [2,3], along with examples of the application of TRAPP to drug discovery [4]. TRAPP includes the molecular dynamics-based perturbation approaches, L-RIP and RIPlig, to explore binding pocket dynamics [5], and it allows data on mutations to be considered [6]. We have applied these and other computational approaches to explore the relation between binding site conformational flexibility and drug binding thermodynamics and kinetics in the anti-cancer target, heat shock protein 90 (HSP90) [7]. The results reveal an unusual relation between binding site flexibility and drug-target residence time: the HSP90-inhibitor complexes with longer residence times have entropically driven binding, with an important contributor being the mobility of a helical region of the binding site in the bound complex. The application of our τ-random acceleration molecular dynamics simulation (τRAMD) method to computing the relative residence times of 70 diverse drug-like HSP90 ligands shows good agreement with experiment, and it allows further features that affect ligand unbinding rates, including transient polar interactions and steric hindrance, to be identified [8].

Acknowledgements. Klaus Tschira Foundation, EU/EFPIA Innovative Medicines Initiative (IMI) Joint Undertaking (grant no. 115366, K4DD), EU 7th Framework Programme (grant no. 603240, NMTrypI), PRACE (Pra12_3089), HLRS Stuttgart (Project Dynathor).

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[3] Stank, A.; Kokh, D.B.; Horn, M. et al. *Nucleic Acids Res* **2017**, gkx277. DOI: 10.1093/nar/gkx277. http://trapp.h-its.org/
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[8] Kokh D.B. et al. Estimation of drug-target residence times by τ-random acceleration molecular dynamics simulations, submitted.

Recent validations of the SIBFA polarizable molecular mechanics/dynamics potential: test cases of inhibitor Zn-metalloenzyme, and of guanine quartet-cation complexes. Further refinements by SAPT analyses. Results on water oligomers and first results of large-scale molecular dynamics simulations

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We first present recent validation results of the polarizable SIBFA potential by comparisons with ab initio QC results in two demanding test cases: inhibitor binding to the Zn-binding site of metallo-β-lactamases [1] and the channeling of monovalent cations along the z axis of two stacked guanine quartets [2]. We then present refinements on the basis of SAPT energy decomposition analyses. Thus, for a given constitutive fragment, we leveraged a procedure automatically optimizing the parameters of each the five energy contributions by least-square minimization of it difference with respect to its QC counterpart in training sets encompassing 20-150 complexes of this fragment with a dipolar and with a dicationic 'probe', namely water and Zn(II). Validation results are presented for a series of 30 water clusters, from hexamers to 20-mers. Preliminary results of large-scale molecular dynamics simulations are discussed.

[1] Kwapien, K.; Damergi, M.; Nader, S. et al. *J. Phys. Chem. B*, **2017,** *121,* 6295-6311.
[2] Gresh, N.; Naseem-Khan, S.; Lagardère, L. et al. *J. Phys. Chem. B,* **2017**, *121*, 3997-4014.

Modeling Lung Surfactant Interactions with Benzo[a]pyrene

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[2]*Department of Physical Chemistry and Electrochemistry, Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Krakow, Poland*

By reducing surface tension of the air-water interface in alveoli, lung surfactant (LS) is crucial for proper functioning of the lungs. It also forms the first barrier against inhaled pathogens. In this study we present the interactions of LS models with benzo[a]pyrene (BaP). BaP, a polycyclic aromatic hydrocarbon, is one of the most dangerous components of respirable particulate matter. It is formed during incomplete combustion of all organic materials, e.g. coal, wood, or automobile fuels, but also tobacco or foods. In human body BaP is metabolized to highly reactive species, such as diol epoxide, quinone or radical cation, which react with DNA, leading to DNA damage, an important first step in carcinogenesis.

Two phospholipids, namely dipalmitoylphosphatidylcholine (DPPC), and 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) and their 1:1 mixture are used as LS models. Pressure-area isotherms are employed to study global properties of the monolayers. We find that addition of BaP has a condensing effect, manifested by lowering the values of surface pressure and shifting the isotherms to smaller areas. Atomistic details of this process are examined by means of molecular dynamics simulations [1]. We show that initially BaP molecules are accumulated in the monolayers. Upon compression, they are forced to the headgroups region and eventually expelled to the subphase. BaP presence results in reduction of monolayer hydration in the hydrophilic region. In the hydrophobic region it induces increased chain ordering, reduction of monolayer fluidity, and advances transition to liquid condensed phase in DPPC system.

Acknowledgements. Support from the Polish National Science Centre, Project No. UMO-2014/13/B/ST4/04995. Calculations were performed at Faculty of Chemistry of Jagiellonian University and at ACK CYFRONET Supercomputer Center.

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Noble gas compounds – theoretical studies of structure and nature of bonding

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The noble-gases (Ng) are usually considered as chemically inert due to their stable electronic structure of valence electrons unfavorable to formation of chemical bonds. The inertness of noble-gases has been used e.g. in the development of matrix isolation technique since the early 1950s.

The first chemical compound containing noble-gas (Ng) atom, $Xe^{+}[PtF_6]^{-}$, was experimentally prepared 56 years ago by Bartlett [1]. The last four decades have introduced a rich and interesting world of noble-gas chemistry.

Recently, a new class of rare gas containing molecules, HNgY, have been prepared and characterized in the IR low-temperature matrices spectroscopy [2-3]. Usually molecules are experimentally prepared in low-temperature matrices by photodissociation of a hydrogen-containing precursor and thermal mobilization of the photodetached hydrogen atoms.

In order to understand the nature of chemical bonds in the molecular systems containing Ng atoms we have applied the electron localization function (ELF), which is an indirect measure of the probability of finding two electrons with the opposite spins [4]. Via ELF analysis we can obtain information of the degree of ionic and covalent bonding in studied molecules.

In the lecture will be presented the results of *ab initio* calculations of structure and properties, the ELF analysis of the nature of chemical bonds of isolated noble-gas hydrides well as noble-gas hydrides involved in molecular complexes.

Acknowledgements. The author thank the Wrocław Centre for Networking and Supercomputing for generous allocation of computer time.

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Imaging bond reorganization by the reaction fragility spectra

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Computational analysis of the energy derivatives over the reaction progress (ξ) along the reaction path ($F_\xi = -dE/d\xi$) has been initiated by Toro-Labbé *et al*. The authors argued that electronic rearrangement may preferentially occur in the transition state region limited by the extremes on the $F(\xi)$ relationship [1] The new method for monitoring the density changes proposed in this present work proves that bonds may be formed or break far beyond of this region. [2]

The analysis has been based on the Hellmann-Feynman force on a nucleus, $\mathbf{F}_A = \int \rho(\mathbf{r})\boldsymbol{\varepsilon}_A(\mathbf{r})d\mathbf{r}$ for the exact density $\rho(\mathbf{r})$. The second component of force on a nucleus is the inter-nuclear repulsion $\mathbf{F}_A^{n-n} = \Sigma_B Z_B \boldsymbol{\varepsilon}_A(\mathbf{R}_B)$. The total force vanishes in an equilibrium; they are nonzero when positions of the nuclei are arbitrarily fixed. However, by the Hohenberg & Kohn theorem the electron density is still in an equilibrium with the electric field of the nuclei and forces may be calculated by exploring the force constants matrix (Hessian).

The Hessian ($3N$ x $3N$) matrix may be transformed to an alternative connectivity matrix (N x N), by collecting the cumulative force constants $C_{AB} = \nabla_A \cdot \left(\mathbf{F}_B + \mathbf{F}_B^{n-n}\right)$. This matrix shows interesting new properties: (i) the elements are independent to the variations of a coordinate system; (ii) the inter-nuclear contributions vanish (by the Laplace equation), hence the elements contain electronic energy contributions exclusively. They characterize atoms ($\nabla_A \cdot \mathbf{F}_A > 0$) and interatomic contacts ($\nabla_A \cdot \mathbf{F}_{B \neq A} < 0$). (iii) $\Sigma_B C_{AB} = 0$ for columns and rows. When a system loses one of its atoms by dissociation, its corresponding elements in the connectivity matrix vanish.

The fragility spectrum for an atom in molecule a_ξ^A has been proposed as the diagram of computed derivative: [2] $a_\xi^A = d(\nabla_A \cdot \mathbf{F}_A)/d\xi$ vs the reaction progress ξ. The spectra clearly demonstrate the bond creation/annihilation around A along the reaction path for the test reactions.

By the conceptual DFT formalism, two important relations have been arrived at:

$$a_\xi^A \propto \frac{S}{N}\int \frac{d\rho(\mathbf{r})}{d\xi}\left[\boldsymbol{\varepsilon}_A(\mathbf{r})\right]^2 d\mathbf{r} \quad \text{and} \quad \nabla_A \cdot \mathbf{F}_{B \neq A} \approx \frac{S}{N}\int \rho(\mathbf{r})\boldsymbol{\varepsilon}_A(\mathbf{r}) \cdot \boldsymbol{\varepsilon}_B(\mathbf{r})d\mathbf{r}$$

The first one provides an explanation for the observed $a_\xi^A(\xi)$ dependence, as it comes from the density variation in the bond region around a nucleus. The second one sheds light on the linear relation between $\nabla_A \cdot \mathbf{F}_{B \neq A}$ elements and corresponding average bond energies.

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[2] Ordon, P.; Komorowski, L.; Jędrzejewski, M. *J. Chem. Phys*. **2017**, *147*, 134109.

Accurate nonrelativistic wavefunctions and energies for the ground state and first excited state of the boron atom

Krzysztof Strasburger

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The energy difference between the lowest states of the boron atom (^2P_u and ^4P_g) has not been measured so far as no intercombination lines between doublets and quartets have been found. [1] The long-term purpose of the present research is to determine its value on the grounds of theory. The (future) calculation of relativistic and low-order QED terms, which are needed for an accurate prediction, will require nonrelativistic wavefunctions of very good quality.

These wavefunctions are expressed as linear combinations of properly symmetrized basis functions

$$\Psi(\mathbf{r}_1,\sigma_1,\mathbf{r}_2,\sigma_2,\ldots,\mathbf{r}_n,\sigma_n) = \sum_{I=1}^{N} c_I \hat{A}[\sigma_1,\ldots,\sigma_n] P \chi_I[\mathbf{r}_1,\ldots,\mathbf{r}_n], \tag{1}$$

where Θ is the appropriate spin function (eigenfunction of total $\hat{S}^2$ and $\hat{S}_z$ operators) and χ_I is a primitive, explicitly correlated Gaussian lobe

$$\chi_I(\mathbf{r}_1,\mathbf{r}_2,\ldots,\mathbf{r}_n) = \exp\left[-\sum_{i=1}^{n}\alpha_{i,I}\left(\mathbf{r}_i-\mathbf{R}_{i,I}\right)^2 - \sum_{i=2}^{n}\sum_{j=1}^{i-1}\beta_{ij,I}\left(\boldsymbol{r}_i-\boldsymbol{r}_j\right)^2\right], \tag{2}$$

The Â operator ensures proper permutational symmetry of Ψ while the spatial symmetry projector $\hat{P}$ is defined accordingly to the chosen irreducible representation of a finite point group. One may realize easily that the basis functions are not the eigenfunctions of the $\hat{L}^2$ operator. $\hat{P}$ annihiliates the contributions with angular momentum lower than the desired value. The proper rotational symmetry is recovered effectively owing to variational energy minimization, which involves the optimization of linear (c_I) and nonlinear ($\alpha_{i,I}$, $\beta_{ij,I}$ and $\mathbf{R}_{i,I}$) parameters of the wavefunction. For the ground state, the energy convergence is comparable to that obtained with other explicitly correlated ansatz. [2]

Acknowledgements. The work was financed by the statutory activity subsidy from the Polish Ministry of Science and Higher Education for the Faculty of Chemistry of Wrocław University of Technology (contract number 0401/0189/17). Most calculations were performed at the Wrocław Centre for Networking and Supercomputing. Additional computer resources were used in the laboratories maintained by Dr. Borys Szefczyk and Dr. Paweł Kędzierski.

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σ-Hole interactions of boron clusters

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Polyhedral boron clusters (boranes, boron hydrides) are large group of compounds with unique properties and unusual noncovalent interactions. It includes 3D aromaticity and abilities to form dihydrogen bonds and σ-hole interactions. Group V, VI and VII elements in neutral heteroboranes have highly positive σ-holes that are responsible for strong σ-hole interactions.[1] We have observed the S···π, Br···π, Sb_2···H-B types of σ-hole interactions of heteroboranes experimentally in the corresponding crystal packings.[2-4] Quantum chemical analysis revealed that these interactions were considerably stronger than in their organic counterparts.[2-4] The remarkable ability of heteroboranes to form strong σ-hole interactions might be attributed to the multicenter bonding, which breaks the classical electronegativity concept. [5]

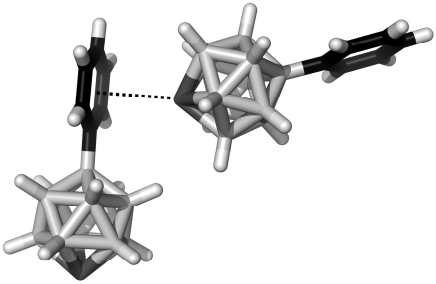

Figure: S···π type of σ-hole bond found in the X-ray structure of phenyl substituted thiaborane. [2]

Ackowledgements. We acknowledge the financial support of the Czech Science Foundation (17-08045S).

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New Methods and Models for Condensed Phase Simulation

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I will discuss new theoretical models and extended Lagrangian methods that address accuracy and tractability for using atomistic polarizable force fields and linear scaling AIMD in the condensed phase. I will highlight a recent application of polarizable models to improve the rate of catalysis by 50X by optimizing electric field environments.

Local surface properties in the design of nanostructured catalysts: Regium bonds and beyond

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Size and local structure are of central importance for determining the reactive properties of many catalytic materials. The most prominent example is gold; crystalline surfaces are chemically inert whereas nanoparticles of gold are efficient catalysts for many reactions. The high catalytic activity of nanostructured gold is due to the presence of low-coordinated gold atoms with high binding affinity for the reactants, typically Lewis-bases. [1] We have recently shown that the surface electrostatic potential [$V_S(\mathbf{r})$] at the binding sites allways is positive, and that the magnitudes of the local maxima ($V_{S,max}$) in $V_S(\mathbf{r})$ at these sites correlate with the binding affinities of Lewis-bases. [1,2] Silver and Copper show similar patterns in $V_S(\mathbf{r})$ and all three metals interact preferentially at their most positive sites. The analogy of these interactions with halogen bonds led us to name them Regium bonds.[2] However, the binding is not purely electrostatic but have significant contributions from charge transfer and polarization, and the relative importance of the different interaction components varies depending upon the ligand (Lewis base) and the metal.

In order to include the effects of charge transfer and polarization in the characterization of Lewis acids we have defined another surface property, the local electron attachment energy [$E_S(\mathbf{r})$]. [3] The $E_S(\mathbf{r})$ is computed from the virtual orbitals of a Kohn-Sham DFT calculation, and has contributions not only from the electrostatic potential but also the exchange correlation potential and the kinetic energy densities of the virtual orbitals. Whereas $E_S(\mathbf{r})$ originally was developed to characterize the reactive properties of molecular systems, it has been shown to be an excellent complement to the $V_S(\mathbf{r})$ in the characterization of nanoparticles and extended crystalline surfaces of transition metal and metal oxide catalysts.[2,4,5] Using these two properties it is possible to construct a ligand-specific interaction map for the surface of a catalyst from a single Kohn-Sham DFT calculation. We will indicate how such interaction maps can be used in the rational design of new catalysts that are optimized with respect to geometrical structure and chemical composition.

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How theory guided experiment in quest for analogs of magnetic precursors of oxocuprate superconductors

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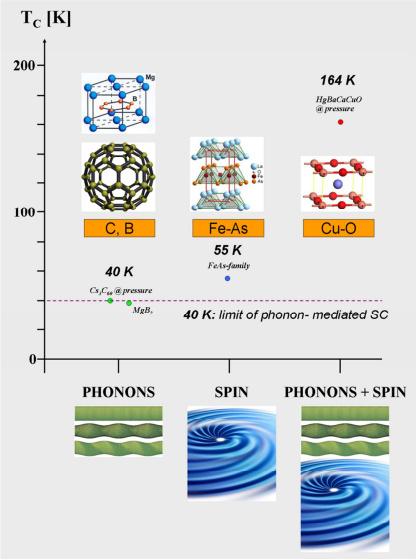

Figure 1: The known families of high-T_C superconducting materials [13].

In this contribution I will describe 18-years lasting theory-based attempts to design from the scratch an entirely new family of superconducting materials [1-11] (Figure 1), together with experimental results which confirmed the theoretical predictions, as well as with those, which did not while the experiment had an unexpected or even quite exotic outcome [12].

