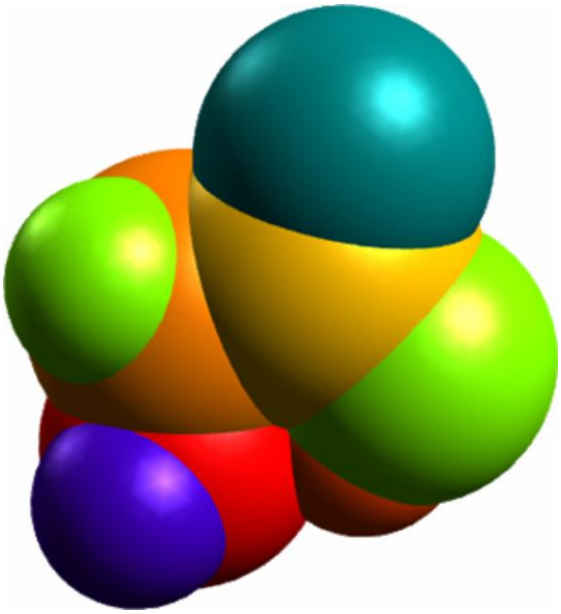
Computational Chemistry Day

Book of abstracts

May 12, 2018
Zagreb, Croatia, EU

Computational Chemistry Day



Book of abstracts

May 12, 2018
Zagreb, Croatia, EU

Foreword

The idea to organize this meeting was born spontaneously out of the impression that we, as computational chemists, need an opportunity to discuss our work, and to share the information and knowledge more than we currently do. We also need to coordinate our efforts in many common aspects, as for example, in provision and use of the computational resources, including the software. The reactions of the colleagues and the response of the whole community made us believe that such a meeting should become a regular event.

We imagine this meeting as an informal professional gathering suited to our needs and possibilities. To ensure continuity and diversity, it should be portable in terms of the hosting institution and specific organizers. Everyone is invited to participate both in the organization as well as in the meeting itself. In future, we would particularly like to include practical and less common content as are, for example, workshops, *crash courses*, and lectures on meta topics. Such contributions will be highly appreciated.

We think that registration fee should not discourage or even prevent anybody from participation which we want to make easy and simple. This year, it was possible owing to the generous financial support, which we gratefully acknowledge to our host – the **Department of Chemistry of the Faculty of Science, University of Zagreb**, and also to the **Croatian Chemical Society**, the **Ruđer Bošković Institute**, the **Croatian Science Foundation** and to the **Ministry of Science and Education**.

We thank the lecturers who readily accepted our invitation to deliver a lecture and alleviated a large part of the organizational burden.

Finally, let us thank you, dear participants, for recognizing this meeting as a good idea and actively taking part in it. We sincerely hope that you had a pleasant and interesting *Computational Chemistry Day* and that you will join us at the next one.

The Organization Board

Program of the *Computational Chemistry Day*

08:50–09:00 ***Opening addresses***

1st session (moderator: **Nađa Došlić**)

09:00–09:30 **Sanja Tomić** (RBI)
Computational studies as an aid to the experiments in revealing the secrets of biomacromolecules

09:30–10:00 **Valerije Vrček** (FBF)
Chemical fate of pharmaceuticals and design of organometallic nucleobases – two different probes for computational methods

10:00–10:30 **Marko Hanževački** (RBI)
The binding free–energy calculation using molecular dynamics: from macrocycles to proteins

10:30–11:00 ***Coffee break***

2nd session (moderator: **Ivan Ljubić**)

11:00–11:30 **Sanja Koštrun** (Fidelta)
Macrolide inspired macrocycles – novel templates towards drugs for un met medical needs

11:30–12:00 **Ivan Kodrin** (PMF)
Molecular electrostatic potential values as a tool for prediction of supramolecular interactions in coordination compounds

12:00–12:30 **Ivan Marić** (Srce)
Croatian scientific and educational cloud (HR-ZOO) - Project overview

12:30–14:00 ***Lunch break and* Poster session**

3rd session (moderator: **Marko Cvitaš**)

14:00–14:30 **Robert Vianello** (RBI)
Computational insight into the selectivity and catalytic activity of monoamino oxidase for targeting neurodegenerative diseases

14:30–15:00 **Mario Vazdar** (RBI)
Arginine "magic": guanidinium like-charge ion pairing from aqueous salts to cell penetrating peptides

15:00–15:30 **Tomica Hrenar** (PMF)
Strategies for full conformational analysis

15:30–15:35 ***Closing remarks***

15:35–17:00 **Poster session *with more coffee***

Table of contents

Lectures

L 1. Computational studies as an aid to the experiments in revealing the secrets of biomacromolecules

Sanja Tomić

Sanja.Tomic@irb.hr

Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb

Molecular recognition, binding and catalysis are ongoing processes in all known living organisms. Understanding these processes helps understanding development of life, the cause of diseases and ways to treat them. In our laboratory we apply combined computational and experimental approaches to address the questions like: How proteins and nucleic acids recognize and interact with their binding partners? How do proteins behave in an environment that resembles a natural one? How metal ions influence the macromolecular function? How to explain an enzyme mechanism? Since our potentials (number of people, available experimental devices, and knowledge) are very limited, we often collaborate with scientists from other laboratories and institutes. In my talk today I will describe a few of such joint research activities related to the conservation of the conformational dynamics and ligand binding within M49 enzyme family, identification of new inhibitors of human dipeptidyl peptidase III (hDPP III), understanding hDPP III catalyzed peptide hydrolysis and how this can help in rationalization of the hDPP III mutants (in)activity, as well as just started research on Keap1-DPP III interaction and on the metal exchange mechanism in hDPP III.

L 2. Chemical fate of pharmaceuticals and design of organometallic nucleobases – two different probes for computational methods

Valerije Vrček

vvrcek@pharma.hr

Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, Zagreb, Croatia

Given the environmental importance of the occurrence of pharmaceuticals in (waste)waters, it is necessary to fully describe their chemical fate in the aquatic medium. Of special significance are reactions between pharmaceuticals and chlorinating species, which are frequently used for wastewater/drinking water treatment. Modern computational techniques may be used to consider all possible transformations, induced by chlorinating species, and locate degradation products related to ecotoxicological profile of the original drugs. Along with analytical methods, quantum-chemical methods represent robust machinery for determining the mechanism of chemical transformations relevant for pharmaceuticals [1-3].

The use of quantum-chemical methods in the design of structures and synthesis optimization is a novel contribution to the search for biologically active organometallic derivatives of nucleobases (OrDeNs). Despite the importance and number of characterized/described OrDeNs in scientific publications, the quantum-chemical approach to the study of these compounds is missing. A thorough review of the literature, spanning from first preparation of ferrocenyl-adenine in 1980, does not reveal a single example of the use of computational methods in the study of OrDeNs. It is therefore imperative to use various theoretical models to describe the structural and electronic properties of OrDeNs. According to recent (and our) experience in the application of theoretical models in the field of bioorganometallic chemistry, density functional theory (DFT) methods are the optimal choice for describing OrDeNs [4,5].

Acknowledgement: This work is, in part, sponsored by the Croatian Science Foundation (IP-2016-06-1137).

References:

[1] F. Achrainer, D. Šakić, V. Vrček, H. Zipse, *Org. Biomol. Chem*. **11** (2013) 4232-4239.

[2] D. Šakić, P. Šonjić, T. Tandarić, V. Vrček, *J. Phys. Chem. A* **118** (2014) 2367-2376.

[3] Šakić, D.; Hanževački, M.; Smith, D. M.; Vrček, V. *Org. Biomol. Chem*. **13** (2015) 11740-11752.

[4] J. Lapić, V. Havaić, D. Šakić, K. Sanković, S. Djaković, V. Vrček, *Eur. J. Org. Chem*. (**2015**) 5424-5431.

[5] K. Kowalski, L. Szczupak, S. Saloman, D. Steverding, A. Jablonski, V. Vrček, A. Hildebrandt, H. Lang, A. Rybarczyk-Pirek, *ChemPlusChem*. **82** (2017) 303-314.

L 3. The binding free–energy calculation using molecular dynamics: from macrocycles to proteins

Marko Hanževački and David M. Smith

mhanzev@irb.hr

Division of Physical Chemistry, Group for Computational Life Sciences, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

Computational modelling of the structure and thermodynamics of chemical systems provides a tool for investigation of the mechanistic aspects of important biochemical processes. Molecular dynamics simulations at atomistic level provide a detailed insight into the system behavior and events that are sometimes not easy to understand from the experimental data. However, the interplay between the experiment and molecular simulations is crucial for explaining the problems observed in modern science of life.

In this research we briefly present the usage of two fundamentally different methods that are often referred to when it comes to the binding free–energies estimations. The first method is Umbrella Sampling (US) which is based on enhanced sampling of the conformational phase space hindered by the form of the system's energy landscape. This procedure is often used together with the non–equilibrium Steered Molecular Dynamics (SMD). The second method is Molecular Mechanics Poisson–Boltzmann Surface Area (MM/PBSA) which is popular method to estimate the free–energy of binding of small ligands to proteins based on the continuum implicit solvation approach.

Calculations of the affinity and thermochemical properties were based on three case studies. These cases are model host–guest complexes and are illustrated taking β–Cyclodextrin (β–CD) macrocycle and two proteins, Protein Kinase and Pyruvate Formate-Lyase (PFL), as model receptors. The inclusion of the adamantane derivative guest in the hydrophobic cavity of the β–CD host was investigated in three different solvents using molecular dynamics, where computed binding free–energies show excellent agreement with an experiment. The binding affinities of nine non–covalent inhibitors of the Activin Receptor Type IIA Protein Kinase (ActRIIA) were investigated by means of molecular dynamics simulations where the dissociation constants were evaluated and compared to the available experiments. The process of flexible substrate, Coenzyme A, entry into the PFL protein interior was also investigated using advanced molecular dynamics techniques, where chemical change in the active site directly influence the conformational equilibrium of the protein, which plays a crucial role in substrate binding.

L 4. Macrolide inspired macrocycles – novel templates towards drugs for un-met medical needs

Sanja Koštrun, head of CADD group

Sanja.Kostrun@glpg.com

Fidelta Ltd., Zagreb, Croatia

Protein–protein interactions play an important role in key biological processes, and their modulation is an ongoing challenge in the field of drug design [1]. There is an increased number of success stories with macrocycles being effective inhibitors of protein-protein interactions (PPI) [2].

Macrocyclic molecules are an obvious choice for binding to large and flexible surface areas of PPI's. They also offer diverse functionalities and stereochemical complexity in a conformationally restricted manner. This can enable them to be highly potent as well as selective when key functional groups interact with biological targets. Macrocyclic drugs typically include a 12 or more membered ring architecture which often do not fit into the "rule of five" properties. However, many macrocycles benefit from favourable drug-like properties that can include good solubility, optimal lipophilicity, low binding to plasma proteins, improved metabolic stability and oral bioavailability [3].

Our novel macrolide inspired macrocyclic library was built upon macrolide clinical relevance [4-10] as well as our long-term experience and in-house knowledge on the chemistry and pharmacology. Macrolide inspired macrocycles are designed to diversify and enrich chemical space with different ring sizes, a variety of 3D shapes and potential pharmacophoric features.

A target based approach as well as extensive phenotypic screening in anti-bacterial and anti-inflammatory area has been performed. The physico-chemical and ADME properties have been profiled [3, 11] showing that compounds are highly soluble, with low PPB and lipophilicity appropriate for oral drugs. These properties can be difficult to achieve by small molecules designed against "hard targets".

