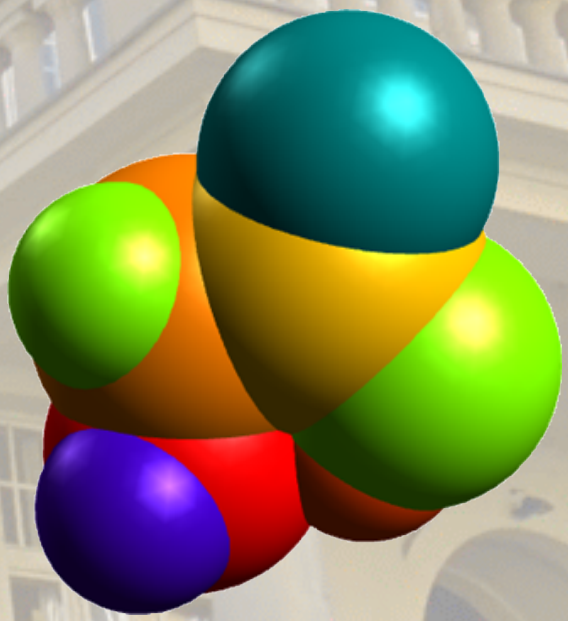
Computational Chemistry Day 2019



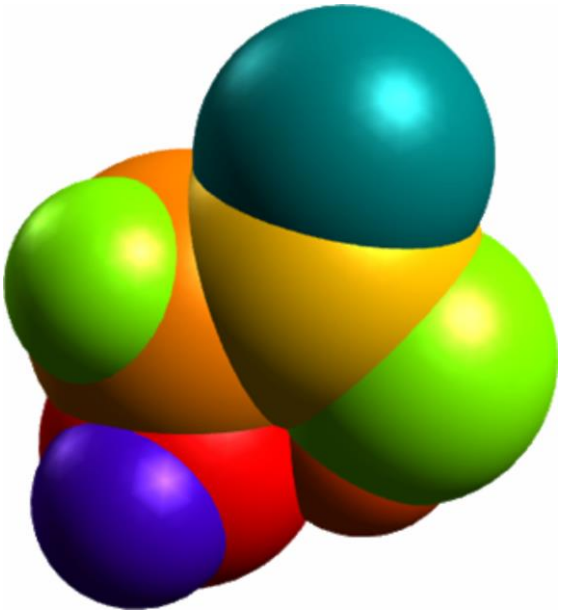
Book of abstracts

University of Zagreb Faculty of Pharmacy and Biochemistry

May 11, 2019

Zagreb, Croatia, EU

Computational Chemistry Day 2019



Book of abstracts

University of Zagreb Faculty of Pharmacy and Biochemistry

May 11, 2019
Zagreb, Croatia, EU

Foreword

Dear colleagues, we are happy to welcome you again! The time from the last year's meeting passed quickly, yet we got many new results and findings to share at the second *Computational Chemistry Day*. We gathered again to learn about the results from our colleagues and to present our own ones. Although many of us meet each other regularly at the working place, there are not many chances to talk about the matters we deal with, except with those directly involved. Speaking to somebody out of the circle always carries the possibility of a new insight or a different view to the problem. Besides, presentation of the results to colleagues from the local community has special charm and raises additional challenge. Meetings like CCD are not only a place for information exchange but also an opportunity to personally acquaint fellow researchers and make grounds for collaboration and joint research.

We are lucky to work in one of the most propulsive and fastest developing fields today. The software tools are getting increasingly numerous and available, and the modelling methods are becoming more and more powerful. Nowadays simulations are on the verge of reality, and our explanation and prediction capabilities have practical significance, with fascinating perspective. The dreams are coming true – many science fiction ideas are not fiction anymore, just the science! On the other side, it is getting more and more difficult to keep up with the pace of new developments. Sharing knowledge and experience with colleagues helps us to stay informed and to adopt new practices more quickly and easily.

We thank the lecturers for providing us the outline of the meeting. We also thank the poster presenters and all the other participants for making this event valuable, interesting and cheerful.

We gratefully acknowledge financial support from *Croatian Science Foundation*, *The Ministry of Science and Education of the Republic of Croatia*, *Chemistry Department of the Faculty of Science of the University of Zagreb*, *Croatian Academy of Sciences and Arts*, and *The Ruđer Bošković Institute*, *Zagreb*. Their support made possible to cover all the organization expenses without participation fees. Finally, we thank the hosting institution – *The Faculty of Pharmacy and Biochemistry of the University of Zagreb*, for hospitality and help in the organization of the meeting.

The Organization Board of the *Computational Chemistry Day 2019*

Program of the *Computational Chemistry Day 2019*

09:00–09:30 ***Opening addresses***

1st session (moderator: **Valerije Vrček**)

09:30–10:00 **Zlatko Mihalić** (PMF, Zagreb)
Computational chemistry today, or how to obtain accurate numbers with minimum effort

10:00–10:30 **Marina Šekutor** (RBI)
Configuration and reactivity of diamondoids on a Cu(111) surface

10:30–11:00 **Antonija Tomić** (RBI)
Development of new zinc ion parameters suitable for classical MD simulations of zinc metallo-peptidases

11:00–11:30 ***Coffee break***

2nd session (moderator: **Mario Vazdar**)

11:30–12:00 **Larisa Zoranić** (PMF, Split)
Conformational adaptivity of designed antimicrobial peptides

12:00–12:30 **Hrvoje Rimac** (FBF)
Formation of a ternary human serum albumin-indomethacine-quercetin complex and energy transfer

12:30–13:00 **Vatroslav Letfus** (Fidelta)
Rational design, synthesis and biological profiling of new JMJD2C inhibitors

13:00–14:00 ***Lunch break***

3rd session (moderator: **Danijela Barić**)

14:00–14:30 **Zlatko Brkljača** (RBI)
Insights into translocation of charged species along membrane proteins using advanced free energy calculations

14:30–15:00 **Marin Sapunar** (RBI)
Tracking excited electronic states in nuclear coordinate space

15:00–15:30 **Tana Tandarić** (RBI)
Computational insight into the MAO B enzyme irreversible inhibition

15:30–16:00 **Karlo Sović** (PMF, Zagreb)
Conformational analysis of fused ring systems using tensor decomposition methods

16:00–16:05 ***Concluding remarks***

16:05–18:00 **Poster session *with more coffee***

Table of contents

Lectures

L 1. Computational chemistry today, or how to obtain accurate numbers with minimum effort

Zlatko Mihalić

mihalic@chem.pmf.hr

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

After fifty years of fast development and two awarded Nobel prizes, the computational chemistry finally occupies its rightful place. A third approach to the natural science emerged, the computer experiment, which established itself as indispensable tool for better understanding of all chemical phenomena. A huge computing power increase during the last few decades enabled development and routine usage of new theoretical methods capable of reproducing and predicting the experimental data. Today new force fields are being developed, treatment of electron correlation is better and faster, simulations of many-particle dynamics are usable. The number of available theoretical methods significantly increased in last twenty years since the first stable implementation of DFT, new approach based on electron density. Thankfully, the effort towards speeding up more exact and inherently slower WFT methods has not ceased.

Since the number of available theoretical methods is huge and constantly increasing, nonspecialist user is confronted with serious dilemmas. This can be illustrated by the fact that contrary to many papers comparing existing functionals and selecting the best among them, top places on the density functionals popularity lists still hold twenty years old (but 'proved') functionals like B3LYP and PBE0. In this lecture, an overview of modern computational chemistry methods will be given, with author's estimates of their suitability for obtaining accurate numbers for right reasons, illustrated with various examples from both the literature and author's own research.

L 2. Configuration and reactivity of diamondoids on a Cu(111) surface

Marina Šekutor

msekutor@irb.hr

Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička c. 54, 10 000 Zagreb, Croatia

Diamondoids, bulky cage hydrocarbons consisting of fused cyclohexane rings [1], are good model systems for assessing the influence of London dispersion (LD) on molecular self-assembly [2]. Since LD interactions are capable of directing on-surface orientations of bulky molecules and thereby prevent randomness during ensembles formation, targeted reactivity of the formed scaffolds can be achieved [3].

We explored the reactivity of a selected diamantane diacid on metal surfaces upon thermal annealing with a combination of experimental and computational techniques [3]. The experimentally observed diamantyl chains that formed on the copper surface were modelled in order to determine their on-surface configuration and to propose the corresponding reaction mechanism (Figure 1). For that purpose the semiempirical GFN-xTB approach developed by Grimme *et al.* was used [4].

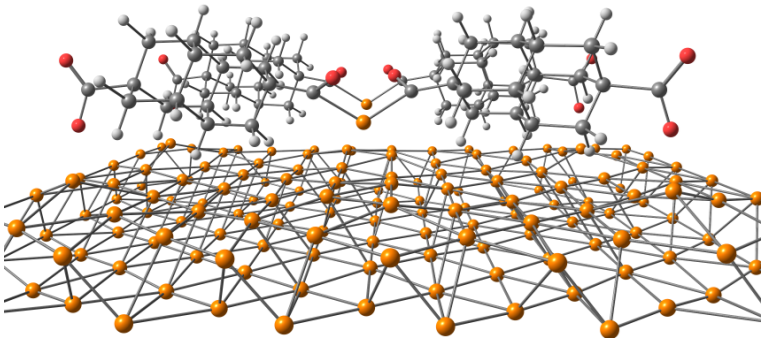


Figure 1. Computed Cu-containing double chains anchored by diamantyl scaffolds on Cu(111).

References:

[1] M. A. Gunawan, J.-C. Hierso, D. Poinsot, A. A. Fokin, N. A. Fokina, B. A. Tkachenko, P. R. Schreiner, *New J. Chem.* **38** (2014) 28–41.

[2] D. Ebeling, M. Šekutor, M. Stiefermann, J. Tschakert, J. E. P. Dahl, R. M. K. Carlson, A. Schirmeisen, P. R. Schreiner, *ACS Nano* **11** (2017) 9459–9466.