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Multiscale modelling for chemical biology

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Biomolecular simulations have advanced to the stage where they can provide reliable predictions of enzyme mechanisms, selectivity, thermoadaptation and and inhibition. Many types of application require different levels of treatment, which can be effectively combined in multiscale models to tackle a range of time- and length-scales [1]. Simulations can identify mechanisms of catalysis in biosynthesis and drug resistance [2]. Simulations can identify and characterise catalytic interactions and determinants of chemo-, regio- and stereospecificity in biocatalysts. Increasingly, simulations are contributing to the design and engineering both of natural enzymes and of de novo biocatalysts [3]. Classical molecular dynamics (MD) simulations can allow predictions of substrate binding, and reveal and predict dynamical changes associated with thermoadaptation and temperature optima of enzyme catalytic activity [4]. For modelling reactions within large systems such as proteins, multiscale combined quantum mechanics/molecular mechanics (QM/MM) methods are a good, practical approach, e.g. for modelling transition states and reaction intermediates, and to analyse structural and electronic determinants of reactivity. QM/MM methods treat the active site with a QM electronic structure method, while the effect of the enzyme environment is included by a simpler (MM) approach. Projector-based embedding techniques allow highly accurate correlated ab initio QM methods to be applied in QM/MM calculations [5].

Acknowledgements. AJM thanks EPSRC and BBSRC for support.

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The Thermodynamic and Kinetic Description of the Reactions in Solutions with Constant pH

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Solutions with constant pH represent from the thermodynamic point necessity of additional Legendre transformation of Gibbs free energy to the new thermodynamic Gibbs-Alberty potential: $G' = G - n_C(H)\mu(H^+)$. Within this description, chemical reactions do not run into the equilibrium concentrations as suppose according to the Guldberg-Waage dynamic principle but to the chosen value of hydrogen chemical potential. In this way modified equilibrium constant K' has to be defined as a function of proton concentration in solution:

$$K' = \frac{(\sum[C])(\sum[D])}{(\sum[A])(\sum[B])}.$$

According to this description, reaction is no longer dependent of concrete molecular forms taken into the equilibrium constant but pH dependent mixture of all relevant forms, which vary by number of active protons.

For the pH dependent rate constants, the formalism of branch reaction need to be considered, e.g. if B and C in the following reactions differ by one active proton:

$A + B \overset{k_1}{\rightarrow} R$ and $A + C \overset{k_2}{\rightarrow} S$ then the product ratio can be evaluated in the form of effective rate constants: $\frac{[R]}{[S]} = \frac{k_1.[B]}{k_2.[C]} = \frac{k_1.[HB]}{k_2.[B^-]} = \frac{k_1}{k_2}.K_a.[H^+] = \frac{x_1.k_1}{x_2.k_2} = \frac{k_1^{eff}}{k_2^{eff}}$

All forms with different number of active protons represent individual reaction channels mutually interconnected via Henderson-Hasselbalch equation of fast acid-base equilibrium:

$$\mathrm{pK_a} = \mathrm{pH} + \log\left(\frac{[\mathrm{HA}]}{[\mathrm{A^-}]}\right)$$

For this kind of description all dominant forms must be included together with some additional forms in those cases the transition barriers are sufficiently low (with relatively high rate constants) despite of possibly low concentrations of corresponding forms.

Several examples will be presented to demonstrate both thermodynamic and kinetic formalisms.

Semi-empirical computational approach to analyze multistep biological and chemical reactions

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Semi-empirical computational approach to analyze multistep biological and chemical reactions is proposed. It has been successfully applied to study the interaction between 2′-deoxycytidine and cis-2-butene-1,4-dial, a metabolite of furan. The new method comprises a combination of few steps. They include the prediction of the reaction mechanism, calculation of Gibbs free energies for the reaction pathway, and conversion of barrier energies to rate constants. Basing on the results of previous steps, corresponding kinetic equations are constructed and solved. Such a procedure allows one to indicate the definite concentration of reaction species (reactants, intermediates, and products) at any moment in time. Obtained results show that 2′- deoxycytidine reacts with cis-2-butene-1,4-dial to form primary products, which are represented by four polycyclic diastereomers. These primary products further transform to more stable secondary products by dehydration, which is catalyzed by acid. The obtained data demonstrate that cis-2-butene-1,4-dial plays a key role in furan-induced carcinogenesis.

Further examples illustrate the application of mentioned approach for environmental science. It has been applied to predict a kinetic behavior of some energetic compounds in the reaction of an alkaline hydrolysis to decompose them.

Study of intermolecular interactions in polymorphic modifications of biologically active compounds

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The properties of organic compounds in the solid state are known to depend on the intermolecular interactions in a crystal. The polymorphic modifications of a same compound are the best object for studying of such a phenomenon. Usually the analysis of crystal structure obtained by X-ray diffraction includes describing of intermolecular hydrogen bonds, halogen bonds, stacking interactions, etc. However the mutual positions of molecules in a crystal are provided by not only specific interactions but also non-specific ones like general dispersion and electrostatics. Interactions of such a type are noted to be very complicated for estimation and might be studied only by quantum-chemical methods.

The suggested earlier method of crystal structure analysis based on quantum-chemical calculations of interaction energies between neighboring molecules in a crystal [1] takes into account all possible types of interactions. The application of this method allows not only to classify organic crystals but also to study the principles of their formation and the role of intermolecular interactions in this process.

The comparison of the crystal structure type and biological activity of polymorphic modifications observed experimentally allows to predict not the crystal structure but its properties and to develop principles of crystal engineering. Such a task is very important for the pharmaceutical industry, creating the basis for controlled crystallization of active pharmaceutical compounds.

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Bottom-up approach to the biocatalyst design: from *ab initio* models to effects of point mutations on the catalytic activity

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The goal of this work was to develop a methodology capable of prediction of the change of catalytic activity upon mutation, which is crucial for both the biocatalyst design and our understanding of existing enzymes. Presented approach, called bottom-up, is based on a hierarchy of computational methods defined by the perturbation theory of intermolecular interactions. Which leads to the Differential Transition State Stabilisation (DTSS) framework[1]. Its main advantage is that it is firmly based on ab initio methodology, as well as a possibility for systematic incorporation of corrections and approximations, depending on the computational complexity of particular problem. This strategy is opposed to conventional, top-down, approaches, which are focused on description of many different phenomena (for example, an exploration of phase space), mostly at the cost of empirical parametrization decreasing the ability of the model to make extrapolated predictions. A particular attention is paid to electrostatic approximation of DTSS, represented by means of Cumulative Atomic Multipole Moments (CAMM)[2] and catalytic fields[1].

The model was tested ono two series of mutated enzymes: one emerging from ketosteroid isomerase (KSI)[3] and another being derived from theozyme KE07 in directed evolution experiments[4]. In the first case, the model was successfully tested on a multistep reaction. In the second one, the detailed role of mutations introducing charged residues was revealed; it was also an example apllication of CAMM library for amino acid rotamers, derived during the research. Both cases show a good agreement of model with experimental values, which justifies its possible usefulness for biocatalyst design, competitive to commonly applied protocols.

Acknowledgements. Support from Polish Ministry of Science an Higher Education (‘Diamond Grant’ No. DI2012 016642, *Application of dynamic catalytic fields to a biocatalyst design*). Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

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closo-Carborane derivatives of indomethacin methyl ester

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The 1,2-dicarba-*closo*-dodecaborane(12) (*ortho*-carborane) derivative of indomethacin methyl ester is a potent and COX-2 selective cyclooxygenase inhibitor, but the *meta*- and *para*-carborane isomers are inactive against COX (Figure 1).[1] Molecular docking calculations predicted a similar binding mode for all three isomers with an uncertain preference for the *ortho* isomer.[2] Subsequent quantum chemical calculations did not improve the agreement with the experimental trend.[2] On the other hand, molecular dynamics simulations of all three isomers bound with COX-2 suggest that only the *ortho*-carborane derivative forms a stable complex, and provide insight into the possible molecular basis for isomer-dependent binding.[3]

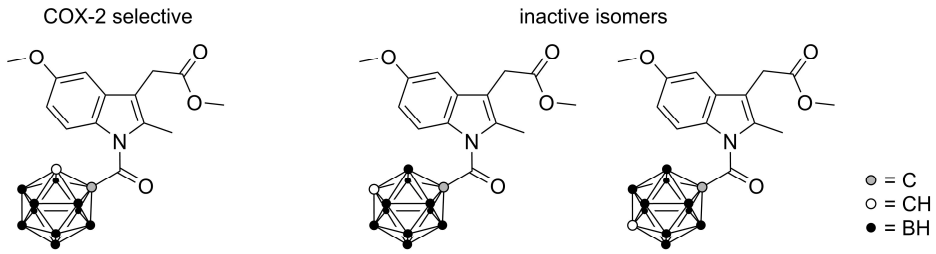

Figure 1. *ortho*-, *meta*- and *para*-carborane derivatives of indomethacin methyl ester.

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Mechanistic insights into selective UV-induced self-repair of DNA lesions

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Cyclobutane pyrimidine dimers (CpDs) are considered as the most common DNA lesions arising during the exposure of the biopolymer to UV light. While these lesions can be repaired in living organisms by e.g. photolyases, such sophisticated repairing factors were absent on Archean Earth. Recent experimental findings suggested that specific DNA sequences exhibit fascinating self-repairing capabilities, which could efficiently protect them from the detrimental effects of pyrimidine dimerization. [1] Nevertheless, the exact molecular mechanism of this process remained obscure until recently, owing to considerable challenges associated with synthesis of selectively damaged sequences. In this talk, I will describe the mechanistic details of the self-repair process determined by means of MD simulations and highly accurate quantum-chemical calculations involving the algebraic diagrammatic construction to the second order method, ADC(2). [2] In particular, the most recent results revealed that the UV-induced self-repair of the GAT=T sequence is triggered by sequential electron transfer process operating downhill along the slope of the potential energy surface in the lowest excited singlet state. I expect that the assessment of the efficiency and availability of this process in other DNA sequences would enable us to identify the most UV-resistant oligomers which could survive in the harsh environment of early Earth.

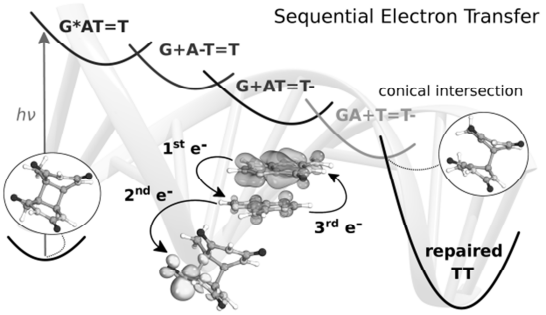

Figure: The UV-induced sequential-electron transfer mechanism enabling efficient repair of the CpD in the GAT=T DNA tetranucleotide.

Acknowledgements. This contribution is supported by a fellowship from the Simons Foundation (494188, R. S.).

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Some advances in energy decomposition analysis

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I will discuss some recent developments in variational energy decomposition analysis (EDA), using absolutely localized molecular orbitals. The first part of the talk will focus on non-bonded interactions, while the second will discuss chemical bonds.

With respect to non-bonded interactions, I will concentrate on the adiabatic EDA. It connects energetic contributions such as the frozen, polarization, and charge-transfer terms to shifts in observables such as structure and vibrational frequencies from their values for non-interacting monomers. Such considerations can be used to interpret experimental observables. Another application is to assess the validity of different definitions of charge transfer, which we shall also discuss.

With respect to EDA for chemical bonds, I will discuss the analysis of bond-formation in terms of frozen interactions augmented by spin-coupling for the electron pair bond. Polarization is augmented by an orbital contraction term. The relative magnitudes of the resulting terms, including charge transfer, comprise a fingerprint that distinguishes different classes of chemical bonds (covalent, ionic, charge-shift, etc) in both familiar and unfamiliar cases. The analysis permits a reassessment of the role of kinetic energy lowering in chemical bond formation with some surprising results.

Excited State Dynamics at Nanoscale Interfaces for Solar Energy Harvesting: Time-Domain Ab Initio Studies

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Photo-induced processes play key roles in solar applications of numerous nanoscale materials. They require understanding of material's response to photo-excitation on atomic and nanometer scales. Our non-adiabatic molecular dynamics techniques, [1] implemented within time-dependent density functional theory, [2-4] allow us to model such non-equilibrium response in real time. The talk will focus on photo-initiated charge and energy transfer in representative examples, involving semiconducting [5-7] and metallic [8] quantum dots, polymers, [7] hybrid organic/inorganic perovskites, [9-12] graphene, [13] MoS_2 [14] and related two dimensional materials, [15] TiO_2, [8,9,13] etc. [16,17] Charge and energy transfer, Auger-type processes, energy losses and charge recombination create many challenges due to large differences between molecular and periodic, and organic and inorganic matter. Our simulations provide a unifying description of quantum dynamics on the nanoscale, characterize rates and branching ratios of competing processes, resolve debated issues, and generate theoretical guidelines for development of novel systems for solar energy utilization.

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Molecular dynamics study ionic liquids: temperature dependence of ionic conductivity

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Ionic liquids (IL) are salts that are liquid near ambient conditions. ILs have many potential applications and are considered as "green" chemicals, with less negative impact on the environment than the classical solvents. Unique physicochemical properties of ILs can be tuned by altering the ions and their combinations. Recently ILs have been successfully used as electrolytes in thermoelectrochemical cells, [1] which offer an innovative alternative to solid-state thermoelectric converters utilizing semiconductor materials. Transport coefficients of ionic liquids are important for optimization of ionic-liquid based thermoelectrochemical devices. In this work, we applied the classical molecular dynamics (MD) simulations to study dynamical properties of several ILs.

Our simulations show that dynamical properties (diffusion, viscosity, conductivity) are very sensitive to intramolecular potentials, especially total charges of ions. In our recent paper [2] we investigated the influence of the charge scaling, the size of the simulated system and the temperature factor on calculated density, radial distribution function and the diffusion coefficients of the cation and anion of two methylpyridinium based ionic liquids: 1-butyl-4-methylpyridinium tetrafluoroborate ([b4mpy][BF4]) and 1-butyl-4-methylpyridinium chloride ([b4mpy][Cl]). Scaling down all partial charges by a factor of 0.88 gives an adequate description of ionic mobility and its changes with temperature. MD simulations are able to predict viscosity and ionic conductivity, however, the error is highly dependent on the charge scaling factor. In case of [b4mpy][BF4] ionic liquid, the estimation error was up to 50%.

In this study we have extended our simulations to other ionic liquids ([EMIM][TFSI], [HMIM][PF6], [EMIM][DCA], [EMIM][CF3SO3]) and compared several protocols for partial charge calculations: scaled antechamber AM1-BCC charges for single ions, RESP (fit to ab initio ESP) charges for single ion pair, RESP charges averaged over several ion pair conformations, RESP charges for single ion pair surrounded by other ion pairs.

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DAD's not in charge of Me

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The most accepted hypothesis of the origin of the rate enhancement in enzymes is the relative stabilization of the transition state (TS) with respect to the reactant state (RS), as originally proposed by Pauling. [1] In other words, the reaction catalyzed by an enzyme has a lower free-energy barrier than the counterpart reaction in aqueous solution. Based on molecular simulations, this reduction of the free-energy barrier has been attributed to electrostatic preorganization of the protein that stabilizes the TS with respect to the RS. Nevertheless, other proposals have appeared to explain the efficiency of these complex biologiological machines. For instance, it has been suggested that specific protein fluctuations might reduce the donor–acceptor distance (DAD) for enzyme catalyzed S_N2 reactions. This would diminishing the potential-energy barrier height and/or width and enhancing the rate by increasing the number of reactive trajectories over and through the barrier. The controversial contribution of protein motions to modulate the DAD, originally proposed in enzymatic hydride transfer reactions, has been extended to other enzymes such as methyltransferases.

In this commmunication we report results derived from QM/MM theoretical studies of reactions catalyzed by enzymes and, in particular, in hydride transfer catalyzed reactions and methyltransferases to test whether experimental observations of rate-constant reductions and variations in kinetic isotope effects (KIEs) should be attributed to changes in the DAD. We will show how compression cannot explain the experimental results. On the contrary, electrostatic properties in the active site, together with a certain plasticity of the protein, correlate with the catalytic activity of wild type and mutants in the enzymes studied in our laboratory.

Acknowledgements. Support from the *Spanish Ministerio de Economía y Competitividad* and FEDER funds (project CTQ2015-66223-C2), Universitat Jaume I (project P1•1B2014-26) and the USA National Institute of Health (Ref No. NIH R01 GM065368).

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Rational design of covalent inhibitors of EGFR by QM/MM mechanistic modeling

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The aberrant activity of EGFR is one of the main cause leading to the insurgence of non-small cell lung cancer (NSCLC). Gefinitib, a first-generation inhibitor of EGFR is widely employed as first-line therapy for patient affected by NSCLC displaying activating mutations (i.e., L858R) of this kinase. Although patients display good responses to this 4-anilinoquinazoline drug, most of them acquire resistance within 1-year treatment, which is often driven by the insurgence of a mutation at the gatekeeper position of the ATP binding site. In details, Thr790, which undertakes a water-mediated H-bond with the quinazoline moiety of gefitinib, is replaced by a methionine residue leading to a reduction in the inhibitory potency of this drug [1]. The introduction of an acrylamide warhead capable of alkylating a non-catalytic cysteine (Cys797) in the scaffold of compounds targeting the ATP binding site of EGFR allows these inhibitors to overcome the unfavorable effect caused by the presence of M790. However, the presence of this highly electrophilic warhead remains a toxicity burden. In this scenario, the availability of groups able to form a covalent bond with Cys797, but less reactive than typical acrylamide moieties would facilitate the development of safer inhibitors able to overcome resistance in NSCLC. In the present talk, I'll present our multiscale computational strategy, based on hybrid QM/MM methodology coupled with enhanced sampling approaches [2], to drive the design and synthesis of novel irreversible inhibitors of EGFR active on T790M-postive cells and yet featured by low reactivity toward free thiols.