This talk will present how the experimental NMR and theoretical computational techniques are coupled together to rationally design, develop and predict behaviour of complex macrocyclic structures [12, 13].

References:

[1] J. Mallinson, I. Collins, *Future Med Chem.* **4** (2012) 1409-1438.

[2] S. P. Liu, L. A. Dakin, L. Xing, J. M. Withka, P. V. Sahasrabudhe, W. Li, M. E. Banker, P. Balbo, S. Shanker, B. A. Chrunyk, Z. J. Guo, J. S. M. Chen, J. A. Young, G. Y. Bai, J. T. Starr, S. W. Wright, J. Bussenius, S. Tan, A. Gopalsamy, B. A. Lefker, F. Vincent, L. H. Jones, H. Xu, L. R. Hoth, K. F. Geoghegan, X. Y. Qiu, M. E. Bunnage, A. Thorarensen, *Sci. Rep.* **6** (2016) 30859.

[3] V. Stepanić, D. Žiher, V. Gabelica-Marković, D. Jelić, S. Nunhuck, K. Valko, S. Koštrun, *Eur. J. Med. Chem.* **47** (2012) 462-472.

[4] O. Čulić, V. Eraković, M. J. Parnham, *Eur. J. Pharmacol.* **429** (2001) 209-229.

[5] M. Shinkai, M. O. Henke, B. K. Rubin, *Pharmacol. Ther.* **117** (2008) 393-405.

[6] K. Hamada, K. Mikasa, Y. Yunou, T. Kurioka, T. Majima, N. Narita, E. Kita, *Chemotherapy* **46** (2000) 49-61.

[7] K. Mikasa, M. Sawaki, E. Kita, K. Hamada, S. Teramoto, M. Sakamoto, K. Maeda, M. Konishi, N. Narita, *Chemotherapy* **43** (1997) 288-296.

[8] S. L. Andersen, A. J. Oloo, D. M. Gordon, O. B. Ragama, G. M. Aleman, J. D. Berman, D. B. Tang, M. W. Dunne, G. D. Shanks, *Clin. Infect. Dis.* **26** (1998) 146-150.

[9] M. Bukvić Krajačić, M. Perić, K. S. Smith, Z. Ivezić Schönfeld, D. Žiher, A. Fajdetić, N. Kujundžić, W. Schönfeld, G. Landek, J. Padovan, D. Jelić, A. Ager, W. K. Milhous, W. Ellis, R. Spaventi, C. Ohrt, *J. Med. Chem*. **54** (2011) 3595-3605.

[10] M. S. Whitman, A. R. Tunkel, *Infect. Control Hosp. Epidemiol.* **13** (1992) 357-368.

[11] V. Stepanić, S. Koštrun, I. Malnar, M. Hlevnjak, K. Butković, I. Ćaleta, M. Dukši, G. Kragol, O. Makaruha-Stegić, L. Mikac, J. Ralić, I. Tatić, B. Tavčar, K. Valko, S. Zulfikari, V. Munić, *J. Med. Chem.* **54** (2011) 719-733.

[12] S. Koštrun, V. Munić Kos, M. Matanović Škugor, I. Palej Jakopović, I. Malnar, S. Dragojević, J. Ralić, S. Alihodžić, *Eur. J. Med. Chem.* **133** (2017) 351.

[13] S. Alihodžić, M. Bukvić, I. J. Elenkov, A. Hutinec, S. Koštrun, D. Pešić, G. Saxty, L. Tomašković, D. Žiher, *Progress in Med. Chem*. 2018, in press, http://doi.org/10.1016/bs.pmch.2018.01.002.

L 5. Molecular electrostatic potential values as a tool for prediction of supramolecular interactions in coordination compounds

Ivan Kodrin and Marijana Đaković

ikodrin@chem.pmf.hr

Department of Chemistry, Faculty of Science, University of Zagreb, 10 000 Zagreb, Croatia

One of the primary challenges of crystal engineering is to deliver solids with a desired physical property or response. A deeper understanding of driving forces governing the recognition and association processes of molecules is a key step toward a more efficient design of new materials. The concepts introduced by M. C. Etter as set of three general rules predominantly tackle the self-assembly of small organic molecules through hydrogen bonds. According to these rules, the best hydrogen bond donor preferentially interacts with the best hydrogen bond acceptor. Molecular electrostatic potential values were suggested as a practical and fast way to rank affinities of hydrogen bond donors toward acceptors. This approach is also applicable for an explanation and prediction of other types of intermolecular interactions, halogen as well as hydrogen bonds. Although it is commonly used for strictly organic systems, there are only a few papers regarding the supramolecular interactions between metal complexes. In order to make this method applicable to a variety of inorganic systems including 1-D coordination polymers, we proposed a new approach for relatively fast calculation of molecular electrostatic potential values of such infinite polymeric chains [1]. By variation of the position of nitrogen atoms and groups on the aromatic rings of coordinated ligands and utilizing different transition metal ions, the strength of hydrogen and halogen bond donors and acceptors can be easily tuned resulting with different molecular recognition events. The obtained results have been rationalized in the context of calculated molecular electrostatic potential values in order to provide some general guidelines for a synthesis of crystalline coordination compounds with controllable elastic bending properties.

Acknowledgement: This work was fully supported by the Croatian Science Foundation under the project UIP-11-2013-1809.

References:

[1] M. Đaković, Ž. Soldin, B.-M. Kukovec, I. Kodrin, C. B. Aakeröy, N. Baus, T. Rinkovec, *IUCrJ* **5** (2018) 13–21.

L 6. *Croatian scientific and educational cloud* (HR-ZOO) - Project overview

Ivan Marić

Ivan.Maric@srce.hr

University Computing Centre (SRCE), University of Zagreb, Zagreb

The main objective of the project *Croatian scientific and educational cloud* (*HR-ZOO*) is building up of the computing and data cloud as the core component of the national e-infrastructure. The project involves establishing of the national sites (in Osijek, Rijeka, Split and Zagreb), grid sites with clusters for scientific computation, HPC site for particularly demanding computations, cloud-sites with the general purpose computing and data resources, dedicated hardware for storing large data collections and the new high speed backbone of the national academic network. A specialized expert team will maintain and further develop *HR-ZOO* as well as provide support to the users. In the presentation, the current status of this strategic project will be reviewed with an emphasis on the time schedule of the project activities, on the portfolio of planned services as well as on the questions of long term sustainability and of the management model of *HR-ZOO*.

L 7. Computational insight into the selectivity and catalytic activity of monoamino oxidase for targeting neurodegenerative diseases

Robert Vianello

robert.vianello@irb.hr

Computational Organic Chemistry and Biochemistry Group, Ruđer Bošković Institute, Zagreb, Croatia

Monoamine oxidase (MAO) is a flavoenzyme responsible for metabolizing a large variety of biogenic and dietary amines together with many neurotransmitters in the brain, such as dopamine and serotonin, whose imbalance is extensively linked with the development and progression of many neurological disorders including Parkinson and Alzheimer disease. That is why MAO has been a central pharmacological target in treating neurodegeneration for over 60 years [1]. Still, despite decades of extensive research, neither its catalytic nor inhibition mechanisms have been unambiguously determined. Elucidating precise atomistic details about MAO activity is of paramount importance in designing novel and effective inhibitors as transition state analogues, particularly since current drugs show serious adverse effects and tend to address only the symptoms rather than the cause of the dysfunction.

On the basis of QM calculations and EVB QM/MM simulations, we have proposed a new two-step hydride mechanism for the MAO catalytic activity [2a-b], which is fully corroborated by recent ^{13}C kinetic isotope effect measurements [3]. Calculations of the pK_a values of three tyrosine residues [2c] revealed that MAO active site is hydrophilic, but turns hydrophobic upon the substrate entrance. MAO selectivity was studied in the case of histamine [2d], which is not a physiological MAO substrate, yet is efficiently metabolized by MAO upon the *N*-methylation of the imidazole ring. This fact raises a very important and intriguing question: *For such a promiscuous enzyme, what is the origin of its unexpected selectivity towards two very similar compounds, yet fully equal in their reactive ethylamine parts?* Our results rationalize this in terms of a lower activation energy and more favorable reaction exergonicity and active-site binding for *N*-methylhistamine, while underlining the important role of Ile199, Leu171 and Leu328 in properly orienting substrates for the reaction. The insight gained through these studies led us to propose several strategies of preventing neurodegeneration [2e-f].

References:

[1] R. R. Ramsay, A. Albreht, *J. Neural Transm.* (2018), DOI: 10.1007/s00702-018-1861-9.

[2] a) R. Vianello, M. Repič, J. Mavri, *Eur. J. Org. Chem.* (2012) 7057-7065; b) M. Poberžnik, M. Purg, M. Repič, J. Mavri, R. Vianello, *J. Phys. Chem. B* **120** (2016) 11419-11428; c) R. Borštnar, M. Repič, S. C. L. Kamerlin, R. Vianello, J. Mavri, *J. Chem. Theory Comput.* **8** (2012) 3864-3870; d) A. Maršavelski, R. Vianello, *Chem. Eur. J.* **23** (2017) 2915-2925; e) M. Pavlin, M. Repič, R. Vianello, J. Mavri, *Mol. Neurobiol.* **53** (2016) 3400-3415; f) R. Vianello, C. Domene, J. Mavri, *Front. Neurosci.* **10** (2016) 327.

[3] J. R. Tormos, M. B. Suarez, P. F. Fitzpatrick, *Arch. Biochem. Biophys.* **612** (2016) 115-119.

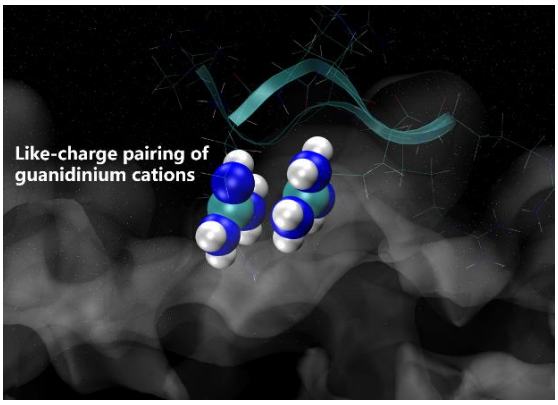
L 8. Arginine “magic”: guanidinium like-charge ion pairing from aqueous salts to cell penetrating peptides

Mario Vazdar

mario.vazdar@irb.hr

Laboratory for chemistry in model biological systems, Division of organic chemistry and biochemistry, Ruđer Bošković Institute, Zagreb, Croatia

It is a textbook knowledge that charges of the same polarity repel each other. For two monovalent ions in the gas phase at a close contact this repulsive interaction amounts to hundreds of kilojoules per mole. In aqueous solutions, however, this Coulomb repulsion is strongly attenuated by a factor equal to the dielectric constant of the medium. The residual repulsion, which now amounts only to units of kJ/mol, may be in principle offset by attractive interactions. Probably the smallest like-charge pair, where a combination of dispersion and cavitation forces overwhelms the Coulomb repulsion, consists of two guanidinium cations in water. Indeed, by a combination of molecular dynamics and electronic structure calculations and electrophoretic as well as spectroscopic experiments we have demonstrated that aqueous guanidinium cations form (weakly) thermodynamically stable like-charge ion pairs.



