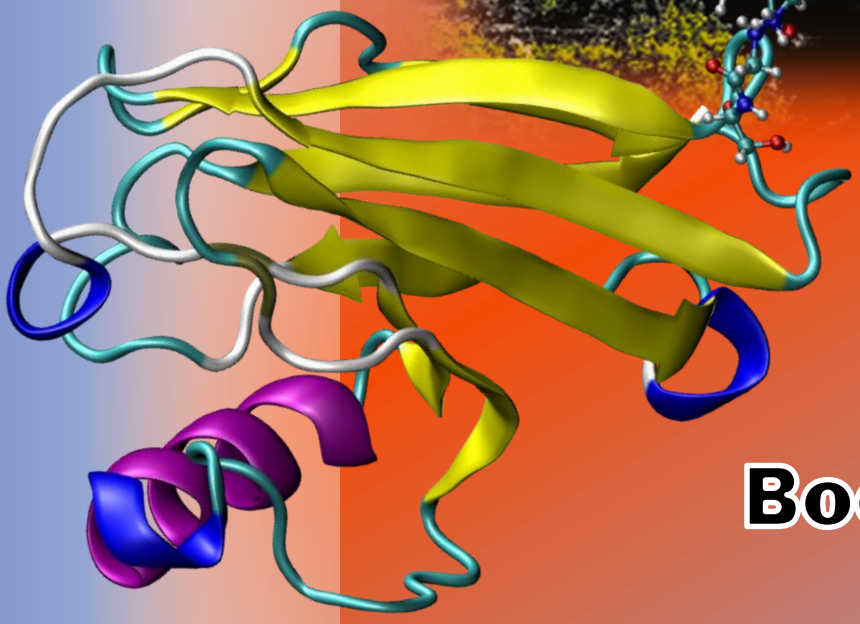
MIB'23

Modeling Interactions in Biomolecules IX

Průhonice, 10th – 14th September 2023



Program & Book of Abstracts

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Contents

Průhonice

Průhonice is a village with a population of 2,120 inhabitants, which lies about 15 km south-eastwards from the Prague city centre. The Průhonice Park, the Castle with its Romanesque Church of the Virgin Mary's birth (originally a chapel) and the Dendrological Garden rank among the most significant monuments of this beautiful place. The first mention of a local community dates back to 1187, depicting the consecration of the Romanesque Chapel (now the Church) of the Virgin Mary's birth, then in 1270 when Zdislav and Oldřich of Průhonice were appointed the Prague Castle burgraves.

The **Průhonice Park** is a UNESCO World Heritage Site and Czech National Historic Landmark. Its area consists of 250 hectares with about 23 km of footpaths. It was founded in 1885 by the Count Arnošt Emanuel Silva-Tarouca who had the whole Castle area rebuilt in the Czech "Neo-Renaissance" style. Průhonice Park is a masterpiece of European landscaping with a unique combination of local and imported exotic tree species. Visitors can see around 1,800 different tree taxa and cultivars. The most famous genus grown in Průhonice Park is rhododendron and a part of the park is also formed by a unique 3-hectare alpine garden with numerous rocks and hillsides where 3,000 alpine plants, perennials, and trees are grown.

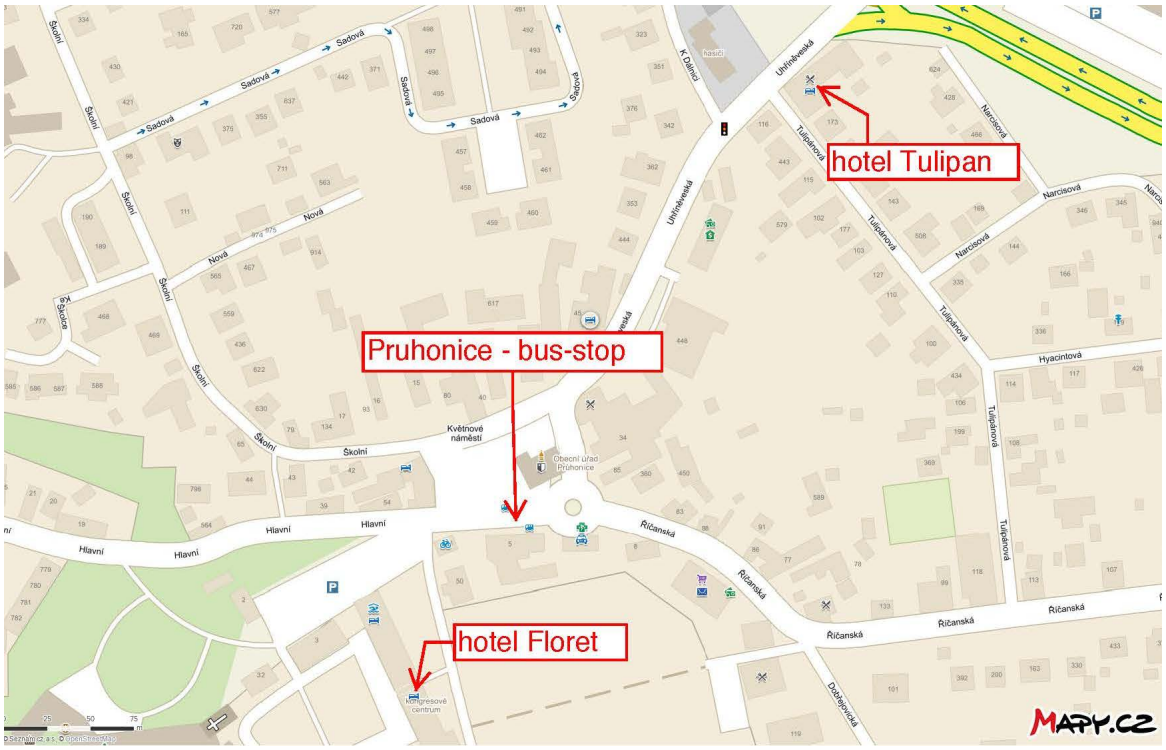
In the mid-seventies of the 20th century the Dendrological Garden was founded in Průhonice and nowadays covers 73 hectares. About 5,000 tree taxa and perennials are concentrated here, making the garden one of the largest ornamental plant collections within the Czech Republic. The garden is uniquely organized with stress placed on individual groups of plants used within the landscaping.

Travel information

The best connection to Prague represents the bus – lines **357**, **363**, and **385**, which takes you to (or from) Opatov, the closest metro station. There you change to metro line C (towards Letňany) going to the city centre and also stopping at the Main Train Station ("Hlavní nádraží"). The Průhonice bus stop is located in the square about 100m from the Cogress Centre (see a map below) and bus departures from Průhonice (towards Opatov) and from Opatov (towards Průhonice) are collected on the following page. Metro operates from around 4:45 a.m. and the last train leaves the terminal station at midnight. Travelling to the Prague centre takes about 40 minutes and a (5-zone) ticket you need costs 50 CZK. It is valid for 90 minutes on any type of public transport from its validation (How to travel around Prague).

For any connection in Prague and its surroundings, you can check online timetable on following webpages: `https://pid.cz/en/find-a-connection` or `https://idos.idnes.cz/en/pid/spojeni` or ask anybody from organizators. We will be happy to help you.

Locations of hotels and the bus stop in Průhonice:



Bus departures from Průhonice towards Opatov:

	357 (16 min)			**363** (16 min)			**385** (7 min)		
	WD	WE		WD	WE		WD	WE	
4			**4**	17 47	45	**4**			**4**
5	43		**5**	29 59	45	**5**	22		**5**
6	14 44		**6**	24 34 54	50	**6**	07 37	39	**6**
7	15 45	20	**7**	04 24 34 59	50	**7**	07 37	39	**7**
8	29	19	**8**	49	49	**8**	07 37	39	**8**
9	19	49	**9**	49	19	**9**	12	39	**9**
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11	19	49	**11**	49	19	**11**	52	39	**11**
12	19	49	**12**	49	19	**12**	52	39	**12**
13	19	49	**13**	49	19	**13**	52	39	**13**
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21	47	47	**21**	18	18	**21**	50	37	**21**
22	47	47	**22**	18	17	**22**	50	37	**22**
23			**23**	29	29	**23**	50	50	**23**

WD - working day, WE -weekend; Travel time is stated in parenthesis

Bus departures from Opatov towards Průhonice:

	357 (15 min)			**363** (16 min)			**385** (7 min)		
	WD	WE		WD	WE		WD	WE	
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19	45	15	**19**	00 15 30	45	**19**	10	00	**19**
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21	45	45	**21**	15	15	**21**	10	10	**21**
22	45	45	**22**	15	15	**22**	12	12	**22**
23	45	45	**23**	15	15	**23**	12	12	**23**
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WD - working day, WE -weekend; Travel time is stated in parenthesis

MIB'23

in memoriam of

Prof. PETER POLITZER

Biography of Prof. Peter Politzer (December 12, 1937 - June 10, 2022)

Neither a one-page bio nor a curriculum vitae can adequately capture the life of Peter Politzer. Such papers give facts but can only hint at the essence of Peter's life. Peter Politzer was born in Prague, Czechoslovakia less than a year before the Munich Pact of late September 1938 was signed by leaders of Great Britain, Germany, France and Italy, granting the ribbon-like band of the Sudetenland in Czechoslovakia to Germany. In March and December of 1939, the Politzer family fled Czechoslovakia in stages with the long-range aim of settling in the United States of America (USA). Their first step to this goal was a year and one half spent in Brazil waiting to be included in the quota to come legally to live and work in the USA. Peter's father was a chemical engineer, first in Czechoslovakia, then in Brazil and then finally in Cleveland, Ohio. His parents Alfred and Anna instilled in Peter by their examples a tremendous work ethic, which Peter carried with him until his final days. Peter's work was his passion. He attended Western Reserve University in Cleveland, Ohio, where he received his B.A. in chemistry in 1960, his M.S. in physical chemistry in 1961 and his Ph.D. in physical chemistry in 1964. His Ph.D. dissertation, directed by Ralph Petrucci, dealt with the chemisorption of CO on metals and metal oxides. After two years as a postdoctoral research associate with Harrison Shull at Indiana University, Peter joined the chemistry faculty at the Louisiana State University in New Orleans (later renamed the University of New Orleans) in 1966. He was awarded the rank of Boyd Professor of Chemistry in 1993, and retired from teaching in the spring of 2006. Peter was the mentor and research advisor for many Ph.D. students, including Jane Murray, Per Sjöberg, Tore Brinck, Dariush Habibollazadeh, Zenaida Peralta-Inga, Yuguang Ma, Ping Jin, and others. His research interests ranged from theoretical concepts such as electronegativity and chemical hardness to applications of electrostatic potentials and average local ionization energies to molecular interactive behavior and bonding, as well as to the study of chemical reactions and the reaction force in a variety of disciplines, including energetic materials. He is a world-renowned leader in halogen bonding and other σ-hole bonding interactions and other areas of theoretical and computational chemistry, with over 520 research publications in scientific journals and books. Peter was active in research until the late spring of 2022.

Peter had such a joie de vivre, matched only by his work ethic. He attended many meetings and symposia over the course of his career, and enjoyed particularly attending the MIB and MDMM conferences in the Czech Republic and Poland starting in 2003. In early January 2012, he was surprised in Santiago, Chile by the Politzer Conference organized there by Alejandro Toro-Labbé and his group at the Pontificia Universidad Católica de Chile. Peter was, for the first time in his life, an attendee for every talk at a meeting! He enjoyed the science at meetings but also liked to have time to explore the local scene in every city and country he visited. Peter found everything interesting, which made it a pleasure to be in his company. He was truly a renaissance man and will be sorely missed by all who knew him well.

Jane S. Murray, Cleveland, Ohio July 9th, 2023

Scientific program

Tuesday Wednesday Thursday

Sunday

13:00–16:00	**Registration**	
chairman	*T. Clark*	
16:00–16:20	M. Rokyta	Conference opening
16:20–17:05	D. Salahub	Quantum Quantum Effects and Biology
17:05–17:50	P. Slavíček	Revealing Intermolecular Interactions with Liquid Phase Photoemission Spectroscopy
17:50–18:35	C. Adamo	Nonempirical Double Hybrids Functionals: how far can we go?
19:00–21:00	**Welcome party**	

Monday

chairman	*N. Gresh*	
9:00–9:40	J. Murray	Two Topics Motivated by MIB-VII (2015): Counter-intuitive Halogen Bonding/The Role of "Excluded" Electronic Charge in Noncovalent Interactions
9:40–10:10	T. Brinck	Anomalous π-bonding between Boron-Silicon Lewis Acids and Molecular Nitrogen
10:10–10:40	A. Michalak	Theoretical Modeling of Catalytic Activity in Complex Processes Involving Multiple Reaction Pathways: an Example of CO_2-Epoxide Copolymerization
	Coffee break	
chairman	*J. Rak*	
11:00–11:30	W. A. Sokalski	Covalent versus Noncovalent Interactions in Catalysis
11:30–11:50	Z. Futera	Electronic Conductance of Biomolecules: Tunneling vs. Hopping
11:50–12:20	T. Clark	Ligand Binding and Activation of Class A GPCRs
	Lunch	

chairman	*A. Michalak*	
14:00–14:20	M. Straka	New Components in Molecular Electronics: Memristor and Spinristor
14:20–14:40	P. Imhof	Specificity and Mechanisms in DNA Repair
14:40–15:00	M. Prejano	Computational Investigation of Reaction Mechanism of Mg^{2+}-Dependent Human PAICS, an Emergent Target for Anticancer Therapies
15:00–15:20	Y. Sham	Simulation of Membrane-Stabilizing Copolymer with Lipid Bilayers under Constant Surface Tension
15:20–15:40	M. Janicki	The Origin of the UV-Induced Ring-Opening Mechanism in the Sulphur-Substituted 2-amino-azole
15:40–15:43	**Conference photo**	
	Coffee break	
chairlady	*M. J. Ramos*	
16:00–16:20	E. Dyguda-Kazimierowicz	Attainability of Receptor-Ligand Scoring with MED Nonempirical Interaction Energy Model
16:20–16:40	S. Paul	Molecular Insights into the Aggregation of Human Islet Amyloid Polypeptide
16:40–17:00	G. Rodrigues	Multiconfigurational Pair-Density Functional Theory: Dealing with Strong Correlation at the Protein-Scale.
17:00–17:20	M. Peralta-Moreno	Markov State Models with Fragment Dissolved Molecular Dynamics as a Step Forward in Drug Design
	Dinner	
19:00–21:00	**Poster session**	