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Motion in a crowded environment: the influence of obstacles mobility, size and model of transport

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In general, intracellular and extracellular environments are usually densely crowded and contain different elements like lipids or proteins [1]. We studied the movement of particles in crowded environments by means of extensive Monte Carlo simulations. Two-dimensional coarse-grained model is supposed to mimic a lateral motion of probe molecules in a membrane. For this purpose we employed Single Agent Model where the motion of an object is considered as a random walk without any correlation with other moving elements [2]. The second model of motion was based on the Dynamic Lattice Liquid model, which was based on the cooperative movement concept. Obstacles were fixed or underwent Brownian motion or they can also be formed of flexible chains [3]. The conditions at which anomalous diffusion appeared in the system were analyzed. The influence of obstacles mobility, size and concentration on the static and dynamic percolation threshold, on the mobility and the character of motion, on critical exponents and on the shape of molecules trajectories were studied.

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Development of nanosensors based on graphene

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It will be presented a summary of research on the design and manufacturing of tailored non-enzymatic sensors for the exclusive detections of hydrogen hydroxide and dopamine in water matrix. The single wall carbon nanotubes, graphene nanoribbons and holey graphene oxide were tested as possible anchor materials. The electrochemical method was employed for the surface modification of nanomaterials, and for the determination of their new properties. New method of electrochemical production of holey graphene oxide from graphite was proposed and evaluated. Manufactured sensors were extensively characterized for their properties, conditions, detection limits and stability.

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Towards Improvement of Solar Cell Efficiency: Computational Approach

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Following rapid population growth our society faces various challenges. National Science Foundation identified grand challenges involving three interconnected areas: food, energy and water. The research grand challenges are design to help understanding the complex, coupled processes of balances of Earth reserves. In addition, such research will assist in development of modern, efficient technologies to better utilize available natural resources.

This talk will reveal how Computational Chemistry methods could be efficiently used to assist with better application of new materials in the areas of global challenges. Our new results that could guide development of more efficient solar cells will be discussed.

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Effective One-Electron Potentials - Route for Condensed Phase Quantum Chemistry

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Exploring biological phenomena at the molecular scale is oftentimes indispensable to develop new drugs and intelligent materials of the future. Properties of a chemical system are usually strongly affected by intermolecular interactions with the nearby environment such as solvent. [1,2] Studying such molecular aggregates requires an accurate quantum mechanical approach, the computational cost of which grows extremely fast with the number of particles. Therefore, one of the major tasks of Quantum Chemistry is to develop mathematical models to simplify equations and implement them in a form that is computationally cheap but still provides high accuracy and reliability.

Fragment-based approaches designed to systematically treat the extended molecular systems and even biomolecules have achieved a considerable success in molecular modelling. [3] Their major strength is deeply rooted in the notion of the importance of the one-electron densities for the overall properties of chemical systems.[4] However, most of the state-of-the art methods of this kind are limited due to the inability to comprehensively include the electron correlation. As a result, applying pure fragment-based methods on the electronically excited states is still an unresolved issue.

In this contribution, we focus on finding a unified way to generalize the effective one-electron potentials and discuss the limits of the effective one-electron approach to the intermolecular interaction energy problem, without the need of introducing Hamiltonian embedding. It is believed that the proposed concept can be helpful in designing future methods tuned to studying electronically excited states in solutions.

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Photochemical Properties of Oxazoline Prebiotic Precursors of RNA Nucleotides

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Prebiotically plausible synthesis of RNA nucleotides and nucleosides has been one of the greatest challenges for the origins of life field. [1] At present, prebiotical reaction sequencies are sought to demonstrate high-efficiency chemical routes leading to RNA monomers from credible feedstock and under the prebiotic conditions on the early Earth. In recent years, there have been many efforts to discover plausible reaction routes leading to the formation of RNA monomers. However, the most intuitive formation of N-glycosidic bond between nucleobases and ribose proved to be highly inefficient for purines and practically impossible for pyrimidines. In addition, no selective and high-yielding sources of pure ribose were identified so far. To bypass the direct glycosilation, oxazolines having preformed N-glycosidic bond were proposed as the key intermediates and were successfully used to furnish ribonucleotides in the final parts of the syntheses. [2,3] One of the crucial factors determining lifespan of molecules on the Archean Earth is photostability. Since UV-irradiation is an important element of many such prebiotically credible reaction sequences, the assessment of photochemical stability of oxazolines should be performed.

To scrutinize the photostability of arabino- aminooxazoline (aAO) and oxazolidinone thione (aOT), we performed computational explorations of excited-state potential energy surfaces to show mechanistic picture of non-adiabatic phenomena. Algebraic diagrammatic construction to the second order [ADC(2)] and complete active space perturbation theory (CASPT2) methods were used to carry out these calculations. Our results indicate efficient radiationless deactivation mechanisms (Fig. 1) of aOT and in conjunction with findings of UV-irradiation experiments, we anticipate that the listed precursor should be photostable on the Archean Earth. By contrast, our calculations suggest that aAO precursor does not absorb in the range of the sunlight spectrum that reached the surface of the early Earth. This indicates that aAO would survive in the prebiotic environment.

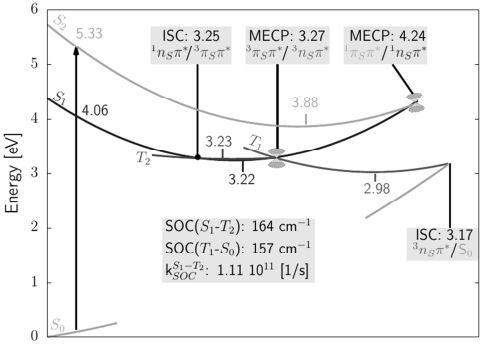

Figure: Schematic picture of plausible nonradiative deactivation channels of aOT estimated at the ADC(2)/cc-pVTZ level.

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A simulation environment for efficient modeling of proteins and their peptide complexes: CABS-flex and CABS-dock

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The conformational flexibility of protein structures is crucial for their functions. However, simulations of protein flexibility using classical modeling tools remain computationally costly for most of protein systems. Here, we present CABS-dock and CABS-flex standalone, which are Python packages for highly efficient simulations of protein-peptide docking and protein structure flexibility. The methods combine highly efficient CABS coarse-grained protein model [1] with reconstruction to all-atom representation.

The standalone applications are designed to allow for easy access to the extensive power of CABS computations and complete control over simulation process. In comparison to the previous implementations (in the forms of web servers [2,3]), the standalone versions are equipped with new features and functions. The new features include: multimeric and large-size protein support, contact map visualizations, and analysis of similarity to the reference structure. Additionally, the key stages of the protocol are configurable. The user may modify, for example, the simulation parameters, the distance restraints, and the options of structural clustering and filtering. Altogether, the packages offer a new, flexible simulation and analysis environment that can be easily extended to other methodologies. The standalone applications are available at https://bitbucket.org/lcbio/cabsdock and https://bitbucket.org/lcbio/cabsflex.

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Interactions of hyaladherins with hyaluronan and its neutral analog

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Hyaluronic acid (HA, hyaluronan), an alternating co-polymer of glucuronic acid and N-acetylglucosamine ([4)-β-D-GlcpA-(1→3)-β-D-GlcpNAc-(1→]n), is a major component of extracellular matrix of animal connective tissues. It plays various roles in signaling cascades and is thus involved in inflammation, progression of various diseases including cancer, and wound healing. HA-binding proteins, hyaladherins, which serve as mediators of these processes, are both membrane-bound (CD44, LYVE-1, RHAMM) or soluble (TSG-6). TSG-6 structure is known from numerous NMR experiments that indicate its interaction with HA, heparin and chondroitinsulfate [1]. We applied molecular-dynamics simulations to study the binding of HA oligosaccharides by TSG-6. Two binding sites were identified, one of which is identical with the HA-binding site described previously [2], but the other one, so far unknown, partially overlaps with the binding site of heparin [3] and also for chondroitinsulfate [1]. The specificity of the binding sites for HA and charged oligosaccharides in general was investigated by the comparison of HA with its neutral HA analog containing the glucuronic acid residue instead of glucose [4]. This molecule can be bound by both these sites, but the Helmholtz energies of complex dissociation determined by the umbrella sampling method show a remarkably lower stabilization of the analog in the first site, while in the other site the analog binding is even more stable than that of HA. The second binding site is thus less HA-specific and is able of binding various oligosaccharides independently of their negative charge. It indicates the possibility of designing artificial ligands of hyaladherins with a potential pharmaceutical application.

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Microsecond scale MD study of a protein-heparin complex

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Glycosaminoglycans (GAGs) are a group of long unbranched negatively charged polysaccharides. Every GAG consists of repeatable disaccharide unit which is made up of one aminosugar and one uronic acid. GAGs are located in the extracellular matrix and are involved in many cellular processes such as cell proliferation, angiogenesis, anticoagulation, adhesion and signalling cascades via interactions with protein. Since GAGs are negatively charged, most of their interactions are electrostatic driven. Heparin is a GAG consisting of a 2-O-sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine with a -4 charge per disaccharide unit. As a part of proteoglycans, heparin binds its protein targets such as chemokines and grow factors which allows to actively participate in multiple cell signaling processes.

Complexes of Fibroblast Growth Factor (FGF) with GAGs are most studied ones among protein-GAG complexes both experimentally [1] and computationally [2]. Usually Molecular Dynamics (MD) simulations of such systems are done in nanoscale. With our approach, we aimed to examine our complex of FGF with heparin in microscale (10 μs of MD). Results of analysis corresponding to heparin (sugar ring conformations, glycosidic linkages etc.) for unbonded heparin and in complex with FGF were compared with computational data from shorter simulation of free heparin (5 μs of MD) [3], while those corresponding to FGF-heparin complex with our previously obtained nanoscale MD results [4]. Analysis of aforementioned complex involved free energy calculations (MM-GBSA) for whole complex and per residue as well as calculations of entropy contribution with use of the Potential of Mean Force (PMF), Normal Mode analysis (NM) and Quasi Harmonic analysis (QH). The obtained data are important for understanding molecular base of protein-GAG systems.

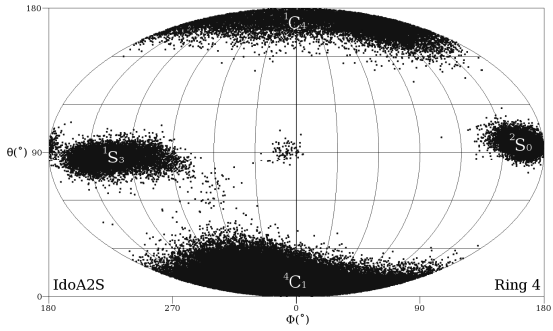

Figure: IdoA2S pucker on sinusoidal projection of puckering space representing ring conformations occuring during MD simulation.

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Ligand-driven conformational dynamics influences selectivity of UbiX

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UbiX is a flavin prenyltransferase that catalyzes a biosynthesis of prenylated flavin mononucleotide (prFMN),[1] which acts as a cofactor in enzymatic decarboxylation reactions of α,β-unsaturated organic acids.[2] The biosynthesis of prFMN requires two substrates: flavin mononucleotide (FMN) and dimethylallyl-monophosphate (DMAP). Up until now, it remained elusive why UbiX utilizes DMAP instead of dimethylallyl-diphosphate (DMAPP),[1] which is a very common isoprenoid precursor,[3] whereas DMAP is scarcely used in metabolic pathways.

Herein, we demonstrate that the UbiX's selectivity may be governed by its conformational dynamics. Depending on which ligand (DMAP or DMAPP) is bound to the enzyme, its interactions with the active site either favors the proper positioning of substrates for the reaction to occur (DMAP) or a proper positioning is rarely obtained (DMAPP). We also found that DMAPP may induce diffusion of FMN from the active site - this diffusion is strictly correlated with structural changes within the active site (Figure 1).

Even though calculated binding energies exhibit a preference for DMAP over DMAPP, we believe that this difference is not as pivotal towards selectivity of UbiX as is the positioning of ligands within the active site. We also discuss the possible effects of mutual polarization of ligands and active site's heavy atoms, its possible implication on the selectivity of UbiX and feasibility of using classical force fields.

Conformational dynamics analysis was performed based on multiple-replica MD simulations with fixed-charge force fields approach. Binding energies were calculated using the MMPBSA/MMGBSA methods, whereas polarization study was performed on QM cluster models of the UbiX's active site with either DMAP or DMAPP bound.

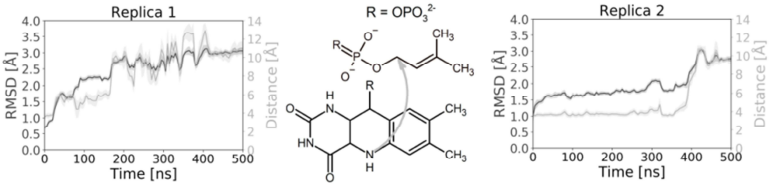

Figure: A correlation between interatomic distance and RMSD of active site's heavy atoms.

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Theoretical perspective on photochemical properties of hydroxocobalamin and aquacobalamin

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The main objective of the study was to investigate the photochemical properties of hydroxocobalamin (OHCbl) and aquacobalamin(H_2OCbl) in terms of theoretical chemistry. From an experimental point of view, both the above complexes do not undergoes photodissociation when excited by the wave ~400 nm and at this wavelength, the formation of a dissociation product, i.e. a cobalt(II) system, is not observed. On the other hand, the OHCbl complex at shorter wavelength excitation ~270 nm, undergoes partial photolysis.

The structure employed in the present work is cobalamin model complex, in which the lower base was replaced with imidazole, while the amide and methyl groups of side chains of the corrinmacrocycle were replaced by hydrogen atoms. All the calculations, were performed by DFT and TD-DFT methods using BP86 functional. The def2-TZVPP basis sets was used and the presence of water as a solvent is taken into account using COSMO model solvent. Excitation energies and characters of the excited states were determined and calculational results are compared with experimental data. Potential energy surfaces for S_1 and S_0 states were also found. In the case of the OHCbl complex, on the S_1 surface there are two low-energy states: n/d→π* MLCT and n/d→σ* LF, while H_2OCbl has one minimum with the character π→σ* LMCT.The initial stage of photoprocess is the disconnection of axial base and then in the LF excited state, takes place deactivation to the ground state.

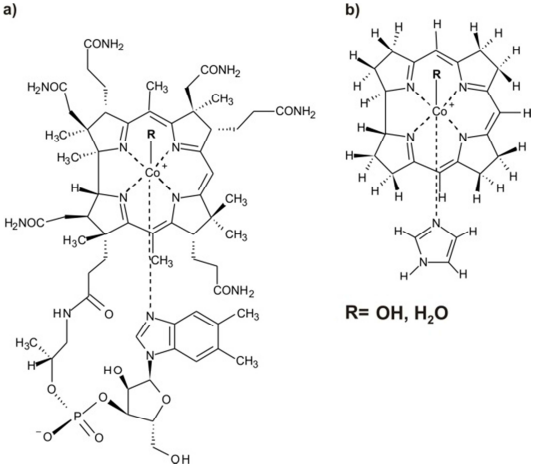

Figure: a) Molecular structure of hydroxocobalamin (OHCbl) and aquacobalamin (H2OCbl), b) structural model employed in present work.

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Posters

Electron density reorganization study by the atomic fragility spectra for the Kemp elimination

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Atomic fragility spectra calculated for the minimum energy coordinate on the reaction path have been recently proved to provide a neat picture of the density changes around atoms as well as within the bonds. By applying the technique to the Kemp reaction[1], a landmark for the studies of the catalytic reaction mechanism, the sequence of bond reorganization in this process has been exposed. The NO pair of the izoxazole ring was proved to be the sensitive and unstable point of the system. Small disturbances at this point by an external field are critical to the catalytic effect on the reaction. The divergences of Hellman-Feynman forces calculated for the bonds have been shown to provide an original and precise index of their binding power, well correlated with common bond energies. The results demonstrate the promising power of the technique for the reaction imaging[2].

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

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Vibrational Solvatochromism - From Simple Experiments in Solution to Complex Biomolecules

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Although many state-of-the-art experimental techniques offer methods that can accurately and precisely measure primary structures of biomolecules, probing the high-order organization beyond covalent interaction in condensed phases such as a cytosol still poses a great challenge of modern Science. In effect, the native structure of biomolecule is oftentimes unknown or highly unclear, greatly limiting our understanding of biochemical processes governing life. In particular, short living structural rearrangements within biomolecules could play an important role in signal transduction, but probing and understanding those subtle processes is still a field of extensive study.