The importance of pairing of guanidinium cations in aqueous solutions goes beyond a mere physical curiosity and has significant biochemical implications. Guanidinium chloride is known to be an efficient and flexible protein denaturant. This is due to the ability of the orientationally amphiphilic guanidinium cations to disrupt various secondary structural motifs of proteins by pairing promiscuously with both hydrophobic and hydrophilic groups, including guanidinium-containing side chains of arginines.

The fact that the cationic guanidinium moiety forms the dominant part of the arginine side chain implies that the like-charge ion pairing may also play a role for interactions between peptides and proteins. Indeed, arginine-arginine pairing has been frequently found in structural protein databases. In particular, when strengthened by a presence of negatively charged glutamate, aspartate, or C terminal carboxylic groups, this binding motif helps to stabilize peptide or protein dimers and is also found in or near active sites of several enzymes.

The like-charge pairing of the guanidinium side chain groups may also hold the key to the understanding of the arginine “magic”, i.e., the extraordinary ability of arginine-rich polypeptides to passively penetrate across cellular membranes. Unlike polylysines, which are also highly cationic but lack the ease in crossing membranes, polyarginines do not exhibit mutual repulsion. Instead, they accumulate at the membrane, weaken it, and may eventually cross in a concerted, “train-like” manner. This behavior of arginine-rich cell penetrating peptides can be exploited when devising smart strategies how to deliver in a targeted way molecular cargos into the cell.

L 9. Strategies for full conformational analysis

Tomica Hrenar

hrenar@chem.pmf.hr

University of Zagreb Faculty of Science, Department of Chemistry, Horvatovac 102a, Zagreb, Croatia

Conformational analysis presents a critical step in many theoretical investigations. Molecules usually exist in variety of conformers and according to their distribution, different chemical reactions take place. To obtain a reliable theoretical results all these conformers should be taken into account. Procedures for full conformational analysis of cyclic and non-cyclic molecules will be presented using the three independent theoretical approaches: a stochastic search, a grid search and *ab initio* molecular dynamics coupled with tensor decomposition methods.

Stochastic search within the multilevel scheme consists of random generation of structures, geometry optimization at the molecular mechanics level and clustering of obtained conformers. Next stage includes optimization of clustered geometries by using higher level of the theory. Additional clustering of the high-level quantum chemical results gives the appropriate estimate of the conformational space.

The second approach is the *grid search* that relies on generation of all possible conformations for a given molecule by rotation around single bonds for discrete amounts. For all generated conformations the electronic energy is calculated and the *n*-dimensional potential energy surface (PES) is build. Conformers are the strict local minima on this *n*-dimensional PES. This approach is not suitable for molecules with larger number of single bonds (>10).

The third approach includes conducting low-level *on-the-fly ab initio* molecular dynamics simulations at high temperatures. It has the advantage over the stochastic search because it starts with the electronic structure calculations and over the grid search since it samples the conformational space in a "smart" way. Structural data collected from the molecular dynamics trajectory are arranged in *n*-dimensional array of numbers and tensor decomposition methods are used for analysis and classification. Results obtained from tensor decomposition allow investigation of molecular dynamics trajectories in significantly reduced space and their statistical analysis presents a wealth of information, including "smart" initial guess for full conformational space of the investigated system regardless of its structure.

Acknowledgement: This work was supported by the *Croatian Science Foundation* (Project No: IP-2016-06-3775, Activity and *in silico* guided design of bioactive small molecules, ADESIRE).

Posters

P 1. Why does ferulic acid scavenge radicals more effectively than caffeic acid? A DFT study.

Ana Amić

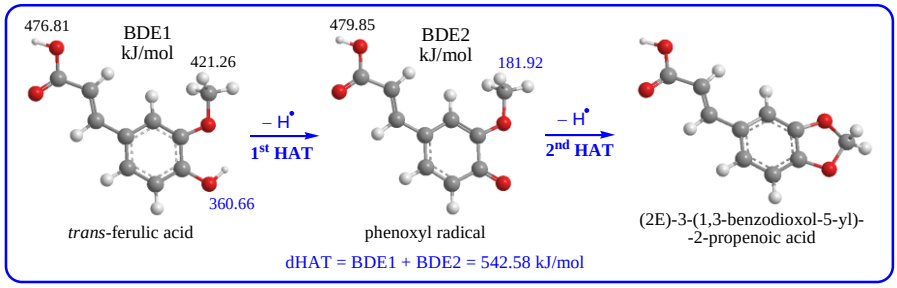
aamic@kemija.unios.hr

Department of Chemistry, Josip Juraj Strossmayer University of Osijek, Cara Hadrijana 8a, 31000 Osijek

Caffeic acid (CA) and ferulic acid (FA) are widespread in plant kingdom and are constituents of a diet rich in fruits and vegetables. Both acids are also abundant colon catabolites of diverse polyphenolic compounds and may appear in systemic circulation in low μM concentrations. Due to high bioavailability, they possess potency to scavenge excess of intracellular radical species and thus may help in supressing age-related diseases [1].

In vitro assays indicated FA as more efficient radical scavenger than CA [2]. It is an unexpected result because CA possesses catechol group (two vicinal OHs) which is a well- known powerful antiradical moiety. FA possesses guaiacyl group (vicinal OH and OCH_3) for which the role in radical scavenging is only scarcely investigated [3].

This research tries to explore the antioxidant mechanisms which enable better antiradical activity of FA in comparison with CA. DFT calculations of thermodynamics of double hydrogen atom transfer (dHAT) and double sequential proton loss electron transfer (dSPLET) were performed in water and pentyl ethanoate as solvents at SMD/M06-2X/6-311++G(d,p) level of theory. Obtained results for dHAT mechanism are depictured below.



Contrary to experimental results, single HAT mechanism, i.e., BDE1 value indicates CA as better antioxidant. Experimental findings can be explained by considering dHAT: pathway *via* guaiacyl moiety of FA is less energy demanding than *via* catechol group of CA. It is known that

lower BDE value is related to faster radical-trapping kinetics. These facts could explain higher antiradical activity of FA. Analogous results are obtained for dSPLET mechanism. Thus, the role of guaiacyl moiety in radical-trapping should not be neglected, as mainly was the case previously. In addition, Gibbs free energy changes in studied mechanisms indicate both acids as effective scavengers of a set of ten radicals. Again, FA is the more potent radical scavenger.

References:

[1] D. Del Rio, A. Rodriguez-Mateos, J. P. E. Spencer, M. Tognolini, G. Borges, A. Crozier, *Antioxid. Redox Signal*. **18** (2013) 1818-1892.

[2] Y.-Z. Cai, M. Sun, J. Xing, Q. Luo, H. Corke, *Life Sci*. **78** (2006) 2872-2888.

[3] A. Amić, Z. Marković, E. Klein, J. M. Dimitrić Marković, D. Milenković, *Food Chem*. **246** (2018) 481-489.

P 2. Development of new parameters for the Zn^{2+} ion for the specific environment of the DPP III enzyme catalytic site

Antonija Tomić,[a] Michael Ramek[b] and Sanja Tomić[a]

atomic@irb.hr

[a]Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička 54, 10 000 Zagreb, Croatia

[b]Institute of Physical and Theoretical Chemistry, Graz University of Technology, Stremayrgasse 9, 8010 Graz, Austria

The dipeptidyl peptidase III (DPP III) is a two-domain metallopeptidase that requires the zinc cation for its activity. Computational studies performed so far used the non-bonding parameters for the zinc ion. These parameters describe the metal-ligand interactions only through electrostatic and van der Waals potentials. Treating zinc metal in a non-bonded fashion resulted in a strong preference for octahedral zinc coordination that was not observed in the DPP III structures determined by the X-ray diffraction. In the experimentally determined DPP III structure the zinc ion is mostly tetrahedrally coordinated by two histidines, glutamate and one water or the substrate/inhibitor molecule. The quantum mechanics - molecular mechanics (QMMM) calculations showed an exchange of the four- and five-coordinated zinc ion during the reaction. In order to generate zinc ion parameters that will show better agreement with experimental findings and the results of QMMM calculations, several different strategies for metal ion modeling were tested. So far the hybrid model [1,2] that combines bonded and non-bonded approaches in a way that new bonds between the metal ion and protein residues are defined while leaving all other ligands unrestrained has shown the most promising results. The existing dummy atom model [3] where the metal center is described by a set of cationic dummy atoms (CaDA) connected to the central atom in the tetrahedral coordination geometry to mimic the electron orbitals has not proved suitable for simulating the DPP III active site zinc ion. However, we are working on a modification and improvement of the available CaDA parameters.

More accurate description of the Zn-protein interactions should aid to understand the factors governing specificity and coordination geometry around the metal center crucial for the novel DPP III ligands development.

References:

[1] W. Yang, B. T. Riley, X. Lei, B. T. Porebski, I. Kass, A. M. Buckle, S. McGowan, *J. Biomol. Struct. Dyn.* (2017), DOI: 10.1080/07391102.2017.1364669.

[2] P. Li, K. M. Merz, *J. Chem. Inf. Model.* **56** (2016) 599−604.

[3] http://www.mayo.edu/research/labs/computer-aided-molecular-design/projects/zinc-protein-simulations-using-cationic-dummy-atom-cada-approach

P 3. Substituent effects on the stability of 1,4-benzodiazepin-2-one tautomers. A density functional study

Barbara Pem[a,b] and Valerije Vrček[a]

bpem@imi.hr

[a]Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, 10000 Zagreb, Croatia

[b]Institute for Medical Research and Occupational Health, Ksaverska cesta 2, 10000 Zagreb, Croatia

Since their discovery in the 1960s, benzodiazepines have established themselves as essential pharmaceuticals for the treatment of various psychological disorders [1]. The basis of their action mechanism is the 1,4-benzodiazepin-2-one scaffold, with the differences in pharmacodynamic and pharmacokinetic properties of each molecule stemming from the variations of their functional groups [2]. Since they possess a –CH-C(=O)-NH- group, 1,4-benzodiazepin-2-ones can exist in three tautomeric forms: keto (amide), enol and iminol. Tautomerization in benzodiazepines is important for both their pharmacological and biochemical properties, because it can influence activity [3], biodegradation [4] and also lead to racemization [5].

This study investigates tautomerization of various commercially available benzodiazepines, as well as some novel biologically active molecules, with the aim of determining substituent effects on their respective stabilities. The relative stabilities were calculated at the M06 and ωB97XD levels of theory, with the 6-31+G(d,p) basis set. In all observed cases keto tautomer was the most stable, followed by the iminol and then the enol. However, the stability of iminol tautomers can be increased by substituting the benzene ring with a heterocycle, whereas the enols are stabilized by adding an electron-withdrawing substituent at the C3 position. Therefore, substituent effects on the relative stability of tautomers should be considered during the design of novel benzodiazepines with specific chemical and biological properties.

References:

[1] J. Spencer, R. P. Rathnam, B. Z. Chowdhry, *Future Med. Chem.* **2** (2010) 1441-1449.

[2] B. Kuila, Y. Kumar, D. Mahajan, K. Kumar, P. Singh, G. Bhargava, *RSC Adv.* **6** (2016) 57485-57489.

[3] J. Klaminder, T. Brodin, A. Sundelin, N. J. Anderson, J. Fahlman, M. Jonsson, J. Fick, *Environ. Sci. Technol.* **49** (2015) 10406-10412.