Tuesday

chairman	*X. Lopez*	
9:00–9:30	F. De Proft	The Linear Response Function: Investigation of Different Approximations following the Coupled-Perturbed Approach for Atoms and Molecules and Application to Noncovalent Interactions
9:30–10:00	S. Záliš	Electron Transfer Through Solvated Metallo-Labeled Protein Chains Containing Tryptophan Units. QM/MM Molecular Dynamics Simulations.
10:00–10:30	F. J. Luque	HYPHAR: A Journey from Continuum Solvation Models to Virtual Screening in Drug Discovery
	Coffee break	

chairman	*J. Urban*	
10:50–11:20	J. Rak	How Does Nature Defeat the Devastating Force of Solvated Electrons?
11:20–11:50	R. Marek	Interaction of Platinum Drugs with Macrocyclic Carriers
11:50–12:20	M. J. Ramos	Studies on Enzyme-Catalysed Reactions
	Lunch	
14:00–19:00	**Sightseeing tour**	starts from the Floret hotel in Průhonice
19:00–20:15	**Concert**	Faculty of Mathematics and Physics Malostranské náměstí, refectory of one of our historical buildings

Wednesday

chairlady	*J. S. Murray*	
9:00–9:30	S. Grimme	New 'Low-Cost' Electronic Structure Methods for Large Systems
9:30–10:00	T. Borowski	Experimental and Computational Studies on a Bifunctional Enzyme - Hyoscyamine 6β-hydroxylase
10:00–10:30	J. Pittner	Molecular Dynamics with Non-adiabatic and Spin-Orbit Effects: Theory and Applications
	Coffee break	
chairman	*D. Malenov*	
10:50–11:20	I. Conti	Combination of Time-Resolved Spectroscopies and Theoretical Models to Disentangle Ultrafast Photoprocesses. Double Thionated Pyrimidine: a Molecular Tools with Tunable Photoproperties
11:20–11:50	L. Rulíšek	What Are the Minimal Folding Seeds in Proteins? Experimental and Theoretical Assessment of Secondary Structure Propensities of Small Peptide Fragments
11:50–12:20	N. Gresh	Further Advances and Challenges in Refining Polarizable Molecular Mechanics/Dynamics Potentials. Applications of Polarizable MD for Major Groove, Sequence-Selective Targeting of B-DNA.
	Lunch	

chairman	*F. J. Luque*	
14:00–14:20	M. Srnec	Off-diagonal Thermodynamics and Its Effect on Reactivity
14:20–14:40	J. Korchowiec	From Bulk to Surface – Transferability of Water Atomic Charges
14:40–15:00	M. Mitoraj	Kinetic and Potential Energy Contributions to a Chemical Bond from the Charge and Energy Decomposition Scheme ETS-NOCV
15:00–15:20	D. Rutkowska-Zbik	Dioxygen Activation on Binuclear Transition Metal Centres
15:20–15:40	V. Jha	Investigating Substrate Site and Allosteric Site Inhibitors of MTHFD2 by Computational Modeling
	Coffee break	
chairman	*J. Korchowiec*	
16:00–16:20	I. Öztürk	Interaction of Radiopharmaceuticals with Somatostatin Receptor 2 Revealed by Molecular Dynamics Simulations
16:20–16:40	A. Stachowicz-Kuśnierz	Molecular Dynamics Study of Nanoplastics in Lipid Environment
16:40–17:00	M. Melicherčík	Will Chloroquine Be Able to Treat Malaria Again?
17:00–17:20	L. Chomicz-Mańka	How May Metronidazole Work as a Radiosensitizer?
	Dinner	
19:00–21:00	**Poster session**	

Thursday

chairman	*D. Salahub*	
9:00–9:30	S. Zarić	Differences and Similarities in Benzene/Benzene and Water/Water Interactions
9:30–10:00	X. Lopez	Interaction of High-Valent Metals with Intrinsically Disordered Proteins and Peptides: Insight from Simulations
10:00–10:30	N. Russo	Photodynamic Therapy. A Computational Viewpoint
	Coffee break	

chairman	*W. A. Sokalski*	
10:50–11:20	P. Bouř	Emergence of the Spectroscopy of Resonance Raman Optical Activity
11:20–11:50	K. Świderek	Towards a New Protocol for Computer-Assisted Biocatalysts Design
11:50–12:20	Concluding remarks	

Poster presentations

Poster no.	Author name	Poster title
1	E. Andris	Hydrogen bonding in complexes of coinage metals
2	Z. Chval	Cis/Trans Effects in the Pt(II)-Complexes
3	E. Delgado Curiel	Molecular Structure and Fluorescence Spectrum Analysis of Fisetin.
4	S. Dobrev	Gallium as an Antibacterial Agent: A DFT/SMD Study of the Ga^{3+}/ Fe^{3+} Competition for Binding Bacterial Iron Acquisition Systems
5	J. M. Granadino-Roldán	Fragment Dissolved Molecular Dynamics, Uncovering New Opportunities in Drug Design
6	G. W. Jonnalagadda	Charge Transport Properties of Cytochrome b_{562} in Junctions between Metal Contacts
7	T. Kalvoda	Design of Potent Cyclic Peptides for Lead Detoxification using Quantum Mechanics Methods
8	P. Kędzierski	Catalytic Fields as a Tool to Compare Homologous Enzyme Variants and Reaction Mechanisms
9	J. Kessler	Monitoring Biomolecules by Chiral Raman Spectroscopy and Molecular Dynamics
10	J. M. Kormaník	Protein Fragments as Modular Parts for Metalloprotein Design
11	P. Kulhánek	Base-Pair Opening in Biased Molecular Dynamics Simulations
12	D. Malenov	Coordinated Water as Hydrogen Bond Acceptor: Crystallographic and Quantum Chemical Study
13	C. Morgado-Pérez	Conformational Classes, Conformational Preferences, and Conformational Transitions of Various DNA Dinucleotide Steps. Molecular Dynamics of Drew-Dickerson Dodecamer Revisited.
14	H. Mun	Computational Analysis of Zinc Binding Groups for Carbonic Anhydrase Inhibition
15	J. Novotný	Paramagnetic Host-Guest Complexes of Ruthenium(III) Compounds and Cyclodextrines
16	J. A. Piceno	Computational Study of Conformational Possibilities of Separate Deoxynucleosides to the Formation of Various Conformational Classes of Minimal Fragments of DNA Chain
17	M. Pospíšil	Halloysite as Suitable Adsorbent of Atrazine and Diuron
18	M. Rózga	Theoretical Description of Peptide Bonds in Selected Systems Based on ETS-NOCV Method
19	J. Rubio-Martinez	Quest for Compounds that Selectively Activate the Pro-apoptotic Bax Protein
20	F. Šebesta	Factors Influencing Charge Separation in Azurin Protein Mutants with Trp Residues. QM/MM/MD Simulation.

21	Y. Sham	Discovery of a Potent Broad-Spectrum Metallo Beta Lactamase Inhibitor for Rescuing Beta Lactam Antibiotic Resistance
22	A. Szczyrba	8-substituted Adenine Derivatives as Potential Radiosensitizers. A Computational Study
23	O. Tichý	QM/MM Study of the Electron Hopping Processes of the Two Lowest Singlet Excited States of Cytosine, Its Aza-Derivatives and Carotenoids
24	T. Trnka	Efficient Pipe Interface Between the Amsterdam Modeling Suite and External Software
25	A. Vavrečka	QM/MM Study of the Electron Hopping Processes of Conjugated Systems
26	G. Vila Julià	Establishing a Binding Model for Bombesin to Bombesin Receptors
27	O. Żurowska	ETS-NOCV and Molecular Electrostatic Potential-Based Picture of Chemical Bonding

Talk Abstracts

Quantum Quantum Effects and Biology

Dennis Salahub

Department of Chemistry, Department of Physics and Astronomy, CMS-Centre for Molecular Simulation, IQST – Institute for Quantum Science and Technology, Quantum Alberta, University of Calgary, Canada,

dsalahub@ucalgary.ca

By "quantum quantum" I mean effects beyond the normal quantum chemistry of Born-Oppenheimer (free-) energy surfaces. I will review some of the following topics:

1) Quantum criticality at the origin of life [1], biomolecules appear to inhabit the "poised realm" between order and chaos.

2) Spins in biology – the radical-pair mechanism and bio-chemical-physics in magnetic fields [2–5]

3) Quantum machine learning – could quantum computers play a significant role in, e.g., drug discovery? [6, 7]

[1] Vattay, G.; Salahub, D. R.; Csabai, I.; Nassimi, A.; Kauffman S. A. Proceedings of 7$^{\text{th}}$ International Workshop DICE 2014 Spacetime – Matter – Quantum Mechanics *J. Phys: Conference Series* **2015**, *626*, 012023.
[2] Zadeh-Haghighi H.; Simon, C. *J. R. Soc. Interface* **2022**, *19*, 20220325.
[3] Smith, J.; Zadeh-Haghighi, H.; Salahub, D.; Simon, C. *Sci. Rept.* **2021**, *11*, 6287.
[4] Rishabh; Zadeh-Haghighi, H.; Salahub, D.; Simon, C. *PLS Comput. Biol.* **2022**, *18*, e1010198.
[5] Deviers, J.; Cailliez, F.; Zuniga-Gutierrez, B.; Kattnig, D. R.; de la Lande, A. *Phys. Chem. Chem. Phys.* **2022**, *24*, 16784.
[6] Naseri, M.;Gusarov S.; Salahub, D. R. "Quantum Machine Learning in Materials Prediction: A Case Study on ABO3 Perovskite Structures" *J. Phys. Chem. Lett.* **2023**, in final preparation.
[7] Chu, Y.; Zhang, Y.; Wang, Q.; Zhang, L.; Wang, X.; Wang, Y.; Salahub, D. R.; Xu, Q.; Wang, J.; Jiang, X.; Xiong, Y.; Wei, D.-Q. *Nature Machine Intelligence* **2022**, *4*, 300–311.

Revealing Intermolecular Interactions with Liquid Phase Photoemission Spectroscopy

Petr Slavíček

Department of Physical Chemistry, University of Chemistry and Technology, Prague

Photoemission spectroscopy is routinely used in surface science and solid-state physics. The liquid microjet technology allowed for the transplantation of this powerful technique to aqueous solutions. However, interpreting the experimental data requires heavy assistance of *ab initio* approaches.

The photoemission spectrum covers directly emitted electrons as well as the secondary electrons of the Auger types. Together, they provide surprisingly detailed information on the structure, speciation, and intermolecular interactions in the disordered systems. I will emphasize here the novel types of spectroscopies based on the non-local types of Auger decay. [1]

In the presentation, I will briefly discuss the theoretical methods that can be used for modeling photoemission in the liquid phase: [2] from simple dielectric-based models, QM/MM polarizable techniques to various types of fragmentation methods. [3] I will then demonstrate the applicability of liquid-phase photoemission spectroscopy for exploring interactions in biomolecules. In particular, the structure of ATP/magnesium complexes, [4] nucleic acid components, [2], indole [5] and saccharides [6] will be discussed in detail.

Acknowledgements: Support from the Czech Science Foundation, project number 21-26601X, is acknowledged.

[1] Unger, I.; Seidel, R.; Thürmer, S.; Pohl, M. N.; Aziz, E. F.; Cederbaum, L. S.; Muchová, E.; Slavíček, P.; Winter, B.; Kryzhevoi, N. V. *Nature Chemistry* **2017**, *9*, 708.
[2] Pluhařová, E.; Slavíček, P.; Jungwirth, P. *Acc. Chem. Research* **2015**, *48*, 1209.
[3] Tóth, Z.; Kubečka, J.; Muchová, E.; Slavíček, P. *Phys. Chem. Chem. Phys.* **2020**, *22*, 10550.
[4] Mudryk, K.; Lee, C.; Tomaník, L.; Malerz, S.; Trinter, F.; Hergenhahn, U.; Neumark, D. M.; Slavíček, P.; Bradforth, S.; Winter, B., arXiv:2306.05352, **2023**.
[5] He, L.; Tomaník, L.; Malerz, S.; Trinter, F.; Trippel, S.; Belina, M.; Slavíček, P.; Winter, B.; Küpper, J. *submitted* **2023**.
[6] Malerz, S.; Mudryk, K.; Tomaník, L.; Stemer, D.; Hergenhahn, U.; Buttersack, T.; Trinter, F.; Seidel, R.; Quevedo, W.; Goy, W.; Wilkinson, I.; Thürmer, S.; Slavíček, P.; Winter, B. *J. Phys. Chem. A* **2021**, *125*, 6881.

Nonempirical Double Hybrids Functionals: how far can we go?