With the advancement of high-precision ultrafast vibrational spectroscopy, invaluable and unprecedented insights into many dynamical processes that occur in proteins and nucleic acids on timescales of the order of picoseconds were obtained. [1] Since molecular vibrations are extremely sensitive to even tiniest structural changes of the probe or its environment, vibrational spectroscopy has a great advantage over the other experimental approaches.[2] Unfortunately, as the response functions that dictate the concomitant band positions and lineshapes are usually very complicated and depend on the quantum mechanical properties of the vibrational oscillator, the interpretation of the experimental output is not a straightforward task. As a result, too simplistic theoretical models are often used to translate the structural and dynamical information from vibrational spectra.

The presentation will discuss on the direction of research that focuses on tightening the link between molecular structure and its vibrational characteristics and its application to interpret convoluted experimental data. The state-of-the-art approach based on the physically well-defined intermolecular interactions, the solvatochromic effective fragment potential method (SolEFP) along with its biomolecule-fragmented extension, [3] will be presented as a promising candidate for an accurate and efficient {\em ab initio} vibrational map in proteins. The inclusion of Pauli exchange-repulsion and dispersion interactions, inaccessible by most of previous approaches, will be highlighted in particular. The discussion on a future perspectives of this approach will also be presented.

Acknowledgements. M.C. was supported by IBS-R023-D1 grant. B.B. thanks the Wrocław Centre for Networking and Supercomputing (WCSS) at Wrocław University of Science and Technology in Poland for support. L.J. W. was supported by the Welch Foundation (F-1722).

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Excited state dynamics of conjugated polyenes. Ab-initio and semiempirical calculation of electronic absorption spectra

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Correct quantum chemical calculation of absportion spectra and excited state dynamics of linear conjugated polyenes has been a challenging task for long decades. Here, we present an extensive computational study describing properties of linear conjugated polyenes from ethene up to polyene with 22 carbon atoms in the main chain. For calculation of the electronic absorption spectra we use many ab-initio quantum chemical methods, TDDFT approach and semiempirical methods. These static calculations were a prerequisite for excited state dynamics of said polyenes, which were employed using Tully surface hopping combined with the OM1 method.

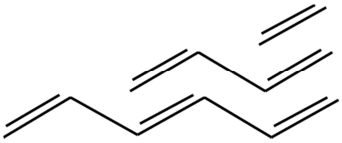

Figure: Ethene, butadiene and hexatriene

Ab-initio calculations of electronic spectra were carried out using CASSCF, CIS, TDHF, CIS(D), EOMCCSD and SAC-CI methods on ethylene along with TDDFT (and TDADFT aproximation) using functionals CAM-B3LYP, LC-ωPBE and ωB97XD. All methods were used with the augmented Dunning correlation consistent basis set aug-cc-pvdz and basis-size dependence was explored. The best results for ethylene spectra were obtained with TDDFT methods CAM-B3LYP, ωB97XD and surprisingly with CIS and TDHF methods, all of which provide correct order of at least first four excited states and standard mean deviation from experimental energies of first five excited states less than 0.12 eV.

These methods were used for calculation of spectra for longer polyenes; here the CIS and TDHF method fail to provide sufficiently correct results even for the most important B_u excited state. TDDFT methods correctly describe this B_u state with deviation from experiment less than 0.1 eV, although not even the correct order of first two excited states is reproduced.

As for semiempirical calculations, we used the MNDO, MNDOC, OM1, OM2, OM3, PM3 and AM1 methods combined with GUGA-CI formalism with various active space configurations. Here, best results were obtained with the OM1 method, which provides correct order of the first two excited states; i. e., dark A_g and bright B_u state; mean standard deviation of their excitation energies is about 0.25 eV.

This calculation allowed subsequent calculation of excited state dynamics. Here, we obtained reliable mean lifetimes of A_g and B_u excited states for ethylene, butadiene, hexatriene and oktatetraene; moreover we have an initial guess of these lifetimes for polyenes with 20 and 22 carbon atoms. All of these results are in agreement with experimental data. There is ongoing work focused on refining existing lifetimes and obtaining them for remaining polyenes.

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Molecular and functional aspects of proMMP-9 homotrimerization

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Matrix metalloproteinase (MMP)-9 is a highly flexible, multidomain protein of endoproteolytic activity. Type I, IV, V and IX collagens, elastin, laminin and the aggrecan core protein belong to its main substrates. Due to such substrate specificity MMP-9 is directly involved in tissue remodelling, wound healing, but it also contributes to activation and deactivation of signalling biomolecules like cytokines and growth factors. In pathological conditions MMP-9 contributes to the development of rheumatoid arthritis or cancer progression and metastasis.

MMP-9 is synthetized in a latent state (proMMP-9), in which the propeptide occupies the catalytic cleft. In order to acquire catalytic activity it has to dissociate, involving hydrolysis by another enzyme, or at least to bend away. On the other hand, inhibition of MMP-9 is performed by the tissue inhibitor of metalloproteinases (TIMP)-1, which has the ability to form two kinds of complexes with MMP-9 – the inhibitory one, where it bloks the active site of the MMP-9 catalytic domain, or noninhibitory one resulting in the binding to the hermopexin-like domain. The latter often is formed even before MMP-9 is released from the cell. Its worth noticing that there are only four known TIMP proteins which regulate the activity of all MMPs (23 known in humans) and that they can function also as regulatory molecules. Free TIMP-1 itself was reported to have growth factor-like and antiapoptotic properties [1].

Recent findings show that proMMP-9 can form homotrimeric, circular structures in two forms differing in their diameters. Facts that those forms were released by neutrophils, which are unable to synthetize TIMP-1, and that they exhibit significantly a higher affinity to TIMP-1 than monomers suggest that such trimers may play the regulatory role by binding free TIMP-1 [2], and not the catalytic one.

Here, we present results supporting this hypothesis. Using molecular modelling approach we show that in a smaller, more frequent homotrimer, the most common path of activation is inactivated. The bait region of propeptide, where initial cleavage by MMP-3 takes place is unavailable for the hydrolysis due to its interactions with the hemopexin domain.

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http://unres-server.chem.ug.edu.pl
portal for coarse-grained simulations of proteins

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Faculty of Chemistry, University of Gdańsk

UNRES is a highly reduced protein model with only two interaction sites per residue: united side chain and united peptide group. Owing to this reduction, it offers 1000-4000-fold speed up in molecular dynamics simulations compared to all-atom models. The UNRES effective energy function has been defined as a potential of mean force of polypeptide chains in water, which has been subsequently expanded into Kubo cluster cumulant functions. In contrast to most of the protein coarse-grained models, owing to its physics-based origin, the UNRES force field can be used in simulations without ancillary information from structural databases; however, the implementation includes the possibility of using restraints. UNRES has been used with success in protein-structure prediction, studying protein-folding kinetics and free-energy landscapes as well as to solve biological problems. [1]

Recently, we have implemented a server based on the UNRES package, which enables a user to submit jobs using a web-based interface. [2] Three types of calculations are available: (i) single local energy minimization, (ii) single-trajectory canonical MD and (iii) multiplexed replica-exchange molecular dynamics (MREMD). For the MREMD type of calculation, a production simulation is followed by running weighted histogram analysis method (WHAM) to compute the probabilities of conformations, thermodynamic quantities and ensemble averages, and cluster analysis of the ensemble at the desired temperature to construct the final models. This procedure copies our physics-based protein-structure prediction procedure that has been tested in the CASP exercises. The final models are converted into all-atom and subjected to a short refinement.

The user-supplied input includes protein sequence and, optionally, restraints from secondary-structure prediction or small x-ray scattering (SAXS) data, and simulation type and parameters which are selected or typed in. Oligomeric proteins, as well as those containing D-amino-acid residues and disulfide links can be treated. Distance distribution from SAXS measurements are incorporated into the target function as a maximum-likelihood term that guides the shape of the simulated structures towards that defined by SAXS. [3]

The output is displayed graphically (minimized structures, trajectories, final models, analysis of trajectory/ensembles); however, all output files can be downloaded by the user.

Acknowledgements. Support from National Science Center of Poland (Narodowe Centrum Nauki, NCN) [UMO-2017/25/B/ST4/01026, UMO-2017/26/M/ST4/00044] is acknowledged. Computational resources were provided by (i) the Informatics Center of the Metropolitan Academic Network (CI TASK) in Gdańsk, (ii) the Interdisciplinary Center of Mathematical and Computer Modeling (ICM), University of Warsaw (grant GA-71-23), (iii) the Polish Grid Infrastructure (PL-GRID), (iv) our cluster at the Faculty of Chemistry, University of Gdańsk.

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Tuneable Aromaticity of para-Substituted Benzene Derivatives

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For aromatic species, substituent effect is a phenomenon which has a strong impact on properties of these systems.[1,2] Thus, the question of the relationship between aromaticity and substituent effect arises. This work investigates changes in aromaticity in para-substituted benzene derivatives exposed to external electric fields of different intensities. Three systems, namely *para*-aminophenol, *para*-nitrobenzonitrile and *para*-nitrophenol, with various substituent electron-accepting/donating properties are studied (see Figure 1 for spatial orientation of these systems).

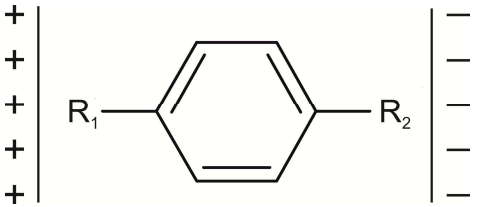

Figure 1: Orientation of para-substituted benzene derivatives in an external electric field.

The interrelation between aromaticity and the substituent effect appears to be of a competitive nature.[3] It is shown that the aromaticity of the benzene ring (and the substituent effect) in such systems can be tuned by changing the intensity of the external electric field. [3] Such tuning is most effective for a system substituted with one electron-donating and one electron-accepting substituent.

Acknowledgements: Calculations were carried out using resources provided by the Wroclaw Centre for Networking and Supercomputing (http://wcss.pl), grant No. 118.

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Vanadium centres introduced into BETA zeolite – theoretical and experimental characterization

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There is an increasing interest in the production of lower alkenes because of their importance in the chemical industry. Oxidative dehydrogenation (ODH) is an attractive catalytic reaction of formation of light alkenes from light alkanes:

$$C_nH_{2n+2} + 0.5\ O_2 \rightarrow C_nH_{2n} + H_2O$$

What is more, the energy demand for this reaction is much lower than that for conventional catalytic cracking and even than that of dehydrogenation processes [1]. Vanadium-based systems constitute an important class of ODH catalysts.

The aim of this work was to analyse the nature of the V species introduced into the Beta zeolite by two-step post-synthesis method [2] and characterize obtained samples both theoretically and experimentally.

We studied the nature of the introduced vanadium. Its coordination, oxidation state, and the existence of proximal hydroxyl groups were assessed by the experimental approaches with an aid from computations. The chemical composition of the samples was confirmed with XRF, phase composition by XRD, BET provided surface area and porosity. Reducibility was measured with H_2-TPR method, while NH_3-TPD gave information on the type and strength of acid centers.

The theoretical investigations were performed within Density Functional Theory (DFT), with Perdew-Burke-Ernzerhof (PBE) functional and the basis set of def2-TZVP type with Turbomole computer program. In the first instance, theoretical cluster models of the possible vanadium active centres were constructed, based on the available literature data as to the geometry and environment of the V-sites in zeolites, in particular the theoretical studies regarding SOD and BETA zeolites [3].

Acknowledgements. This work was supported by the National Science Centre, Poland within project no 2016/23/B/ST4/02854.

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Structure and redox properties of nitroaromatic compounds and cyclic nitroamines adsorbed on a silica surface. M05 computational study

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Nitrocompounds, especially nitroaromatic compounds encountered in drugs, dyes, and explosives, represent a group of hazardous contaminants which could be dispersed in the environment during production, processing, destruction, and recycling. Sorption of organic chemicals to soil is a major process that can affect their mobility, degradation and toxicity by reducing their availability. A fundamental understanding of sorption and desorption mechanisms is therefore essential for the accurate prediction of the fate and impact of organic contaminants in soils and groundwater. Adsorption of nitrocompounds by soil components is one area that has been actively studied both experimentally and theoretically searching for efficient methods for removing them from the environment. It was shown that different fractions of soil adsorb nitrocompounds and facilitate their transport. Since silica is one of the most investigated fractions of soil, adsorption of nitroaromatic compounds, such as trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), 2,4-dinitroanisole (DNAN), 5-nitro-2,4-dihydro-3H-1,2,4-triazol-3-one (NTO), 5-amino-3-nitro-1H-1,2,4-triazole (ANTA), and cyclic nitroamines, such as hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX), and 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20) on (001) surface of α-quartz was studied at the M05/tzvp level using cluster approximation.

Structure and redox properties of adsorbed nitrocompounds were compared with those of gas-phase and hydrated species by calculation of the geometrical parameters, ionization potential, electron affinity, oxidation and reduction Gibbs free energies, oxidation and reduction potentials. It was found that adsorption and solvation decrease gas phase electron affinity, ionization potential, and Gibbs free energy of reduction and oxidation, and thus, promote redox transformation of nitrocompounds. However, in case of solvation, the changes are more significant than for adsorption. This means that nitrocompounds dissolved in water are easier to transform by reduction or oxidation than adsorbed ones. Nitroaromatic compounds are more active in reduction process than cyclic nitramines. Among the considered nitroaromatic compounds, TNT was found to be the most reactive in an electron attachment process and the least reactive for an electron detachment transformation.

Initial Excited-state Relaxation of Ring-locked Retinal Chromophore Model. An Insight from Coupled Cluster and Multireference Perturbation Theory Calculations

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Retinal is a chromophore of various photoactive proteins responsible for e.g. vision at higher organisms and active transport of ions in bacteria. The chromophore is covalently bound to the protein through protonated iminium moiety (RPSB, Figure) and its light-induced photoisomerization is the first step that triggers biochemical cascades leading to various activities of retinylidene proteins.

Due to remarkable rate of the photoisomerization (the first intermediate is formed in merely 200-250 fs), the theoretical chemistry methods played an invaluable role in revealing the most probable mechanism of the photoprocess. Nevertheless, the experimental studies of rhodopsin pigment comprising the artificial RPSB with the photoreactive bond incorporated into eight-membered ring have shown that discussed photoreaction can be accelerated as concluded from the excited-state lifetime of the artificial pigment being shorter than of the native rhodopsin without loss of its remarkably high quantum yield. The present contribution is an assessment of complete active space self-consistent field (CASSCF) and approximated second-order coupled cluster (CC2) quantum chemistry methods in reference to extented multiconfiguration quasidegenerate second-order perturbation theory XMCQDPT2 approach for description of initial geometrical excited-state (the S_1 state) relaxation of locked-11.8 retinal model (Figure). The relaxation in terms of energy difference between the Franck-Condon and the excited-state equilibrium structures as well as emission energies from the latter were calculated with various multireference perturbation theory approaches (e.g. XMS-CASPT2 or XMCQDPT2 with modified energies of active orbitals).

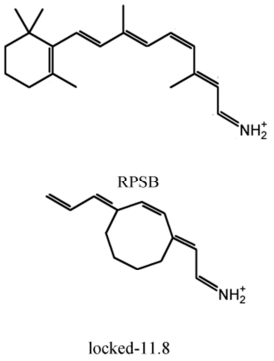

Figure: Comparison of full (RPSB) and investigated (locked-11.8) models.

Our analysis clearly shows that the S_1 state minimum energy structures are predicted to be too strained (twisted) according to CC2 and CASSCF approaches (being in a very good agreement) as compared to XMCQDPT2 method predictions. As a consequence, the emission energies are underestimated for the former geometries. Furthermore, less extensive structural and energetical relaxation in locked-11.8 conformers as predicted by XMCQDPT2 method may have some implications for treating investigated RPSB model as an ultimate goal for designing super fast and efficient photoswitches.

Acknowledgements. This work was financed by Wroclaw Research Centre EIT+ under the project BIOMED "Biotechnologies and advanced medical technologies" (POIG 01.01.02-02-003/08). Calculations were performed at the Wroclaw Centre for Networking and Supercomputing.

Quantum-chemical studies of homoleptic Iridium(III) complexes in OLEDs: *fac* versus *mer* isomers

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Phorphorescent transition-metal complexes have recently attracted significant attention because of their unique photophysical properties for appliactions such as dopants for OLEDs (organic light-emitting diode),convenient fluorescent markers for biological system as well as photocatalysts in light accelerated processes [1]. The most popular phosphorescent systems are based on coordination compounds of heavy metals such us Ir, Pt, Os or Pd in which the central metal atom is stabilized by cyclometalated organic ligands of various structures [2]. In particular, iridium complexes deserve much attention, due to efficient triplet emission as an effect of very strong spin-orbit coupling, which causes mutual isoenergetic transition from the singlet to the triplet state, known as intersystem crossing (ISC) [3].

In the present work computational studies have been carried out with the aim of better understanding the photophysical and stereochemical properties of homoleptic iridium (III) compounds with benzoquinoline. Homoleptic triscyclometalated Ir complex may have two geometrical isomers: meridonial (mer) and facial (fac) [4].

To compare both isomeric forms the geometric and electronic structures and phosphorescent properties of a series of iridium(III) complexes have been investigated by using density functional theory (DFT) with Becke's three parameter hybrid method combined with the Lee-Yang-Parr correlation functional (B3LYP). The calculations were performed using the 6-311++G(d,p) basis set for H,C,N,O and F atoms. For Ir metal center SDD basis set was selected as it contains effective core pseudopotential. The frontier orbital energies HOMO and LUMO and energy gaps between HOMO and LUMO have been calculated. Previous studies indicated that the energy gap between molecular orbitals is a critical parameter in determining molecular electrical transport properties because it may serve as an approximate a measure of electron conductivity.