[4] J. Seifert, S. Pezeshki, A. Kamal, K. Weisz, *Org. Biomol. Chem.* **10** (2012) 6850-6860.

[5] S. K. Yang, *Chirality* **7** (1995) 365-375.

P 4. Chemical shift GIPAW-DFT calculations and ssNMR measurements for two amino-acid anthracene conjugates

Berislav Perić,[a] Gábor Szalontai[b] and Srećko Kirin[a]

Berislav.Peric@irb.hr

[a]Laboratory for solid state and complex compounds chemistry, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia
[b]NMR laboratory, University of Pannonia, Veszprém, Hungary

Solid-state NMR (ssNMR) differs from liquid phase NMR due to the absence of rapid molecular motions simplifying many of NMR-specific interactions. To reliably simulate ssNMR spectra of crystalline solids, calculations of parameters have to incorporate full periodicity of the samples. Full-periodic calculation procedure for NMR chemical shifts (shieldings), GIPAW procedure, incorporates magnetic-field dependent phases into Projector Augmented Wave (PAW) method used for obtaining wave functions from pseudopotential plane-wave DFT calculations [1]. Today GIPAW procedure is a part of several pseudopotential plane-wave DFT programs and is used for simulation and interpretation of the ssNMR spectra. Here we present the GIPAW-DFT calculations and ^{13}C ssNMR measurements for two 9,10-substituted amino-acid anthracene conjugates (**1** and **2**) for which structures have been obtained using single-crystal X-ray diffraction method. After full periodic geometry optimization, calculation of NMR chemical shieldings (shifts) has been performed by using GIPAW procedure in the Quantum Espresso program [2]. Electron density functional used was PBE [3] with energy cut-off of 90 Ry and 3×3×3 (for **1**) or 3×2×2 (for **2**) for Monkhorst-Pack k-point grids. ^{13}C CP and CPNQS MAS ssNMR measurements were performed using a Bruker Avance II NMR spectrometer (9.38 T) on a 4 mm MAS probe.

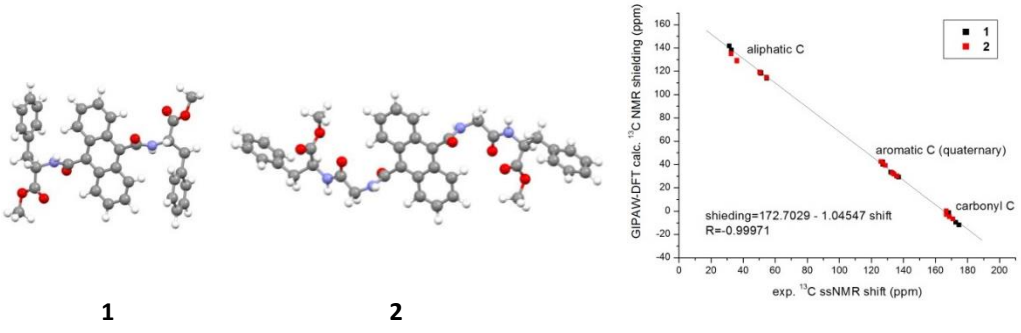


Figure 1. Structures of two amino-acid anthracene conjugates **1** (left) and **2** (middle) with comparison of the GIPAW calculated NMR shieldings and ^{13}C ssNMR measured shifts (right).

References:

[1] C. J. Pickard, F. Mauri, *Phys. Rev. B* **63** (2001) 245101.

[2] https://github.com/dceresoli/qe-gipaw; http://www.quantum-espresso.org/

[3] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **77** (1996) 3865-3868.

P 5. Protonation equlibria and optical properties of benzo[*b*]thienopyridil-benzimidazoles studied by spectroscopic and computational methods

Darko Babić,[a] Nataša Perin,[b] Marijana Hranjec[b] and Robert Vianello[c]

darko.babic@irb.hr, robert.vianello@irb.hr

[a]Group for Computational Life Sciences, Ruđer Bošković Institute, Zagreb, Croatia
[b]Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, Zagreb, Croatia
[c]Computational Organic Chemistry and Biochemistry Group, Ruđer Bošković Institute, Zagreb, Croatia

Three new amino substituted benzo[*b*]thieno[2,3-*b*]pyrido[1,2-*a*]benzimidazoles **1**–**3** were synthesized as potential fluorescent pH sensitive probes (Fig. 1). These dye molecules involve highly conjugated pentacyclic planar chromophores with remarkable optical properties including strong fluorescence in the visible spectrum and excellent photostability [1,2]. To determine their analytical features, **1**–**3** were followed over a range of pH values by UV/Vis and fluorescence spectroscopies, which revealed that the protonation/deprotonation induces drastic photophysical changes. For example, the fluorescence intensity of **3** strongly increases upon the exposure to acidic conditions [3] (Fig. 2). Determination of the protonation forms responsible for the observed spectroscopic trends was attempted by combining the factorization of the titration spectra with computation of the protonation equilibria constants and electronic spectra. Our analysis indicates that this requires titration spectra recorded at greater resolution (0.2 - 0.3 pH units). While these are still lacking, here we present the preliminary results obtained at resolution of 1 pH. In view of their analytical applicability, we propose the synthesis of two additional promising systems (**4**, **5**), characterized by improved acid/base (pK_a = 7–9) and spectroscopic features.

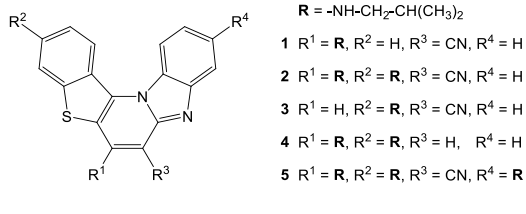


Figure 1. Investigated fluorescent benzo[*b*]thieno [2,3-*b*]pyrido[1,2-*a*]benzimidazole derivatives.

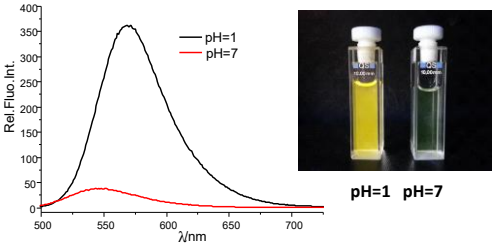


Figure 2. Fluorescence emisson spectra of compound **3** at pH = 1 and pH = 7.

References:

[1] N. Perin, M. Hranjec, G. Pavlović, G. Karminski-Zamola, *Dyes Pigm.* **91** (2011) 79–88.

[2] N. Perin, K. Bobanović, I. Zlatar, D. Jelić, V. Kelava, S. Koštrun, V. Gabelica Marković, K. Brajša, M. Hranjec, *Eur. J. Med. Chem.* **125** (2017) 722–735.

[3] M. Hranjec, E. Horak, D. Babić, S. Plavljanin, Z. Srdović, I. Murković Steinberg, R. Vianello, N. Perin, *New J. Chem.* **41** (2017) 358–371.

P 6. Role of N-centred radicals' stability in intramolecular C-H amidation reactions

Davor Šakić,[a] Hendrik Zipse[b] and Valerije Vrček[a]

dsakic@pharma.hr

[a]Faculty of Pharmacy and Biochemisrtry, University of Zagreb, Croatia
[b]Department of Chemistry, LMU, Munich, Germany

Nitrogen-centered radicals are involved in numerous and diverse type of reactions, including degradation of proteins and peptides, environmental fate of pharmaceuticals, and targeted synthesis of amines and amides. Contrary to well investigated substituent effects on C-centered radical stability, for many N-centered radicals experimental data is lacking. By using quantum-chemical methods in conjunction with isodesmic reactions, we have connected experimental bond dissociation energies with calculated relative stability of N-centered radicals to fill in the gaps in understanding substitution effects.

Knowledge about relative stability of N-centered radicals and radical cations [1] is of potential relevance in metal-free C-H amidation reactions. Combination with available C-H bond energies for substrate fragments allows for the prediction of reaction enthalpies in 1,5-HAT steps frequently encountered in reactions such as the Hoffman-Löffler-Freytag (HLF) reaction [2].

References:

[1] J. Hioe, D. Šakić, V. Vrček, H. Zipse, *Org. Biomol. Chem.* **13** (2015) 157-169.

[2] D. Šakić, H. Zipse, *Adv. synth. & cat.* **358** (2016) 3983-3991.

P 7. Mechanisms and kinetics of charge transfer in aqueous reactions of free radicals with haloorganic substrates

Ivana Nikšić-Franjić,[a] Iva Džeba,[b] Igor Sviben,[a] Marija Bonifačić,[a] Aleksandar Sabljić[a] and Ivan Ljubić[a]

iniksicf@irb.hr

[a]Division of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia
[b]Division of Materials Chemistry, Ruđer Bošković Institute, Zagreb, Croatia

Free radical reactions in aqueous media typically exhibit a rich variety of fundamentally important mechanisms in close competition [1-3]. Of special interest is proton-coupled electron transfer (PCET), which is ubiquitous in many biological and electrochemical processes that crucially depend upon it. We present a combined experimental and theoretical study of the α-aminoalkyl and α-hydroxyalkyl free radicals, the glycine radical anion and hydrogen atom, in reaction with various haloorganic substrates, such as alkyl halides, haloacetates, 5-bromouracil, iodoacetamide and chloral hydrate. In majority of these systems, the dominant mechanism is shown to be the PCET. Examples of competing pathways include hydrogen atom transfer (HAT), halogen abstraction, and free radical substitutions and additions. These reaction systems are especially suitable for studying the PCET owing to their compactness, which renders them tractable to accurate quantum chemical methods, and a number of readily controllable experimental parameters. The physiologically relevant pH range is maintained throughout the reaction with the use of standard buffer systems (bicarbonate and phosphate), which is useful for assessing the in vivo impact of this class of C-centered free radicals and hydrogen atom. In addition, the studied haloorganic substrates find important biological and medical applications. The mechanism and kinetic parameters are modeled using density functional theory with the polarizable continuum (PCM) framework used for an implicit description of the water solvent. We compare the performance of a series of density functionals for predicting the reaction rate constants. The best results overall are seen with the M06, followed by the M05-2X functional. The dominant reaction channels are typically characterized by the negative apparent activation energies, and so accurate modeling of the kinetic parameters remains challenging.

References:

[1] I. Ljubić, B. Matasović, M. Bonifačić, *Phys. Chem. Chem. Phys.* **15** (2013) 18001-18011.

[2] I. Ljubić, A. Sabljić, M. Bonifačić, *J. Phys. Chem. B* **120** (2016) 11810-11820.

[3] G. E. Adams, E. M. Fielden, B. D. Michael, *Fast Processes in Radiation Chemistry and Biology*, John Wiley & Sons, 1973, New York.

P 8. Excited state proton transfer in prototypical hydrogen bonded systems

Jurica Novak, Marin Sapunar, Tarek Ayari and Nađa Došlić

jurica.novak@irb.hr

R. Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

Single and multiple hydrogen bonds and related proton or H atom transfer (PT) in the ground and excited electronic states are of fundamental importance. Besides being of importance for potential applications, hydrogen bonds pose some fundamental challenges due to the strongly anharmonic and multidimensional quantum character of their dynamics.

Here we focus on coupled electron and nuclear dynamics that characterizes excited state PT reactions and discuss the mechanisms and time scales of the reactions in prototypical hydrogen bonded systems [1-3].