Carlo Adamo[1]

[1] Chimie ParisTech, PSL Research University, CNRS, I-CLeHS, F-75005 Paris, France

Modern computational approaches based on Density Functional Theory (DFT) provide valuable answers for most of the chemical problems to which they are applied, and this success well correlates with their widespread use. Despite these achievements, DFT still faces some challenges that cannot be ignored in view of their relevance in (Bio)Chemistry, such as noncovalent interactions.
In order to deal with these problems and further expand the domain of applicability of DFT, better performing exchange-correlation functionals are systematically proposed. They can be classified into two broad families, following the procedure used for their construction. The first family is composed by semi-empirical approaches, that is by all the functionals whose internal coefficients are determined by an error minimization procedure with respect to external reference datasets. By opposition, the second family contains nonempirical functionals whose coefficients are fully determined on the basis of theoretical arguments. [1]
In this talk we describe our non-empirical approach [2] which, starting from well-defined theoretical considerations, allows for the definition of new functionals whose performances are comparable with those obtained by semi-empirical approaches. Discussion of selected cases, some of them relevant for applications to biological systems, not only shows the large domain of applicability of non-empirical functionals, but also underlines how increasing the number of theoretical constrains induces an improvement of the numerical performances. [3, 4]

[1] Brémond, E.; Ciofini, I.; Sancho-García, J. C.; Adamo C. *Acc. Chem. Res.* **2016**, *49*, 1503.
[2] Brémond, E.; Sancho-García, J. C.; Pérez-Jiménez, Á. J.; Adamo C. *J. Chem. Phys.* **2014**, *141*, 031101.
[3] Li, H.; Tirri, B.; Brémond, E.; Sancho-García, J. C.; Adamo C. *J. Org. Chem.* **2012**, *86*, 5538.
[4] Brémond, E.; Li, H.; Sancho-García, J. C.; Adamo C. *J. Phys. Chem. A* **2022**, *126*, 2590.

Two Topics Motivated by MIB-VII (2015): Counter-intuitive Halogen Bonding/The Role of "Excluded" Electronic Charge in Noncovalent Interactions

Jane S. Murray

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In 2015, Peter Politzer and I attended MIB-VII in Praha-Průhonice. Peter's talk was entitled "The σ-Hole at Age 10: Healthy but with Some Growing Pains". My talk the next day nearly did not happen, as I was up all night working on it, and barely got to the conference room in time. It was entitled "Electrostatic Potentials and Electronic Densities: Giving Atoms Back their Identities".

The talk that I will be presenting at MIB-IX covers work that ultimately began at MIB-VII. The first part of my talk covers what we call counter-intuitive halogen bonding [1], and stemmed from comments at a number of international meetings involving halogen bonding. The second part discusses adventures in changing contours of the electronic density to gain insight into noncovalent interactions of interacting species, be they inter- or intra-molecular, attractive [2,3] or repulsive [4].

Acknowledgements: This talk is dedicated to Peter Politzer, with eternal thanks for his constant support and encouragement.

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Anomalous π-bonding between Boron-Silicon Lewis Acids and Molecular Nitrogen

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Boron compounds of the type BX_3, where X is a halogen (F, Cl, or Br) are known to be strong Lewis acids and bind Lewis bases, such as NH_3 and CO, by π-hole bonding. [1] In the case of NH_3 and amines, the B-N bond is similar to a covalent bond, both in length and in strength. N_2, on the other hand, interacts only weakly with the BX_3 compounds. However, we recently found that compounds of the type $B(SiR_3)_3$ and $B(GeR_3)_3$ (but not $B(CR_3)_3$) form a relatively strong bond with N_2 with a B-N bond length that is even shorter than the sum of the covalent radii of the B and N atoms. [2] This bond is a consequence of a π-backbonding interaction between the B-Si (B-Ge) σ-bond region and the N_2 π and $\pi^\star$ orbitals. The B-Si and B-Ge bond regions are characterized by a ring shaped area of low average local ionization energy $\overline{I}_S(\mathbf{r})$ [3] that has a minimum ($\overline{I}_{S,min}$) directly above the bond. The value of the $\overline{I}_{S,min}$ is shown to reflect the backbonding capacity of the Lewis acids and decreases (stronger interaction) with electron donating R-substituents. The binding of N_2 also has a significant σ-bond contribution that is largely electrostatic in character, as indicated by the high surface electrostatic potential [$V_S(\mathbf{r})$] above the B atom. π-backbonding provides a mean for activating N_2 for the nitrogen reduction reaction (NRR). Heterogenous electrocatalysts with the B(Si-)$_3$ or B(Ge-)$_3$ bonding motif can be prepared by boron doping of nanostructured silicon or germanium compounds, and particularly hydrogenated silicene is shown to have promising catalytic properties.

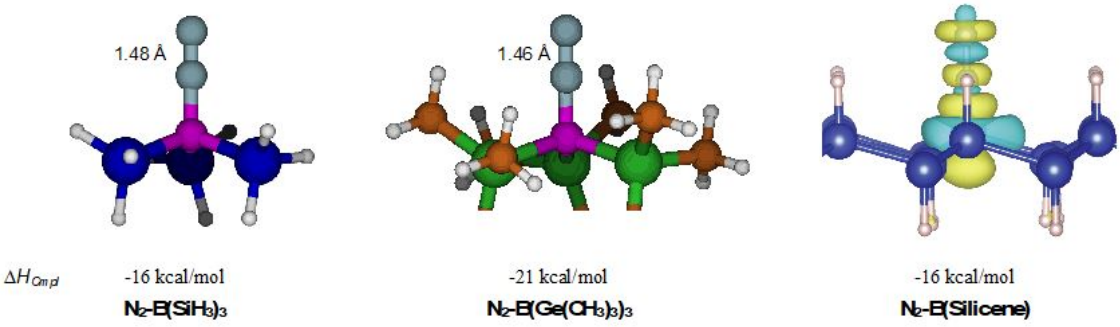

Fig. 1: N_2 binds strongly to $B(SiH_3)_3$ (left), $B(GeH_3)_3$ (middle) and boron doped H-silicene (right). The π-backbonding is indicated by the density difference plot (yellow enhanced, aqua depleted) of the silicene.

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Theoretical Modeling of Catalytic Activity in Complex Processes Involving Multiple Reaction Pathways: an Example of CO_2-Epoxide Copolymerization

Olga Żurowska, Jakub Pawełko, Rafał Wójcik, Aleksandra Roznowska, Karol Dyduch, Monika Srebro-Hooper, Artur Michalak

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Predicting the catalyst activity based on results computational studies is often challenging. In the case of complex processes involving many alternative isomeric complexes, not only the energy barriers for the reaction pathways have to be taken into account, but also the populations of alteranative isomers, determining probability of the reaction pathways [1, 2]. Here, the results of theoretical studies for the epoxide-opening in the process of CO_2/epoxide copolymerization with bifunctional, salen-based cobalt(III) catalysts (Figure 1) will be used as an example.

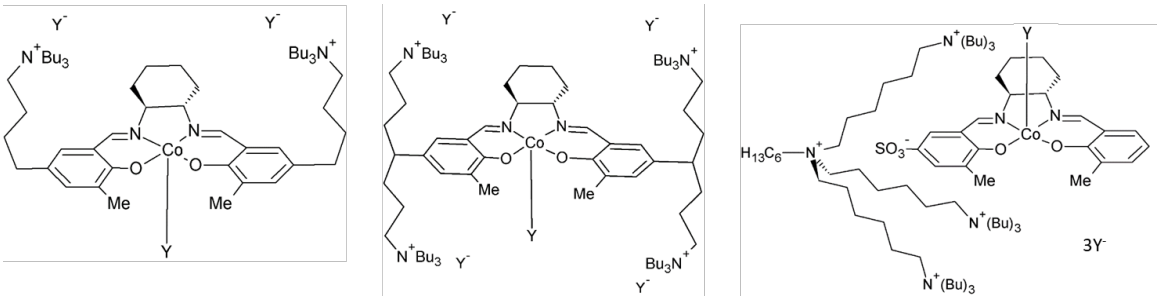

Fig. 1: Examples of bifunctional catalysts for the CO_2/epoxide copolymerization. [3]

Modeling of the processes catalyzed by these complexes are still challenging for computational chemistry. Large number of isomers to be considered, numerous possible conformations of the aliphatic chains, and spatial arrangements of non-covalently bound anions in the co-catalyst salt impose methodological difficulties and high computational cost. Results of our computational studies [2] will be presented, utilizing a computational protocol that combines semiempirical molecular dynamics simulations with DFT to explore the conformational space. The catalyst activity based on thousands of complex geometries and hundreds of considered reaction pathways is predicted, leading to qualitative agreement with experimental data.

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Covalent versus Noncovalent Interactions in Catalysis

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Extremely high turnover numbers of some fastest enzymes, like ketosteroid isomerase KSI, are related to covalent binding of corresponding transition states with active site [1]. The physical nature of such strong interactions could be analyzed by Hybrid Variation-Perturbation Theory, yielding electrostatic multipole, electrostatic penetration, exchange, delocalization and correlation terms [2,3], where covalent nature of interactions could be defined as ratio of delocalization and electrostatic terms [4]. In this contribution preliminary analysis involving dynamic catalytic fields for ketosteroid isomerase will be presented, indicating possible ultrafast coupling of proton zero point oscillations with each stage of catalyzed reaction [5], possibly explaining the origin of extremal activity of KSI. In addition, due to still persisting controversies related to delocalization term or its induction or charge-transfer components [6,7], several variational interaction energy partitioning schemes will be validated against Symmetry Adapted Perturbation Theory results using basis sets approaching Hartree-Fock limit.

Acknowledgements: Research supported by NCN OPUS grant 2017/27/B/ST4/0132701327 „Catalytic fields as the tool for theoretical analysis and design of biocatalysts". Calculations have been performed in WCSS, ICM and PCSS supercomputer centers.

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Electronic Conductance of Biomolecules: Tunneling vs. Hopping

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Redox proteins facilitate electron transfer events in many biological processes, including photosynthesis, respiration cycle, or denitrification reactions. Blue copper proteins such as plastocyanin or azurin and the heme-containing cytochromes often participate in these redox cascades. Recently, these proteins have been utilized in nanobioelectronic devices due to their suitable electron-transfer properties. However, non-expected physical phenomena were observed when the proteins were incorporated between metal contacts or electrodes. While in a native aqueous environment, the electron flow through the system of redox sites proceeds by the thermally activated hopping mechanism, the temperature-independent currents of relatively high magnitudes were detected on protein/metal junctions [1] [2]. These data suggest that the electrons on the bio/metallic interfaces and junctions are transferred by the coherent tunneling mechanism, independently of the redox-active states.

We investigate these charge-transport phenomena by means of computer simulations based on the combination of classical molecular dynamics (MD) and density functional theory (DFT) approaches [3] [4]. While the incoherent hopping could be studied by hybrid quantum-mechanical / molecular-mechanical (QM/MM) techniques [5], coherent tunneling requires a quantum description of the whole interface model. Recently, we applied these methodologies to azurin, small tetraheme cytochrome (STC), cytochrome b562, and cytochrome c. We showed that in all cases, the electron passes the junctions by the tunneling mechanism. At the same time, the hopping is severely hindered by the large potential drop on the protein/metal interfaces [6]. A large density of protein valence states ensures slow distance decay ($\beta = 0.2$ Å^{-1}) and persistence of the tunneling currents over several nanometers with the crossover to hopping at ~ 7 nm in the case of STC.

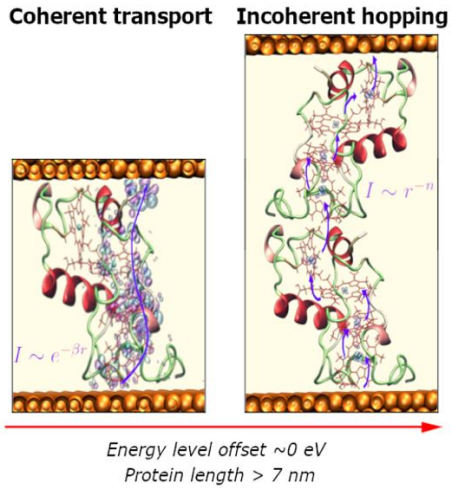

Fig. 1: Tunneling (left) vs. hopping (right) through the STC junctions

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Ligand Binding and Activation of Class A GPCRs

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We have developed metadynamics simulation protocols to characterize ligand binding [1] and receptor activation. [2] These protocols are available *via* PLUMED-Nest and era applicable to almost all Class A GPCRs. The protocols use multi-walker metadynamics to ensure adequate sampling and, in the case of ligand binding, funnel constraints to prevent the ligands wandering in the extracellular medium. The activation/deactivation protocol uses the A^{100} activation index [3] as the single collective variable.
These protocols are finding general acceptance within the GPCR simulation community and have extended our ability to characterize the activation mechanisms of GPCRs significantly, especially with regard to the identification of additional binding sites to the orthosteric one.
In a further development, we have extended the binding/unbinding protocol to enable it to treat peptide ligands, rather than the small-molecule ligands treated originally. We have applied a preliminary version of this protocol to the neuropeptide Y Y4-receptor, [4] and will soon release the optimized protocol, which has been modified to take the stronger binding forces and extended sampling space of large peptide ligands into account.
The results of the simulations are consistent with experiment in all cases and provide an almost complete picture of the GPCR activation mechanism. The missing link is the recruitment of the G-protein by the receptor. We are developing a standard protocol to close this gap.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft as part of Research Training Group GRK 1910 "*Medicinal Chemistry of Selective GPCR Ligands*" and by grants of supercomputer time from the Gauss Alliance on SuperMUC (Project Nr. Pr74su) and from the Erlangen National High Performance Computing Center (NHR@FAU) of the Friedrich-Alexander-University Erlangen-Nuernberg (FAU) (Project Nr b126dc). NHR funding was provided by federal and Bavarian state authorities. NHR@FAU hardware was partially funded by the DFG-Grant No. 440719683.