Acknowledgements: This research was supported in part by PL-Grid Infrastructure.

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Spatial packing of diols and esters with imidazoquinazoline ring - quantum-mechanical modelling

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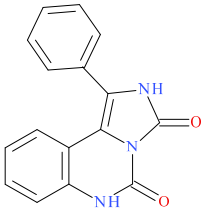

(I)

1-phenyl-2H,6H-imidazo[1,5-c]quinazoline-3,5-dione (I) can react with 2-molar excess of ethyl bromoacetate and diester - 1-phenyl-2,6-bis(ethoxy-carbonylmethyl)imidazo[1,5-c]quinazoli-ne-3,5-dione is formed. In turn, the use of 2-molar excess of ethylene oxide results in an obtaining of diol - 1-phenyl-2,6-bis(2-hydroxyethyl)imidazo[1,5-c]quinazoline-3,5-dione.

These compound are characterized by spectral methods, therein by crystallographic studies [1, 2]. Single-crystal X-Ray diffraction analysis of diester and diol con-firmed the location of substituents at nitrogen atoms No. 2 and No. 6. It revealed also a different way of arranging the diol and diester molecules in the elemental cell and the crystal structure.

In the case of diester, there are four pairs of enantiomers in the unit cell. It was observed that the quinazoline rings are located parallel to each other. They are rotated by 180° in the plane but they are located exactly one above the other.

Quantum-mechanical calculations revealed that it is caused by overlapping of HOMO and LUMO molecular orbitals. Electron transfer is possible due to the difference in the charge distribution in imidazoquinazoline rings of the two molecules (Figure A).

There are also 4 pairs of molecules in the elemental cell of the diol, but these are not exactly enantiomers. There is a slight difference in the position of the phenyl ring relative to the imidazoquinazoline ring. The diol molecules are situated in parallel with the planes of the imidazoquinazoline ring but the rings are shifted from each other (Figure B). There is no electron transfer between diol molecules. Hydrogen bonds formed by hydroxyl groups are responsible for the spatial arrangement of diol molecules.

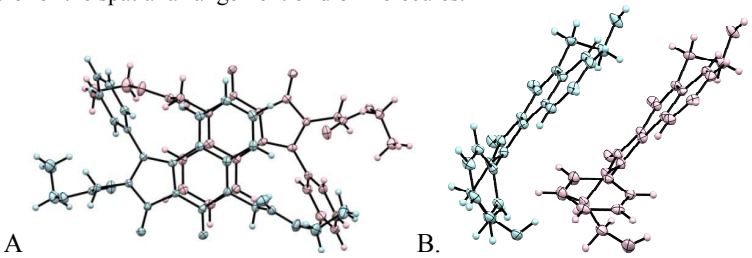

Figure: Spatial arrangement of: (A) ester, (B) diol molecules in crystal.

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Influence of the position of bromine and chlorine atoms on the distribution of electron density for hydroxyalkyl aniline derivatives used as modifiers of unsaturated polyester resins

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Unsaturated polyester resins, i.e., styrene solutions of an unsaturated alkyd, are usually cured by the system consisting of a radical producing initiator, such as benzoyl peroxide or ketone peroxides with some metal salts, as accelerators. Tertiary aromatic amines also reduce the activation energy of peroxide. These amines are used in unsaturated polyester resins compositions with benzoyl peroxide for room temperature curing [1]. The best possible situation is when the amine has two functional groups capable of reacting with carboxylic acids or anhydrides or with diols. The most widely reported industrial formulations are the three-component systems consisting of the polyester dissolved in styrene, peroxy initiator, and a tertiary amine. The formulations where amine is chemically incorporated into polyester chains, already at the stage of its synthesis have somewhat better stability. These accelerators can selectively react with some groups of initiators. Incorporation of such an amine into resin structure may significantly accelerate gelation of the resin because of formation of active RO• radicals that initiate polymerization [2].

The aim of this work was to obtain novel ternary amines that can be used as modifiers and preaccelerators for UP resins. These amines has incorporated chlorine and bromine atoms into structure i.e. substitution of the aromatic ring. The *ortho*-, *meta*- and *para*- derivatives of N,N-bis(hydroxyalkyl)aniline were discussed in terms of the impact on the rate of gelation, because type of atom and its position of substitution affect significantly on the distribution of electron density in aromatic ring. Calculations of distribution of electron density based on the Density Functional Theory (DFT) were made using Gaussian 09 application. Despite the similarity of both elements, their influence on the distribution of electron density in aromatic ring are different. It may result from the type of the substituent and position of its substitution. These effects can be observed not only in quantum-mechanics simulations (e.g. in HOMO orbitals shape) but also in laboratory experiments during gelations time measurenment.

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A novel approximate valence bond model for intramolecular proton transfers and its application to porphyrin and porphycene

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(Bio)molecular processes which occur in the ground or excited electronic states, are described based on the Born-Oppenheimer (BO) approximation. It leads to the potential energy surfaces (PESes), which depend on the atomic positions, and can be used for molecular dynamics simulations. Potential energy values, as well as BO forces acting on the nuclei, can be computed using the conventional quantum mechanical methods, including the density functional theory (DFT). However, such methods are time consuming and restrict possible molecular dynamics simulations, especially when explicit quantum delocalization of the atomic nuclei (e.g. protons) is concerned. A practical solution is to use a fast, quantum generator of the PESes. Such generator has to be parametrized based on more advanced quantum mechanical calculations in order to mimic their results. In the Approximate Valence Bond (AVB) [1] we represent the PES with a function $V(\mathbf{r})$ determined as the lowest eigenvalue of the following set of equations $\sum_{j=1}^{N_M}\left[\mathcal{H}_{ij}(\mathbf{r}) - \delta_{ij}V(\mathbf{r})\right]c_j(\mathbf{r}) = 0$, where $\mathbf{r}$ denote the Cartesian coordinates of the atomic nuclei, and N_M is the total number of local minima of the considered molecule. In the simplest (harmonic) approximation, a symmetric real-valued square matrix $\mathcal{H}(\mathbf{r})$ of order N_M is defined as follows: $\mathcal{H}_{ii}(\mathbf{r}) = \frac{1}{2}(\mathbf{r}-\mathbf{r}_{ii})^T\mathcal{A}_i(\mathbf{r}-\mathbf{r}_{ii}) + \mathcal{B}_i^T(\mathbf{r}-\mathbf{r}_{ii}) + \mathcal{C}_i$ and $\mathcal{H}_{ij}(\mathbf{r}) = \mathcal{B}_i^T(\mathbf{r}-\mathbf{r}_{ij}) + \mathcal{C}_i$. The $\mathbf{r}_{ii}$ denotes vector of coordinates of the i^{th} local minimum, while $\mathbf{r}_{ij}$ stands for a vector of coordinates of the saddle point between the minima i and j, provided that the minima i and j are separated by a single energy barrier. Other elements of the matrix $\mathcal{H}$ are set to 0. $\mathcal{A}, \mathcal{B}$ and $\mathcal{C}$ are the parametric objects of the matrix, vector and scalar type, respectively, and they are optimized to reproduce selected results of the reference quantum mechanical calculations. In a more advanced (anharmonic) approximation, the protonic Cartesian coordinates are replaced by curvilinear angular and Morse type coordinates which allow for describing anharmonic potential wells for the protons motions.

In this study we adapt the AVB method for intramolecular double proton transfer in porhyrin and porhycene molecules, and account for parameterization of the all-atom Hessians in the stationary geometries. We apply combination of internal and Cartesian coordinates and use the normal transformation [2] to ensure rotational invariance of PES, without increasing cost of the analytical derivates, for arbitrary number of atoms. The potential is tested applying quantum-classical molecular dynamics simulations (MD/AVB) for porphyrin and porphycene, including motions of their internal protons.

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Unusual bonding in boron clusters

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Bonding in boron clusters is predominantly of multicenter nature, usually referred to as 3-center-2-electron (3c2e) bonding. Two types of 3c2e bonds, the B-B-B and B-H-B triangles, occur in boranes, which often breaks the classical electronegativity concept.[1] Such bonding also results in unusual noncovalent interactions (in crystals, with biomolecules). Group V, VI and VII elements in neutral heteroboranes have highly positive σ-hole and they can thus form strong σ-hole interactions.[2] We have observed the S···π, Br···π, Sb_2···H-B types of such interactions of heteroboranes in the corresponding crystal packings.[1,3,4] Quantum chemical analysis revealed that these interactions were considerably stronger than in their organic counterparts.[1,3,4]

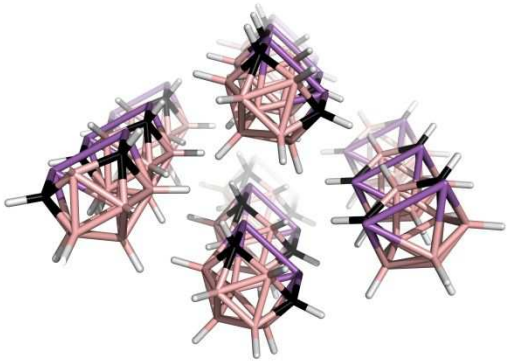

Figure: Pnictogen type of bonding due to σ-hole found in the X-ray structure of a nido-distiba-dicarbaborane.[4]

Acknowledgements: We acknowledge the financial support of the Czech Science Foundation (17-08045S).

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Modelling of h-CBN band structures on a metal surface

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h-CBN monolayers, two-dimensional sheets of carbon, boron, and nitrogen, are structural analogs to the more well-known graphene and h-BN monolayers, and have been highly sought as potential alternatives due to their band-gaps being intermediate to that of semi-metallic graphene and insulating h-BN. Recent successes, for example a recent synthesis of a graphenic h-CBN monolayer on an Ir(111) substrate [1], have spawned further interest, and have, alongside their proposed structures, led to experimental measurements of the h-CBN electronic structure.

In this presentation, theoretical studies of h-CBN band structures on Ir(111) and Rh(111) substrates are explored in depth, with the goal of validating the atomistic and electronic structures of the h-CBN monolayers that have been discussed. Density functional theory is used to help explain the features of the band structure, and to relate the band structure with the distribution of C, N, and B atoms about the lattice. Simulations are further used to help unravel the role of the substrate in activating the precursor molecule and in guiding their migration.

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Random coils and solvation shell of hyaluronan in electrolyte solutions

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Hyaluronic acid (HA, hyaluronan), an alternating co-polymer of glucuronic acid and N-acetylglucosamine ([4)-β-D-GlcpA-(1→3)-β-D-GlcpNAc-(1→]n), is a major component of extracellular matrix of animal connective tissues with a variety of biological roles and technological application. In aqueous solution, HA molecules form random coils the size of which was studied experimentally many times and the dependence of the radius of gyration (R_g) on the identity and concentration of different salts in the solution was described. In general, the random coils shrink when the salt concentration increases. The aim of our work is to simulate the electrolyte effects on HA random coils by molecular dynamics and to describe the key phenomena driving the random coil formation. A HA oligosaccharide of 48 monosaccharide residues was simulated in appropriate solvent for 80 ns and, subsequently, large random coils were composed of its randomly selected fragments connected in accord with the statistics of the dihedral-angle couples of the glycosidic bonds between the residues. R_g was then determined from a statistically significant ensemble of the coils generated this way. The results show a good agreement with experiment regarding the both the absolute R_g value and its dependence on electrolyte concentration [1]. However, a similar behavior was observed also for a neutral HA analog containing glucose instead of glucuronic acid which indicates that the repulsion of the negative charges of the carboxylate groups are not the key factor determining the random-coil shape. Therefore, we analyze the structure of the solvation shell of both the polymers using a cumulative solvation-shell diagrams in which the surroundings of all residues of the same kind within several simulation frames is superimposed to one 2D plot. Using this and other analyses we identify the differences in the water structure of different polysaccharides, distributions of ions and variations in the molecular geometry. The results indicate that the random-coil shrink as a consequence of disturbing the solvation shells by weakly bound ions that increase the chain conformational entropy and thus induce the closer packing of the molecule.

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Quantum chemical calculations of complexes of 10-methylthio colchicine with lithium

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Colchicine is a tropolone alkaloid of Colchicinum autumnale. It shows antifibroatic, antimitotic and anti-inflammatory activity [1]. Colchicine thio derivatives are less toxic and can be used as anticancer agents [2]. Furthermore, complexes of lithium may form strong bonds with other elements [3] and mediate a lithium bond [4].

Geometric and electronic structure was studied, within DFT framework at M06/6-31+g(d,p) level of theory [5-6]. To access the impact of solvent on results calculations were performed with PCM model [7]. We used the same solvent as in complex synthesis which was methanol.

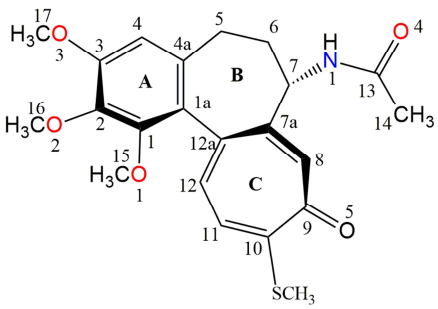

Fig. 1: 10-methyltio colchicine molecule

According to ESI MS studies it was found out that 10-methylthio colchicine can form stable complexes with lithium of two different stoichiometry: 1:1 and 2:1. Five different interaction schemes were considered excluding 10-methyltio colchicine coordinating via sulphur atom.

The most energetically favoured complexes of 10-methylthio colchicine with lithium cation are obtained when one or both molecules of colchicine coordinate via O4 and O5 oxygen atoms. Moreover, our calculation showed that amongst all studied complexes the most energetically favoured interaction is Li+…O4.

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Hydrolitic and electron transfer pathways in oxaliplatin biotransformation

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The work constitutes a part of our project: "Theoretical studies of biotransformation mechanism of platinum(II) cytostatic complexes" [1,2]. The aim of this presented studies was to find the most plausible reaction courses, which conduct of pro-drug into forms capable to interact efficiently with target biomolecules. Implementing the theoretical methodology and *in silico* tools, two alternative reaction courses, hydrolytic and based on dissociative electron attachment, were evaluated. The results were obtained with applying the B3LYP-def2tzvp treatment. The hydrolytic transformation starts from the impact of water molecule on oxaliplatin, where reagents are: [Pt(C6H14**N**2)(**O**OC-CO**O**)] + $2H_2O$. It was confronted with electron-induced pathways, where reagents include: [Pt(C6H14**N**2)(**O**OC-CO**O**)] + e^- + H_2O. The computational simulations of nucleophilic substitution (by the H_2O impact) and dissociative electron attachment (by impact of electron donor molecules, free electrons, hydrated electrons) provided the values of structural and thermodynamic parameters, which allowed to track the fate of drug along the different metabolic pathways. The most concurrent pathways represent the sequence of reactions initiated by electron attachment

Conclusions: contrary to the commonly accepted idea, the hydrolytic pathway cannot be considered as an only mechanistic mode of oxaliplatin bioactivation; comparing the concurrent pathways we can opt for the hybrid mechanism, including electron impact on aquated oxaliplatin.

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Addressing halogen bonding with the revised non-empirical scoring model

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Hybrid Variation-Perturbation Theory (HVPT) [1] introduces partitioning of the Möller-Plesset second-order interaction energy (E_{MP2}) into the multipole electrostatic ($E_{EL,MTP}^{(10)}$), penetration ($E_{EL,PEN}^{(10)}$), exchange ($E_{EX}^{(10)}$), delocalization ($E_{DEL}^{(R0)}$) and correlation ($E_{CORR}^{(2)}$) terms:

$$E_{int} = E_{MP2} = \underbrace{E_{EL,MTP}^{(10)}}_{R^{-n}} + \underbrace{E_{EL,PEN}^{(10)} + E_{EX}^{(10)} + E_{DEL}^{(R0)}}_{e^{-\alpha R}} + \underbrace{E_{CORR}^{(2)}}_{R^{-6},\ e^{-\alpha R}} \approx \underbrace{E_{EL,MTP}^{(10)} + E_{Das}}_{R^{-n},\ e^{-\alpha R}}$$

These contributions could be divided into long- and short-range interactions varying with the intermolecular distance R as R^{-n} or $e^{-\alpha R}$, respectively. Our non-empirical $E_{EL,MTP}^{(10)} + E_{Das}$ model, [2] which is based on the long-range components of interaction energy only, utilizes Das function [3] to approximate computationally demanding dispersion interactions. The latter is fitted to the dispersion ($E_{disp}^{(20)}$) and exchange-dispersion ($E_{exch-disp}^{(20)}$) interaction energy terms, defined within Symmetry-Adapted Perturbation Theory (SAPT).