References:

[1] J. Novak, M. Mališ, A. Prlj, I. Ljubić, O. Kuehn, N. Došlić, *J. Phys. Chem. A* **116** (2012) 11467-11475.

[2] J. Novak, A. Prlj, N. Basarić, C. Corminboeuf, N. Došlić, *Chem. Eur. J.* **23** (2017) 8244-8251.

[3] R. J. Squibb, M. Sapunar, A. Ponzi, R. Richter, A. Kivimäki, O. Plekan, P. Finetti, N. Sisourat, V. Zhaunerchyk, T. Marchenko, L. Journel, R. Guillemin, R. Cucini, M. Coreno, C. Grazioli, M. Di Fraia, C. Callegari, K. C. Prince, P. Decleva, M. Simon, J. H. D. Eland, N. Došlić, R. Feifel, M. N. Piancastelli, *Nat. Commun.* **9** (2018) 63.

P 9. Optical stability of oxazepam and chiral 1,4-benzodiazepines. DFT study of the racemization mechanism

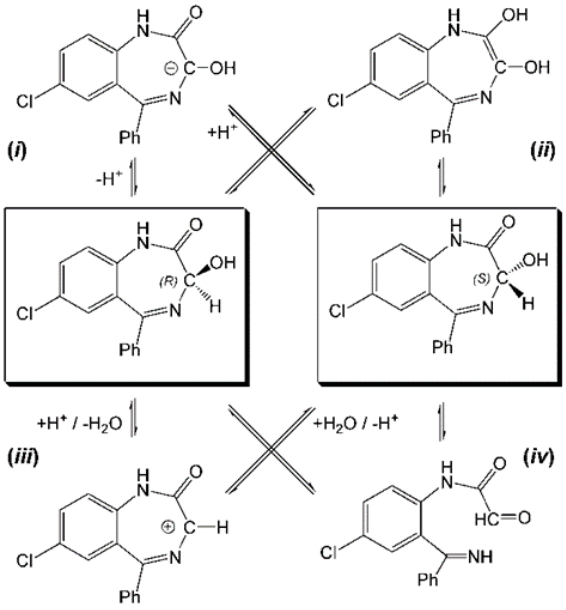
Lucija Božičević, Helena Sremec, Lucija Hok, Davor Šakić and Valerije Vrček

lbozicevic@student.pharma.hr, hsremec@student.pharma.hr

Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, Zagreb, Croatia

Optical stability is of utmost importance in pharmaceutical chemistry and biomedicine. In this work, the attention is focused on oxazepam which displays extreme chiral instability under physiological conditions (37 °C, pH 7.4), and may serve as a model for the whole family of 1,4-benzodiazepin-2-ones.

Several reaction mechanisms underlying the racemization of oxazepam were proposed in the literature (Scheme 1). In several kinetic studies the reaction rate constant *k* was measured and values varied from 0.16 min^{-1} (23 °C, pH 7) to 0.02 min^{-1} (20 °C). According to the Eyring equation, these values correspond to the free energy barrier range of 87 – 91 kJ/mol. We assume that all processes below or close to the target experimental barrier ($\Delta G^{\ddagger} \leq 91$ kJ/mol) may contribute to the measured reaction rate.



Scheme 1. Four different reaction mechanisms of racemization process in oxazepam, as reported throughout the literature: **(i)** C3-H/H exchange reaction (SE1 type), **(ii)** keto-enol tautomerization, **(iii)** solvolytic (H_2O) identity reaction, and **(iv)** ring-chain tautomerization.

We used quantum chemical models to calculate geometries and energies of respective intermediates and transition state structures. All structures were optimized with the B3LYP functional and the standard basis set 6-31+G(d). We also determined the Gibbs energies of solvation using the SMD continuum solvation model at the B3LYP/6-31+G(d) level (ε = 78.4). Initial configurations of water complexes were created using a locally modified version of the stochastic search method (http://andrija.pharma.hr/Andrija/SCRIPT.html)

According to our computational results we claim that the enantiomerization of oxazepam in water follows the mechanism of the ring-chain tautomeric rearrangement. No other mechanism, suggested earlier in the literature, matches the experimental data in terms of Gibbs free energy.

P 10. Chlorination of 5-fluorouracil: reaction mechanism and ecotoxicity assessment of chlorinated products

Lucija Hok,[a] Lea Ulm,[b] Tana Tandarić,[c] Adela Krivohlavek,[b] Davor Šakić[a] and Valerije Vrček[a]

lucija.hok@gmail.com

[a]Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, Zagreb, Croatia
[b]Andrija Štampar Teaching Institute of Public Health, Mirogojska 16, Zagreb, Croatia
[c]Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička 54, Zagreb, Croatia

5-Fluorouracil (5-FU) is a pyrimidine antimetabolite introduced in the clinic as an anticancer drug. The reaction between 5-FU and hypochlorous acid (HOCl) is the fundamental process which can occur in activated neutrophils in cancer patients [1] or during chemical treatment of wastewaters [2]. This study combines synthesis, NMR and MS spectroscopy, quantum chemical calculations, and toxicity experiments on *Daphnia magna* to investigate chemical fate of 5-FU in chlorinated environment. All structures were fully optimized with the B3LYP functional. The standard 6-31+G(d) basis set was used for geometry optimizations and frequency calculations. Improved energetics have been calculated using B2K-PLYP functional and 6-311+G(3df,2p) basis set. Gibbs energies of solvation were determined using the SMD continuum solvation model at the B3LYP/6-31+G(d) level (ε = 78.4). Two explicit water molecules were found as „the ideal number of solvent molecules" for a reliable description of the corresponding potential energy surfaces.

The first chlorinated product chlorohydrin **3a** was less toxic than the parent 5-FU, suggesting the beneficial effect of chlorination (Figure 1). Further chlorination leads to N1-chlorinated intermediate **6**, that undergoes pyrimidine ring opening reaction. The final product **11** was obtained after the loss of the chlorinated urea fragment. This is the most potent compound in the reaction sequence, with toxicity parameter EC_{50} more than twice lower compared to the parent 5-FU. Interplay between experimental and theoretical procedures, to properly describe reaction pathways and provide more information on toxicity profiles, is a way forward in environmental science research.

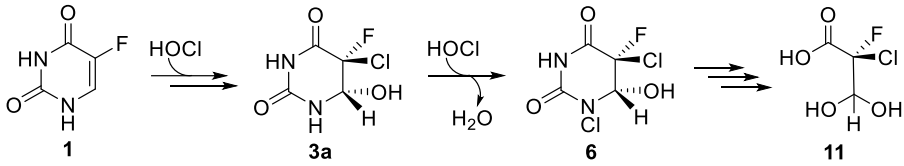


Figure 1. Chlorination and ring opening in 5-FU.

References:

[1] C. C. Winterbourn, A. J. Kettle, M. B. Hampton, *Ann. Rev. Biochem.* **85** (2016) 765-792.

[2] J. L. Acero, F. J. Benitez, F. J. Real, G. Roldan, *Water Res.* **44** (2010) 4158-4170.

P 11. MD and DFT study of glycerol binding in B_{12}-dependent diol dehydratase

Luka Bilić,[a] Marko Tomin,[b] Danijela Barić,[a] Borislav Kovačević[a] and David M. Smith[a]

Luka.Bilic@irb.hr

[a]Division of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia
[b]Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Zagreb, Croatia

During biodiesel production a large amount of glycerol is created as a byproduct [1,2]. Dehydration of glycerol to a more valuable product could be obtained by eco-friendly methods utilizing B_{12}-dependent dehydratases which turn glycerol into 3-hydroxypropanal [3-5]. However, the unusual property of glycerol is that it is both the supstrate and the irreversible inhibitor of B_{12}-dependent dehydratases [6]. The proposed mechanism of inactivation is based on the crystal structure of B_{12}-dependant diol dehydratase (DDH, PDB code: 3AUJ) [7]. This mechanism relies on the position of the hydroxyl group at C(3) atom of glycerol being oriented towards the serine residue (Ser301) in the active site. However, incompleteness of the enzyme in crystal structure (missing adenosyl group), poor resolution (2.1 Å) and small electron density aroud C(3) call for further research. Herein we compare geometrical parameters of the active site of DDH obtained by molecular dynamic simulations (MD) and quantum chemical calculations (DFT) with the crystal structure, and investigate various patterns of glycerol binding in the active site.

References:

[1] J. C. Thompson, B. B. He, *Appl. Eng. Agric.* **22** (2006) 261–265.

[2] A. S. Aldiguier, S. Alfenore, X. Cameleyre, G. Goma, J. L. Uribelarrea, S. E. Guillouet, C. Molina-Jouve, *Bioprocess Biosyst. Eng.* **26** (2004) 217–222.

[3] (a) T. Toraya, *Cell. Mol. Life Sci.* **57** (2000) 106–127; (b) T. Toraya, *Chem. Rev.* **103** (2003) 2095–2127.

[4] (a) K. L. Smiley, M. Sobolov, *Arch. Biochem. Biophys*. **97** (1962) 538–543; (b) J. Pawelkiewicz, B. Zagalak, *Acta Biochim. Polon*. **12** (1965) 207–218.

[5] (a) T. Toraya, S. Fukui, *Eur. J. Biochem*. **76** (1977) 285–289; (b) T. Toraya, S. Kuno, S. Fukui, *J. Bacteriol*. **141** (1980) 1439–1442; (c) R. G. Forage, M. A. Foster, *Biochim. Biophys. Acta* **569** (1979) 249–258.

[6] W. W. Bachovchin, R. G. Eagar Jr., K. W. Moore, J. H. Richards, *Biochemistry* **16** (1977) 1082-1093.

[7] K. Doitomi, T. Kamachi, T. Toraya, K. Yoshizawa, *Biochemistry* **51** (2012) 9202-9210.

P 12. DFT study of the ammonia N–H bond activation by dicyclopalladated azobenzene complex

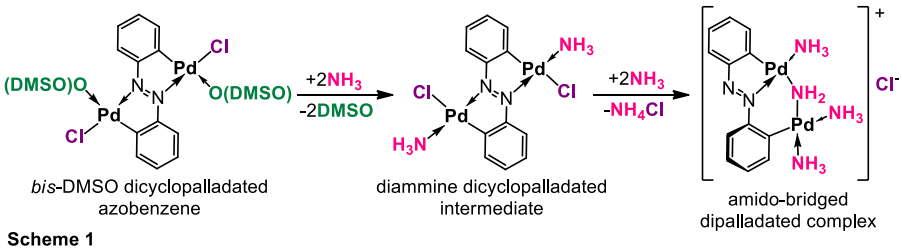
Marina Juribašić Kulcsár,[a] Ana Budimir[b] and Manda Ćurić[a]

marina.juribasic@irb.hr

[a]Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia
[b]Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, 10000 Zagreb, Croatia

Metal-mediated ammonia N–H bond activation is extensively studied as the first step in catalytic transformation of inexpensive ammonia into more precious N-containing compounds [1]. Ammonia activation is usually hindered by the strong ammonia N–H bond and, in case of late-transition metals, preferential formation of ammine Werner-like adducts over amido complexes comprising the amido (NH_2) group [1].