[3] H.-Y. Gao, M. Šekutor, L. Liu, A. Timmer, H. Schreyer, H. Mönig, S. Amirjalayer, N. A. Fokina, A. Studer, P. R. Schreiner, H. Fuchs, *J. Am. Chem. Soc.* **141** (2019) 315–322.

[4] S. Grimme, C. Bannwarth, P. Shushkov, *J. Chem. Theory Comput.* **13** (2017) 1989−2009.

L 3. Development of new zinc ion parameters suitable for classical MD simulations of zinc metallo-peptidases

Antonija Tomić,[a,c] Gordan Horvat,[b] Michael Ramek,[c] Dejan Agić,[d] Hrvoje Brkić[e,f] and Sanja Tomić[a]

atomic@irb.hr

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

[b]Department of Chemistry, Faculty of Science, University of Zagreb,10 000 Zagreb, Croatia

[c]Institute of Physical and Theoretical Chemistry, Graz University of Technology, 8010 Graz, Austria

[d]Faculty of Agrobiotechnical Sciences Osijek, Josip Juraj Strossmayer University of Osijek,31 000 Osijek, Croatia

[e]Faculty of Medicine, Josip Juraj Strossmayer University of Osijek,31 000 Osijek, Croatia

[f]Faculty of dental medicine and health, Josip Juraj Strossmayer University of Osijek,31 000 Osijek, Croatia

Reliable representation of the systems with transition metals is still a weak point of the force field based molecular modeling methods. We tested different strategies for modeling the zinc ion in classical molecular dynamics simulations based on nonpolarizable (nonbonded, hybrid bonded/nonbonded and cationic dummy atom models) as well as on polarizable (Drude-2013) potentials using human dipeptidyl peptidase III (DPP III) as a template. In the experimentally determined human 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. Since neither of the strategies based on the nonpolarizable potential showed good agreement with experimental findings and the results of QMMM calculations, and the simulations utilizing the polarizable potential turned out to be extremely expensive, we modified the approach of Yang et al. [1] by extending the region used in quantum mechanical (QM) calculations based parametrization procedure. Namely, the zinc-coordinated water molecule and the residues constituting the second metal ion coordination sphere were included in QM calculations resulting with a new set of the zinc ion parameters, so called 4-ligand-extended parameters, to be used within the AMBER force fields ff12SB and ff14SB. These parameters enabled realistic modeling of the active site configuration in different DPP III orthologues as well as in distant peptidases like thermolysin, neprilysin and aminopeptidase N.

References:

[1] W. Yang, B. T. Riley, X. Lei, B. T. Porebski, I. Kass, A. M. Buckle, S. McGowan, *J. Biomol. Struct. Dyn.* **36** (2018) 2595-2604.

L 4. Conformational adaptivity of designed antimicrobial peptides

Yogesh Sonavane and Larisa Zoranić

larisaz@pmfst.hr

Department of Physics, Faculty of Science, University of Split, Split, Croatia

Today's society is facing the challenge of battling infectious diseases due to the rapid emergence of resistant bacterias, mostly attributed to the overuse and misuse of antibiotics, but also the lack of new treatments. An alternative may be the use of antimicrobial peptides (AMPs), which are the first line of defence against the invading pathogens in all living organisms [1]. In this lecture, we present the molecular dynamics simulation studies of novel AMPs, design by home-made algorithms and expert knowledge [2]. The simulations of kiadins, GLY-LYS rich peptides based on the tandem-repeat of small natural host defence peptide PGLa-H, highlighted that helical structuring and its amphipathic arrangement observed in different environments are influenced by both number and positions of the induced GLY mutations. Our second example is flexampin which is constructed by starting from an adaptable, dynamic turn tandem motif in a central location, characteristic of some ranatuerins from the skin secretions of ranid frogs, and by adding designed helix-forming cationic amphipathic arms. The high flexibility of the central segment enables the best matching amphipathic and hydrophobic microenvironments it encounters, as simulations of the peptide in solutions and in the presence of solvated neutral and anionic membrane showed. The possible applicability is tested by comparing the peptide's bactericidal activity and toxicity against human cells.

References:

[1] M. Zasloff, *Nature* **415** (2002) 389–95.

[2] (a) T. Rončević, D. Vukičević, N. Ilić, L. Krce, G. Gajski, M. Tonkić, I. Goić-Barišić, L. Zoranić, Y. Sonavane, M. Benincasa, D. Juretić, A. Maravić, A. Tossi, *J. Med. Chem.* **61** (2018) 2924–2936; (b) D. Juretić, Y. Sonavane, N. Ilić, G. Gajski, I. Goić-Barišić, M. Tonkić, M. Kozić, A. Maravić, F.-X. Pellay, L. Zoranić, *BBA Biomembranes* **1860** (2018) 2655-2668.

L 5. Formation of a ternary human serum albumin-indomethacine-quercetin complex and energy transfer

Hrvoje Rimac

hrimac@pharma.hr

Department of Medicinal Chemistry, Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, 10 000 Zagreb

Human serum albumin (HSA) is a plasma protein capable of binding and transporting a wide variety of ligands, both endogenous and exogenous. It serves as a depot for xenobiotics, prolonging their half-life in circulation and regulating their blood concentration. It consists of three domains (I-III), each of which is comprised of two subdomains (A and B) and the two most important binding sites for drugs are situated in subdomains IIA and IIIA, which are also called warfarin and benzodiazepine site, respectively (Figure 1). Quercetin is a plant product abundant in everyday diet, which has many salutary effects, of which its antioxidative, cardiovascular, and anticarcinogenic are the most extensively studied. It binds to the IIA site of HSA, suggesting that its binding may cause displacement of drugs from these binding sites, leading to adverse effects. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID), a derivative of methylated indole. It binds to the IIA HSA binding site >99% which means it can potentially interact with quercetin.

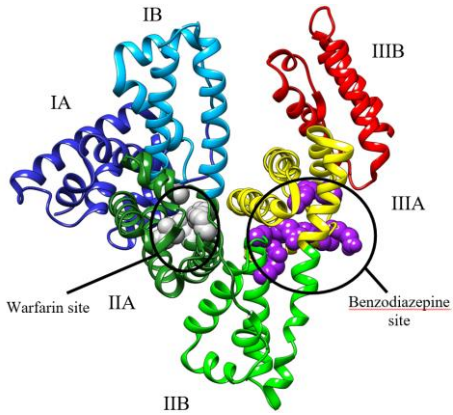


Figure 1. Structure of human serum albumin with two most important binding sites shown.

In this work, spectrofluorimetry, docking and molecular dynamics simulations (MD) were used to obtain an insight of quercetin – indomethacin interactions in binding to HSA. Spectrofluorimetric data showed an increase of quercetin fluorescence in presence of indomethacin, which suggests stronger quercetin – HSA interactions. Further docking and MD simulations showed difference in interactions between quercetin and HSA in presence and absence of indomethacin, with indomethacin pushing quercetin deeper into the hydrophobic cleft and changing the nature of quercetin – HSA interactions from cation – π stacking to hydrogen bonding. The obtained results are consistent with the experimental fluorimetric data and provide additional insight into the xenobiotics - HSA binding mechanism.

L 6. Rational design, synthesis and biological profiling of new JMJD2C inhibitors

Vatroslav Letfus, Dubravko Jelić, Ana Bokulić, Adriana Petrinić Grba and Sanja Koštrun

Vatroslav.Letfus@glpg.com

Fidelta d.o.o., Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia

JMJD2 is an enzyme family of human histone demethylases that have been linked to diseases such as prostate and breast cancer. Thus, these enzymes are considered oncogenes and their selective inhibition might be a possible therapeutic approach to treat cancer [1]. Majority of currently known inhibitors suffer from the low permeability and low selectivity between the enzyme isoforms [2].

This project used information from the available x-ray structures of JMJD2C and homologous JMJD2A complexes with small molecules and peptides. A computational analysis of protein-ligand interactions was applied using structure based drug design, and new JMJD2C inhibitors based on toxoflavin motif with improved biological activity and *in vitro* ADME properties were designed and synthesized.

Although toxoflavin is a known toxin, structural modifications of parent molecule in order to minimize its redox potential, introduction of substituents with different electronic properties to toxoflavin scaffold was performed.

A number of synthesized compounds possess interesting activity profiles in target-specific, biochemical assay against JMJD2C enzyme (IC_{50} = 8-16 nM). Inhibitors also displayed good passive cellular permeability and metabolic stability. However, diminishing of redox liability and consequently non-specific influence on cell viability still remains a challenge. Nevertheless, a step towards strong potency has been made with good starting point for further optimization.

References:

[1] P. A. C. Cloos, J. Christensen, K. Agger, A. Maiolica, J. Rappsilber, T. Antal, K. H. Hansen, K. Helin, *Nature* **442** (2006) 307-311.

[2] N. R. Rose, E. C. Y. Woon, G. L. Kingham, O. N. F. King, J. Mecinović, I. J. Clifton, S. S. Ng, J. Talib-Hardy, U. Oppermann, M. A. McDonough, C. J. Schofield, *J. Med. Chem.* **53** (2010) 1810-1818.

L 7. Insights into translocation of charged species along membrane proteins using advanced free energy calculations

Zlatko Brkljača, Sanja Škulj and Mario Vazdar

zlatko.brkljaca@irb.hr

Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Zagreb, Croatia

Molecular dynamics simulations are a powerful tool for the investigation of complex systems in atomistic detail. In the last 20 years, these methods have been extensively used to study biological systems, such as DNA, proteins and membranes. In this study we focus on the latter subject, particularly on the phenomenon of membrane permeation, which governs biological processes and underlying cell mechanisms. In this respect, while the neutral species can quite readily permeate the cell bilayer, the unmediated transport of charged species is usually quite slow, and does not occur on biologically relevant timescales. The transport of such species is thus generally occurring via supporting mechanisms, which commonly involve transmembrane proteins, used to arbitrate their passage through the membrane [1].