Das function has been extended to comprise 6 more atoms (marked in blue in Figure). Importantly, the revised Das function covers all halogen atoms, thus halogen bonding in protein-ligand complexes can be studied with our $E_{EL,MTP}^{(10)} + E_{Das}$ model. Here, the function with novel parameteres is used for the first time in the $E_{EL,MTP}^{(10)} + E_{Das}$ model with phosphodiesterase type 5 (PDE5) inhibitors, which are substituted with a series of halogen atoms. [5] The results are compared to E_{MP2} and VinaXB, an empirical scoring function dedicated to halogenated compounds. Apparently, the simple $E_{EL,MTP}^{(10)} + E_{Das}$ model performs well on such inhibitors, yielding much better results than employed empirical function.

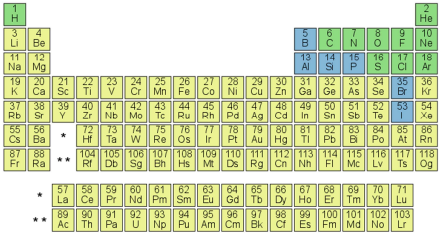

Figure: Atoms covered by Das function. Green - already published parameters; [3] Blue - new parameters.

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Fragility of the proton exchange reactions between H_2NCHO and H_2NCHS molecules

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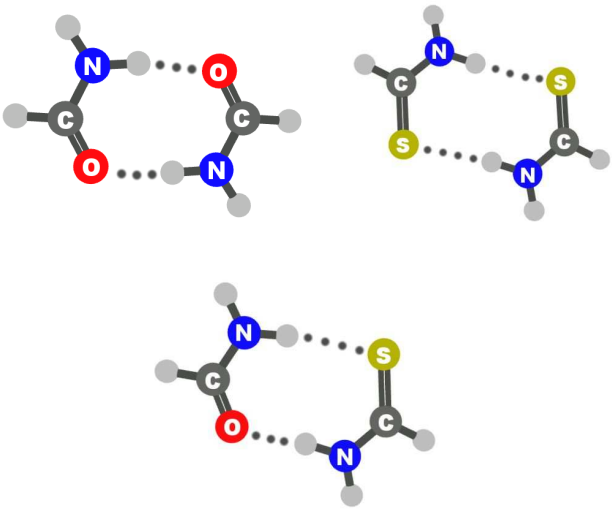
The double proton transfer reactions belong to classical group of processes extensively studied both experimentally and by computational methods. [1] Jaque and Torro-Labbé have given a concise review of the kinetic studies aimed at describing the process by means of the reaction force formalism.

Application of the fragility spectra to the reaction seemed most natural; the newly proposed method directly describes the bond reorganization and associated density change along the bonds. [2,3] The results clearly expose the difference between the N-H…O and N-H…S bonding patterns.



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Structural studies of the L_carbamoylase with active site bound mono/dinuclear Co^{2+} - MD simulation study

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L-carbamoylase (*Geobacillus Stearothermophilus*) involved in a pathway, which is responsible for the production of L-amino acid by hydrolyzing amide bonds of L-N-carbamoyl-amino acids. This enzyme exists as a functional homodimer and uses Co^{2+} as a cofactor for catalysis. Dinuclear divalent metal ions have been observed in the active site of homolog enzymes, whereas, in L-carbamoylase single Co^{2+} was observed in each of the active sites, when no cobalt salt was added during protein purification/crystallization. Moreover, crystallization with $CoCl_2$ did not change the occupancy of the active sites by Co^{2+}. Thus, the question whether the enzyme works with a mono or dinuclear Co^{2+} active sites is still open.

To answer the above, 75 ns, metal ion non-bonded model MD simulations were carried out for mono and dinuclear Co^{2+} bound L carbamoylase, respectively. It has been observed that in case of mononuclear Co^{2+} L_carbamoylase, there is the formation of water mediated interaction instead of direct interaction between Co^{2+} and active site residue. In dinuclear L_carbamoylase there is loss of some conserved interactions and formation of new. Next bonded model MD (40 ns) simulations were performed and coordination of active site residues with Co^{2+} were observed to remaining conserved. Since the available crystal structure of homolog enzymes with ligand bound in the active site have domain closed conformation. Thus, to get more structural insights on the role of ligand in domain closing, MD simulations of mono and dinuclear Co^{2+} L_carbamoylase, respectively, docked with L-N-Ala-Carbamoylase, were carried out. During MD simulation, it has been observed that water molecule bound to Co^{2+} was bumped out. Thus, to resolve it restrained nonbonded model MD (60 ns) simulations were performed, water molecules coordinated with Co^{2+} were considered as nonbonded by applying harmonic restraint while active site residues were kept bonded with Co^{2+}. Cluster analysis of whole trajectory shows that coordination of Co^{2+} with active site residues remain throughout the trajectory.

The present study shows non-bonded and bonded metal ion model unable to model the coordination of Co^{2+} with active site residues. To unravel preference of mono/dinuclear Co^{2+} for catalysis by L_carbamoylase and role of ligand binding in domain movement, further docking and protein-ligand MD simulation (restrained nonbonded) will be performed.

Acknowledgments. This research project was supported by grant No UMO2014/14/E/NZ1/00053 from the National Science Centre, Poland and by PL-Grid Infrastructure. Calculations were performed at the Academic Computer Centre Cyfronet AGH.

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Interactions of levamisole with iron octacarboxyphthalocyanine. Experimental and DFT study

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Phthalocyanines were discovered in the early 20th century. They are structural analogues of porphyrins. These compounds have a conjugated system of 18 delocalized π-electrons. The inner part of the macrocycle can complex almost all metal ions from the periodic table [1]. Complexes of phthalocyanines with iron ions are of particular interest due to the possibility of using them as catalysts in different redox reactions [2]. This property can be used to remove pharmaceuticals and personal care products, which are present as contaminations in water. Due to their potential negative impacts on natural ecosystems and humans these pollutants could be very harmful.

The subject of our research is the interaction of levamisole with iron and metal-free octacarboxyphthalocyanine (FePcOC and H_2PcOC, respectively). Levamisole is a drug used to treat parasitic worm infection. The aim of our study is to examine the type and energy of interaction of levamisole with phthalocyanine (fig.1). The geometric structures of the axial and equatorial complexes of FePcOC or H_2PcOC with levamisole both in the gas phase and in aqueous solution were optimized at the M06-2X/6-31G* level of theory using Gaussian 09.

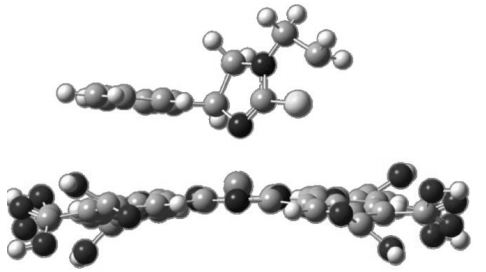

Fig. 1. Structure of axial FePcOC – levamisole complex calculated at M06-2X/6-31G* level of theory.

Acknowledgments: All calculations were carried out in Wrocław Centre for Networking and Supercomputing.

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About the nature of halogen bond interaction under the spatial confinement

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Nowadays, much attention is put toward the description of noncovalent complexes, exposed to the high pressure or embedded in confining environments. [1-3] Such conditions may strongly modify the physical and chemical properties of molecular systems. This study focuses on the theoretical description of the confinement induced changes in geometry and energetic parameters of the halogen bonded FCl···CNF complex. A model analytical potential is applied to render the effect of orbital compression. In order to analyze the nature of halogen bond interaction, in the presence of spatial confinement, the supermolecular approach together with the symmetry-adapted perturbation theory are used. Furthermore, a thorough analysis of topological parameters, characterizing the halogen bond upon orbital compression, is performed within the Quantum Theory of Atoms in Molecules. The calculations are carried out using the ωB97x and CCSD(T) methods in connection with the aug-cc-pVTZ basis set. Among others, the obtained results indicate that the spatial confinement not only modifies the nature of halogen bond interaction, but also induces the appearance of completely new form of the studied FCl···CNF system. [4]

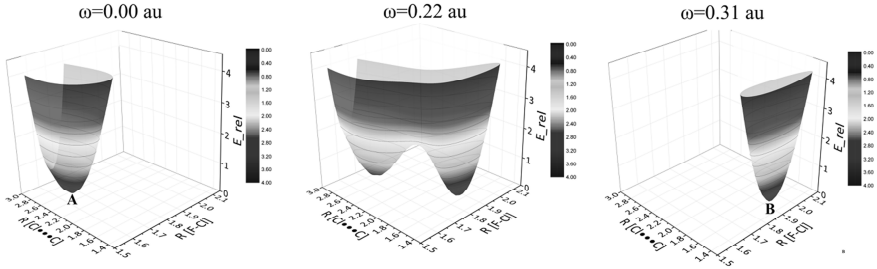

Figure: Changes in the total energy values, as a function of F-Cl and Cl···C distances obtained for the FCl···CNF complex for different ω values.

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The Role of DPPG in Lung Surfactant Model Exposed on Benzo[a]pyrene

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Lung surfactant (LS) appears at water-air interface in alveoli. Its main function is to reduce the work needed to expand alveoli during inhalation and to prevent alveolar collapse during exhalation. Disturbance of this complex interfacial system by the uptake of pollutant molecules can lead to changes in fluidity, permeability, phase separation and domain formation, and in turn can lead to serious disorders in lung functionality. The knowledge of LS-pollutant interactions is essential for understanding the mechanism of this process. In this presentation we illustrate the impact of benzo[a]pyrene (BaP) on DPPC, DPPG and their 4:1 mixture used as LS models. It is an extension of our previous studies [1]. Pressure-area isotherms and molecular dynamic simulations are employed to study properties of LS monolayers. It was found that addition of BaP has a condensing effect, manifested by lowering the values of surface pressure. The compression of monolayer during respiratory cycle may expel BaP to bulk solution. It was demonstrated that DPPG is an active component preventing the BaP molecule to enter the water subphase but as minority LS component can only reduce this process. The presence of BaP in LS monolayer is manifested by reduction of monolayer hydration in the hydrophilic region and increased chain ordering in the hydrophobic region. The changes in monolayer fluidity and phase behavior properties may be a source of different lung disorders.

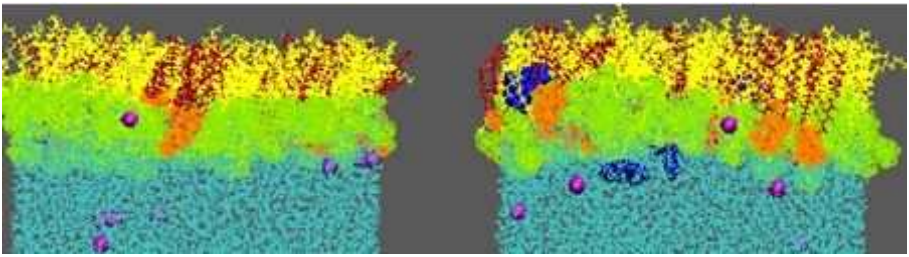

Figure: Side view of DPPC/DPPG LS monolayer model without (left) and with DPPC/DPPG LS monolayer with perturbing BaP molecules. The color code is as follows: DPPC chains – yellow, DPPG chains – red, DPPC headgroups – green, DPPG headgroups – orange, BaP molecules – blue, water – cyan, Na^+ counterions – magenta.

Acknowledgements. Support from the Polish National Science Centre, Project No. UMO-2014/13/B/ST4/04995. Calculations were performed at Faculty of Chemistry of Jagiellonian University and at ACK CYFRONET Supercomputer Center.

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Looking for a mechanisms of pathogenic effect of mutated mitofusin 2 using molecular modeling

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Charcot-Marie-Tooth disease type 2A (CMT2A) is an autosomal dominant axonal peripheral neuropathy caused by mutations in the mitofusin 2 gene (*MFN2*). In some patients harboring *MFN2* gene mutations disease phenotype additionally includes neuropathy and impairment of the central nervous system, and these abnormalities can vary with severity and time of onset. More than 100 *MFN2* gene mutations have been reported so far, with majority located within the GTPase domain encoding region.

Interestingly, these domain-specific mutations cause a wide range of symptoms with significant differences associated with different amino acid substitutions in the same position. This accentuates functional mutation heterogeneity of CMT2A. Therefore, we asked the question whether changes in the protein structure caused by various MFN2 mutations can help to explain diseases phenotypes.

Of all identified mitofusin 2 mutations within the GTPase domain, in which an amino acid in a given position was replaced by at least two other amino acids, 68 were selected for further analysis. Using a stable protein model developed by us earlier, we evaluated the effects of each substitution on the MFN2 structure and predicted the molecular consequences of such alterations. In parallel, clinical features associated with a given mutation were carefully analyzed and an internal score of neurological deficits have been proposed. Finally, both analyses were cross-referenced to establish whether the predicted changes in the mitofusin 2 structure due to mutation positions and properties of the substituted amino acids correlate with the observed symptoms. We found that modeling of the MFN2 mutations is an effective approach capable to predict associated pathogenic impacts, and that these correlate with clinical outcomes. The proposed methodology may aid an early diagnosis and prediction of symptoms of the disease progression in CMT2A patients.

Acknowledgements: These studies were supported in part by IMDiK PAN (Z-526, topic 21), and in part by Faculty of Physics, University of Warsaw (BST-176600/BF/22). Computations were carried out using infrastructures financed by POIG.02.03.00-00-003/09 and POIG.02.01.00-14-122/09 (IMDiK PAN and Faculty of Physics UW, respectively).

The new vs the old concept of aromaticity. Prediction of geometric and magnetic indexes of aromaticity

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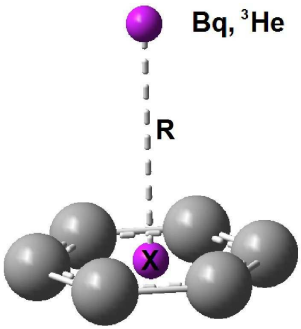
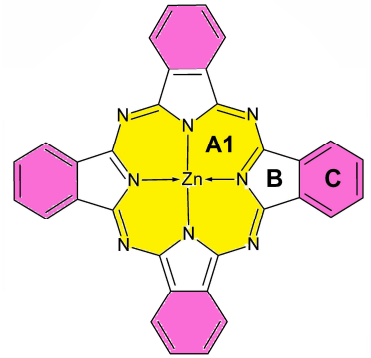
Benzene is an example of typical aromatic molecule. It is a planar, six-membered ring structure with all CC bonds equal. It contains six delocalized π-electrons and it is a stable chemical compound. On the contrary, unsaturated compounds with C=C bonds are significantly more reactive. The aromaticity of benzene (and other rings systems) could be modified by electron-donating or electron-accepting substituents. Harmonic oscillator model of aromaticity [1] (HOMA) and nucleus-independent chemical shift [2] (NICS) has been used as structural and magnetic indexes of aromaticity, respectively.

In this paper we will discuss the problem of aromaticity using benzene, pyrene, pyridine as model compounds [3]. In the next step we will discuss the local aromaticity of five- and six-membered ring subunits in ZnPc [4].

All calculations using ab initio and density functional theory (DFT) were performed with Gaussian 09 version E.01 program package.





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Lessons learned from the experimental and theoretical study of halogen bonding in the class A GPCRs

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Halogen bond (XB) is a non-covalent interaction defined as a directional bond between a covalently bound halogen atom (acting as a donor) and a Lewis base as an acceptor [1-3]. The XB strength is comparable to weak or moderate hydrogen bonds and increases in the order of Cl < Br < I. XB has been indicated to play an essential role in supramolecular systems, liquid crystal engineering, nanomaterials, nanowire formation, catalysis, and also recently, in drug design and lead optimization processes [4,5].

The family A of G protein-coupled receptors (GPCRs) are the largest subfamily and make up about half of all GPCRs including hormones, neurotransmitters and light receptors. Moreover, GPCRs A constitute the largest family of proteins targeted by approved drugs [6]. However, to date, no systematic and comprehensive studies on the role and significance of halogen bonds in family A GPCRs have been published. There are also no studies showing the use of the concept of halogen bonds in the rational design of potential ligands of these receptors.

Thus, we report on a conclusions made on the systematic theoretical and experimental study of the halogen bonds for class A GPCRs. The performed studies include: theoretical prediction and experimental validation of the XB amino acid hot spots (both by synthetized library and virtual screening), and indication the roles of halogen atoms in the interaction of ligands (using XSAR libraries) with protein targets using all crystallized receptors of family A GPCRs (i.e. steric hindrances, interactions of positive σ-hole with negatively charged atoms of the protein).

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Alteration on biochar material to fit environmental applications

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Present and emerging environmental issues are in need of new solutions with a wide range of applications. An example of the sustainable approach is a conversion of waste-considered biomass to biochar, semi-nano carbon-based material. Depending on the size of particles and available surface area, biochar could be a suitable material for the further surface-alteration, similarly to carbon nanotubes.

We are summarizing an experimental data on manufacturing biochar from various raw biomasses. Obtained products have been investigated through physical and chemical characterization needed for the impending alterations to fit custom-designed applications. The reasonable prediction of sought properties could be done through modeling built on initial experimental data.

Four types of biomass (pine needles, cow manure, pine bark and cypress mulch) have been obtained from local Mississippi areas, and pyrolyzed at 400 °C and 700 °C to produce various biochars. Each biochar was characterized with FTIR and SEM-EDX. For example, biochar derived from cow manure (CM) showed presence of C – H bending in the fingerprint region (780 – 790 cm^{-1}) and a strong peak showing presence of C – O stretching (1031 – 1036 cm^{-1}).