Recently, a reversible N–H bond activation of gaseous ammonia has been achieved using a solid dicyclopalladated azobenzene, $[Pd_2Cl_2$(**AZB**-2H)$(O$-DMF$)_2]$, as well as by its reaction in ammonia-rich DMSO solution [2]. Spectroscopic monitoring of the reaction by *in situ* solid-state Raman method as well as by UV-vis spectroscopy in DMSO solution showed a stepwise activation (Scheme 1) yielding the first dipalladated amido complex with a Pd^{II}-(μ-NH_2)-Pd^{II} bridge, $[Pd_2(\mu$-$NH_2)$(**AZB**-2H)$(NH_3)_3]$Cl, *via* a stable diammine dicyclopalladated intermediate $[Pd_2Cl_2$(**AZB**-2H$)_2(NH_3)_2]$ [2].



bis-DMSO dicyclopalladated azobenzene — diammine dicyclopalladated intermediate — amido-bridged dipalladated complex

Scheme 1

Here we describe a computational study that has supplemented the experimental data in elucidation of the mechanism of the presented heterolytic N–H bond activation by the dicyclopalladated azobenzene. DFT calculations support the stepwise mechanism assisted by exogenous ammonia that consists of ammonia coordination, chloride elimination and ammonia-assisted cleavage of the ammonia N–H bond by palladium.

References:

[1] a) M. P. Betoré, M. A. Casado, P. García-Orduña, F. J. Lahoz, V. Polo, L. A. Oro, *Organometallics* **35** (2016) 720–731, and refs cited therein; b) J. L. Klinkenberg, J. F. Hartwig, *Angew. Chem. Int. Ed.* **50** (2011) 86–95; c) J. I. van der Vlugt, *Chem. Soc. Rev.* **39** (2010) 2302–2322; d) Y. Aubin, C. Fischmeister, C. M. Thomas, J.-L. Renaud, *Chem. Soc. Rev.* **39** (2010) 4130–4145.

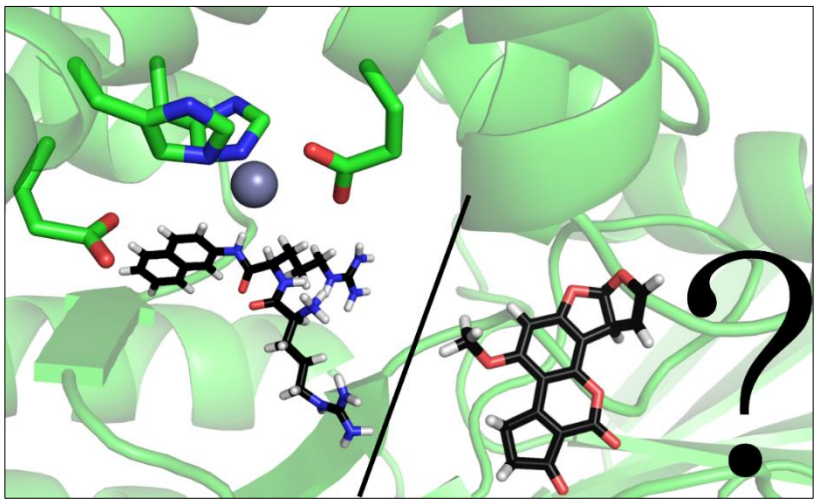
[2] M. Juribašić Kulcsár, I. Halasz, A. Budimir, K. Užarević, S. Lukin, A. Monas, F. Emmerling, J. Plavec, M. Ćurić, *Inorg. Chem.* **56** (2017) 5342–5351.

P 13. Oxidase or peptidase? A putative DPP III from *Armillariella tabescens*

Marko Tomin

marko.tomin@irb.hr

Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia



An enzyme isolated from the fungus *Armillariella tabescens* has been reported to break down aflatoxin B1 (AFB1), a potent toxin and carcinogen commonly found in food and animal feed, and subsequently dubbed aflatoxin oxidase (AFO) [1]. However, AFO shares high sequence similarity with dipeptidyl peptidase III (DPP III) while its recently determined crystal structure reveals an active site resembling the one of DPP III [2]. Further on, recent studies report no oxidase activity [3] while the peptidase activity was reported using both natural and synthetic substrates [2,3].

In order to elucidate the role of the putative *A. tabescens* DPP III, docking and long MD simulations of its complexes with Arg_2-2-naphthylamide and AFB1 were performed and respective binding energies were calculated using the MM-PBSA approach. In case of the AFB1 complex, two possible binding modes were considered. Both conventional and steered molecular dynamics were employed in an attempt to observe long-range conformational motions and locate the non-catalytic, so-called "open", form of the enzyme, present in other DPP III orthologs [4].

In addition to the crystallographically determined "closed" form, an open form of the enzyme was identified, which is consistent with previous findings within the DPP III family. Docking results suggest that AFB1 binding to the enzyme is unfavorable, supporting the findings of Karačić et al [3]. The synthetic substrates, namely dipeptidyl-2-naphthylamides, bind antiparallel to the conserved ^{384}GINL β-sheet which is in line with crystallographic data for human DPP III [4].

References:

[1] D. L. Liu, D. S. Yao, R. Liang, L. Ma, W. Q. Cheng, L. Q. Gu, *Food. Chem. Toxic.* **36** (1998) 563-574.

[2] T. Xu, C. Xie, D. Yao, C.-Z. Zhou, J. Liu, *Biochem. Biophys. Res. Commun.* **494** (2017) 621-625.

[3] Z. Karačić, Ž. Ban, P. Macheroux, *Current Topics in Peptide & Protein Research* **18** (2017) 41-48.

[4] G. A. Bezzerra, V. Dobrovetsky, R. Viertlmayr, A. Dong, A. Binter, M. Abramić, P. Macheroux, S. Dhe-Paganon, K. Gruber, *Proc Natl Acad Sci USA* **109** (2012) 6525-6530.

P 14. Ferrocenoyl-purines: regioselective synthesis and acylation mechanism

Mateja Toma,[a] Alma Filipović,[a] Jasmina Lapić,[a] Senka Djaković,[a] Davor Šakić[b] and Valerije Vrček[b]

mtoma@pbf.hr

[a]Faculty of Food Technology and Biotechnology, University of Zagreb,Pierottijeva 6, Zagreb, Croatia

[b]Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, Zagreb, Croatia

Ferrocene nucleobase conjugates are organometallic compounds where the ferrocene moiety is covalently linked through various "linkers" with heterocyclic nucleobases [1]. The synthesis of ferrocenoyl-purines is based on acylation [2] of purine anions with ferrocenoyl-chloride and in most cases both N7- and N9- isomers were detected by NMR spectroscopy and isolated. In this study we combined synthesis, NMR spectroscopy and quantum chemical calculations to investigate the steric effect of C6-substituent of purine anions on N9/N7 ferrocenoylation.

It is found that N9/N7-regioisomers ratio is dependent on the C^6–substitution of the purine system. It is possible that the bulkier substituent at C6-position causes shielding of the N7 position which inhibits N7-acylation of purine anions. When adenine anion was ferrocenoylated, the N9-isomer was the major product (79%). For N^6-methyl adenine and N^6, N^6-dimethyl adenine the acylation resulted in increased yield of N9-isomer, leading to reaction regiospecificity in case of the $N(Boc)_2$-adenine where only N9-regioisomer was formed. The ratio of N9 : N7 isomers, determined quantitatively by integration of signals in ^{1}H NMR spectra of the reaction mixture, is strongly correlated to the effective (Charton's) and calculated multidimensional (Sterimol) steric parameters of the C6-substituent. Finally, quantum-chemical calculations (B3LYP/6-31+G(d) level) suggest that the barrier for the N7-isomer formation is higher than the corresponding barrier for N9-isomer formation. The calculated energy barrier difference for N7 and N9 –acylation reaction is in correlation with N9/N7 product ratio and steric parameters of C6-substituents, which nicely supports experimental results.

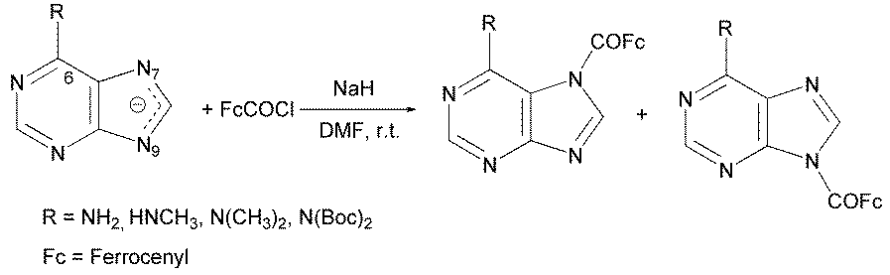


Figure 1. Acylation of purine anion with ferrocenoyl-chloride.

References:

[1] K. Kowalski, *Coord. Chem. Rev.* **317** (2016) 132–156.

[2] J. Lapić, V. Havelić, D. Šakić, K. Sanković, S. Djaković, V. Vrček, *Eur. J. Org. Chem.* **24** (2015) 5424-5431.

P 15. Influence of metal ion and non-coordinating alkyl chain type on the properties of Co(II), Ni(II) and Cu(II) complexes with *N*-alkylated iminodiacetamides: a DFT computational study

Ozren Jović and Neven Smrečki

ozren.jovic@chem.pmf.hr

University of Zagreb, Department of Chemistry, Faculty of Science, Horvatovac 102a, 10000 Zagreb, Croatia

Iminodiacetamide, $HN(CH_2CONH_2)_2$ (imda) is a diamide of iminodiacetic acid (IDA), which is a precursor to nitrilotriacetic acid, ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA). It has been shown that partial or complete amidation of the carboxylic groups in such ligands may enhance their selectivity towards particular metal ions [1,2]. This selectivity may be utilized for the separation of lanthanides [1] or treatment of lead poisoning [2]. Metal complexes with N-substituted iminodiacetamides are scarce in the literature [3-5]. We have studied complexation reactions of iminodiacetamide (H-imda) and *N*-alkyliminodiacetamides Meimda, Etimda, *n*-Primda, *i*-Primda, *n*-Buimda, *i*-Buimda and *t*-Buimda; Me = methyl, Et = ethyl, *n*-Pr = *n*-propyl, *i*-Pr = isopropyl, *n*-Bu = *n*-butyl, *i*-Bu = isobutyl and *t*-Bu = *tert*-butyl) with nickel(II), cobalt(II) and copper(II) nitrates in vacuum and in water. For all 24 metal-ligand combinations we performed geometry optimizations, energy evaluations, frequency calculations, including calculations of thermodynamic properties, HOMO-LUMO energies and population analysis using different levels of theory (mostly using B97-D/def2-TZVP//B97-D/6-311G**). By optimizing geometry and calculating energies for all corresponding *trans*- and *cis*-complexes, we also explained why all synthesized complexes are *trans* isomers. The calculated spectra and molecular geometry agree well with the experimental results despite the presence of extensive hydrogen bonding networks in these systems. The stability of the complex cation $[M(Rimda)_2]^{2+}$ (expressed in term of binding energy between the cation M^{2+} and two Rimda molecules in the gas phase) increases for both Ni(II) and Co(II) with rising length of the alkyl chain. The approximate energy difference between Ni(II) and Co(II) complexes for calculated Gibbs free energy of reaction with corresponding ligands is –2 kcal/mol in water treated as dielectric polarizable continuum.

References:

[1] L. A. Clapp, C. J. Siddons, D. G. Van Deerver, J. H. Reibenspies, S. B. Jones, R. D. Hancock, *Dalton Trans.* (2006) 2001-2007.

[2] E. S. Claudio, M. A. Horst, C. E. Forde, C. L. Stern, M. K. Zart, H. A. Godwin, *Inorg. Chem.* **39** (2000) 1391-1397.