In this work, we use advanced MD simulations to obtain detailed insight into the translocation of charged species along membrane proteins. In particular, we use state-of-the-art umbrella sampling along the pathway technique to obtain an in-depth view at the energetics of the transportation of charged species across the bilayer, thereby comparing it to standard free energy calculations. In this respect, we propose two distinct methods for the generation of initial translocation pathway of the species of interest, based on electrostatic potential map of the protein and rough free energy map of the charged specie around protein surface, respectively. The model system we use to test the proposed methodology is a transmembrane protein adenine nucleotide translocase 1 (ANT 1), which serves in the translocation of charged species across cell membranes [2].

References:

[1] N. P. Bethel, M. Grabe, *Proc. Natl. Acad. Sci. U. S. A.* **113** (2016) 14049-14054.

[2] Y. Wang, E. Tajkhorshid, *Proc. Natl. Acad. Sci. U. S. A.* **105** (2008) 9598-9603.

L 8. Tracking excited electronic states in nuclear coordinate space

Marin Sapunar,[a] Tomislav Piteša,[a] Davor Davidović[b] and Nađa Došlić[a]

marin.sapunar@gmail.com

[a]Department of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia
[b]Center for Informatics and Computing, Ruđer Bošković Institute, Zagreb, Croatia

Overlaps between many-electron wave functions play an important role in photochemical studies as they offer an intuitive and straightforward way to track the electronic character of the states along different nuclear geometries. As such, they are often used for constructing multi-state, multi-dimensional potential energy surfaces (PES) for quantum dynamics. They are also extensively used in nonadiabatic dynamics simulations and in calculations of photoionization observables.

In this contribution, we present recent work on developing two algorithms for calculating overlaps between CIS (or TDDFT) type excited state wave functions [1], one based on an expansion of overlap determinants [2] into level 2 minors (OL2M) and the other based on an expansion of the wave functions into natural transition orbitals [3] (ONTO). The developed algorithms are significantly faster than previously available algorithms, with the ONTO algorithm reducing the cost of a single overlap element calculation by a factor of the square of the number of occupied orbitals in the system. The algorithm exhibits orders of magnitude faster calculations for large systems and significantly increases the size of systems for which TDDFT based nonadiabatic dynamics simulations can be performed. We also provide examples of applications for wave function overlaps outside the context of nonadiabatic dynamics, focusing on using an assignment algorithm to track excited electronic states.

References:

[1] M. Sapunar, T. Piteša, D. Davidović, N. Došlić, *submitted manuscript.*

[2] F. Plasser, M. Ruckenbauer, S. Mai, M. Oppel, P. Marquetand, L. González, *J. Chem. Theory Comput.* **12** (2016) 1207–1219.

[3] (a) I. Mayer, *Chem. Phys. Lett.* **437** (2007) 284-286; (b) P. Surján, *Chem. Phys. Lett.* **439** (2007) 393-394.

L 9. Computational insight into the MAO B enzyme irreversible inhibition

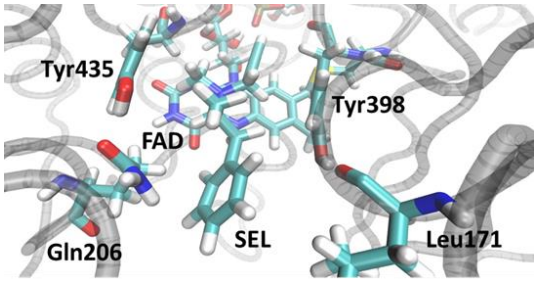
Tana Tandarić and Robert Vianello

Tana.Tandaric@irb.hr

Computational Organic Chemistry and Biochemistry Group,
Ruđer Bošković Institute, Bijenička cesta 54, Zagreb

Monoaminooxidases A and B (MAO A and B) are mammalian flavoenzymes responsible for regulating the levels of amine neurotransmitters. These enzymes represent the main pharmacological target in the treatment of depression and neurodegenerative diseases. Two isoforms are present in the human body, MAO A and MAO B, which share about 70% of the identical amino acids in the primary sequence but exhibit significant differences in the substrate selectivity and especially in inhibitory specificity [1]. The focus of this work are selective irreversible MAO B inhibitors, selegiline and rasagiline, widely used in alleviating the symptoms of Parkinson's and Alzheimer's diseases.

In this work we used molecular dynamics simulations (MD) to obtain insight into MAO B interactions with both inhibitors in the active site. It has been shown that Tyr398 and Tyr435 form an aromatic cage responsible for interaction with the aromatic part of the inhibitor. Ile199 is characterized as being structurally responsible for the selectivity towards inhibitors, which confirms the experimentally obtained results [2]. The binding free energies, obtained using MM-GBSA tools, reveal that selegiline binds better than rasagiline, being consistent with the experimental IC_{50} values [3].



Quantum-chemical analysis employing the enzyme cluster model suggests a completely new chemical mechanism of MAO inhibition through a 3-step reaction, whereby the first step determines the overall reaction rate in which FAD cleaves the hydride ion from the inhibitor's α-methylene group, being in a complete analogy with the MAO catalytic mechanism [4]. The obtained reaction profiles and the final structure of the inhibited enzyme are consistent with the experimental data [1,2]. The obtained results provide new guidelines for the development of more efficient and more effective MAO B inhibitors for clinical use in the fight against neurodegenerative diseases.

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.

L 10. Conformational analysis of fused ring systems using tensor decomposition methods

Karlo Sović and Tomica Hrenar

karlo.sovic@chem.pmf.hr

University of Zagreb Faculty of Science, Department of Chemistry, Division of Physical Chemistry, Horvatovac 102A, Zagreb, 10000

A new procedure for full conformational analysis [1] comprising statistical analysis of molecular dynamics trajectory was applied on fused ring systems like decalin, bicyclo[3.3.0]octane and bicyclo[2.2.0]hexane. This method includes a coordinate space sampling using molecular dynamics simulations with *on-the-fly* calculation of forces, which serves as a sampling space for locating the initial guess structures for further geometry optimization at a higher level of calculation and conformer clustering. The initial guess structures are extracted from those points in phase space which are strict local maxima in a probability distribution of molecular geometry coordinates.

Idea behind this is that during the molecular dynamics run, the investigated molecule would statistically spend more time in and closely around the minima points on the potential energy surface and that, consequently, the probability distribution of the molecular structures in these points of the phase space would have a strict local maxima. Dimensionality of this search is firstly reduced using 2nd-order tensor decomposition tool principal component analysis on the internal coordinate space of investigated molecule. In this reduced space of score values, *n*-dimensional probability distribution is generated and subjected to a procedure for finding all strict local maxima. Further investigation of this method included multi-way analysis of temperature dependent trajectories for fused ring systems using fixed total number of steps in molecular dynamics runs for comparison of obtained conformational spaces. Molecular dynamics simulations were performed using our own program ***qcc*** [2] where the forces were calculated using the PM7 method [3] implemented in MOPAC2016 [4] and numerical integration with the Velocity Verlet algorithm. Multi-way analysis of trajectories was performed using our own program ***moonee*** [5].

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. Primožić, D. Fijan, M. Majerić Elenkov, *Phys. Chem. Chem. Phys.* **19** (2017) 31706.

[2] T. Hrenar, ***qcc***, Quantum Chemistry Code, rev 0.6826-01646.

[3] J. J. P. Stewart, *J. Mol. Modeling* **19** (2013) 1-32.

[4] MOPAC2016, James J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA, HTTP://OpenMOPAC.net (2016).

[5] T. Hrenar, ***moonee***, Code for Manipulation and Analysis of Multi- and Univariate Data, rev 0.6826-03952.

Posters

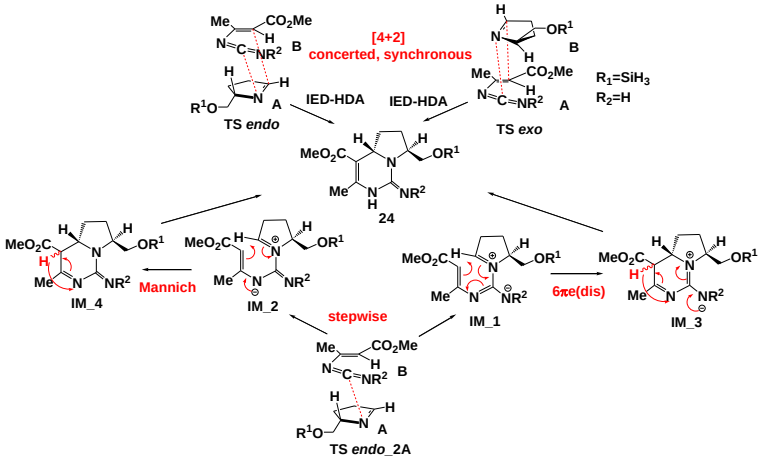
P 1. DFT study of Diels-Alder cycloaddition process through the *endo*- or *exo*- transition states of vinyl carbodiimides with *N*-alkyl imines

Akmaral Kussayeva, Zoran Glasovac and Davor Margetić

akmaral.kussayeva@irb.hr

Ruđer Bošković Institute, Bijenička 54, Zagreb, Croatia

Guanidines are commonly occurring functionality in nature and amino acid arginine plays an important role in biosynthesis of proteins [1]. Various synthetic methods were employed in synthesis of guanidines, and cycloaddition reactions involving guanidines and cycloaddition reactions employed in the synthesis of cyclic guanidines are not well explored [2]. Here we present the results of computational study of Diels-Alder cycloadditions of vinyl carbodiimides with *N*-alkyl imines which were used in synthesis of bicyclic guanidines, but the mechanism was not fully investigated [3]. DFT calculations using the B3LYP hybrid functional and 6-31G(d) basis set indicate that the asynchronous concerted [4+2] cycloaddition process proceeds through the *endo*- or *exo*- transition states.



Mechanism of the cycloaddition reaction between *N*-alkylimine A and vinyl carbodiimide B

References:

[1] D. A. Bender, Amino Acid Metabolism, Wiley-Blackwell, Chichester, 2012, pp. 157-223.

[2] D. Margetić, Cycloadditions of guanidines, in: Cycloaddition Reactions: Advances in Research and Applications, D. Margetić, (Ed.), Nova Science Publishers, New York, 2019.