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New Components in Molecular Electronics: Memristor and Spinristor

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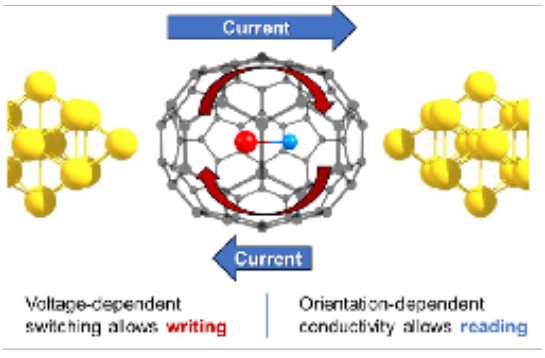
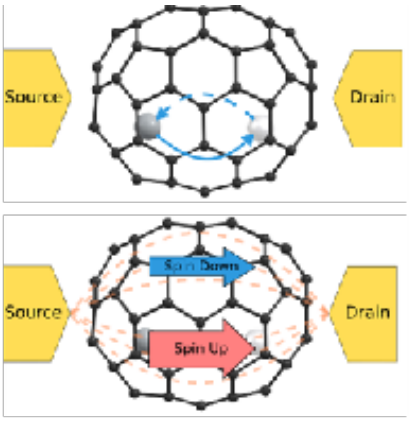
The holy grail of miniaturization of electronic circuits is replacing circuit components by single molecules which blossomed in a whole scientific field – **molecular electronics** (ME). Here we present proof-of-concept studies of endohedral fullerene based electric-field driven molecular switches that can variably rectify electric current and filter the spin. A **molecular memristor** [1–3] is based on an MX@C70 fullerene connected to electrodes, where MX is a dipolar system (M: metal, X: non-metal) enclosed in the cage. We demonstrate *in silico* that (a) the position of MX in the cage can be forced ("written") by applied (large) voltage on electrodes, while (b) the conductivity of MX@C_{70} changes with the position of MX and can be retrieved ("red") also by (a small) applied voltage. This is a behaviour of a memristor – a resistive component, the conductance of which depends on the current that has passed through. The concept of **molecular spinristor** aka spin-filtering memristor [4] goes further and uses an open-shell metal atom, here Ti, enclosed in a fullerene cage, here C_{70}. Again, one can use electric field to move Ti atom among different local minima, each of which feature different rectification properties. Here, in addition, the open-shell electronic structure of Ti@C70 provides spin-filtering function, that can be switched. Proposed systems may function as components for **in-memory computing** that overcomes classical von-Neumann bottleneck of communication between the processing unit and the memory.



Fullerene memristor



Fullerene spinristor

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Specificity and Mechanisms in DNA Repair

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DNA damages are a constant threat to the integrity of the genome. Damages of the DNA bases can arise from oxidation or aberrant methylation. Deamination of (methyl-)cytosine bases, for example, results in (T)U:G mismatches which ultimately lead to mutations in the encoded protein. The Base excision repair system (BER) is a machinery of enzymes, recognising and removing damaged/wrong bases and replacing them with the correct one. Thymine DNA glycosylase (TDG) is a glycosylase that recognises thymine in T:G mispairs and cleaves the glycosidic C1'-N1 bond between base and sugar. In the cognate complex the mispaired base is in an extrahelical conformation, flipped out of the DNA and into the active-site of the enzyme. Our simulations show that the recognition is in part by the intrinsic deformation the DNA exhibits at the site of the T:G, a partially-open base pair with partially-flipped thymine, that is further stabilised by the interaction with the enzyme [1]. Moreover, the interactions of the enzyme's active-site with mispaired thymine are more favourable than those with non-cognate cytosine [1]. Simulations of the base excision reaction afforded us to identify the role of important residues in the step-wise, dissociative cleavage mechanism. Most importantly, His151 in its protonated form facilitates the departure of the excised base as a leaving group [2]. This latter effect is most pronounced upon a proton transfer from His151 to the thymine base, significantly reducing the barrier of the glycosidic bond dissociation. Since a cytosine substrate cannot accept such a transferred proton, His151 also contribuets to TDG's specificity [2].

In addition to thymine, TDG also operates on the higher oxidised forms of methyl-cytosine, formyl-cytosine and carboxyl-cytosine, whereas cytosine, methyl -, and hydroxylmethyl-cytosine remain unprocessed. According to our molecular dynamics simulations of the TDG-DNA complexes with perturbation and thermodynamic integration, TDG has indeed a higher binding affinity to the higher oxidised forms, at least when in their extra-helical state [3]. This can be attributed to an important interaction with H151 in its protonated form and a hydrogen-bonded interaction with the backbone of Thy152.

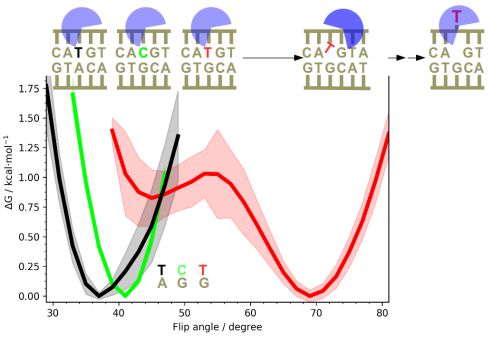

Fig. 1: Thymine DNA glycosylase recognises and excised mispaired thymine.

Acknowledgements: Support from DFG grant IM141/1 is acknowledged. Calculations were performed at the Erlangen National High Performance Computing Center (NHR@FAU) of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)

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Computational Investigation of Reaction Mechanism of Mg^{2+}-Dependent Human PAICS, an Emergent Target for Anticancer Therapies

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Human PAICS (phosphoribosylaminoimidazole carboxylase and phosphoribosylaminoimidazolesuccinocarboxamide synthetase) is an enzyme that catalyzes the conversion of aminoimidazole ribonucleotide (AIR) to N-succinylcarboxamide-5-aminoimidazole ribonucleotide (SAICAR), in steps 6 and 7 of *de novo* purine biosynthesis. [1] Due to its involvement in this important biological pathway, PAICS has emerged as a target for new medical therapies, in particular in the field of cancer treatment, being the enzyme overexpressed in various tumors and linked to malignant cells proliferation. [2] PAICS is a bifunctional enzyme and promotes the production of SAICAR in two consecutive reactions, which take place in two different domains, the AIRc and the SAICARs. In the former, AIR is first carboxylated (carboxylation reaction) and later, in the latter, converted to SAICAR in an ATP-dependent reaction (phosphorylation-condensation reaction). The understanding of the PAICS catalytic mechanism can be of crucial relevance for the therapies targeting the enzyme, inspiring the rational design of new enzyme inhibitors. For this reason, a detailed computational investigation of the PAICS reaction mechanism has been carried out. Two big active sites models, on for each domain, were built starting from available crystal structures, to shed light on the reaction mechanism and to rule out several available mechanistic proposals. In particular, the investigation highlighted the catalytic role of three Mg^{2+} in the phosphorylation-condensation reaction, which are not only involved in substrate binding, but furthermore stabilize all the transition states and intermediates along the reaction.

Acknowledgements: financial support from Carl Tryggers Foundation is acknowledged

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Simulation of Membrane-Stabilizing Copolymer with Lipid Bilayers under Constant Surface Tension

Taylor Kuebler, Evelyn M Houang, Joseph M Metzger, Yuk Yin Sham*

Ischemia/reperfusion injury (IRI) is a key contributor to Ischemic heart disease (IHD) mortality. Synthetic copolymers have been shown to stabilize muscle membranes in animal models with IRI. Our lab has previously shown that inserted copolymers in POPC increase bilayer's resistance to mechanical rupture and their effect is dependent on its overall hydrophobicity composition. To further investigate the molecular interactions governing membrane protection, we have developed novel pipeline for the construction of architecturally diverse copolymers within multi-component lipid bilayers as model system to investigate effect of 1) lipid composition and 2) linear vs branch copolymers on membrane stability. Knowledge gained will contribute to the development of novel therapeutics for I/R injury and other conditions arising from membrane damage.

The Origin of the UV-Induced Ring-Opening Mechanism in the Sulphur-Substituted 2-amino-azole

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Sulphur substitutions in biochromophores have resulted in discovering new properties currently being tested in various fields. [1] For instance, thiated nucleosides are characterized by an efficient singlet-triplet intersystem crossing leading to the efficient population of triplet excited states, which are used to generate reactive singlet oxygen molecules in photodynamics therapy.[2] However, despite extensive experimental-theoretical investigations of the photochemistry of sulphur-substituted chromophores, excited-state properties of thiazole-like compounds in a water solution are still largely unknown. One example of this class of compounds is 2-aminothiazole,[3] which has been used as a molecular scaffold in several market drugs.[4] Recently, the mentioned molecule has also found an application as a plausible prebiotic precursor in ribonucleotide synthesis from complex sugar mixtures.[3] Since 2-aminothiazole and its derivatives can readily absorb UV-B and UV-C light, the photoreactivity of the molecular scaffold should be investigated to understand the potential influence of UV light on the structure of 2-aminothiazole.

To elucidate the photochemical reactivity of 2-aminothiazole in a water solution, we performed joint experimental-theoretical studies, which allowed us to characterize the photodynamics of the chromophore. The performed ADC(2) non-adiabatic molecular dynamics simulations of 2-aminothiazole with three quantum-chemical water molecules have revealed that the UV-excited studied system quickly populates the $^1\pi\sigma^*_S$ excited state resulting in the ultrafast C-S bond breaking in the vicinity of the S_1/S_0 surface crossing. For the biradical ring-opened structure of 2-aminothiazole, we simulated the UV absorption spectrum, at the XDW-CASPT2 level, that is characterized by a broad absorption band with a maximum of 480 nm. The conducted time-resolved transition absorption measurements of 2-aminothiazole in a water solution have shown that the transient absorption spectrum lasts up to 100 ps and possesses an absorption band in the 300-500 nm matching very well with the simulated spectrum. Thus, the interdisciplinary studies have demonstrated that the UV excitation of aqueous 2-aminothiazole leads to the formation of the long-lived biradical state (ring-opened structure), which could be used to perform desirable high-energy chemical reactions or it might lead to damage of the initial structure.

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Attainability of Receptor-Ligand Scoring with MED Nonempirical Interaction Energy Model

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It remains a challenge to accurately assess the inhibitory activity of ligands considering that the commonly used empirical scoring functions are still inadequate in their performance [1]. Specifically, no individual empirical scoring function has the ability to generate reasonable estimates of binding affinity for all protein-ligand complexes [2] and it yields no insight into the physical nature of ligand binding. Nevertheless, performing accurate quantum chemical calculations is infeasible for routine in silico screening of a ligand library due to the high amount of resources required.

In order to surmount these challenges, we propose a ligand scoring model MED [3] based on first principles and accounting for two long-range interaction energy components: multipole electrostatic and approximate dispersion [4] terms. By combining computational efficiency with the absence of arbitrary parameterization, it serves as a robust tool for predicting the relative binding energy in receptor-ligand complexes. The MED model has proven to be successful in a number of cases, including the challenging small molecule inhibitors of protein-protein interaction [5]. Herein we demonstrate the performance of MED model for diverse protein-ligand systems in comparison with the empirical scoring to assess the predictive capabilities of MED scheme.

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Molecular Insights into the Aggregation of Human Islet Amyloid Polypeptide

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The aggregation of human islet amyloid polypeptide (hIAPP) is associated with the pathogenesis of Type II Diabetes (T2D), which is a metabolic disorder suffered by nearly 460 million people worldwide and is expected to increase in the near future. One of the possible therapeutic approach to control the progression of this disease is to prevent the aggregation of hIAPP. The random coil structure of hIAPP monomers transforms into β-sheet conformers, which leads to the amyloid plaques formation. This pathway of transition is analyzed via Markov State Model (MSM) [1]. Further, we have investigated the inhibitory effect of small inhibitor norepinephrine molecule [2], large ATP molecule [3] and boron nitride (BN) nanotubes (BNNTs) and nanosheet (BNNS) of different curvatures [4] on the aggregation of hIAPP.

We observed that norepinephrine preferentially interacts with the C-terminal region of hIAPP. ATP has a greater affinity towards the terminal residues and also the turn region. Moreover, the contribution of hydrophobic adenosine towards ATP contact with hIAPP exceeds that of the hydrophilic triphosphate group. We also find that With increase in curvature of BN from BNNS to (5,5)BNNT, the hydrophobicity decreases, and the interaction preference shifts from hydrophobic C-terminal to the N-terminal region.

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Multiconfigurational Pair-Density Functional Theory: Dealing with Strong Correlation at the Protein-Scale.

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Among different methods that have been proposed for combining DFT with MCSCF, the multiconfigurational pair-density functional theory (MC-PDFT) [1] approach is one of the most popular. In MC-PDFT, instead of taking spin-densities as our functional arguments as in standard spin-density DFT (SDFT), we define it in terms of the total density ρ and the on-top pair density Π. This idea is a generalization of KS-DFT and it was already suggested in 1995 by Becke, Savin and Stoll [2], upon realizing that SDFT can lead to nonphysical results, e.g. failing to describe the degeneracy of the three triplet components.
The standard SDFT functionals can be translated to PDFT functionals so that they give identical results for a single determinant by using the relations between ρ, Π and the usual spin-densities: $\rho(r) = \rho_\alpha(r) + \rho_\beta(r)$ and $\Pi(r) = 2\rho_{\alpha(r)}\rho_{\beta(r)}$, resulting in a pair of solutions that correspond to α and β densities:

$$\rho_{\alpha/\beta} = \frac{\rho \pm \sqrt{\rho^2 - 2\Pi}}{2} \tag{1}$$

In this work, we present an implementation of MC-PDFT that comprises two important new aspects: a definitive SDFT to PDFT exchange-correlation functional translation that considers the complex nature of eq. 1 in cases where $\rho^2 - 2\Pi$ is negative; and derived wavefunction gradients that were used for a fully variational MC-PDFT implementation. The implementation was done in the very efficient massively parallel MultiPsi [3] code and it is noteworthy that the resulting algorithm is more efficient than standard MCSCF, at roughly the cost of regular DFT for small to medium active spaces.