[3] N. Smrečki, B.-M. Kukovec, M. Đaković, Z. Popović, *Polyhedron* **93** (2015) 106-117.

[4] N. Smrečki, O. Jović; K. Molčanov; B.-M. Kukovec; I. Kekez, D. Matković-Čalogović, Z. Popović, *Polyhedron* **130** (2017) 115-126.

[5] N. Smrečki, O. Jović, B.-M. Kukovec, E. Šimunić, S. Vuk, A. Skuhala, M. Babić, T. Rončević, N. Ilić, I. Kekez, D. Matković-Čalogović, Z. Popović, *Inorg. Chim. Acta* **471** (2018) 521-529.

P 16. Molecular dynamics simulations of UCP2 protein – an insight to physiological function

Sanja Škulj, Zlatko Brkljača and Mario Vazdar

sanja.skulj@irb.hr

Laboratory for Chemistry in Model Biological Systems, Rudjer Bošković Institute, Zagreb, Croatia

Mitochondrial uncoupling protein 2 (UCP2) is a transmembrane protein localized in mitochondrial inner membrane working as a mitochondrial carrier. UCP2 belongs to a class of α-helical polytopic proteins and contains 309 residues. It is known that UCP2 protein is involved in maintaining proton gradient across cellular membranes with a help of fatty acids (FA). The mechanism how UCP2 protein and FA work together is still unknown [1]. NMR structure of UCP2 protein was published in 2011 [2], but according to recent results it has been shown that the extraction of UCP2 protein by detergents induces structural perturbations and distortions leading to physiologically irrelevant structure which has a large water channel connecting the two sides of a membrane [3].

In order to get the physiologically relevant structure, we obtained and compared 1 μs of MD simulations of two different structures – the published NMR structure and the homology modeled structure based on crystallographic structure of mitochondrial ADP/ATP carrier (ANT1) and primary UCP2 amino acid sequence. According to extensive MD simulations, the modeled structure appears to be more physiologically relevant than the NMR structure because it is more occluded and impervious to water as compared to the published NMR structure. The modeled UCP2 structure presents an excellent starting point for future MD simulations of functional properties of UCP2 protein in membranes.

References:

[1] M. J. Berardi, J. J. Chou *Cell Metabolism* **20** (2014) 541-552.

[2] M. J. Berardi, W. M. Shih, S. C. Harrison, J. J. Chou, *Nature* **476** (2011) 109-114.

[3] M. Zoonens, J. Comer, S. Masscheleyn, E. Pebay-Peyroula, C. Chipot, B. Miroux, F. Dehez, *J. Am. Chem. Soc.* **135** (2013) 15174−15182.

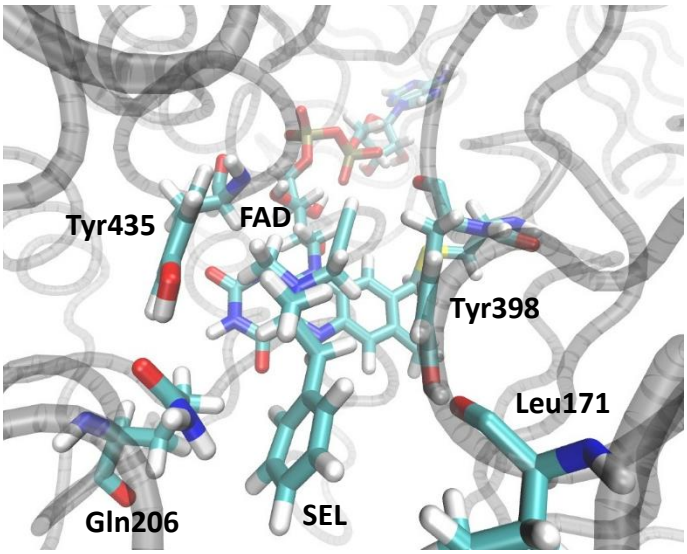
P 17. Irreversible inhibition of monoamine oxidase B enzyme. A computational insight.

Tana Tandarić and Robert Vianello

Tana.Tandaric@irb.hr

Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb

Monoamine oxidases A and B (MAO A and B) are mammalian flavoenzymes responsible for the regulation of amine neurotransmitter levels. These enzymes represent main pharmacological target for the treatment of depression and neurodegenerative diseases. Two isoforms of this enzyme are present in human body, MAO A and MAO B, which share about 70% of the identity in the primary sequence, but show significant differences in substrate selectivity and inhibitor specificity in particular [1]. Focus of this work are selective irreversible inhibitors of MAO B, selegiline and rasagiline, widely used in the treatment of symptoms of Parkinson and Alzheimer disease. Both inhibitors form covalent bond with organic cofactor flavin adenine dinucleotide (FAD). In that way they prevent MAO B enzyme's further catalytic activity.



Here, we used a molecular dynamics (MD) simulations, to simulate 300 ns of interaction of MAO B with both inhibitors. It is shown that Tyr398 and Tyr435 form aromatic cage responsible for interaction with aromatic part of inhibitor. Ile199 is characterized as structurally responsible for the selectivity of the inhibitor, which confirms the experimentally obtained results [2]. Aromatic interactions between the inhibitors and the aromatic cage amino acids as well as the hydrogen bonds between the inhibitors and the flavin cofactor carbonyl oxygen O8 orient the inhibitors in a favorable position for the reaction leading to the covalent binding with the FAD inhibitor. Using MM-PBSA tools, binding free energy values were obtained. The results show that selegiline binds better than rasagiline by 1.4 kcal/mol which is consistent with experimental IC50 values [3].

Quantum-chemical analysis within the enzyme cluster model showed that MAO inhibition proceeds through a 4-step reaction, with the first step determining the total reaction rate, in which FAD cleaves the hydride ion from the α-methylene group of the inhibitor in a complete analogy with the MAO catalytic mechanism [4]. The resulting reaction profiles and the final structure of the inhibited enzymes are in excellent agreement with the experimental data. The obtained results are of great importance for the development of new and more effective MAO B inhibitors for clinical use.

References:

[1] R. R. Ramsay, *Curr. Top. Med. Chem.* **12** (2012) 2189–2209.

[2] F. Hubálek, C. Binda, A. Khalil, M. Li , A. Mattevi, N. Castagnoli, D. E. Edmondson, *J. Biol. Chem.* **280** (2005) 15761-15766.

[3] M. B. H. Youdim, A. Gross, J. P. M. Finberg, *Br. J. Pharmacol.* **132** (2001) 500–506.

[4] R. Vianello, C. Domene, J. Mavri, *Front. Neurosci.* **10** (2016) 327-351.

P 18. DFT and NMR rationalization of diastereoselectivity in glycomimetic synthesis by modified Passerini reaction

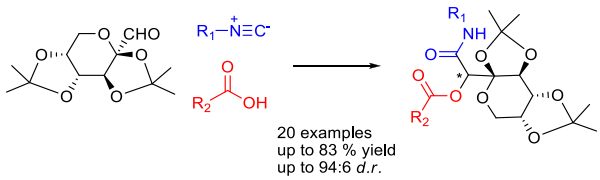
Kristina Vlahoviček-Kahlina,[a] Mario Vazdar,[a] Andreja Jakas,[a] Vilko Smrečki[b] and Ivanka Jerić[a]

smrecki@irb.hr

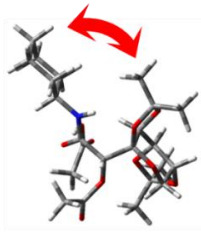
[a]Ruđer Bošković Institute, Division of Organic Chemistry and Biochemistry, Bijenička cesta 54, 10000 Zagreb, Croatia

[b]Ruđer Bošković Institute, NMR Centre, Bijenička cesta 54, 10000 Zagreb, Croatia

The *bis*-isopropylidene-protected D-fructose-derived aldehyde was utilized in the Passerini reaction with various acids and isocyanides thus obtaining functionalized glycomimetics in high yields and diastereoselectivities.

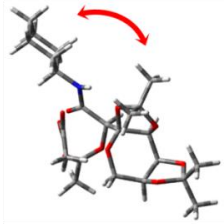


To ascertain the stereochemistry of the newly created stereocentre, NOE contacts observed in 2D NOESY NMR experiments were compared to calculated interatomic distances in optimized structures of four different Passerini products. The measured correlation between hydrogen atom of the new stereocentre and neighbouring hydrogen atoms was not decisive on observed stereospecificity of the product.



final-a = *S* product

In order to elucidate the observed stereoselectivity of Passerini reactions performed with sugar aldehyde, we conducted DFT calculations at the SMD/M062X/6-311++G(2d,p)//M062X/6-31G(d) level of theory employing dichloromethane as a solvent starting from two different configurations leading to the final product with *S* (path-a) and *R* (path-b) configuration, following the mechanistic pathway proposed recently by Ramozzi and Morokuma [1]. The reason for different stability of intermediates, transition states and final products lies in the stabilizing noncovalent van der Waals interactions between nonpolar cyclohexyl and adjacent isopropylidene fragments which are especially pronounced in the final product with *S* configuration due to their closer proximity [2].



final-b = *R* product

References:

[1] R. Ramozzi, K. Morokuma, *J. Org. Chem.* **80** (2015) 5652–5657.

[2] a) J. D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **10** (2008) 6615–6620; b) L. Yang, C. Adam, G. S. Nicholand, S. L. Cockroft, *Nat. Chem.* **5** (2013) 1006–1010.

P 19. Conformational analysis of *cis*-decalin by principal component analysis of molecular dynamics trajectory

Karlo Sović and Tomica Hrenar

ksovic@chem.pmf.hr

University of Zagreb Faculty of Science, Department of Chemistry, Horvatovac 102a, Zagreb, Croatia

A new procedure for full conformational analysis [1] comprising statistical analysis of molecular dynamics trajectory was applied on *cis*-decalin. This method includes a coordinate space sampling using molecular dynamics simulations, reduction of dimensionality using tensor decomposition tools, determination of probability distributions in a reduced space, and finally the search for all of the strict extrema points in probability distributions. These extracted extrema points formed an initial guess for geometry optimization and clustering of conformers.

Molecular dynamics simulations were performed using *on-the-fly* calculations of forces in each point of the simulation and integration with the Velocity Verlet algorithm. The forces were calculated using the PM7 method [2] implemented in MOPAC2016 [3]. All molecular dynamics simulations were performed using our own program ***qcc*** [4]. To ensure that most of the phase space relevant to the conformational space of the investigated compounds was adequately sampled, the initial temperature for the Maxwell distribution of velocities was set at 1298.15 K, and this temperature was kept constant throughout simulations using a Velocity scaling algorithm. The step size was 0.5 fs and the total length of simulation was 5.0 ns (a total of 10000000 steps). In the analysis of trajectory, reduction of data was achieved using 10 principal components with the amount of total variance >90 %. All statistical analyses were performed using our own program ***moonee*** [5]. After the clustering, structures obtained as initial guess were optimized using B3LYP-D3/6-311++G(d,p) level of the theory. Full conformational space was determined and all conformers were structurally examined and their relative content at the room temperature were determined from Maxwell-Boltzmann distribution. Comparison to the conformational space of *trans*-decalin will also be made.

Acknowledgement: This work was supported by the *Croatian Science Foundation* (Project No: IP-2016-06-3775, Activity and *in silico* guided design of bioactive small molecules, ADESIRE).