[3] M. A. Arnold, K. A. Day, S. G. Durón, D. Y. Gin, *J. Am. Chem. Soc.* **128** (2006) 13255-13260.

P 2. Two-state reactivity in radical scavenging by ferulic acid

Ana Amić[a] and Dejan Milenković[b]

aamic@kemija.unios.hr

[a]Department of Chemistry, Josip Juraj Strossmayer University of Osijek,
Ulica cara Hadrijana 8a, 31000 Osijek, Croatia
[b]Bioengineering Research and Development Center,
P. Stojanovića 6, 34000 Kragujevac, Serbia

Ferulic acid (FA), phenolics abundant in plant derived diet and highly bioavailable, may protect cells from damage caused by overproduction of radical species. By scavenging a radical (*via* HAT, PCET, SET-PT or SPLET mechanism) FA produces phenoxyl radical which is able to scavenge another radical by radical-radical coupling mechanism that occurs on two potential energy surfaces (PES), the phenomenon known as the two-state reactivity [1]. Since the C5 site of FA phenoxyl radical is the most reactive site for nucleophilic attack we chose the C5–•OH distance as the scan coordinate (Figure 1). All calculations were performed at M06-2X/6-311++G(d,p) level of theory. Singlet state energy continuously decreases from reactants to product, whereas in the triplet spin states reactants and product are separated by an energy barrier, i.e., transition state (TS), confirmed by IRC calculation. Reactants are more stable in the triplet state. As they approach each other, the energy slightly increases up to the spin crossing point (SCP) between the two PES, where spin inversion occurs, providing lower energy pathway towards a much more stable singlet product. Reaction rate for the first (PCET) and second (radical-radical coupling) mechanism was calculated.

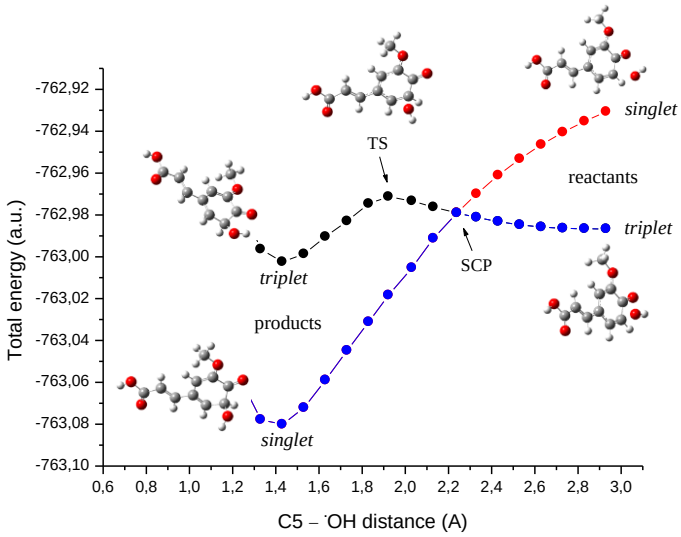


Figure 1. Energy profiles for •OH-phenoxyl radical coupling pathways in the singlet (red line) and triplet (black line) states. Blue line indicates suggested reaction path.

References:

[1] (a) D. Schröder, S. Shaik, H. Schwarz, Acc. Chem. Res. 33 (2000) 139–145; (b) J. Tošović, S. Marković, *Food Chem*. **278** (2019) 469–475.

P 3. A DFT study of gas-phase basicity of cyclic guanidine derivatives

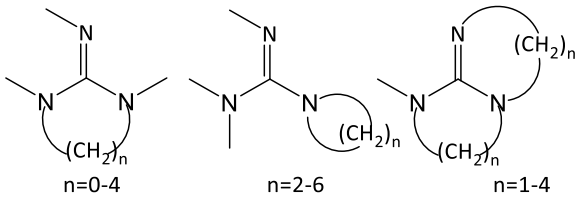
Anamarija Briš, Zoran Glasovac and Davor Margetić

abris@irb.hr

Ruđer Bošković Institute, Bijenička 54, Zagreb, Croatia

Natural and synthetic guanidines are drawing a much interest due to their interesting physico-chemical properties [1]. Guanidines are commonly occurring functionality in nature, therefore, a lot of research has been done in bioorganic chemistry with the aim to discover and design pharmacologically active guanidine derivatives [2]. Also, the very high basicity (superbasicity) of neutral organic guanidine compounds is commonly employed in homogeneous catalysis [1]. There are already many different studies on basicity of different guanidine derivatives with the focus on finding new organic superbases and developing synthesis of those compounds [3].

Herein, we report our methodical study of the gas-phase basicity (GB) of various cyclic guanidine derivatives by Density Functional Theory (DFT) calculations. Considered guanidines differ in the number of nitrogen atoms incorporated in heterocyclic rings as well as in the size of heterocyclic rings (Scheme 1). To locate the most stable structures of the neutral and protonated forms, a set of possible conformations were optimized. The most important structural parameters beneficially contributing to the stability of the structure are identified.



Scheme 1. Schematic representation of the studied guanidine derivatives

This work was supported by the Ministry of Science, Education and Sport of Croatia (grant No. HrZZ IP-2018-01-3298 CycloGu).

References:

[1] D. Margetić, Physico-Chemical Properties of Organosuperbases, in Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts, T. Ishikawa, (Ed.), Wiley, 2009, Chichester, pp: 9-48.

[2] R. G. S. Berlinck, S. Romminger, *Nat. Prod. Rep.* **33** (2016) 456-490.

[3] V. Štrukil, I. Antol, Z. Glasovac, *Croat. Chem. Acta* **87** (2014) 423-430; Z. Glasovac, F. Pavošević, V. Štrukil, M. Eckert-Maksić, M. Schlangen, R. Kretschmer, *Int. J. Mass Spect.* **354/355** (2013) 113-122; Z. Glasovac, M. Eckert-Maksić, Z. B. Maksić, *New J. Chem.* **33** (2009) 588-597.

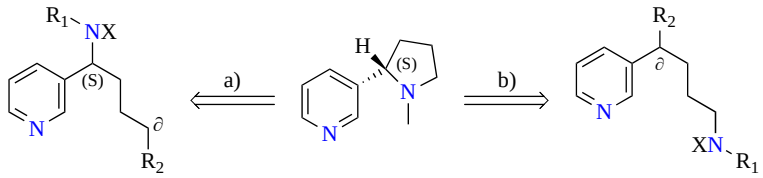
P 4. Role of substituents in Hofmann-Löffler-Freytag synthesis of nicotine. A quantum chemical study

Davor Šakić and Sofia Shkunnikova

dsakic@pharma.hr

University of Zagreb, Faculty of Pharmacy and Biochemistry

Recently, synthesis of S-nicotine has been achieved by using Hofmann-Löffler-Freytag (HLF) methodology [1]. Original procedure using the same methodology has been done at the beginning of the 20th century, but the products were a racemic mixture [2]. Crucial step in the HLF reaction pathway is hydrogen atom transfer (HAT) from the *N*-radical to *C*-radical. Del Castillo and Muniz have achieved retention of stereoconfiguration by using a protective group on nitrogen and an additional activation of primary C atom via O-methylation.



Retrosynthetic C-N bond disconnection

In this work we quantified substitution effects in the HAT step of the reaction on both nitrogen and carbon atom in order to find better synthetic routes both for the original (racemic mixture) product and the stereoselective one. In this study we will focus on the details of the rate determining HAT step. Earlier work [3] was focused exclusively on defining relative *N*-centered and *C*-centered radical stabilization energies (RSE) between commonly used fragments in this field, which can be used to estimate of the thermodynamics of the reaction. Our focus is now on defining energy barriers of the intermolecular HAT reactions of model substituted amines with ethane and reactions of model substituted alkanes with methylamine. Obtained results are then used to narrow down potentially successful substituents for different precursors to nicotine synthesis. Intramolecular HAT reaction of Löffler and Muniz are compared, and more efficient synthesis routes are presented.

References:

[1] E. Del Castillo, K. Muniz, *Org. Lett*. **21** (2019) 705–708.

[2] K. Löffler, S. Kober, *Chem. Ber*. **42** (1909) 3431–3438.

[3] D. Šakić, H. Zipse, *Adv. Synth. Catal.* **358** (2016) 3983–3991.

P 5. Synthesis and electrochemistry of switchable NIR dyes based on triarylamine-anthracene containing complexes

Eduard Kovalski,[a] Marcus Korb,[a,b] Paul J. Low[b] and Alexander Hildebrandt[a]

eduard.kovalski@s2014.tu-chemnitz.de

[a]Technische Universität Chemnitz, Faculty of Natural Sciences, Institute of Chemistry, Inorganic Chemistry, Straße der Nationen 62, 09107 Chemnitz, Germany
[b]University of Western Australia, School of Molecular Science, 35 Stirling Highway, Crawley, Perth, Western Australia 6009, Australia.

The combination of triarylamines and anthracene derivatives led to dyes which display intense π-π* transitions in the visible spectrum [1-2]. In this work, the π-system was extended across an alkyne bridge to metal containing moieties and therefore introduce an acceptor to this electron-rich system. By this strategy we were able to obtain a donor-π-acceptor Ru-based dye whose π-π* transitions exhibit charge transfer character in the mono- and tricationic oxidation state [3]. Furthermore, time dependent (TD)-DFT calculations based on the optimised structures were performed and gave insight into the nature of its electronic transitions. Additionally first studies on platinum complexes of the triarylamine-anthracenes were performed to further increase the understanding of this system's nature and electrochemistry.

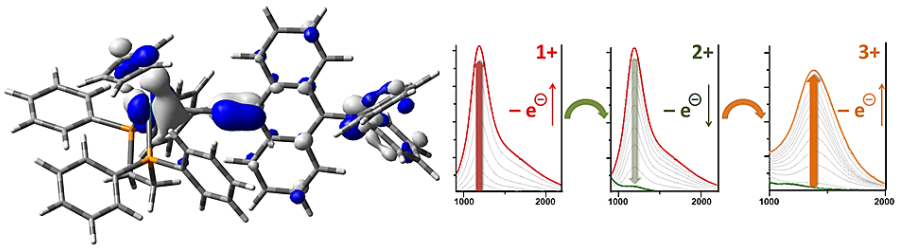


Figure 1. TD-DFT calculation (left) and NIR spectra (right) of the ruthenium halfsandwich.