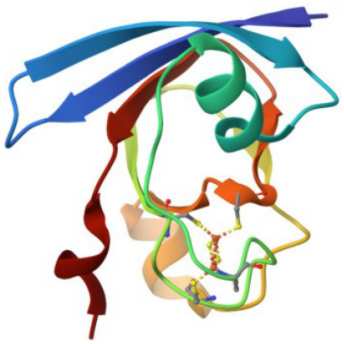

Fig. 1: Ferredoxin I protein

We tested its accuracy by benchmarking a series of singlet-triplet splittings from diradical molecules while its performance was tested with a CAS(10,10)-MC-PDFT calculation of the Ferredoxin I proteinas showed in Fig. 1. Although the protein has more than 1000 atoms each SCF iteration was still completed in one hour using 8 nodes of 32 cores each.

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Markov State Models with Fragment Dissolved Molecular Dynamics as a Step Forward in Drug Design

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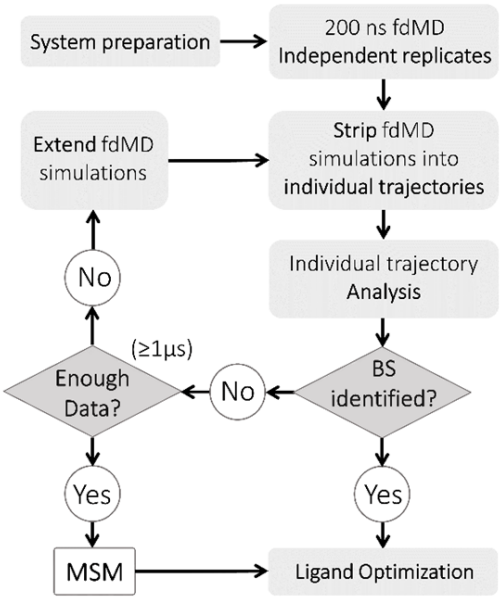

Fig. 1: fdMD-MSM Workflow

Fragment dissolved Molecular Dynamics (fdMD) is a methodology that aims to explore potential binding sites of target proteins to identify small ligands with strong binding affinities [1]. While its primary focus lies on fragments that exhibit prolonged interaction during the complete simulation, there are cases where the fdMD methodology encounters recurrent association/dissociation events that can mislead the identification of the binding site.

In this context, kinetic Markov State Models (MSMs), commonly applied for extremely long MD simulations or multiple MD replicates to identify the most significant long-timescale system processes [2, 3], have been implemented as an alternative further step in the fdMD workflow. Therefore, to evaluate effectiveness of combining both techniques, a set of different systems with available experimental information has been studied to validate the fdMD-MSM methodology. As a result, significant improvements have been achieved in the identification of binding sites and the prediction of related kinetic constants.

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The Linear Response Function: Investigation of Different Approximations following the Coupled-Perturbed Approach for Atoms and Molecules and Application to Noncovalent Interactions

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Density Functional Theory is a well-suited theory for the introduction of chemical concepts, also known as reactivity indices. These are introduced as response functions of the energy E of the system with respect to either the number of electrons N, the external potential $v(\mathbf{r})$ or both. [1,2] These definitions have afforded the non-empirical calculation of these reactivity indices and applications in many fields of chemistry have been studied.

In this lecture, attention will be focused on one of these response functions, the second functional derivative of E with respect to the external potential at constant number of electrons, $\left[\frac{\delta^2 E}{\delta v(\mathbf{r})\delta v(\mathbf{r}')}\right]_N$. This kernel, usually written as $\chi(\mathbf{r},\mathbf{r}')$, is commonly referred to as the Linear Response Function (LRF). The LRF in its time- or frequency-independent context has received comparatively less attention from a chemical reactivity perspective although it has recently been used to qualitatively describe electron delocalisation, (anti-)aromaticity and inductive and mesomeric effects, etc. [3] We computed the LRF at four levels of approximation (the independent particle approximation, the random phase approximation, the Hartree-Fock approximation and the (exact) DFT (Density Functional Theory) expression, using functionals from the first four rungs of Jacob's ladder of exchange-correlation energy functionals. [4] The impact of these approximations is scrutnized. Next, the atom-condensed LRF is used to investigate noncovalent interactions for a series of hydrogen and halogen bonded complexes.

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Electron Transfer Through Solvated Metallo-Labeled Protein Chains Containing Tryptophan Units. QM/MM Molecular Dynamics Simulations.

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Dynamic factors controlling electron-hopping rate and efficiency in modified azurin systems that include a rhenium(I) sensitizer, $Re(His)(CO)_3(dmp)^+$ (dmp = 4,7-Me_2-1,10-phenanthroline), two tryptophans (W122, W124), and a Cu^I center were theoretically investigated in order to account for previous experimental observations that two closely spaced (3-4 Å) tryptophan residues dramatically accelerate long-range electron transfer (ET) from Cu^I to the photoexcited sensitizer. The accelerating effect being much larger when tryptophans were placed in the ET pathway. [1] The ET sequence has been theoretically described as a time evolution of the sensitizer-localized Re→dmp ^{3}CT, and two charge-separated triplet states ^{3}CS1 and ^{3}CS2 where the hole resides on W122 and W124, respectively. The mechanism of an electron transfer was investigated by quantum mechanical (QM) / molecular mechanical (MM) / molecular dynamic (MD) simulations in an aqueous solution. The QM part consisted of $Re(His)(CO)_3(dmp)^+$ and the protein chain up to W122, the rest of the protein and water surrounding were treated by MM. QM calculations employed DFT with the PBE0 functional and D3 dispersion, TDDFT/MM approach was applied for a study of ET between ^{3}CT and CS states, simulations of ET between CS1 and CS2 states utilized UKS/MM methodology.

QM/MM/MD trajectories of low-lying triplet excited states of the $Re(His)(CO)_3(dmp)^+$–W124(–W122) within protein and solvent media exhibited crossings between ^{3}CT and CS1/CS2 or between CS1 and CS2 states. Dynamic fluctuations of the solvated Re-tryptophan-azurins create situations where oxidation of one of the tryptophans by an electronically excited Re complex is energetically feasible. Calculated electronic couplings H_{ab} between ^{3}CT and both ^{3}CS or between ^{3}CS1 and ^{3}CS2 states in the crossing region revealed the hopping pathway and effects of the interplay of mutual orientations of the tryptophan indoles and the Re photosenzitizer. Simulations highlighted the importance of the fluctuational flexibility the the ET-active cofactors and stress the importance of structural and solvational dynamics in driving ET in biomolecules labelled with photoactive metal complexes.

Acknowledgements: Support from the Czech Science Foundation (GAČR) Grant No. 21-05180S is acknowledged. Calculations were performed at the Czech IT4-Innovations National Supercomputing Center (project OPEN-20-8).

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HYPHAR: A Journey from Continuum Solvation Models to Virtual Screening in Drug Discovery

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This talk will discuss the development and validation of the quantum mechanical (QM)-based hydrophobic (HyPhar) descriptors derived from the IEFPCM/MST continuum solvation model, which have been parametrized for water and a variety of organic solvents. The performance of the model for predicting the solvation free energy and the partition coefficient of bioorganic compounds has been calibrated for the blind tests along the series of SAMPL challenges devoted to the calculation of partition coefficients and distributions.
The Hyphar parameters rely on the partitioning into atomic contributions of the solvent's response to the embedding of the solute into the continuum medium that simulates the surrounding solvent. Partitioning of the cavitation and van der Waals components of the solvation free energy exploits the contribution of each atom to the solute/solvent boundary. With regard to the electrostatic term, partitioning relies on a perturbation treatment of the electrostatic response, leading to the combination of the in vacuo wavefunction of the solute with the fully polarized solvent's reaction field. Overall, this procedure provides a 3D distribution map of the atomic contribution to the solvation in a given solvent, and hence to the partitioning into aqueous and organic (i.e., *n*-octanol) solvents.
Taking into account the relationships between the solute's hydrophobicity and the maximal affinity that can be attained for a druggable target, the Hyphar parameters have been examined in the framework of structure–activity relationship studies, hydrophobic similarity and docking. The analysis of the graphical representation of the hydrophobic maps provides a direct linkage with the pattern of interactions found in ligand-target complexes, thus complementing the interpretation afforded by other descriptors. Efforts have also been conducted to develop a structure-based, pH-dependent lipophilicity scale of amino acids from continuum solvation calculations, thus paving the way to a hydrophobic-guided docking of drug-like compounds.

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How Does Nature Defeat the Devastating Force of Solvated Electrons?

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The unexpected discovery of single-strand breaks (SSBs) formation induced by the attachment of low energy electrons to dry DNA under ultrahigh vacuum (UHV) was preceded by numerous experiments in which hydrated electrons were not able to produce SSBs in an aqueous solution. These, at first glance, contradictory findings may be explained by proton transfer (PT) facilitated in water. Indeed, if electrons produced in copious amounts by ionizing radiation in water were as harmful to DNA as under a vacuum, radiotherapy would not be a routine modality of anticancer treatment.

To explain this confusing situation crossed electron-molecular beam (CEMB) and anion photoelectron spectroscopy (aPES) experiments coupled to density functional theory (DFT) modeling were used against model molecules that were designed to demonstrate the fundamental importance of proton transfer (PT) to the radical anions. Three molecular systems were investigated: 5′-monophosphate of 2′-deoxycytidine (dCMPH), where PT in the electron adduct is feasible, and two ethylated derivatives, 5′-diethylphosphate and 3′,5′-tetraethyldiphosphate of 2′-deoxycytidine, where PT is blocked due to substitution of labile protons with the ethyl residues. CEMB and aPES experiments confirmed the cleavage of the C3′/C5′–O bond as the main dissociation channel related to electron attachment in the ethylated derivatives. In the case of dCMPH, however, electron attachment (in the aPES experiments) yielded its parent (intact) radical anion, $dCMPH^-$, suggesting that its dissociation was inhibited. The aPES-measured vertical detachment energy of the $dCMPH^-$ was found to be 3.27 eV, which agreed with its B3LYP/6-31++G(d,p)-calculated value and implied that electron-induced proton transfer (EIPT) had occurred during electron attachment to the dCMPH model nucleotide. In other words, EIPT, subduing dissociation and facilitated in water compared to the dry environment, appeared to be somewhat protective against SSB.

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Interaction of Platinum Drugs with Macrocyclic Carriers

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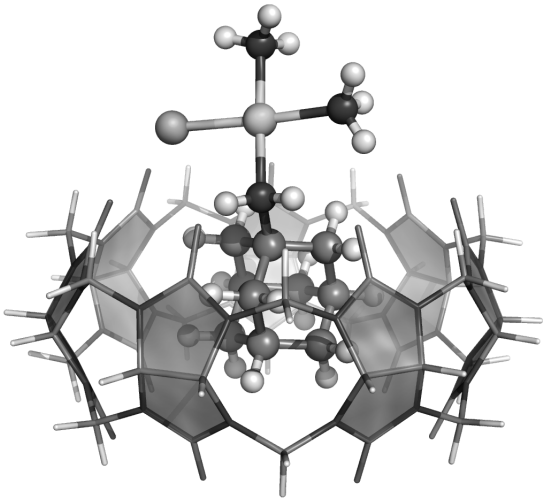
Platinum-based anticancer drugs are actively being developed using lipophilic ligands or drug carriers for the efficient penetration of biomembranes, reduced side effects, and tumor targeting [1]. In addition to bifunctional cisplatin derivatives, monofunctional platinum(II) compounds can also be significantly effective for antitumor therapy. [2]
In this work, we introduce new monofunctional platinum complexes with the general structure *cis*-$[Pt^{II}(NH_3)_2(4\text{-R-py})Cl]^+NO_3^-$ as direct analogs of pyriplatin and investigate their activation by an aquation process stimulated by host-guest interaction with the cucurbit[7]uril (CB7) macrocycle [3]. The host-guest (HG) binding and the aquation process on the platinum core-investigated in detail by using NMR spectroscopy and relativistic DFT calculations—will be discussed. The HG interactions with macrocycles will also be briefly demonstrated on ruthenium(III) compounds. [4]



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Studies on Enzyme-Catalysed Reactions

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This talk is concerned with the computational needs that we come across to figure out results within computational enzymology. Calculations devised to study protein interactions and circumvent problems in some relevant enzymatic systems will be reported as well as recent developments in the establishment of some catalytic mechanisms. We have resorted to different methodologies and altogether different studies [1–4] in order to analyze the energetics of processes related to the systems under study and evaluate their feasibility according to the available experimental data.

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New 'Low-Cost' Electronic Structure Methods for Large Systems

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All widely used semi-empirical quantum chemical methods like PM6, DFTB, or GFN-xTB are formulated in a (almost) minimal basis set of atomic orbitals, which limits the achievable accuracy for many important chemical properties. Recently, we proposed a new special purpose tight-binding (TB) electronic Hamiltonian termed PTB [1] which is expressed in an accurate polarized valence double-zeta AO basis set (vDZP). The basis has been specially optimized in molecular DFT calculations using standard ECPs for all elements up to radon [2]. The PTB method aims primarily at reproducing the one-particle density matrix of a DFT reference calculation with the ω B97X-V range-separated hybrid density functional [3] in exactly the same AO basis. The combination of ω B97X(-V) with vDZP/ECP and an adjusted D4 dispersion correction defines a new member in our hierarchy of efficient composite electronic structure methods, termed ω B97X-3c [2] and is used as reference. The PTB procedure is non-self-consistent employing only two matrix diagonalizations, includes new non-local potentials, as well as established parts from GFN-xTB and requires only simple overlap integrals as input. Compared to ω B97X-3c calculations, speedups of 3-4 orders of magnitude are achieved so that runs for molecules with 100-200 atoms are completed in a few seconds of computation time on standard desktop computers. The use of the PTB density in typical computational chemistry applications as well as for non-SCF-iterative DFT-GGA schemes is discussed.