References:

[1] T. Hrenar, I. Primožič, D. Fijan, M. Majerić Elenkov, *Phys. Chem. Chem. Phys.* **19** (2017) 31706.

[2] J. J. P. Stewart, *J. Mol. Model.* **19** (2013) 1.

[3] MOPAC2016, J. J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA, 2016, http://OpenMOPAC.net

[4] T. Hrenar, ***qcc***, Quantum Chemistry Code, rev. 0.682, 2018.

[5] T. Hrenar, ***moonee***, Program for Manipulation and Analysis of Multi- and Univariate Data, rev. 0.6827, 2018.

P 20. Grid search conformational analysis of carnitine and acetylcarnitine

Marija Bakija, Ana Mikelić, Karlo Sović and Tomica Hrenar

bakija.marija@gmail.com, amikeli1@gmail.com

University of Zagreb Faculty of Science, Department of Chemistry, Horvatovac 102a, Zagreb, Croatia

Carnitine has physiologically important function of decreasing triglycerides content, very low density lipoproteins and cholesterol. Considering these facts, it may be important in the reduction of cardiovascular diseases. Initial geometries for the conformational analysis of carnitine and acetylcarnitine were obtained by systematic search of potential energy surfaces (PES) scans calculated at the semiempirical level [1]. PES were spanned in the space of five and six torsional coordinates for carnitine and acetylcarnitine, respectively. Optimization procedure for finding strict local minima utilizing a brute-force search for arbitrary number of ways (*n*-way space) was applied and all strict local minima on PES were identified [2]. These local minima found at the semiempirical level were subsequently optimized using density functional theory (B3LYP-D3/6-311++G(d,p)). To ensure that optimized structures were indeed local minima, harmonic frequency calculations were carried out and normal modes were examined visually. Full conformational spaces were determined and all conformers were structurally examined and their relative content at the room temperature were determined from Maxwell-Boltzmann distribution. Furthermore, the potential for internal rotation of trimethylamino group in both molecules will be calculated and analyzed.

Acknowledgement: This work was supported by the *Croatian Science Foundation* (Project No: IP-2016-06-3775, Activity and *in silico* guided design of bioactive small molecules, ADESIRE).

References:

[1] T. Hrenar, ***qcc***, Quantum Chemistry Code, rev. 0.682, 2018.

[2] T. Hrenar, ***moonee***, Program for Manipulation and Analysis of Multi- and Univariate Data, rev. 0.6827, 2018.

P 21. Effects of a flexible pinning on the fluctuations of a membrane

Josip Augustin Janeš,[a,b] Daniel Schmidt[a] and Ana-Sunčana Smith[a,b]

jjanes@irb.hr

[a]PULS Group, Department of Physics & Cluster of Excellence: EAM, Friedrich-Alexander University, Erlangen-Nürnberg, Nägelsbachstrasse 49b, 91052 Erlangen, Germany
[b]Department of Physical Chemistry, Ruder Boškovic Institute, Bijenicka c. 54, 10000 Zagreb, Croatia

Mechanical characteristics of freely suspended 2D membranes are commonly determined from their fluctuation spectrum [1]. However, this task is significantly more challenging for the case of membranes attached by proteins to underlying scaffolds. Actually, a complete theoretical description of the effect of a pinning on the dynamic correlations in a membrane is still missing. The difficulty lies in the coupling of plane wave modes by the bond [2]. Here we rectify this situation by modeling the static and dynamic correlations by several complementary analytic methods. We construct a complete theoretical framework for the problem in question and validate our approach by obtaining excellent agreement with the explicit Langevin simulations [3].

References:

[1] C. Monzel, D. Schmidt, C. Kleusch, D. Kirchenbüchler, U. Seifert, A.-S. Smith, K. Sengupta, *Nat. Commun.* **6** (2015) 8162.

[2] D. Schmidt, T. Bihr, U. Seifert, A.-S. Smith, *EPL* **99** (2012) 38003.

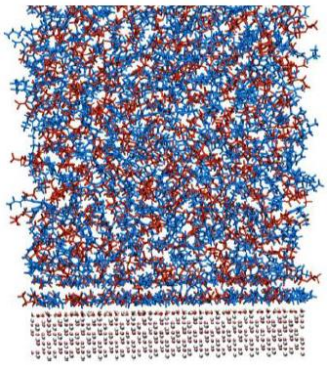
[3] J. A. Janeš, D. Schmidt, A.-S. Smith, *in preparation*.

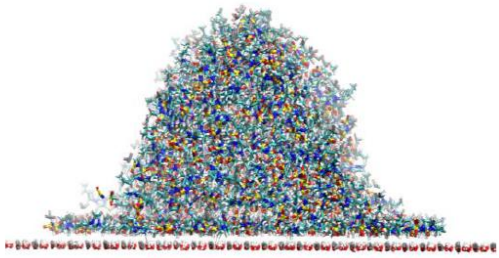
P 22. Static and dynamic properties of $[C_2Mim][NTf_2]$ ionic liquid on neutral sapphire surface

Nataša Vučemilović-Alagić,[a,b] David M. Smith[a,b] and Ana-Sunčana Smith[a,b,c]

nvucemil@irb.hr

[a]EAM, Cluster of Excellence, FAU, Erlangen, Germany
[b]Ruđer Bošković Institute, Zagreb, Croatia
[c]Institute for Theoretical Physics I, FAU, Erlangen, Germany





Understanding the molecular-level behavior of ionic liquids (ILs) at IL-solid interfaces is of fundamental importance with respect to their application in, for example, electrochemical systems and electronic devices [1]. In this respect, we employed atomistic molecular dynamics (MD) simulations to investigate the behavior of an archetypical imidazolium-based IL, namely $[C_2Mim][NTf_2]$, at the neutral sapphire interface [2]. This enabled us to describe the nature of the model IL-solid interface in appreciable detail. More precisely, we observed pronounced structural ordering of the IL constituents in the vicinity of the sapphire surface, which, in turn, induces the multidimensional layering of cations and anions. Moreover, we investigated the surface-wetting capabilities of $[C_2Mim][NTf_2]$ by employing cylindrically shaped nanodroplets [3] with three different radii, thereby measuring the contact angle between the IL and the sapphire surface.

References:

[1] T. Welton, *Chem. Rev.* **99** (1999) 2071-2084.

[2] Z. Brkljača, M. Klimczak, Z. Miličević, M. Weisser, N. Taccardi, P. Wasserscheid, D. M. Smith, A. Magerl, A.-S. Smith, *J. Phys. Chem. Lett.* **6** (2015) 549-555.

[3] J. Driskill, D. Vanzo, D. Bratko, A. Luzar, *J. Chem. Phys.* **141** (2014) 18C517.

Author index

Notes

Impressum

Name of the conference: *Computational Chemistry Day*
Organizers:
Ruđer Bošković Institute
University of Zagreb Faculty of Science
Croatian Chemical Society

Place: Horvatovac 102a, HR-10000, Zagreb, Croatia, EU
Date: May 12, 2018

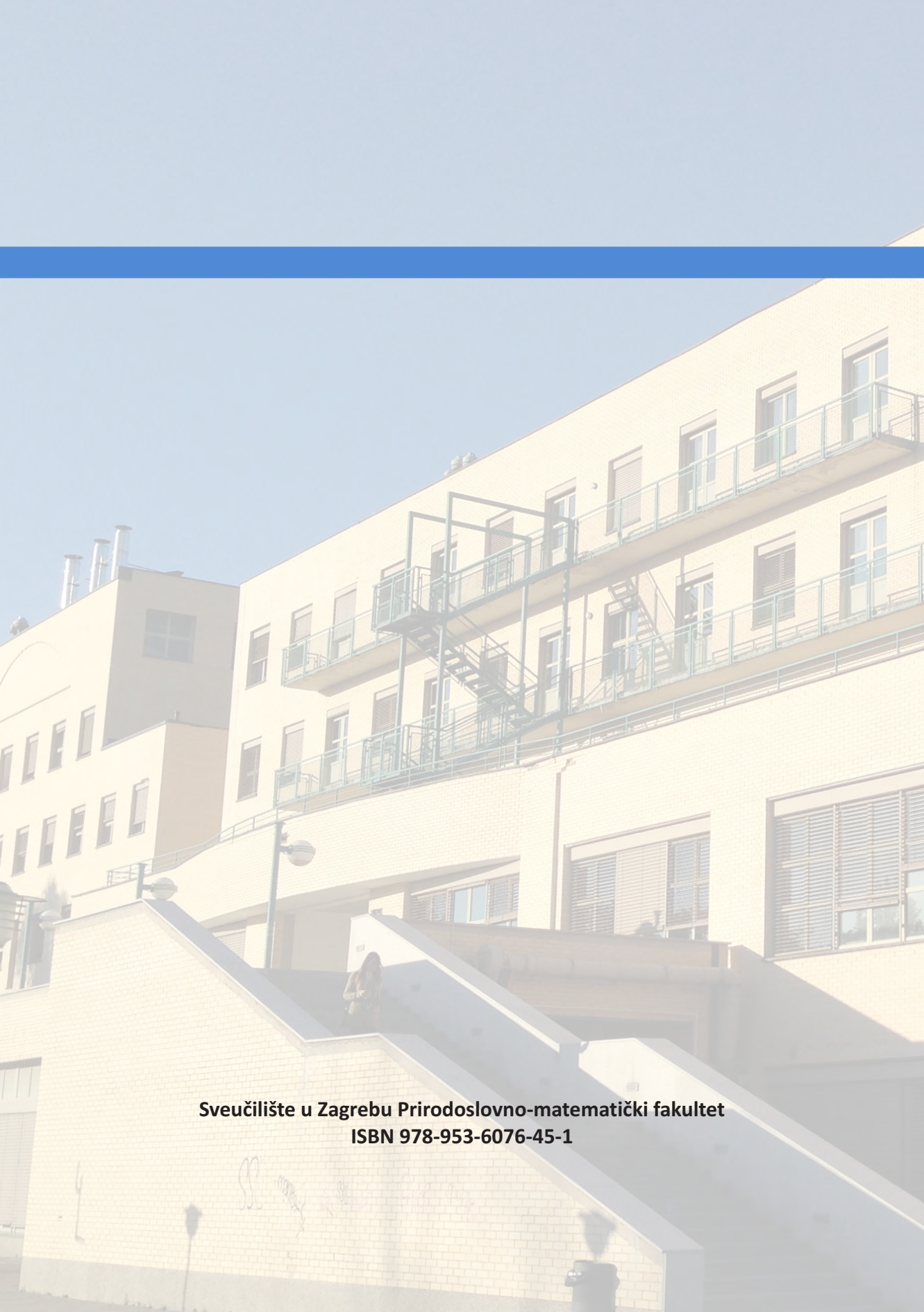
Organization board:
Darko Babić, Danijela Barić, Marko Cvitaš,
Ines Despotović, Nađa Došlić, Marko Hanževački,
Tomica Hrenar, Borislav Kovačević, Ivan Ljubić,
Zlatko Mihalić, Robert Vianello

Abstracts were prepared by the authors.

Publisher: University of Zagreb Faculty of Science
ISBN 978-953-6076-45-1

Organization board warmly thanks the following sponsors for their financial support.

HRZZ Croatian Science Foundation
MINISTARSTVO ZNANOSTI I OBRAZOVANJA
REPUBLIKE HRVATSKE



Sveučilište u Zagrebu Prirodoslovno-matematički fakultet
ISBN 978-953-6076-45-1