SEM – EDX analysis has shown that pore formation was depended on temperature of pyrolysis; for example, the higher comb–like pore formation was observed on biochar produced at the higher temperature. EDX analysis showed higher wt% of C in woody like carbon material rather than more herbaceous cow manure. In addition, besides C and O, minerals found in the tested biochar samples were K, Ca, Mg, Al and Si.

Observed correlations between source of raw biomass, temperature of pyrolysis, protocol of pyrolysis and obtained SEM images of various biochars have shown the necessity of further investigation of alteration-pathways to fit various end-applications.

Acknowledgements. This work was supported by the National Science Foundation: CREST: HRD-1547754, and EPSCoR R-II: OIA-1632899; and by the U.S. Department of Transportation under Grant Award Number 69A3551747130

Molecular modelling of the effects of glycosilation on the structure and dynamics of native and N-terminally tagged hIFNg

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Human interferon gamma (hIFN-γ) is an important antiviral and immunomodulating signaling molecule. It exerts its effects by a high affinity interaction with a species-specific receptor complex (IFNγR). The mature cytokine is a non-covalent homodimer with over 60 % of its amino acids organised in an α-helical globule. Additionally, each monomer has a long unstructured solvent-exposed C-terminal tail, that is susceptible to proteases and thus of variable length.

Natural hIFNγ is a glycoprotein with two N-glycosilation sites in each monomer chain - ASN^{25} and ASN^{97}, which are independently and differentially glycosilated. Glycosilation is not necessary for the activity of the cytokine. Nonetheless, N-linked oligosaccharides are shown to promote the folding and dimerization of the recombinant protein and glycosilation also protects hIFNγ from proteolytic degradation, thus extending its circulatory half-life. [1]

Here, we report the development of model structures of monoglycosilated at either ASN^{25} or ASN^{97} or diglycosilated full-length native and N-terminally tagged hIFNγ dimers. The interaction of the carbohydrate chains with the receptor-binding sites in the cytokine and with its flexible highly positively charged C-termini were explored using molecular dynamics simulations.

We also study the effects of glycosilation on N-terminally labelled with a specific tag peptide hIFNγ, expressed in an insect system. It was found that glycosilation prevents the removal of marker by proteases, [2] arguably, because the carbohydrates cover much of the surface of the cytokine and thus completely or partially protect the tag peptide from proteases. This hypothesis cannot be tested experimentally, which necessitates its *in silico* verification using molecular dynamics simulations.

Acknowledgements. The simulations were performed on the supercomputer Avitohol@BAS and on the HPC Cluster at the Faculty of Physics of Sofia University "St. Kl. Ohridski". This research was supported under the programme for young scientists' career development at the Bulgarian Academy of Sciences (DFNP-17-146/01.08.2017).

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Mechanistic studies on 2-oxoglutarate dependent oxygenases catalyzing atypical oxidation reactions

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2-oxoglutarate dependent dioxygenases (ODDs) belong to a superfamily of enzymes that generate reactive ferryl species [1] which are able to catalyze different chemical reactions, such as hydroxylation (which is the "default" reaction of ODDs), demethylation, desaturation or epoxidation, depending on the chemical nature of the substrate and the structure of the enzyme-ligand complex [2]. For this study we have selected two non-standard ODDs activities that have not been mechanistically studied, i.e. oxidative endoperoxide formation and deamination, which are the final reactions in biosynthesis of verruculogen and kanamacin A, respectively.

Verruculogen is a mycotoxin produced by *Aspergillus* and *Penicillinum* strains. The final step of its biosynthesis is catalyzed by a newly discovered ODD (FtmF) which is so far the only known non-heme enzyme catalyzing formation of an endoperoxide bridge. We have conducted docking, molecular dynamic simulation and DFT studies to investigate the mechanism of this reaction. Our results show that the most probable pathway engages forming of a tyrosine radical which assist in activation of a C-H bond. Direct attack of O2 molecule on the radical yields a peroxo radical. The reaction is quenched by reducing the radical with ascorbate, which explains the requirement for a vitamin C in the reaction mixture to form the endoperoxide.

Kanamycin is an aminoglycoside antibiotic isolated from *Streptomyces kanamyceticus* and used against wide spectrum of bacteria [3]. Its biosynthesis involves an ODD enzyme (KanJ) in its penultimate step, in which kanamycin B is transformed to a 2'-oxokanamycin A. Subsequently formed keto group is reduced to hydroxyl by another enzyme (KanK). In the mechanism proposed for KanJ, the reactive FeIV=O breaks the C-H bond to produce kanamycin B radical [4]. In our studies we have compared two alternative plausible pathways which lead through formation of a hemiaminal intermediate or an imine species. A better understanding of this reaction mechanism might allow for generation of new and possibly more robust antibiotics.

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Absorptive properties of dyes - DSSC technology

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The ability to absorb solar radiation is one of main properties of the dyes critical in dye sensitized solar cell technology. This parameter directly affects the efficiency of the dye sensitized solar cell. The perfect dye has a wide range of absorption (which coincides to the greatest extent with the range of emission spectrum of solar radiation) and high absorption maxima. Those two properties have an impact on increasing the efficiency of the cell [1]. This paper presents the influence of functional groups on the absorption capacity. The dyes were modified by substituting with the following functional groups:-COOH, -NH_2, -OH and -CN. The example of influence of described modifications on the range of absorption of solar radiation absorption is demonstrated on Figure 1.

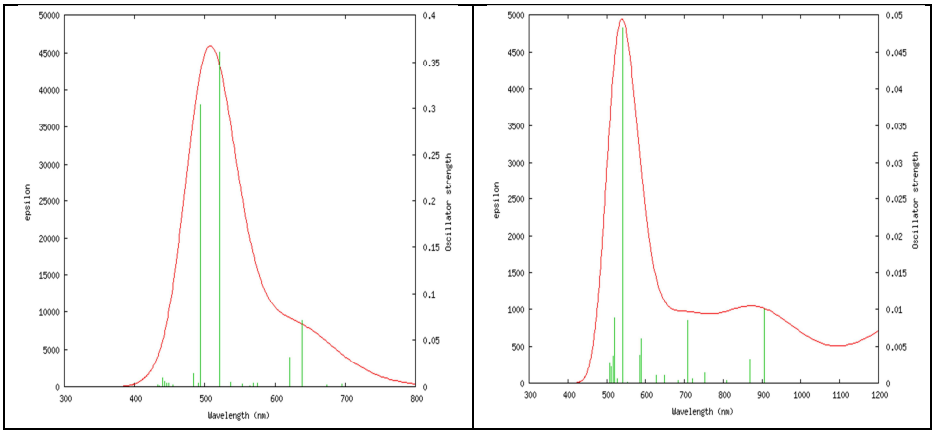

Fig. 1 Absorption spectra of solar radiation a) complex of osmium with groups -COOH b) complex of osmium with groups -COOH and -NH_2

The changes introduced in dye have a direct effect on the absorption capacity and thus on the performance of solar cel. [2]

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Mechanism of reduction process of Pt(IV) complexes in the presence of ascorbic acid

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Platinum (IV) prodrugs are an important class of anticancer compounds that improve the pharmacological properties of platinum (II) complexes. This kind of the drugs are characterized by their kinetically inertness. The reduction process for these Pt (IV) complexes in intracellular environment plays a key role in activating to corresponding Pt (II) structures simultaneously releasing axial ligands. In this work, we focus on the chemical reduction of $PtCl_2OH(NH_3)_2X$, X=SULINDAC ([5-fluoro-2-methyl-1-{4-[methylsulfinyl]benzylidene}-1H-inden-3-yl]aceto), aspirin in the presence of ascorbic acid (AA) regarding to two forms, singly deprotonated (AAH^-) and fully deprotonated (AA^{2-}). Geometries are optimized at the B3LYP-GD3BJ/6-31+G(d)/MWB60/C-PCM level. Single points calculations are carried out using the 6-311++G(2df,2dp) basis set with the consistent extension of pseudoorbitals in combination of the better implicit solvation model – DPCM/scaled-UAKS. Electronic properties of the reduction process are further investigated using NBO and QTAIM analysis. The activation energies are calculated, accordingly, leading to related rate constants. The results show that the lower activation barriers are observed in the case of the AA^{2-} form interacting with the complexes in comparison with the AAH^- in accord with previous study of the satraplatin reduction process[1]. The reduction of the chosen complexes is exothermic with the Gibb free energies ranging from -4.04 kcal/mol to -14.11 kcal/mol.

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Protein kinases - a case study for a new method of computing structural multiple alignments

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Finding optimal multiple alignments in most formulations is a computationally difficult task. It can be performed as a computation of consensus of given pairwise alignments. [1] Here we present DAMA - a theoretical model and an application to bridge a gap between fairly robust alignment methods which are limited to the most simple cases, and more advanced ones, which often have sub-optimal performance on diverse data sets. It delivers robust performance ensured by preservation of whole physico-chemical neighbourhoods of aligned, [2,3] but skipping constraints on the global superposition to provide alignment flexibility, circular permutations and segment swaps. The concept of progressive alignment is used in the initial phase for generating alignments to be further improved by an evolutionary algorithm.

Considering a variety of input structures and structural features to be identified, protein kinases pose a demanding task for structural alignment software. For the purpose of this study we have taken an alignment of 31 kinases prepared by Scheeff and Bourne. [4] This alignment includes 25 typical protein kinases (TPKs) and 6 atypical ones (AKs). Authors described 20 features characteristic for certain kinase families or for all of them. We identified 240 aligned positions in that curated alignment correspond to notable features. We have used this alignment to test two methods performing best on the SISY-multiple set - 3DCOMB and DAMA.

Comparison of DAMA and 3DCOMB on set of 31 kinases revealed eminent accuracy of DAMA. Alignment of secondary structures forming protein cores was resolved nearly equally well by both methods. The only difference concerns position of alignment gaps, which were predicted better by DAMA. DAMA also achieves greater accuracy of detection of conserved residues. Large insertions, often barely conserved in related proteins, are considered troublesome for alignment methods. In this test loops and short insertion in kinked secondary structures were aligned by DAMA with perfect agreement with manually curated reference alignment. This study demonstrates efficiency of the presented methodology and its algorithmic implementation.

Acknowledgements. These studies were supported by Z-156, #21 (IMDiK PAN), BST-180100/BF/22 (UW), DEC-2011/03/D/NZ2/02004 (NSC) and involved infrastructures financed by POIG.02.03.00-00-003/09 and POIG.02.01.00-14-122/09.

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Reaction spectrum for the SN_2 test process: XCH_3+Y

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The recently developed method for imaging the electron density changes that occur in bonds as well as at atoms in a reacting system [1, 2] calls for a systematic studies for the system, where the results of the new method can be readily confronted with the well founded chemical knowledge. The SN_2 test process: XCH_3+Y provides a significant example.

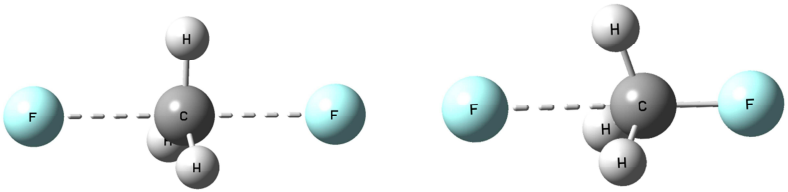

Figure: Calculated atomic fragility spectra provide the sequence of bond breaking and creation of the F–C bond.

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Computer-aided design of peptide-based aldolase mimetics

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De novo enzyme design is promiscuous way for obtaining specific catalysts for various reactions, not only those encountered in nature. The utilization of peptides for this purpose have several advantages. They are available synthetically with broad range of building blocks, not only natural α-L-amino acid but also their enantiomeric or modified counterparts along with β-amino acids. Finally, there are many reports on stabile secondary and tertiary structures composed from as few as 20-40 residues.

Our goal is to mimic enzymatic activity of aldolases from class I (Schiff-base forming) and II (metal-dependent) by reproducing geometric constraints of naturally occurring catalytic sites. Proposed methodology is based on computer-aided design of peptidic structures which would serve as stabile scaffolds for placing catalytic residues by simple mutations at appropriate amino acid positions. The initial projects utilized helix-loop-helix structures modeled in BIOVIA Discovery Studio from experimental 9/10/9/12 helix (composed from α- and cyclic β-amino acids) (1) and oligo-glycyl linker. In the next round of the design flexible glycyl linkers between helices were replaced by rigid repeats of either cyclic β-amino acids or prolyl residues which was then followed by incorporation of third 9/10/9/12 helix into the structures. Simultaneously, the naturally occurring mini-protein MvaT (2) was adapted as synthetically available scaffold. To ensure better packing of hydrophobic core of the designed structures we harnessed Rosetta FastDesign Protocol (3).

Folding to the designed structures was confirmed by structural analysis such as CD or NMR. Retro-aldol activity studies was performed against fluorescent aldol compounds and proved that our strategy is effective enough for obtaining designed catalyst.

Acknowledgements. Support from National Science Centre (NCN) Grant No. 2016/21/B/ST5/00269 is acknowledged.

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Investigating the global and local dynamics of homotetrameric enzyme pteridine reductase by molecular dynamics and enhanced sampling simulations

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Trypanosomatid parasites cause life-threatening human diseases such as leishmaniases and sleeping sickness. There is a need for new therapies and improvement of the existing ones. Inhibiting the folate pathway of these parasites is a potentially useful drug design approach. Pteridine reductase 1 (PTR1) is a key trypanosomatid-specific enzyme of this pathway that needs to be targeted. The role of the PTR1 homotetramer local and global dynamics in enzymatic function is poorly understood. Experimental data in particular suggest that its enzymatic mechanism may be regulated by the long-distance coupling between four binding sites in the homotetramer [1].

In the current study, we use molecular dynamics and related methods to characterize the enzyme dynamical properties and its interactions with substrates and the NADP cofactor. Preliminary analysis has shown different inter-residue network characteristics for PTR1 enzymes from different trypanosomatid species, suggesting that the dynamics may depend on the enzyme variant. Normal mode analysis demonstrated breathing of the homotetrameric enzyme with the correlated movement of substrate loops, which is consistent with the available crystallographic data, and suggests the cooperativity of the dynamics of the binding sites. Finally, a non-equilibrium method, Rotamerically Induced Perturbations, revealed flexibility hot-spots in the homotetramer, and different levels of dynamical coupling between the particular PTR1 monomers.

Acknowledgements. This project has received funding from the Polish National Science Centre (grant no. 2016/21/D/NZ1/02806) and the BIOMS Center for Modelling and Simulation in the Biosciences in Heidelberg. We would also like to acknowledge support of Heidelberg Institute for Theoretical Studies and the Klaus Tschira Foundation. Calculations were performed using resources of the Centre of New Technologies University of Warsaw, Interdisciplinary Centre for Mathematical and Computational Modelling (grant no. GC69-13, GB70-11, G70-13). The authors acknowledge support by the state of Baden-Württemberg through bwHPC and the German Research Foundation (DFG) through grant INST 35/1134-1 FUGG.

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Metal-dependent folding pathways in metallothionein proteins

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Metallothioneins (MTs) are a family of small cysteine-rich proteins presented in all living organisms that are capable to bind metal ions, although the most relevant biological ions are Zn(II) and Cu(I). The relevance of MTs is due to its multiple biological functions, among them metal detoxification and buffering are the most common presented in all animal phylia and plants. Recently, zinc buffering properties have been described in mammalian MT2 [1]. Its capable to maintain the free intracellular Zn(II) ion concentration from nano- to picomolar range through partially Zn(II)-depleted species. However, because of it inherent structure that lacks of aromatic amino acids and secondary structure, insights into partially metal-loaded species is rather complicated. Biophysical studies regarding structural properties are limited even more when considering spectroscopic silent Zn(II) ion coordinated to MT. In this sense, mass spectrometry approaches and molecular modeling simulations are key tools for studying metal-folding MTs pathway. Our latest research gave rise to an overview between the structural and zinc buffering related-to-thermodynamics properties through solving of partially Zn(II)-loaded mammalian MT2 species [2]. The studied focused on the structures and dynamics with the use of classical molecular dynamic (MD) simulations in which the Zn(II) ions were treated with non-bonded approach. In this work, we aimed to explore the metal-folding pathway by Umbrella Sampling (US) simulations. The potential mean force (PMF) was calculated as a function of the distance between the sulfer atom of Cysteine residue and the Zn(II) atom. The reaction coordinate was sampled over 17 windows spaced 0.1 Å. At each window, a harmonic potential of 100 kcal/molÅ^2 was applied, and three-step MD scheme was performed: minimization, NPT equilibration and NVT production phase giving rise to approximately 2000 ps. PMF was extracted from US simulations by the Weighted histogram analysis method, and thus free energy for the binding/unbinding process, as well as the differential free energy contribution of each Cysteine residue to the coordination sphere was determined. Obtained results were able to discern and propose metal-folding pathway in energetic terms regarding Cysteine residue and Zn(II) localization.