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Experimental and Computational Studies on a Bifunctional Enzyme - Hyoscyamine 6β-hydroxylase

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Bifunctional enzymes are especially attractive research targets for someone interested in how enzymes achieve their reaction specificity. Hyoscyamine 6β-hydroxylase (H6H) is a bifunctional non-heme 2-oxoglutarate/Fe^{2+}-dependent dioxygenase that catalyzes the two final steps in the biosynthesis of scopolamine. The first of them is the "canonical" hydroxylation reaction of the tropane ring leading to anisodamine, whereas in the second step anisodamine is oxidatively dehydrogenated with formation of an epoxide ring of scopolamine. Based on high resolution crystal structures of H6H from Datura metel, we have obtained detailed information on substrates binding [1]. UV-vis anaerobic measurement provided information on substrates binding constants, while Mössbauer spectroscopy delivered indirect information on composition and geometry of the iron first coordination shell. The experimentally determined structures served as starting point for classical molecular dynamics simulations and subsequent QM/MM (ONIOM) investigations on the reaction mechanisms [2]. In this contribution we will show how we try to complement experimental data with computational results, and vice versa, and that this approach helps us to propose the most likely mechanism of the reaction and identify factors responsible for reaction specificity.

Acknowledgements: Support from NCN Poland grants No. UMO-2014/14/E/NZ1/00053 and UMO-2022/45/B/ST4/01411 is acknowledged. Calculations were performed at the Academic Computer Centre Cyfronet AGH.

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Molecular Dynamics with Non-adiabatic and Spin-Orbit Effects: Theory and Applications

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Molecular dynamics (MD) represents an important tool for modeling of the behavior of molecular systems in time. When applied to problems from photochemistry, a treatment of excited states and crossings between different potential energy surfaces has to be incorporated in the MD scheme. We present efficient techniques which allow to approximately compute the non-adiabatic couplings and perform surface hopping MD with CASSCF, MRCI, TDDFT, and ADC(2) methods. The performance of the non-adiabatic MD is illustrated on the examples of photoizomerization of azobenzene and internal conversion of excited adenine.

We present surface hopping dynamics on potential energy surfaces resulting from the spin-orbit splitting, i.e., surfaces corresponding to the eigenstates of the total electronic Hamiltonian including the spin-orbit coupling. In this approach, difficulties arise because of random phases of degenerate eigenvectors and possibility of crossings of the resulting mixed states. Our implementation solves these problems and allows propagation of the coefficients both in the representation of the spin free Hamiltonian and directly in the "diagonal representation" of the mixed states. As a test case, we applied our methodology to deactivation of thiophene and selenophene in the gas phase, ethanol solution, and bulk liquid phase.

We also studied halogenated BODIPY derivatives, which are emerging as important candidates for photodynamic therapy of cancer cells due to their high reactivity in triplet states. BODIPY derivatives containing bromine atoms have been found to have significantly stronger SOCs than alkylated BODIPY derivatives outside the Frank–Condon region while they are nearly the same at local minima. Based on calculated TD-DFT vertical excitation energies and SOCs, excited state dynamics of three BODIPY derivatives were further explored with TD-DFT surface hopping molecular dynamics employing a simple accelerated approach. Derivatives containing bromine atoms have been found to have very similar lifetimes which are much shorter than those of the derivatives possessing just the alkyl moieties. However, both bromine atoms and alkyl moieties reduce the HOMO/LUMO gap, thus assisting the derivatives to behave as efficient photosensitizers.

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Combination of Time-Resolved Spectroscopies and Theoretical Models to Disentangle Ultrafast Photoprocesses. Double Thionated Pyrimidine: a Molecular Tools with Tunable Photoproperties

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Recent advances in theoretical models enable to utilize the computational tool as a virtual ultrafast optical spectrometer [1], allowing to deliver and disentangle very different time-resolved optical spectroscopies. The discovery of unpredicted ultrafast photoprocesses opens the door to potential directions of development driving vs future unexpected employments.

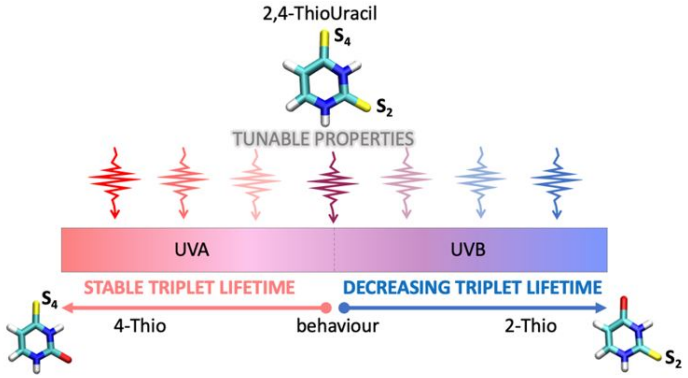

Fig. 1: An overview of the tunable properties of the double thionated 2,4-DTU. The photoinduced properties are smoothly changing by moving across the LA spectrum. The absorption band's extremes closely resemble the singly substituted 4-TU and 2- TU behaviors.

Thiobases [2], sulfur-substituted nucleobase analogs, show entirely different photophysical properties compared to the canonical bases despite having a very similar chemical structure. Instead of high photostability, they exhibit characteristic ISC processes with high yields of triplet states crucial to their applicability in wide range of potential technologies in medicine, structural biology and possibly in the development of organic light-emitting diodes (OLEDs), emerging in ever more applications. However, a comprehensive understanding of the interesting non-negligible wavelength-dependent changes of in the internal conversion (IC) and ISC events, observed for the double thionated thioUracil, is still lacking. Using joint experimental gas-phase time-resolved photoelectron spectroscopy (TRPES) and theoretical quantum chemistry methods we can now explain how different photodecay processes are induced by increasing excitation energies along the entire linear absorption (LA) ultra-violet (UV) spectrum. [2] The disentangled underlying mechanisms reveal that multiple decay processes can be initiated with different ISC rates or triplet state lifetimes that interestingly resemble the distinctive behavior of the singly substituted 2- or 4-Thiouracil, just smoothly moving the pump pulse to decreasing energies. We, then, obtain a clear partition of the LA spectrum, where different photoinduced processes can be obtained by a minor change in excitation wavelength across the UV-A and UV-B windows, conferring significant flexibility advantages to 2,4-DTU over singly substituted Thiouracils. Lifetimes and formation rates of triplet states become properties that can be easily tuned and controlled depending on the criteria required for biological or technological purpose.

What Are the Minimal Folding Seeds in Proteins? Experimental and Theoretical Assessment of Secondary Structure Propensities of Small Peptide Fragments

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Certain peptide sequences, some of them as short as amino acid triplets, are significantly overpopulated in specific secondary structure motifs in folded protein structures. [1] For example, 80% of the EAM triplet is found in α-helices, and only 3% occur in the extended parts of proteins (typically β-sheets). In contrast, the VIV and IYI appear almost exclusively in extended parts (80% and 69%, respectively). [1] In order to determine whether such preferences are structurally encoded in a particular peptide fragment or appear only at the level of complex protein structure, NMR, VCD, and ECD experiments in methanol and N,N-dimethylformamide were carried out on selected tripeptides: EAM (denoted as pro-'α-helical' in proteins), KAM(α), ALA(α), DIC(α), EKF(α), IYI(pro-β-sheet), and VIV(β). The values of the $^{3}J_{NH,H\alpha}$ coupling constants clearly showed that the pro-helical vs. pro-extended propensities start to emerge at the level of tripeptides. This tendency is confirmed by *extensive quantum mechanical conformational sampling* and by VCD and ECD spectra. This enabled us to conclude that the secondary structure of proteins starts to appear at the level of short peptide sequences and these can be considered as minimal "folding seeds". Admittedly, this inherent secondary structure propensity can be overruled by the large intramolecular interaction energies within the folded and compact protein structures. As has been shown previously, there are many patches within the protein chain that may easily have strain (deformation) energies of 5 kcal.mol^{-1} per amino acid. [2] Still, the correlation of experimental and computational data presented herein suggests that the propensity should be considered as one of the key factors that may lead to understanding the underlying physico-chemical principles of protein structure and folding from the first principles. [3]

Acknowledgements: Support of the Czech Science Foundation (GA CR grant 23-05940S) is acknowledged. Calculations were mostly carried out at the IT4Innovations National Supercomputing Center (grant e-INFRA CZ, ID:90254 of the MSMT CZ).

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Further Advances and Challenges in Refining Polarizable Molecular Mechanics/Dynamics Potentials. Applications of Polarizable MD for Major Groove, Sequence-Selective Targeting of B-DNA.

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In the first part of this presentation, we present the present status of refining the SIBFA potential [1] grounded on SAPT/DFT perturbation analyses [2] [3]. These concern cooperativity/anticooperativity, transferability from bi- to multimolecular complexes, the construction of a force-field for proteins and nucleic acids, prospects of MD simulations [4], and how to benefit from machine-learning to extract parameters from SAPT/DFT.
In the second part, we present the design of oligopeptide-intercalators destined to recognize in the major groove of B-DNA a six base-pair palindromic sequence, d(GGCGCC)2, encountered in oncogenes and retroviruses. The MD simulations are done with a polarizable potential, AMOEBA 18 [5]. They support the long-time duration stabilization of complexes in which, the intercalator being anchored at the central d(CpG)2 intercalation site, two arms at two of its symmetric ends bind in-register to O6/N7 of the two successive G bases upstream on both strands [6] [7]. Extension to trisintercalating complexes are done further, with the additional possibility of inducing controlled kinks at the two additional intercalation sites [8].

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Off-diagonal Thermodynamics and Its Effect on Reactivity

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We formulated an original and unique theoretical framework aiming at the prediction of C-H bond activation reactivity. [1–3] In its current form, it features two thermodynamic factors that we named asynchronicity and frustration that together modulate coupled proton-electron transfer reactivity. Only after addition of these two factors to the classical well-documented effect known as linear free energy relationship a complete thermodynamic basis for the control of reactivity/selectivity is formed. In principle, each of the two factors and their combination enable changing the preference of which C-H-bond is likely to be activated that would be otherwise driven by LFER, which favors the weakest C-H bonds in molecules. To demonstrate the power of the approach, we will show and discuss H-atom abstraction reactivity of several transition-metal complexes and organic radicals. Finally, we also discuss the generalization of the approach to reactions with radical group transfer.

Acknowledgements: The financial support of the Grant Agency of the Czech Republic (Grant No. 21-10383S).

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From Bulk to Surface – Transferability of Water Atomic Charges

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The purpose of many molecular dynamics simulations is to describe molecular systems at the interface, for example, water/air interface. The force fields applied often encounter problems with the correct reproduction of the surface tension of water, which affects the surface pressure isotherms of monolayer films. In this work, it was checked to what extent the charge distribution of a water molecule is modified during its movement from the bulk phase to the interface area, and whether such a change may affect the monolayer properties. To describe the transfer process, the method of self-consistent polarization for subsystems citeone, two, three was used. The studies utilized a hundred of hemispherical clusters with different radii (see Fig. 1) cut from molecular dynamics trajectories. It was demonstrated that, both on the surface and in bulk, charge distribution is significantly modified due to the presence of explicit water molecules (isolated molecules charges) as compared to vacuum. The polarization of environment is also important, though the changes in charge distribution were smaller in magnitude then those involved by direct environment effect. Polarization upon transfer of the molecule from the surface to bulk was c.a. 5% relative to the surface charge value, which corresponds to c.a. 0.04 e^-. The modified, interface-derived, charge distribution in water molecule improved its surface tension and had qualitative influence on the results of MD simulations of a DPPC monolayer spread on pure water. Employment of bulk-derived charges did not have such an improving effect on the simulations.

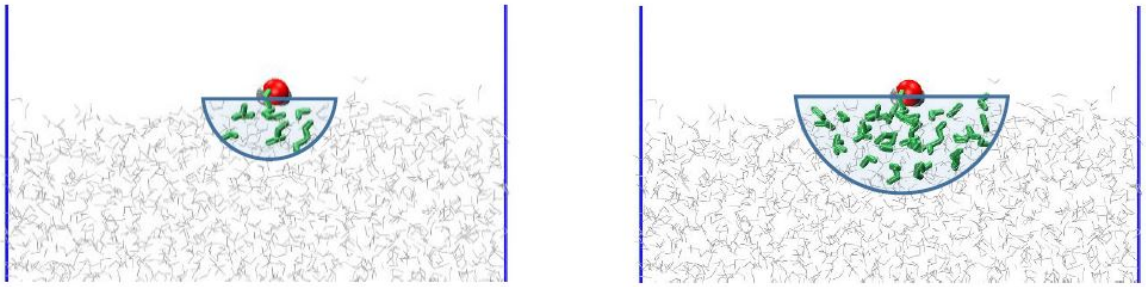

Fig. 1: Side view visualization of hemispherical water clusters used in the self-consistent polarization method for the interfacial water.