References:

[1] M. A. Fox, R. L. Roberts, W. M. Khairul, F. Hartl, P. J. Low, *J. Organomet. Chem.* **692** *(*2007) 3277–3290.

[2] W. Kaim, *Coord. Chem. Rev.* **255** (2011) 2503–2513.

[3] E. Kovalski, M. Korb, A. Hildebrandt, *Eur. J. Inorg. Chem.* **2018** (2018) 671–675.

P 6. Computational study of free radical reactions with halogenated organic molecules in aqueous solutions

Ivana Nikšić-Franjić and Ivan Ljubić

iniksicf@irb.hr

Department of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia

Free radical reactions in aqueous media typically exhibit a rich variety of fundamentally important reaction mechanisms in close competition. In the focus of our research are reactions of several radicals, such as: $^{\bullet}CH(CH_3)NH_2$, $^{\bullet}CH(CH_3)NHCH_3$, $^{\bullet}CH(COO^-)NH_2$ and $H^{\bullet}$ that take place in non-buffered and buffered (bicarbonate or phosphate) aqueous media. We present theoretical studies of the radical reactions with various haloorganic substrates, such as monohaloacetates (chloroacetate, bromoacetate, and iodoacetate) and a modified nucleobase 5-bromouracil. The reaction mechanisms and rates are computed in the framework of density functional theory in conjunction with the polarizable continuum model (PCM) for an implicit description of the water solvent [1–3]. Of special interest is a possibility that the reduction of the haloorganic molecules by the radicals could follow the proton-coupled electron transfer (PCET) route. PCET is a ubiquitous reaction mechanism that is of vast importance to energy conversion in biological and man-made processes as it normally provides the kinetically most favorable means of transfer of the elementary charge (Fig. 1). The prospect of PCET occurring in these systems is fascinating because this would imply disintegration of the H atom to the constituting proton and electron thereby representing the most fundamental instance of the process. The pathways that are expected to be in competition with the PCET are hydrogen transfer (HAT), the direct abstraction of the halogen atoms, substitutions and additions. Especially indicative of the PCET would be increase in the dehalogenation yields in the presence of the basic buffer anions, which fulfill the role of external proton acceptors thus promoting the PCET pathway.

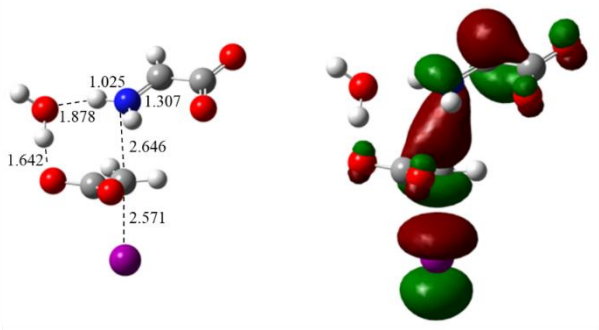


Figure 1. The PCET/H_2O transition state and its singly occupied molecular orbital (SOMO) in the reaction of $^{\bullet}CH(COO^-)NH_2$ with iodoacetate (distances in Å).

References:

[1] I. Džeba, M. Bonifačić, I. Nikšić-Franjić, I. Ljubić, *Phys. Chem. Chem. Phys.* **20** (2018) 19829–19840.

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

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

P 7. Structure and color expression in anthocyanin-based natural dyes: a computational insight

Mariami Rusishvili,[a] Luca Grisanti,[a,b] Sara Laporte,[a] Alessandra Magistrato[c] and Stefano Baroni[a]

lgrisant@irb.hr

[a]Scuola Internazionale Superiore di Studi Avanzati (SISSA), via Bonomea, 265 – 34136 Trieste Italy
[b]Institut Ruđer Bošković (IRB), Bijenička cesta 54 - 10000 Zagreb Croatia
[c]CNR-IOM, via Bonomea, 265 - 34136 Trieste Italy

Anthocyanins are among the most interesting organic dyes in nature, which, depending on the chemical environment (such as acidity and co-pigmentation), give rise to a variety of colors and shades and are responsible for most of the natural hues in the red-purple-blue gamut [1]. The presence of metal also plays a very important role. In spite of the ubiquity and potential applications of anthocyanins in industry, the molecular mechanisms underlying their exceptional photophysical versatility is not yet fully understood. I present the application of use a newly developed multiscale modeling protocol [2] to reveal the intricate relationship existing between the electronic and geometrical factors that determine the optical properties and hence the color function of anthocyanins in a broad pH range (1 to 9) of cyanidin-3-glucoside in water solution, as a prototypical model system. The control on the optical properties is then obtained by addressing not only the charge state (positive flavylium cation, neutral and negative bases) of the relevant chemical species, but also the different tautomers of each charged state. For each species, detailed optical information is obtained by addressing the properties of different conformers, characterized by the slow dynamics of a few internal degrees of freedom. Our study unambiguously reveals that a subtle combination of different structural and electronic traits controls color expression, such as dihedral angles between aromatic moieties, the nature of the bond connecting the two, and the overall charge state of the molecule [3]. Besides, I will introduce some more recent results on metal complexes.

References:

[1] P. Trouillas, J. C. Sancho-García, V. De Freitas, J. Gierschner, M. Otyepka, O. Dangles, *Chem. Rev.* **116** (2016) 4937.

[2] I. Timrov, M. Micciarelli, M. Rosa, A. Calzolari, S. Baroni, *J. Chem. Theory Comput.* **12** (2016) 4423; M. Rosa, M. Micciarelli, Alessandro Laio, S. Baroni, *J. Chem. Theory Comput.* **12** (2016) 4385; M. Rusishvili et. al., *in preparation*.

[3] M. Rusishvili, L. Grisanti, S. Laporte, M. Micciarelli, M. Rosa, R. J. Robbins, T. Collins, A. Magistrato, S. Baroni, *Phys. Chem. Chem. Phys.* (2019) Advance Article, *in press*, doi: 10.1039/C9CP00747D.

P 8. Direct transformation of alkynes to nitriles: quantum-chemical study of the reaction mechanism

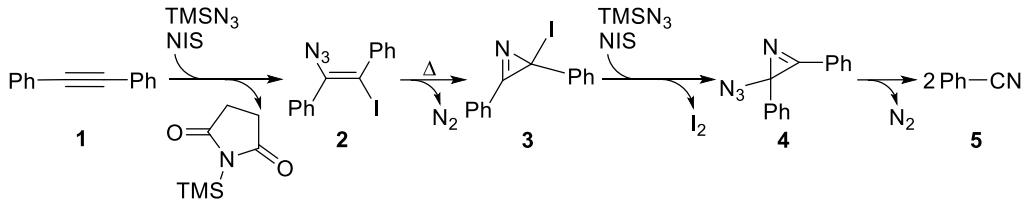
Lucija Hok and Robert Vianello

lucija.hok@irb.hr

Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia

Cleavage of carbon-carbon triple bond is considered to be one of the most challenging targets in modern organic synthesis. Most of the existing methods rely on the oxidative cleavage with toxic organometallic catalysts under harsh reaction conditions [1], which makes their application less desirable. Recently, Yanada et al. [2] reported a metal-free direct cleavage of internal alkynes to nitriles using trimethylsilylazide ($TMSN_3$) as the nitrogen source. Inspired by these experimental advances, in this work, we used density functional theory computations to clarify the mechanism of the mentioned transformation. All structures were fully optimized by the M06-2X/6-31+G(d) model. To account for the solvent effects, Gibbs energies of solvation with acetonitrile were determined using the SMD implicit continuum model at the same level of theory.

After inspecting several mechanistic possibilities, our results show that the cleavage of the C-C triple bond in alkyne **1** is a downhill process ($\Delta_rG \approx$ -193 kcal mol^{-1}), which occurs in six steps (Scheme 1). In the first step, a simultaneous addition of azide from $TMSN_3$ and iodine from *N*-iodosuccinimide (NIS) to C≡C, leads to the formation of iodo vinyl azide **2**. The intermediate **2** undergoes internal rearrangement to obtain 2-iodo-2*H*-azirine **3** which is accompanied by the release of the nitrogen gas under the thermal condition. Addition of $TMSN_3$ to the double bond in **3** with a simultaneous loss of iodine, generates azide azirine **4**. The final cyano compounds **5** are obtained in the last, rate-determining step ($\Delta G^{\#}$ = 33.5 kcal mol^{-1}) which includes breaking the bond in azide moiety and the fragmentation of the unsaturated heterocycle in azide azirine **4**. The obtained free-energy profiles are in agreement with Yanada's experimental results [2], though further investigations on various internal alkynes in solvents with different polarity are in progress.



Scheme 1. Reaction mechanism of the triple bond cleavage in alkyne **1**.

References:

[1] G. Yan, Y. Zhang , J. Wang, *Adv. Synth. Catal.* **359** (2017) 4068-4105.

[2] N. Okamoto, M. Ishikura, R. Yanada, *Org. Lett.* **15** (2013) 2571-2573.