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Systematic studies of the formation of hydrogen bonds by fluorine using quantum-mechanical methods

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In recent years, fluorine has become a very often used substituent in the rational design of biologically active compounds; however, due to its unique properties, it is difficult to determine its effect on the formation of intermolecular interactions, e.g. hydrogen bonds (H-bonds).[1,2] H-bonds are one of the most important interactions in proteins influencing secondary and higher structures as well as contributing to molecular recognition. H-bonds formed by fluorine are relatively rare (compared to nitrogen and oxygen) and the less electronegative donors (CH > NH > OH) are preferred. At the same time, the geometry of H-bonds is poorly directional with a longer acceptor-donor distance.[3]

Herein, we report systematic studies on the role of fluorine in the formation of hydrogen bonds and their comprehensive geometrical analysis with the most common donors occurring in proteins using quantum mechanical methods. For different fluorine-containing molecules (e.g. fluorobenzene, trifluorotoluene, fluoroethane) and H-bond donors (methanol, dimethylamine and ethane) a spherical scan of energy interaction (based on single-point calculations using MP2 functional with cc-pVDZ basis set) was performed.

The results indicated that fluorine forms specific hydrogen bonds, which to a large extent deviate from directionality, as well as depend on the electronegativity of the donor.

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The study of charge transfer through damaged DNA duplexes

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We theoretical studied the charge transfer efficiency for donor-acceptor pairs in DNA duplexes containing damaged nucleosides. The donor was 2-aminopurine (Ap) while the acceptor was guanine (G), 8-oxoguanine (OxoG) or 2,6-diamino-4-oxo-5-formamidopyrimidine (FapyG). The OxoG and FapyG are mutations of normal guanine that occur owing to interaction of DNA with free radicals. The human 8-oxoguanine DNA glycosylase 1 (hOGG1) repair enzyme that performs excision of damaged bases, however, the exact excision mechanism is currently unknown. Recently, we proposed new catalytic scheme for hOGG1 enzyme.[1,2] In the current study we wanted to find out whether the base excision by hOGG1 could be in principle monitored in real time employing fluorescence spectroscopy. In our previous studies on charge transfer the calculated donor – acceptor coupling integrals described successfully modulation of charge transfer efficiency that was measured in DNA molecules.[2,3] In particular, the coupling integrals described quenching of fluorescence radiation from 2-aminopurine by guanine in relation with the hole transfer from Ap to G.[3,4] The calculated coupling integrals indicated that guanine is better quencher than OxoG or FapyG. The results indicated that experimental detection of damaged nucleosides within DNA duplex employing fluorescence spectroscopy is possible.

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Influence of sulfonamide moiety in long-chain arylpiperazines on serotonin affinity: FMO-EDA calculation

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Replacement of carboxamide group with sulfonamide moiety is a common modification used in medicinal chemistry. Although both come under the class of amides derivatives, mentioned modification in the structure of ligands strongly affect physical properties and the spatial orientation of the molecules. Our previous results showed, that varied or similar activities for particular receptors were found for the carboxamides/sulfonamides with *p*-xylyl spacer, while of the two classes of carboxamides and sulfonamides examined, benzyl derivatives of the sulfonamides displayed the highest serotoninergic affinity, in particular to the 5-HT_7 receptors [1].

In this study the structure of four long-chain arylpiperazines complexed with four receptors (5-HT_{1A}R, 5-HT_{2A}R, 5-HT_6R, 5-HT_7R) has been investigated by means of quantum mechanical methods. At the beginning, the test compound was docked to receptors and next optimized with ONIOM method. For thus obtained structures FMO-EDA calculations were performed.

Results shed some lights on the interpretation of the experimental results concerning the affinity to receptors, as well as they provided the reasonable binding energies and binding patterns of ligand-protein interactions.

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Theoretical studies of coumarin dyes used as sensitizers in solar cells

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One of the most important problems in present world is a search for new alternative and renewable sources of energy, that are environmentally friendly and able to eliminate or to limit the use of fossil fuels. As a very promising method to obtain electric current from solar radiation dye sensitized solar cells deserve a special attention. The important part of these kind facilities is dye which due to the light absorption of light is excited to the higher electronic state. It allows for the electron transfer from the sensitizer to semiconductor and finally in the external circuit which is connected to the solar cell, where appear an electric current. At present scientists try to improve properties of DSSC by trying different types of dyes. One of the most promising class is represented by coumarin derivatives. In this work we present exploratory theoretical studies of several coumarin sensitizers. Electronic properties, such as: the distribution of electron density, absorption spectra, DOS and NBO population analysis were calculated. We investigate isolated dyes and dye-semiconductor complexes, (in our works titanium dioxide is used).

In silico driven engineering of penicillin G acylase toward degradation of diverse signal molecules for effective biofilm control

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Penicillin G acylases (PGAs) are enzymes widely utilized in industrial biotransformation processes. Recent studies have indicated a novel role for the PGAs due to their acyl-homoserine lactone acylase activity [1], which renders PGAs as promising bacterial agents facilitating biofilm development control by quorum quenching.

In this study, we have modeled *Escherichia coli* penicillin G acylase wild-type (*Ec*PGA WT) and *Pseudomonas aeruginosa* acyl-homoserine lactone acylase (PvdQ) enzymes in complexes with bacterial quorum sensing signal molecules N-acyl-L-homoserine lactones (AHLs) with varying length of their acyl chain (C4-C12) to study their binding affinity and reactivity. Using molecular dynamics simulations, binding free energy and QM/MM calculations, we have established that *Ec*PGA WT is capable of favorable and productive binding of several investigated AHLs and that the energy profiles of these reactions are in agreement with experimental rates, indicating that this enzyme should also exhibit activity towards AHLs despite indications to the contrary in the literature [2]. After confirming the predicted activity by experimental means, we have designed a set of PGA variants carrying three amino acids mutations in the binding site to mimic the geometry of this site in PvdQ enzyme by narrowing the its entry and extending its length. Nine of the most promising mutants were further analyzed to evaluate effects of mutations on binding and reactivity with the investigated AHLs.

In summary, several of the designed PGA mutants revealed notably enhanced activities towards various AHLs in comparison to *Ec*PGA WT in some cases reaching or even surpassing the activity of PvdQ WT. We have also observed extended specificity of the designed mutants not present in either of the wild-type enzymes that together with the robust properties of PGA and improved activities towards bacterial signaling molecules represents promising foundation towards the development of pharmaceutical agents capable of controlling biofilm development.

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Versatile SGLT1 ligand study based on a novel computational method

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The glucose uptake and metabolism of tumor cells is increased in comparison to the non-tumorous cells. Inhibition of them could provide an increased efficiency of the anti-cancer therapy, but the natural inhibitors do not bind strong enough and design of new efficient inhibitors is hard because the binding site is unknown. Here we present a new computational method based on molecular dynamics and docking that encompasses dynamic changes of protein structure due to thermal movements with relatively small computer power needs. The method provides statistical information about binding strength to SGLT1 of several ligands and an insight of SGLT1 binding site.

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Homology modeling in amyloidogenecity prediction

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Amyloid fibrils are related to several neurodegenerative disorders including Alzheimer's and Parkinson's diseases. Formation of such aggregates strongly depends on short protein fragments called hot spots. Experimental methods of finding hot spots are expensive and time consuming. Therefore using them for testing all candidates is currently not possible.

We proposed homology modeling based method of amyloidogenecity prediction. Structure of a fragment of yeast prion was used as a template for modeling. Energy of resulting structure was compared with energy of the template. We showed that there was noticeable difference in energy between structures obtained using amyloidogenic and non-amyloidogenic sequences.

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The role of the binding pocket of dioxygenase AsqJ in reaction selectivity - a QM/MM study

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AsqJ from *Aspergillus nidulans*, a Fe(II)/2-oxoglutarate dependent dioxygenase (ODD), takes part in biosynthesis pathway of a quinolone antibiotic 4'-methoxyviridicatin, i.e. catalyses a stepwise desaturation and epoxidation of a benzodiazepinone. [1,2] The experimental findings show that the C=C bond formation is most likely initiated by hydrogen atom transfer (HAT) from the benzylic carbon atom (C10) in preference to HAT from the ring moiety (C3 atom). [3] This QM/MM study was done to elucidate the origins of the regioselectivity of the first HAT and to identify the factors that control the desaturation/hydroxylation bifurcation and promote the former pathway.

Our results suggest that, even though the C10-H bond activation is associated with a relatively high intrinsic barrier, the interactions of the substrate with the binding pocket of the protein compensate for the electronic effects and favour HAT at the C10 position. At the final step of the reaction the reaction outcome is determined by the electronic properties of the reactants, i.e. the energy gap between orbital on the radical center and the σ orbital for the C-H bond and their proximity to the electron accepting orbital π* of iron(III) species.

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3-ketosteroid Δ^1-dehydrogenases – comparative analysis of homology models and calculations of ODH reaction mechanism

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3-ketosteroid Δ^1-dehydrogenases (KSDs) are key flavin-depended enzymes of steroid degradation pathway catalyzing oxidative 1-dehydrogenation (ODH) of androst-4-en-3,17-dione (AD) to androst-1,4-dien-3,17-dione (ADD) or 9-OH-AD to unstable 9-OH-ADD. The best-studied KSDs originate from *Rhodoccocus* species, where a number of copies of KSD isoenzymes can be found in each bacteria genome. Recently, for *R. ruber* it was proved that KSDs isoenzymes exhibit functional differences [1]. KSD from denitrifying *Sterolibacterium denitrificans*, cholest-4-en-3-one Δ^1-dehydrogenase (AcmB), is a KSD expressed during anaerobic cholesterol degradation and it catalyzes 1-dehydrogenation not only of AD but also of cholest-4-en-3-one [2]. Moreover, in *S. denitrificans* genome there are two more copies of genes with high sequence similarity and identity (95–99%, 42–44%, respectively). Interestingly, KSDs and AcmB differ not only in the range of substrate spectrum, but also in the pH optimum of the catalyzed reaction. The standard KSDs pH optimum is 8–10 whereas for AcmB we have observed the pH optimum of 6.5.

The aim of our work was to compare a known KSD structure of *Rhodococcus erythropolis* (4C3Y) with modelled structure of AcmB from *S. denitrificans* and its two isoenzymes. For that purpose we used homology modelling approach together with MD simulation and structure clustering. Based on the relaxed AcmB structure we plan to model the reaction mechanisms using quantum mechanical (QM) calculations with DFT. The mechanistic hypothesis for KSD from *R. erythropolis* assumes initiation of the reaction by proton abstraction from C2 by tyrosyl anion (TYR318), formation of transient carboanion, which is stabilized by keto-enol tautomerization and interaction of hydroxyl group of TYR487 with keto group of the substrate [3]. In the last step the hydride is transferred from C1 to the FAD, which triggers again tautomarization and double bond formation. The unusual pH optimum of AcmB suggests different reaction mechanism (due to low probability of tyrosyl anion existence in the acidic condition), although the presence of the of additional (fourth) Tyr residue in the proton relay may influence pKa of catalytic tyrosine making such reaction possible.

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Pushing the limits of the reachable oxidation states of metal atoms

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One of the major goals of inorganic chemistry is to prepare compounds of elements in unusual oxidation states – in these words C. K. Jørgensen started one of his articles over 40 years ago[1]. Nowadays, when scientific world is still looking for new functional materials, fluorinating agents, oxidants, and catalysts, hitherto unknown highest oxidation states are still of great significance. Particularly promising ones seem to be going further beyond +8 oxidation state, which was the impassable boundary until the end of 2009.

Recently, in 2010 it was theoretically predicted, [2] that there can exist IrO_4^+ cation with nonavalent Ir^{IX} transition metal center. Four years later this prediction has been experimentally confirmed. [3] The next step was done in 2016, when kinetically stable, metastable state of cationic molecule with Pt^X atom have been theoretically investigated[4]. These breakthrough discoveries show that nowadays it is not clear at all, what could be the limiting value of the oxidation state depending on the position in Periodic Table, in isolated molecules and with stabilizing conditions.

We want to present the results of our calculations concerning chosen molecules, included neutral ones, which comprise Ir^{IX}, Pt^X, Au^{XI} and Hg^{XII} atoms - isoelectronic analogs of Os^{VIII}. Our calculations were performed at CCSD(T) level of theory and with previously selected and validated DFT functionals.

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Refinement of the OPLS-AA force field parameters for phospholipids. Theoretical studies on triacetin molecule

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The results of the molecular dynamic (MD) simulations depend on the description of the potential energy function and its parameters correlated with an applied force field. Limitations of force fields associated with the standard parametrization methods are most obvious in modelling of lipid membranes, whose dynamics depend on the correct description of the non-bonding interactions. The OPLS-AA is a generic force field, developed by W. L. Jorgensen and used in simulation of small organic molecules, which contain a wide range of various functional moieties [1]. The generic force fields are developed according to the assumption that the proper estimation of the force field parameters is reflected by the reproduction of the properties of condensed phases of considered small organic molecules containing parametrized moiety. The liquid state properties such as density, enthalpy of vaporization and Gibbs free energy of hydration should be validated. Unfortunately, the literature and unpublished data show deficiency in the non-bonding parameters estimation, and in consequence incorrectly reproduce condensed phase properties and large system simulations [2,3,4].

The studies are aimed to extent and refine of OPLS-AA force field to phospholipids, such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC). The project is focused on small molecules, which contains chemical groups present in PC and PE, such as triacetin. The triacetin molecule, which contains moiety present in glycerol backbone of phospholipids has never been considered as a model molecule. It is particularly interesting molecule, since there is large resources of the experimental data obtained for its condensed phase, such as density and enthalpy of vaporization. In the presented studies, we focused on the OPLS-AA parameters such as Ryckeart-Bellman coefficients describing torsional potential and partial charges, which are responsible for reproduction of non-bonding interactions.

The presented data showed the refinement procedure, including QM and ab initio MD calculation, applied for parametrization of triacetin molecule and the effect of the new parameters on reproduction of known liquid state properties of these molecule.

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Insight into reaction mechanism of ATP Sulfurylase. Theoretical studies

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ATP sulfurylase (ATPS) is involved in the first step of the sulfate reduction process occurring in Sulfate Reducing Bacteria (SRB). It catalyzes the activation of ATP to adenosine 5'-phosphosulfate (APS).

$$MgATP + SO_4^{2-} \rightarrow MgPP_i + APS$$

There are two hypothesis about ATPS reaction mechanism. The first is SN-2 direct conversion of ATP to APS and pyrophosphate anion, where SO_4^{2-} attacks the α-phosphorus of the ATP phosphate group and enzymatic reaction proceeds through pentavalent trigonal bi-pyramidal transition state [***1,2,3***]. The second one is two steps SN-1 mechanism, where ATP is cleaved to pyrophosphate anion and AMP anhydride and subsequently AMP anhydride reacts with sulfate anion leading to the APS molecule [***4***]. The ATPS reaction mechanism was investigated with QM methods using hybrid DFT-D3 with the B3LYP functional.

Seven models of ATPS active site were constructed to model its reaction. One with magnesium cation was built based on the Molecular Dynamics (MD) simulation results performed for haxameric form of ATPS from *Saccharomyces Cerevisiae* in complex with APS, Mg^{2+} and pyrophosphate anion (PPi). Six other models were constructed based on the crystal structure, which was solved for ATPS-APS- PPi complex, defined by the 1G8H PDB code [***2***]. Interestingly, in this only crystal structure available for ATPS in complex with both of reaction products magnesium anion is not observed.

The presented computational results suggest that ATPS reaction proceeds by the SN-2 mechanism of direct conversion of ATP to APS with the barrier of about 12 kcal/mol. Interestingly, studies show that ATPS catalyzed reaction of ATP without Mg^{2+}, which is in agreement with 1G8H crystal structure. The presence of magnesium cation affects the conformation of ATP, leading to very high barriers for all tested mechanisms..

What is more SN-1 two steps mechanism has been excluded due to a very high barrier of ATP cleavage and very unstable AMP anhydride.

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Fragility spectra for the internal rotations around the model peptide bonds

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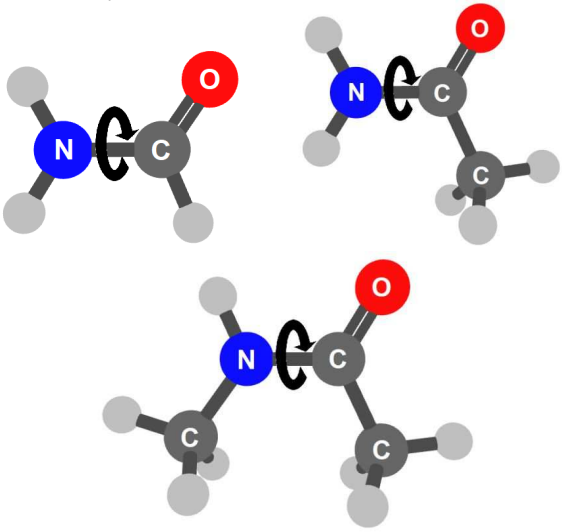
The recently developed method for imaging the electron density changes that occur in bonds as well as at atoms in a reacting system [1, 2] calls for a systematic studies for the system, where the results of the new method can be readily confronted with the well founded chemical knowledge. The peptide bond provides a tempting example. Three model structures have been selected for this study; their three analogues have also been studied.



Calculated atomic fragility spectra and the proposed bond-energy indices for the internal rotation around the HN-CO bond demonstrated unique precision combined with striking sensitivity, by detecting the density changes even at atoms distant from this reaction center ($-CH_3$).

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