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Kinetic and Potential Energy Contributions to a Chemical Bond from the Charge and Energy Decomposition Scheme ETS-NOCV

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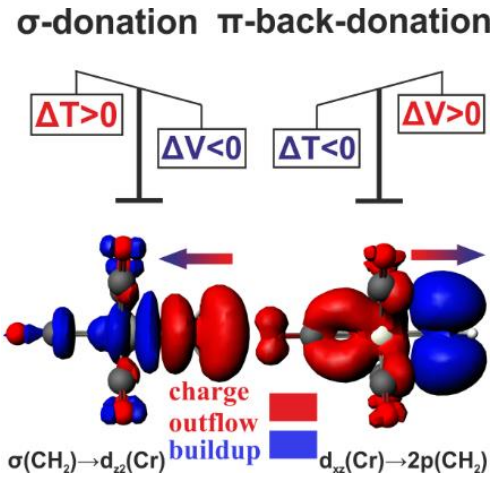
Department of Theoretical Chemistry, Faculty of Chemistry,Jagiellonian University, R. Ingardena 3, 30-060 Kraków, Poland



This talk highlights qualitative and quantitative relation between the Natural Orbitals for Chemical Valence (NOCV) based chemical bonding channels $\Delta\rho_i$ (i= σ, π, δ, etc.) and the corresponding kinetic ΔT_i and potential energy ΔV_i contributions within the charge and energy decomposition scheme ETS-NOCV implemented in the Kohn-Sham based Amsterdam Density Functional (ADF) package. [1] It is unveiled, that inter–fragment dative and covalent-type electron charge reorganizations upon formation of a series of strong and weak bonds employing main-group elements are due to lowering of the negative kinetic energy contributions, as opposed to the intra–fragment charge delocalizations (e.g. hyperconjugations in ethane) which are, in contrary, driven by the potential energy (electrostatic) component. [1] Complementary, formation of π-contributions in $N_2$is accompanied by lowering of both kinetic and potential energy constituents. Remarkably, well-known globally stabilizing back-donation (M $\rightarrow$ ligand, where M is a transition metal) and donation (ligand $\rightarrow$ M) processes, ubiquitous in organometallic species, have been discovered for the first time to be driven by the opposite $\Delta T_i/\Delta V_i$ mechanisms – namely, the former contribution is associated with the negative kinetic term (which outweigh the positive potential energy), whereas the latter charge delocalization into electrophilic transition metals leads to an attractive electrostatic stabilization (and positive kinetic energy), [1] see the attached top-left figure.

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Dioxygen Activation on Binuclear Transition Metal Centres

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The C-H bond activation in alkanes is a cumbersome process. There is a need for active and selective catalyst for precise functionalisation of inert hydrocarbons. Moreover, these catalysts have to meet requirements for sustainable chemical production including environmentally friendly technology and oxidation agents. To approach this challenge, various oxidation catalysts are developed and examined. In the Nature there exist a number of very active and selective oxidation systems, in particular enzymes bearing transition metal centres. While many of them have single metal ions, there are also those with centres containing two metal ions located in proximity to each other. Such binuclear active sites with two iron ions are observed e.g., in soluble methane monooxygenase. Thus, there are two metal ions that are involved in the reaction and can react with various molecules – oxidants what can lead to formation of the reactive oxygen species (ROS).

In this context, we explored the reactivity of the inorganic active sites in enzymes as modelled by Fe, Ni, Co, and Mn porphyrin (Por) dimers towards the dioxygen molecule. Our quantum chemical calculations were performed within Density Functional Theory (DFT) with def2-TZVP basis sets for all atoms. The B3LYP and PBE functionals with the +D3 dispersion correction were employed. All calculations were done with the Turbomole program.

The series of metalloporphyrins placed face-to-face at different distances with O_2 located between the metal ions were studied. This allowed us to explore the influence of the type of metal ions and their separation on the ability to split O_2 and form ROS. Our calculations show that all investigated metal ion pairs can bind the oxygen molecule located between them, what is manifested by elongation of the O-O bond. However, for the Fe(II) ions this effect is the strongest, allowing for the O-O bond dissociation and formation of the high-valent oxo species. The performed calculations allowed to determine the energy barriers connected with the O-O bond splitting and their dependence on the distance between the ions.

Our results are consistent with the DFT studies of analogous metal ions incorporated into zeolite matrices, done in J. Heyrovsky Institute of Physical Chemistry, Prague (JHI), and may be helpful in modelling new catalysts in future.

Acknowledgements: This work was supported by the National Science Centre, Poland grant no. 2020/39/I/ST4/02559 and by the Czech Science Foundation project # 21-45567L, the RVO: 61388955. We gratefully acknowledge Polish high-performance computing infrastructure PLGrid (HPC Centers: ACK Cyfronet AGH) for providing computer facilities and support within computational grant no. PLG/2020/013927.

Investigating Substrate Site and Allosteric Site Inhibitors of MTHFD2 by Computational Modeling

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UPR-dependent metabolic reprogramming diverts metabolites from glycolysis to mitochondrial 1C metabolism, highlighting pharmacological resistance to folate drugs and overexpression of certain enzymes. Methylenetetrahydrofolate dehydrogenase (MTHFD2) is a mitochondrial enzyme that plays a key role in 1C metabolism in purine and thymidine synthesis and is exclusively overexpressed in cancer cells, but absent in most healthy adult human tissues. A close homolog known as MTHFD1 which shares 53.6% sequence similarity with MTHFD2, is present in healthy adult tissue, thus raising selectivity concerns in the development of MTHFD2 inhibitors. To the best of our knowledge, tricyclic coumarin-based compounds (substrate site binders) and xanthine derivatives (allosteric site binders) are the only selective inhibitors of MTHFD2 reported till date. We here present a detailed investigation of available structural data of MTHFD2 in complex with potent and selective inhibitors that occupy either the substrate site or the allosteric site, further providing insights into binding mode, key protein-ligand interactions and conformational dynamics, that correspond to the experimental binding affinities and biological activities. Xanthine derivatives have reportedly shown conformational changes at the allosteric site of MTHFD2, that were further verified by molecular dynamics simulations and RMSF analysis. In addition, we carried out structure-based drug design on the substrate binding site of MTHFD2, by exploiting the cocrystallized structure of MTHFD2 with a tricyclic coumarin-based inhibitor. Structure-based drug design campaign involving R-group enumeration, bioisostere replacement, molecular docking, ADME prediction, MM-GBSA binding free energy calculations and MD simulations, led to a small library of new compounds, capable of selectively inhibiting MTHFD2. To confirm selective MTHFD2 binding, the existing and proposed inhibitors were evaluated by implementing the same computational protocol on the cocrystal structure of MTHFD1. The results reported herein are expected to benefit medicinal chemists working on the development of selective MTHFD2 inhibitors for cancer treatment.

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Interaction of Radiopharmaceuticals with Somatostatin Receptor 2 Revealed by Molecular Dynamics Simulations

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The development of drugs targeting the somatostatin receptor 2 (SSTR2), generally overexpressed in neuroendocrine tumors, is the focus of intense research. A few molecules in conjugation with radionuclides are in clinical use for both diagnostic and therapeutic purposes. These radiopharmaceuticals are composed by a somatostatin analogue bio-vector conjugated to a chelator moiety bearing the radionuclide. To date, despite valuable efforts, a detailed molecular-level description of the interaction of radiopharmaceuticals in complex with SSTR2 has not yet been accomplished. Therefore, in this work, we carefully analyzed the key dynamical features and detailed molecular interactions of SSTR2 in complex with six radiopharmaceutical compounds selected among the few already in use (^{64}Cu/^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{64}Cu-SARTATE) and some in clinical development (^{68}Ga-DOTANOC, ^{64}Cu-TETATATE). Through molecular dynamics simulations exploiting recently available structures of SSTR2, we explored the influence of the different portions of the compounds (peptide, radionuclide, chelator) in the interaction with the receptor. We identified the most stable binding modes and found distinct interaction patterns characterizing the six compounds. We thus unveiled detailed molecular interactions crucial for recognition of this class of radiopharmaceuticals. The microscopically well-founded analysis presented in this study provides guidelines to the design of new potent ligands targeting SSTR2.

Acknowledgements: We gratefully acknowledge "Progetti biennali d'Ateneo Finanziati dalla Fondazione di Sardegna, annualità 2020" (University of Cagliari) and the Health Extended ALliance for Innovative Therapies, Advanced Lab-research, and Integrated Approaches of Precision Medicine partnership (HEAL ITALIA), founded by the Italian Ministry of University and Research, PNRR, mission 4, component 2, investment 1.3, project number PE00000019 (University of Cagliari). We thank Giovanni Serra and Fabrizio Cosimo Muredda (University of Cagliari) for technical assistance with computational resources.

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Molecular Dynamics Study of Nanoplastics in Lipid Environment

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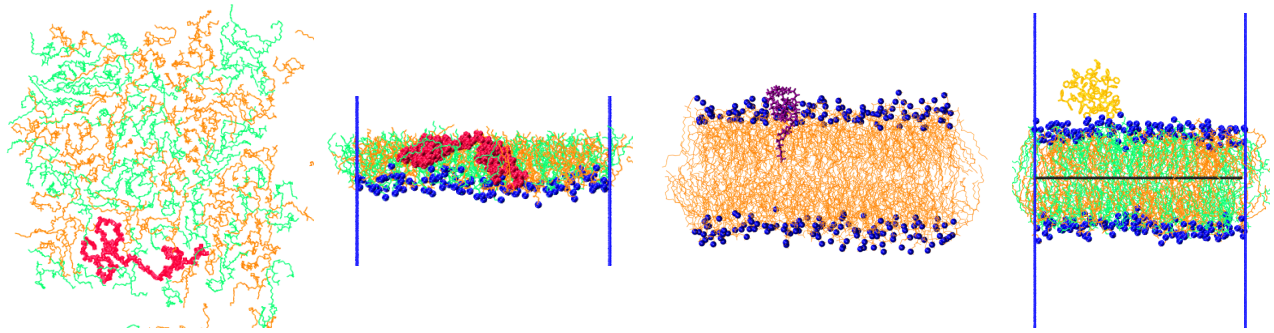
Plastic pollution has art of air pollution. Particles with diameter below 2,5 µm, penetrate the lungs and may enter body tissues. Lipid membranes form barriers which they must cross before entering the body. In lungs this is the lung surfactant (LS) system. It is a surface film spread on alveolar subphase covering pulmonary epithelial cells. On the microscopic level LS has a complex structure composed of a monolayer and multilamellar reservoirs associated with it. After crossing LS, NPs meet cellular membranes which also have to be crossed.

In this study, interactions between model lipid monolayers and bilayers with model NPs was examined by means of classical all-atom molecular dynamics simulations. NPs of polyethylene (PE), polypropylene (PP), polystyrene (PS), and polylactic acid (PLA) with varying size were introduced into phospholipid membranes. Varying composition of the monolayers and bilayers was used in order to mimic different environments, i.e. LS vs epithelial cells' cellular membrane. Adsorption processes, NPs affinity towards lipids, the particle's fate in lipid environment, the impact of NPs adsorption on membrane structure, and vice versa were analyzed.



(a) (b) (c) (d)

Fig. 1: Examples of studied systems: top (a) and side (b) view of PLA in 1:1 DPPC:POPC monolayer; (c) PE adsorbing to POPC bilayer; (d) PS on the surface of 1:1 DPPC:POPC bilayer. Color code: red – PLA, purple – PE, yellow – PS, green – DPPC tails, orange – POPC tails, blue – N atoms from lipid headgroups, water is not shown.

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Will Chloroquine Be Able to Treat Malaria Again?

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Since malaria remains the most prevalent parasitic disease, solution of its suppression is a long-term problem. Over the course of several decades, this solution was the drug chloroquine, but later the resistance to this drug appeared. The main cause of malaria resistance is considered the PfCRT protein, the structure of which was determined in 2019. Mutated resistant versions of this protein render treatment ineffective – the generally accepted hypothesis is that the protein transports drug molecules out of the vacuole. Using molecular dynamics, structural and functional changes of the PfCRT protein influenced by individual mutations and their combinations in selected resistant strains of Plasmodia are described. The effect of structural changes in the PfCRT protein induced by the binding of probable natural substrates (peptides formed by the splitting of heamoglobin) is also studied. In conclusion, the results of the influence of mutations on the ability to transport the drug through the membrane are presented.

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How May Metronidazole Work as a Radiosensitizer?

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Nitroimidazoles are a group of compounds, which – in addition to their antibacterial and antiparasitic properties – can act as oxygen mimetics enhancing radiotherapy of radioresistant tumors. Despite almost half a century of research on nitroimidazoles as radiosensitizers, their mode of action remains unclear. O'Neill's group suggested a radical mechanism, in which hydroxyl radical attacks the pyrimidine ring, producing hydroxypyrimidine radical, which is prone to attach nitroimidazolic compound, leading eventually to DNA single strand break. [1] On the other hand, Edwards suggested that a nitroimidazole drug accepts a secondary electron, and the produced anion radical is then protonated to its neutral radical form. Such a radical should be able to induce oxidative damage to DNA. [2]
To understand the molecular mechanisms of action of nitroimidazolic oxygen mimetics, we analyzed the behavior of their well-known representative – metronidazole – versus two main products of water radiolysis: hydroxyl radicals and secondary electrons. To this purpose, we employed stationary and pulse radiolysis, as well as quantumchemistry and QSAR modeling. Our finding suggests that nitroimidazole's mechanism of action is bound with electrons rather than with hydroxyl radicals. Moreover, we found a path, which shows that nitroimidazoles after electron attachment and protonation may be a source of toxic nitrogen dioxide inside the irradiated cell. We suggest, that NO_2 could be responsible for the sensitization of hypoxic radioresistant cancer cells to irradiation during enhanced radiotherapy. Understanding the mechanisms of action of nitroimidazoles as radiosensitizers should enable the rational design of such type of drugs.

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

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Differences and Similarities in Benzene/Benzene and Water/Water Interactions

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Considering properties of water and benzene molecules, one can expect very different benzene/benzene and water/water interactions. Benzene does not have a dipole moment, while water has. Quantum chemical calculations showed that minima on potential surface of water/water interactions is hydrogen bond, where dipole moment of water plays important role. The calculations show that the minima on potential surface for benzene/benzene interactions are stacking (parallel displaced) geometry and T-shaped geometry.