P 9. Computational study of glycerol binding within the active site of coenzyme B_{12}-dependent diol dehydratase

Luka Bilić, Danijela Barić, Radha Dilip Banhatti, David Matthew Smith and Borislav Kovačević

lbilic@irb.hr

Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

Microbial conversion of crude glycerol (GOL), waste from biofuel production, into compounds of greater industrial value could solve technical difficulties encountered by conventional means of chemical conversion [1]. During microbial conversion the first step GOL undergoes is dehydration by enzymes dehydratases into 3-hydroxylpropionaldehyde (3HPA) [2-3]. Two classes of dehydratases can catalyze dehydration of GOL, B_{12}-independent and B_{12}-dependent dehydratases, from which B_{12}-dependent class is more often used due to its tolerance to aerobic conditions [4]. However, a peculiar property of B_{12}-dependent dehydratases is that the substrate GOL also acts as an irreversible inhibitor [5]. Based on the B_{12}-dependent diol dehydratase (B_{12}-dDDH) crystal structure with GOL (PDB code: 3AUJ) K.Yoshizawa et.al. concluded that the geometry of such bound GOL enables radical reorganization causing inhibition [6]. However, in the recent study on similar enzyme B_{12}-dependent glycerol dehydratase employing classical molecular dynamics we observed GOL in a different geometry [7]. Here we present a detailed study of the GOL geometries within the active site of B_{12}-dDDH and consider implications of our findings for the mechanism of substrate induced inactivation.

References:

[1] Z. Chen, D. Liu, *Biotechnol. Biofuels* **9** (2016) 205.

[2] T. Toraya, *Cell. Mol. Life Sci.* **57** (2000) 106–127.

[3] T. Toraya, *Chem. Rev.* **103** (2003) 2095–2127.

[4] W. Jiang, S. Wang, Y. Wang, B. Fang, *Biotechnol. Biofuels* **9** (2016) 57.

[5] W. W. Bachovchin, J. R. G. Eagar, K. W. Moore, J. H. Richards, *Biochemistry* **16** (1977) 1082−1092.

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

[7] B. Kovačević, D. Barić, D. Babić, L. Bilić, M. Hanževački, G. M. Sandala, L. Radom, D. M. Smith, *J. Am. Chem. Soc*. **140** (2018) 8487–8496.

P 10. DFT study of C–H bond activation in 4,4'-bis(*N,N*-dimethylamino)-azobenzene by palladium(II) acetate

Marina Juribašić Kulcsár, Darko Babić and Manda Ćurić

marina.juribasic@irb.hr

Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia

An important class of catalytic reactions are palladium-mediated processes for which the C–H bond activation, *i.e*. cyclopalladation, is the key step [1]. Among palladium catalysts, trimeric palladium(II) acetate is the most common [1]. Widely accepted mechanism for the C–H bond activation by $[Pd(OAc)_2]_3$ involves the C–H bond activation by a Lewis-acidic metal *via* agostic interaction with the exiting proton and simultaneous acceptance of this proton by a basic ligand *via* an intramolecular hydrogen bond [2]. Reaction is initiated by opening of the trimer $[Pd(OAc)_2]_3$ by either the substrate or an additive, and this process yields a trimeric, dimeric or even monomeric acetate species [2,3]. Similar to the chloride precursors [4], the intermediate complex should be formed by coordination of the substrate to $[Pd(OAc)_2]_3$ before any C–H bond cleavage takes place.

Herein, we present a computational study of activation of two C–H bonds in a symmetric azobenzene substrate, 4,4'-bis(*N,N*-dimethylamino)azobenzene, and its monocyclo-palladated complex yielding mono- and dicyclopalladated products, respectively.

References:

[1] (a) M. Albrecht, *Chem. Rev*. **110** (2010) 576-623; (b) *Palladacycles: Synthesis, Characterization and Applications* (Eds. J. Dupont, M. Pfeffer), Wiley–VCH, Weinheim, 2008; (c) J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev*. **105** (2005) 2527-2572.

[2] (a) D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* **117** (2017) 8649-8709; (b) D. Lapointe, K. Fagnou, *Chem. Lett.* **39** (2010) 1119-1126.

[3] (a) B. E. Haines, J. F. Berry, J.-Q. Yu, D. G. Musaev, *ACS Catal.* **6** (2016) 829-839; (b) J. Váňa, J. Lang, M. Šoltésová, J. Hanusek, A. Růžička, M. Sedlák, J. Roithová, *Dalton Trans.* **46** (2017) 16269-16275; (c) A. Bjelopetrović, S. Lukin, I. Halasz, K. Užarević, I. Đilović, D. Barišić, A. Budimir, M. Juribašić Kulcsár, M. Ćurić, *Chem. Eur. J.* **24** (2018) 10672-10682.

[4] (a) D. Babić, M. Ćurić, D. M. Smith, *J. Organomet. Chem.* **696** (2011) 661-669; (b) M. Juribašić, A. Budimir, S. Kazazić, M. Ćurić, *Inorg. Chem*. **52** (2013) 12749-12757.

P 11. Exploring the stable conformations during binding and unbinding of coenzyme A in pyruvate formate-lyase

Marko Hanževački,[a,b] Karmen Čondić-Jurkić,[a] Radha Dilip Banhatti,[a] Ana-Sunčana Smith[a,b] and David Matthew Smith[a]

Marko.Hanzevacki@irb.hr

[a]Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, Zagreb, Croatia
[b]PULS Group, FAU, Department of Physics, IZNF Cauerstraße 3, 91058 Erlangen, Germany

Pyruvate formate-lyase (PFL) is a glycyl radical enzyme that converts pyruvate and coenzyme A (CoA) into formate and acetyl-CoA in two half-reactions [1]. Recently we showed that the acetylation of PFL active site in the 1st half-reaction induces subtle conformational changes of distal region at the protein surface where a potential CoA entry channel was identified [2]. Entry of CoA into the active site is crucial for the start of the 2nd half-reaction and the overall catalytic cycle is terminated when acetyl transfer to CoA is successful, thereby enabling CoA to dissociate with the attached acyl group from the active site.

Using steered molecular dynamics (SMD) simulations, performed on the acetylated and non-acetylated monomeric PFL model systems, we first of all investigate the possible entry pathways of CoA into the active site and examine the probability of CoA entry to occur through the previously identified channel. We then perform unrestrained molecular dynamics simulations starting from the final structures obtained from SMD and examine the existence of possible bound states of CoA in the near vicinity of the active site. Detailed study of the unrestrained dissociation processes reveal the presence of stable and reactive bound states of CoA close to the active site. The chemical outcomes on the catalysis are discussed. Umbrella sampling, performed on snapshots from unrestrained dynamics, confirms bound states at a position ideal for triggering the 2nd half-reaction, provided CoA goes through the identified channel.

Using one of the acetylated model system that has a higher probability for stable bound state, we present in brief the difficulties and issues that arise in estimating potential of mean force for such process as this, where a flexible substrate enters the active site of an enzyme which also entails an unusually long reaction coordinate of approximately 30 Å.

References:

[1] (a) A. Becker, K. Fritz-Wolf, W. Kabsch, J. Knappe, S. Schultz, A. F. V. Wagner, *Nat. Struct. Bio.* **6** (1999) 969-975; (b) A. Becker, W. Kabsch, *J. Biol. Chem.* **277** (2002) 40036-40042.

[2] M. Hanževački, K. Čondić-Jurkić, R. Dilip Banhatti, A.-S. Smith, D. M. Smith, *Chem. Eur. J.* (2019) accepted, DOI: 10.1002/chem.201900663.

P 12. Human DPP III - Keap1 interactions

Marko Tomin and Sanja Tomić

marko.tomin@irb.hr

Laboratory for Protein Biochemistry and Molecular Modelling, Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia

Kelch-like ECH associated protein 1 (Keap1) is a cellular sensor for oxidative stress and a negative regulator of the nuclear erythroid 2–related factor 2 (Nrf2). A cytosolic metallopeptidase dipeptidyl peptidase III (DPP III) has been shown to interact with the Kelch domain of Keap1 [1] via the ETGE motif located in a flexible loop belonging to the upper domain [2]. Using the previously developed models of the DPP III - Keap1 complex [3], we are trying to identify the conformation of the ETGE-containing loop in the complex, as well as the work required to achieve the active conformation for Keap1 binding.

Although the DPP III - Keap1 interaction through the conserved ETGE motif has been experimentally confirmed [4], the extensive MD simulations of the human DPP [2,5] suggest that the loop is attached to the upper domain of DPP III at all times. In order to quantify the thermodynamic barrier and the work required for the loop translocation, as well as the subsequent complex formation, we have used steered MD simulations, adaptive steered MD simulations and conventional MD simulations in conjunction with the MM-PBSA energy calculations.

References:

[1] Y. Liu, J. T. Kern, J. R. Walker, J. A. Johnson, P. G. Schultz, H. Luesch, *PNAS* **104** (2006) 5205-5210.

[2] A. Tomić, M. González, S. Tomić, *J. Chem. Inf. Model* **52** (2012) 1583-1594.

[3] M. Gundić, A. Tomić, R. C. Wade, M. Matovina, Z. Karačić, S. Kazazić, S. Tomić, *Croat. Chem. Acta* **89** (2016) 217-228.

[4] K. Lu, A. L. Alcivar, J. Ma, T. K. Foo, S. Zywea, A. Mahdi, *Cancer Res.* **77** (2017) 2881-2892.

[5] A. Tomić, M. Berynskyy, R. C. Wade, S. Tomić, *Mol. biosys*. **11** (2015) 3068-3080.

P 13. *Ab initio* calculation of dielectric function for plasmonic metal alloys

Matej Bubaš and Jordi Sancho Parramon

mbubas@irb.hr

Ruđer Bošković Institute, Zagreb, Croatia

Electromagnetic response of material requires knowledge of dielectric function in the spectral range of interest. A dielectric function can be modified by the shape and thickness of materials such as nanoparticles and thin films [1]. Noble metals such as gold and silver are known plasmonic materials, and show promise in enhancing light harvesting efficacy and water splitting [2].

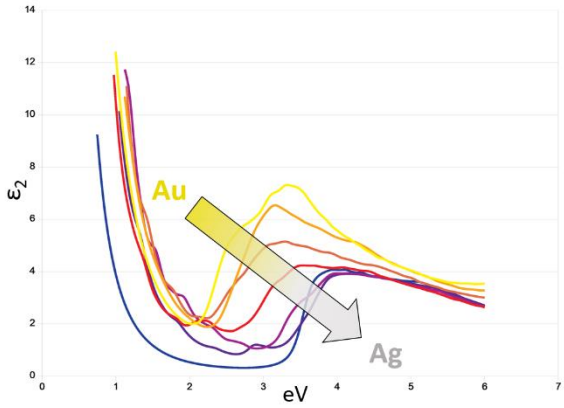


Figure 1. Change of calculated ε_2 with Au-Ag alloy composition

For alloy based materials, the shape of dielectric function can be changed by modifying the alloy composition. This can be used to tune the absorption of a material in a desired spectral range [3]. Experimentally exploring the compositional dependence of dielectric function can be time demanding and expensive. Therefore, approaching this problem computationally, using density functional theory (DFT), could prove to be advantageous. Currently there are few studies focusing on alloy dielectric function calculations using DFT, especially for noble metals. For that reason, we are presenting a theoretical framework for dielectric function calculation of noble metal alloys, along with some preliminary results.

References:

[1] (a) S. Eustis, M. A. El-Sayed, *Chem. Soc. Rev.* **35** (2006) 209-217; (b) S. Laref, J. Cao, A. Asaduzzaman, K. Runge, P. Deymier, R. W. Ziolkowski, M. Miyawaki, K. Muralidharan, *Opt. Express* **21** (2013) 11827-11838.

[2] X. Shi, K. Ueno, T. Oshikiri, *Nat. Nanotech.* **13** (2018) 953-958.

[3] O. Peña-Rodríguez, M. Caro, A. Rivera, J. Olivares, J. M. Perlado, A. Caro, *Opt. Mater. Express* **4** (2014) 403-410.

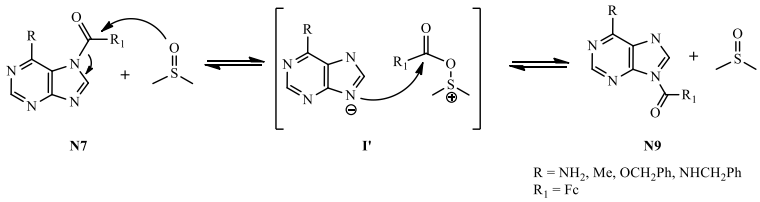
P 14. Reaction mechanism of transferrocenoylation of purines. A DFT study

Mateja Toma, Lucija Božičević, Davor Šakić and Valerije Vrček

mtoma@pharma.hr

Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

Ferrocenoyl-purines are organometallic derivatives combining redox-active and biogenic parts. In the reaction of ferrocenoyl chloride and purine anion, two isomers (N7 and N9) were formed, with the ratio depending on the C6-purine substituent. We found that each of the isomers (N7 and N9) in DMSO undergoes transacylation reaction with the ratio approaching to the equilibrium state. The mechanism of transacylation in ferrocenoylated purines (R = NH_2, CH_3, O-CH_2Ph, NH-CH_2Ph) starts with the nucleophilic attack of the sulfur atom of DMSO on the carbonyl group at the N7-(or N9) position, and follows the S_N2-like mechanism. The reaction mechanism was explored by the use of DFT models. To locate stationary points (transition states and minima), we introduced two explicit molecules of DMSO by the stochastic procedure. The conformational analysis revealed the relative energy range of approximately 100 kJ/mol, which shows that searching for the optimal position of explicit solvent molecules is prone to large errors. Gibbs free energy barriers were calculated at the SMD-M06L/6-311+G(d,p)/SDD and SMD-B3LYP/6-31G(d)/SDD level. In the case of adenine (R = NH_2), the introduction of the first explicit DMSO molecule sets the barrier to $\Delta G^{\ddagger} > 130$ kJ/mol, but the second one lowers the energy close to the experimental value: $\Delta G_{exp}^{\ddagger} \approx 104$ kJ/mol, $\Delta G_{calc}^{\ddagger} \approx 108$ kJ/mol (M06L/6-311+G(d,p)/SDD).



Scheme 1. Reaction mechanism of N7/N9 transacylation in ferrocenoyl purines.

P 15. Magnetic interaction of Mn and Cr atoms on Ag(001) modified by graphene adsorption

Mihovil Bosnar,[a] Ivor Lončarić,[a] Predrag Lazić,[a] Igor Žutić[b] and Kirill D. Belashchenko[c]

mbosnar@irb.hr

[a]"Ruđer Bošković" Institute, Bijenička cesta 54, Zagreb, Croatia
[b]University at Buffalo, Buffalo, New York, USA
[c]University of Nebraska-Lincoln, 1400 R St, Lincoln, Nebraska, USA

We study the magnetic exchange between Mn or Cr atoms adsorbed on Ag(001) surface. By fitting DFT results on the Ising model, we show that this interaction is antiferromagnetic in both cases. We also show that when graphene is laid on top of the adatoms, the exchange interaction changes because of the bonding of graphene and the adatoms. For Cr adatoms the result of adsorption is reduction in the magnitude of the exchange parameters, but the character stays the same. For Mn adatoms bonding completely changes the exchange and opens up a possibility of a novel spin ordering.

P 16. Static and dynamic properties of $[C_2Mim][NTf_2]$ ionic liquids

Nataša Vučemilović-Alagić,[a,b] Robert Stepić,[a,b] David Matthew Smith[a,b] and Ana-Sunčana Smith[a,b]

nvucemil@irb.hr

[a]Ruđer Bošković Institute Bijenička cesta 54, Zagreb, Croatia,
[b]PULS Group, Institute for Theoretical Physics, Department of Physics & Cluster of Excellence: Engineering of Advanced Materials, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany

In the last decades it has become a common practice to use ionic liquids (IL) films in the context of catalysis. A particular advantage of these systems is their low vapor pressure and powerful solvation. Understanding the solvent effects both in the context of interface wetting and chemical reactions is vitally important for the technological applications of ILs, however, the understanding of these processes is still not satisfactory. To address this problem, we employ atomistic molecular dynamics (MD) simulations and investigate the behavior of the archetypical imidazolium-based IL $[C_2Mim][NTf_2]$ [1]. We systematically study the role of the IL model introduced through the force field, and determine their static and dynamic properties at interfaces with a hydroxylated sapphire or vacuum. We establish a model which reproduces the experimentally observed X-ray reflectivity, surface tension and diffusion coefficients with reasonable accuracy. We use this model to study the structuring of IL and the changes of its transport properties as a function of the distance from the interface of choice.

References:

[1] Z. Brkljača, M. Klimczak, Z. Miličević, M. Weisser, N. Taccardi, P. Wasserscheid, D. M. Smith, A. Magerl, A.-S. Smith, Complementary Molecular Dynamics and X-ray Reflectivity Study of an Imidazolium-Based Ionic Liquid at a Neutral Sapphire Interface, *J. Phys. Chem. Lett.* **6** (2015) 549–555.

P 17. Mechanism of the water-gas shift reaction in the supported ionic liquid phase

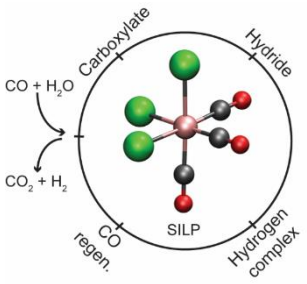
Robert Stepić,[a,b] Christian Wick,[a] Vinzent Strobel,[c] Daniel Berger,[d] Nataša Vučemilović-Alagić,[a,b] Marco Haumann,[c] Peter Wasserscheid,[c] Ana-Sunčana Smith[a,b] and David Matthew Smith[a,b]

rstepic@irb.hr

[a]Institute for Theoretical Physics, FAU, Cauerstraße 3, Erlangen, Germany
[b]Group for Computational Life sciences, RBI, Bijenička cesta 54, Zagreb, Croatia
[c]Lehrstuhl für Chemische Reaktionstechnik, FAU, Egerlandstraße 3, Erlangen, Germany
[d]Helmholtz Institut Erlangen-Nürnberg, Fürther Straße 249, Nürnberg, Germany

Supported ionic liquid phase (SILP) catalysis enables a highly efficient, Ru-based, homogeneously catalyzed water-gas shift reaction (WGSR) between 100°C and 150°C [1]. The active Ru-complexes have been found to exist in imidazolium chloride melts under operating conditions in a dynamic equilibrium, which is dominated by the $[Ru(CO)_3Cl_3]$- complex [2].

We here present state-of-the-art theoretical calculations to elucidate the reaction mechanism of WGSR catalyzed by the anionic transition metal complexes in more detail. We show that the mechanism includes the intermediate formation and degradation of hydrogen chloride, which effectively reduces the high barrier for the formation of the requisite dihydrogen complex. Process of decarboxylation and the formation of a hydride is shown to be the rate limiting step of the reaction.



The hypothesis that the rate-limiting step involves water, enabling the formation of the six membered ring in the transition state leading to significant reduction in the calculated barrier, is supported by using D_2O in continuous catalytic WGSR experiments. The resulting mechanism constitutes a highly competitive alternative to earlier reported generic routes involving nucleophilic addition of hydroxide in the gas phase and in solution [3].

References:

[1] T. Bauer, R. Stepic, P. Wolf, F. Kollhoff, W. Karawacka, C. R. Wick, M. Haumann, P. Wasserscheid, D. M. Smith, A.-S. Smith, J. Libuda, *Catal. Sci. Technol.* **8** (2018) 344-357.

[2] S. Werner, N. Szesni, M. Kaiser, R. W. Fischer, M. Haumann, P. Wasserscheid, *ChemCatChem* **2** (2010) 1399-1402.

[3] R. Stepić, C. R. Wick, V. Strobel, D. Berger, N. Vučemilović-Alagić, M. Haumann, P. Wasserscheid, A.-S. Smith, D. M. Smith, *Angew. Chem. Int. Ed.* **58** (2019) 741-745.

P 18. Saturated fatty acids with different lengths in DOPC phospholipid bilayers - free energy and apparent pK_a calculations

Sanja Škulj and Mario Vazdar

sanja.skulj@irb.hr

Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Zagreb, Croatia

Long chain fatty acids (LCFA) are important nutrients which regulate the storage and energy resources in living systems. LCFAs can diffuse through phospholipid bilayers and affect the biophysical properties of the mitochondrial inner membrane by increasing H^+ conductance across the phospholipid bilayer [1]. LCFAs activate uncoupling proteins (UCPs) embedded in biological membranes – in particular, FAs increase the UCP1 and UCP2 dependent H^+ leak [2,3].

In order to understand the details of the H^+ transport, we considered neutral and deprotonated form of **three LCFA** with different lengths: **myristic** (C14:0), **palmitic** (C16:0) and **stearic** (C20:0) **acid** in dioleoyl-sn-glycero-3-phosphocholine (DOPC) bilayer. We calculated free energy profiles using all atom molecular dynamic (MD) simulation using umbrella sampling technique. Free energy profiles suggest that neutral forms of LCFA are located deeper in DOPC bilayer than deprotonated forms and stabilization inside the bilayer increases with the chain length for both neutral and deprotonated forms. On the other hand, free energies of flip-flop of both neutral and anionic forms are constant upon the prolongation of the fatty acid. Based on the free energy curves, we also calculated apparent fatty acid p$K_{a,app}$ values in the bilayer which are 7.0, 7.2 and 6.3 for myristic, palmitic and stearic acid and are increased by several pK_a units compared to the corresponding pK_a values in water. We found that spontaneous protonation of fatty acid anions takes place in the bilayer interior at ca. 1.4 nm from the bilayer center for all studied fatty acids [4]. Presented results are one step more in the clarification of mechanism of the H^+ transport and could help in future studies of the H^+ transport across more realistic biological membranes.

References:

[1] L. Wojtczak, R. J. Wieckowski, *J. Bioenerg. Biomembr.* **31** (1999) 447-455.

[2] A. Fedorenko, P. V. Lishko, Y. Kirichok, *Cell* **151** (2012) 400-413.

[3] O. Jovanović, A. A. Pashkovskaya, A. Annibal, M. Vazdar, N. Burchardt, A. Sansone, L. Gille, M. Fedorova, C. Ferreri, E. E. Pohl, *Free Radic. Biol. Med.* **89** (2015) 1067-1076.

[4] S. Škulj, M. Vazdar, Calculation of Apparent pKa Values of Saturated Fatty Acids With Different Lengths in DOPC Phospholipid Bilayers, submitted.

P 19. Calculation of redox potential in ferrocene derivatives. The effect of the exact exchange fraction in hybrid DFT methods.

Tea Kuvek, Mateja Toma and Valerije Vrček

tkuvek@student.pharma.hr

Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia

The B3LYP method, the most popular hybrid density functional, is regularly applied in state-of-the-art computational models for predicting redox potentials. Benchmark calculations of absolute reduction potential of ferricinium/ferrocene couple, the IUPAC-proposed reference in nonaqueous solution, include the SMD-B3LYP/6-31G(d)/LanL2TZf protocol [1]. We used this procedure to calculate redox potential for a series of ferrocene derivatives (see Figure).

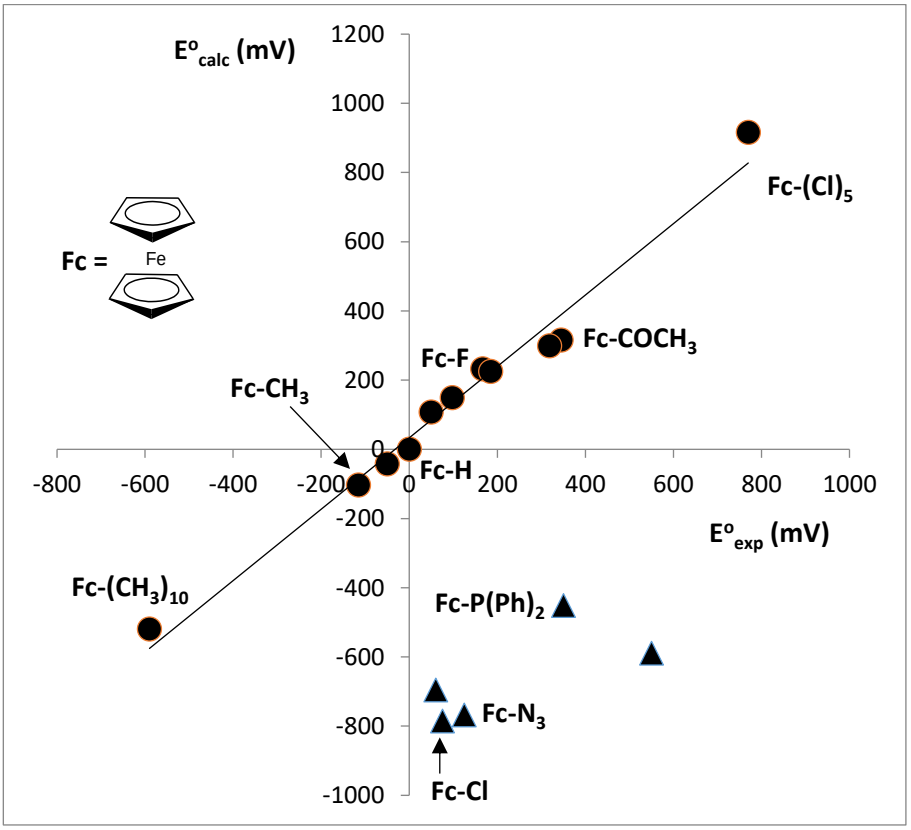


Figure 1. Correlation between experimental and calculated (SMD-B3LYP/6-31G(d)/LanL2TZf method) redox potential for a series of ferrocene derivatives

In a number of cases a significant discrepancy between experimental and calculated data was detected. The cases include substituents bonded to ferrocene system via C, S, N, B, or P atom. Most of them are monosubstituted, some are disubstituted, including *ansa*-derivatives.

The same error appeared in a large number of ferrocene derivatives collected throughout the literature. This DFT method overestimates the stability of oxidized ferrocene species (ferricinium radical). Therefore, the calculated value of redox potential for specific ferrocene derivative is too low, and the compound appears/pretends as an extremely strong reducing agent. The deviation amounts to 1000 mV, which corresponds to energy equivalent of 100 kJ/mol. Three variables were assessed to detect a possible origin of the observed failure: functional, basis set, and solvation model. It comes out that the Hartree-Fock exchange fraction in hybrid DFT methods is the main source of the error.

References:

[1] M. Namazian, C. Y. Lin, M. L. Coote, *J. Chem. Theory Comput*. **6** (2010) 2721-2725.

P 20. Application of machine learning for herbicide characterization

Vesna Pehar,[a] Davor Oršolić[b] and Višnja Stepanić[b,c]

stepanic@irb.hr

[a]Croatian Defense Academy "Dr. Franjo Tuđman", Zagreb, Croatia
[b]Centre of Research Excellence for Marine Bioprospecting – BioProCro
[c]Division of molecular medicine, Ruđer Bošković Institute, Zagreb, Croatia

Herbicides are chemical molecules used for destruction of weeds. Massive usage of herbicides has resulted in two global problems: increase in weed resistance and harmful impact of human health [1, 2]. In order to facilitate development of novel, more specific herbicides and of strategies for impeding the weed resistance, we have carried out extensive *in silico* analysis of the set of herbicides. Herein, we present results revealing links between structural, physicochemical, ADME (Absorption, Distribution, Metabolism, Excretion) and toxic features for herbicides (Figure 1). The analysis has been done by using proper machine learning approaches.

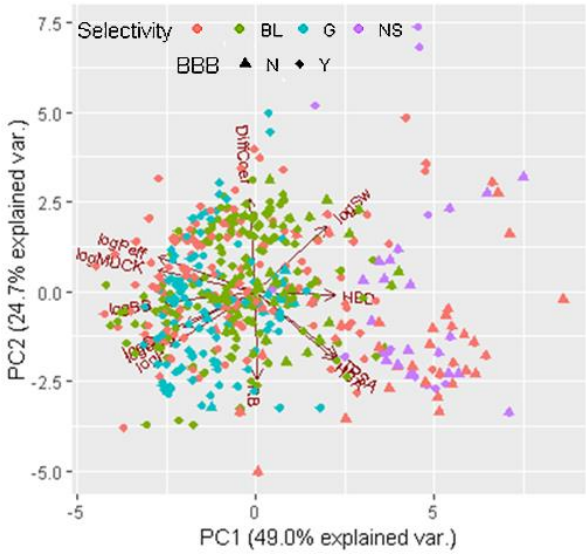


Figure 1. Herbicides in PCA space of calculated permeabilities and important physchem properties and simple structural parameters. BBB (Y or N) denotes compound's ability to penetrate blood-brain barrier. Selectivity classes describe herbicide effectiveness against broadleaved plants (BL), grass species (G) as well as nonselective herbicides (NS).

References:

[1] A. Forouzesh, E. Zand, S. Soufizadeh, S. S. Foroushani, *Weed Res.* **55** (2015) 334-358.

[2] V. I. Lushchak, T. M. Matviishyn, V. V. Husak, J. M. Storey, K. B. Storey, *EXCLI J.* **17** (2018) 1101-1136.

Author index

Notes

Impressum

Name of the conference: *Computational Chemistry Day 2019*
Organizers:
University of Zagreb Faculty of Pharmacy and Biochemistry
Ruđer Bošković Institute
University of Zagreb Faculty of Science
Croatian Chemical Society

Place: University of Zagreb Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, HR-10000, Zagreb, Croatia, EU
Date: May 11, 2019

Abstracts were prepared by the authors.

Publisher: University of Zagreb Faculty of Science
ISBN 978-953-6076-51-2

Organization of the Computational Chemistry Day 2019 was financially supported by:
- The Croatian Science Foundation, through the projects: UIP-2017-05-9537, IP-2014-09-7540, IP-2014-09-3386 and IP-2016-06-1142
- The Ministry of Science and Education of the Republic of Croatia
- The Croatian Academy of Sciences and Arts
- University of Zagreb Faculty of Science, Department of Chemistry
- The Rudjer Boskovic Institute, Zagreb

Sveučilište u Zagrebu Prirodoslovno-matematički fakultet
ISBN 978-953-6076-51-2