Analysis of the data in the crystal structures in the Cambridge Structural Database (CSD) revealed the most frequent benzene/benzene and water/water geometries. Majority of the benzene/benzene interactions in the crystal structures in the CSD are stacking interactions with large horizontal displacements, and not geometries that are minima on benzene/benzene potential surface. Large number of the water/water contacts in the CSD are hydrogen bonds, 70% of all attractive water/water interactions. In addition water/water contacts with two water forming antiparallel interactions are 20% of all attractive water/water contacts. In these contacts O-H bonds of water molecules are in antiparallel orientation (Fig. 1). In benzene/benzene interactions at large horizontal displacements two C-H bonds also are in the antiparallel orientation (Fig. 1).

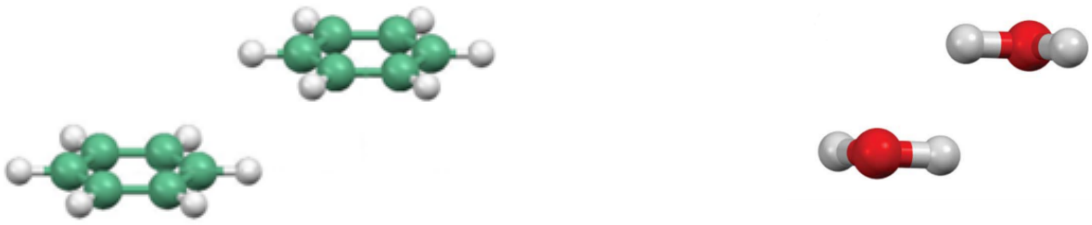

Fig. 1: Examples of benzene/benzene interaction at large horizontal displacement and antiparallel water–water interaction

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Interaction of High-Valent Metals with Intrinsically Disordered Proteins and Peptides: Insight from Simulations

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Metals play a very important role in biological systems. They can act as catalytic and structural cofactors, and although present in small quantities, they are fundamental for the normal function of biological systems. However, they can also be important toxins, when non-biological metals are present in the cell or the correct homeostasis of biometals are altered. Elucidating the effect of a multivalent metals in biological systems require the understanding of their physico-chemical characteristics, and an understanding of how they interact with biological molecules. In this sense, high-level computational modeling is a fundamental tool to characterize these interactions. In the present talk we revise recent work carried out in the group in this area. In particular we will show examples of how metal interaction is key to induce structure in intrinsically disordered proteins and peptides (IDPPs). Due to their prevalence in disease, the study of IDPPs has become of utmost importance. We will analyze how the binding of the metal alters the conformational landscape of disordered peptides and the effect that this change has on the conformational entropy of the system. We consider as a test case a 13mer KSPVPKSPVEEKG, a multiphosphorylation domain of certain neurofilaments. Finally, we will analyze mimosine-derived disordered peptides as a promising new type of metal chelators.

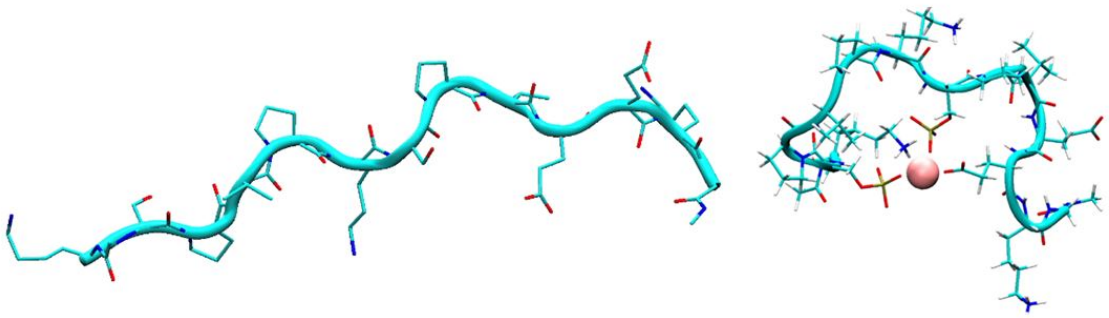

Fig. 1: Metal biding to a phosphorylated IDP

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Photodynamic Therapy. A Computational Viewpoint

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Photodynamic Therapy (PDT) is a non invasive medical treatment used in different field including different type of cancer and infections from bacteria. The main ingredients of PDP are a source of light at given wavelenghts, a photosensitizer and molecular oxygen. The contribution of theoretical and computational chemistry in the field should be presented and discussed. In particular, the discussion will be focused on the possibility to design new drug active in both chemo- and photo-dynamic therapy, by using density functional theory. The photophysical properties (absorption wavelengths, singlet-triplet energy gaps and spin-orbit matrix elements) of a series of photosensitizers should be presented.

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Emergence of the Spectroscopy of Resonance Raman Optical Activity

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Raman optical activity (ROA) has been first observed in 1973. [1] It measures tiny difference in scattering of the left and right circular polarized light. It can discriminate absolute configuration, and is more sensitive to conformation than unpolarized Raman spectroscopy. Typical applications involve sugars, proteins, and nucleic acids in aqueous solutions. Conveniently, the spectra can be simulated and interpreted using analytical density functional theory (DFT) methods. [2] With some computational tricks, spectra of proteins of several thousands of atoms can be calculated. [3]

However, Raman scattering is a very inefficient process. In addition, typical ROA/Raman signal ratio is only 10^{-4}. Therefore, several attempts to increase the sensitivity were proposed in the past. One of them is measuring the spectra of color absorbing samples. The excitation laser frequency is "in resonance" with an electronic transition. This condition can dramatically increase Raman signal, and even more the ROA component.

First such experiments were quite problematic, samples were often decomposing, and interpretation of the spectra was difficult. "Bizarre" results were obtained, such as ROA of non-chiral solvents. [4] Only lately, measurement techniques improved (e.g., using rotation cells), parasite signals stemming from electronic circular dichroism and chiral Raman scattering could be reliably subtracted (the ECD-Raman effect, Figure 1), and "true" vibrational resonance ROA spectra are available. [5] They provide unique information not only about geometrical, but also electronic molecular structure.

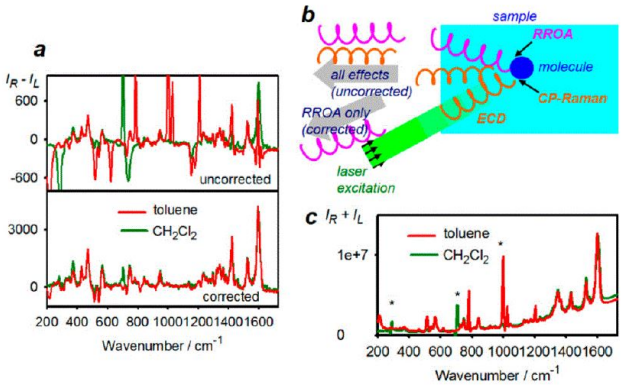

Fig. 1: a, c) ROA and Raman spectra of a resonance nickel complex is a mixture of solute and solvent signals, b) because of several events going on during light scattering in a color sample. These must be considered for correct interpretation. [6]

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Towards a New Protocol for Computer-Assisted Biocatalysts Design

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The origin of enzyme catalysis remains a question of debate despite much intense study. The biggest challenge is to define the common property responsible for speeding up chemical reactions in active sites of enzymes. In this presentation, we focus on three not related enzymatic models i.e protease of HIV-1 (PR), [1] glycine N-methyltransferase (GNMT) [2], and HG.3 and HG3.17, de novo design enzyme Kemp eliminase [3, 4] in order to investigate their common features crucial for catalysis.

Herein, we report the results of QM/MM theoretical studies for (a) peptide bond cleavage in a multi-step reaction catalyzed by HIV-1 PR, (b) the SN2 methyl transfer reaction catalyzed by GNMT, and (c) kemp elimination catalyzed by two de novo enzymes, HG3.17, and HG.3. In general, our studies indicate the importance of the electrostatic properties of the protein in the active site. Thus, in the multi-step reaction catalyzed by HIV-1 PR, the electric field created by the protein in the active site of the enzyme emerges as being critical for the electronic reorganization required during the chemical process. Additionally, the decomposition of the electrostatic forces generated by the protein in the scissile peptide bond on the rate-limiting transition state would favor the peptide bond cleavage.

Finally, a rational QM/MM molecular dynamics strategy based on combining the best electrostatic properties of enzymes with activity in a common reaction is presented. The computational protocol has been applied to the re-design of the protein scaffold of an existing promiscuous esterase from Bacillus subtilis Bs2 to enhance its secondary amidase activity. After the alignment of Bs2 with a non-homologous amidase Candida antarctica lipase B (CALB) within rotation quaternions, a relevant spatial aspartate residue of the latter was transferred to the former to favor the electrostatics of transition state formation, where a clear separation of charges takes place. [5]

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Poster Abstracts

Hydrogen bonding in complexes of coinage metals

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Gold(I) complexes with charged ammonium groups represent some of the rare examples of metal-hydrogen bonds. [1, 2] We have recently predicted that similar interactions, albeit weaker, could be possible with lighter coinage metals – silver and copper, [3] given appropriate geometry-enforcing ligand scaffold. In this contribution, we will summarize our findings of gold(I)-hydrogen bond and also present the results of our experimental attempts to identify hydrogen bonding in AgCl and CuI complexes various ligands, including protonated Me-DalPhos (Figure 1), where such interactions might be enforced by complex's geometry. The complexes, which so far could not be isolated in condensed phase, have been studied by measuring their infrared spectra in the gas phase using helium-tagging infrared photodissociation spectroscopy.

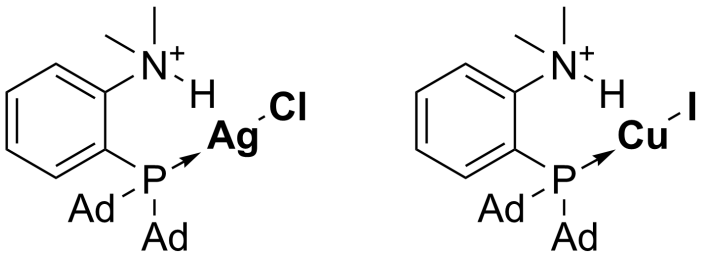

Fig. 1: Structures of studied complexes

Our results indicate that metal-hydrogen bonding might be realized, given enough constraints, also in exotic systems such as Ag(I) complexes. Even though such interactions are unlikely to important for determining chemical structure, they might play a role in modulation of chemical reactivity of metal centers.

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Cis/Trans Effects in the Pt(II)-Complexes

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Cis/trans effects were studied on the *cis/trans*-$[PtCl(NH_3)_2(pyrX)]^+$ and *cis*-$[PtCl_2(NH_3)(pyrX)]$ (pyr = pyridine; X = H, CH_3, NO_2, NH_2) complexes. The influence of the substitution effects of the pyrX ligand on the kinetics of the first activation step (hydrolysis reaction) of the complexes and their properties were studied, and both Cl^- ligands were considered as possible leaving groups in the case of the latter complexes.
The substitution of the pyrX ligand led to quantitatively similar changes in the reactivity of the Pt(II) complexes with respect to the *cis*-Cl^- / trans-Cl^- leaving ligands. The neutral *cis*-$[PtCl_2(NH_3)(pyrX)]$ complexes exhibited lower sensitivity of the reaction rates with respect to the pyrX ligand modifications than the positively charged ones, probably due to lower differences in electron donation.
No intrinsic difference in the lability of the two Cl^- ligands in the *cis*-$[PtCl_2(NH_3)(pyrX)]$ complexes was found: the binding energies were almost exactly the same, even though the *cis*-Cl^- ligand exhibited higher electron donation due to the lower trans-effect of the trans-positioned NH_3 ligand compared to the pyrX ligand. Indeed, no preferable site for the nucleophilic attack was detected in the water solvent. In the gas phase, the preferred site for the nucleophilic attack to cis-amminedichloropyridineplatinum was clearly the trans-Cl^- ligand due to electrostatic stabilization of the transition state.

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Molecular Structure and Fluorescence Spectrum Analysis of Fisetin.

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Fisetin (F), also known as 3,3',4',7-tetrahydroxyflavone, is part of a group of natural substances called flavonoids which offers a lot of benefits to human health having anti-inflammatory, anticarcinogenic and antioxidant properties [1]. F can be found in a wide variety of comestible plants, fruits and vegetables such as strawberry, apple, grape, onion and many others [2].
In this work we compute absorption's and emission's characteristic wavelength and energies of Fisetin´s molecule in vacuum and a solvent, based on the Density Functional Theory (DFT) using Gaussian16 and the Minnesota functional M06-2X with the 6-31++G(d,p) basis set. These calculations are compared with F powder´s fluorescence (FL) spectrum and also FL spectrum of F solutions in methanol and propylene glycol.

	Absorption		Emission	
	Vacuum	Methanol	Vacuum	Methanol
ΔE (eV)	4.01	3.91 (3.86)	4.30	3.11 (3.2)
λ (nm)	309	317 (321)	354	398 (388)

Table 1: Absorption and emission characteristic wavelength and energies of F molecule for enol O3 configuration.

	Absorption		Emission		FL maxima	
	Vacuum	Methanol	Vacuum	Methanol	Powder	Methanol solution (0.16 mM)
ΔE (eV)	2.8	2.85 (3.06)	2.5	2.29 (2.63)		
$\lambda(nm)$	443	435 (405)	498	543 (472)	527	509

Table 2: Absorption and emission characteristic wavelength and energies of F molecule for keto O3 configuration.

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Gallium as an Antibacterial Agent: A DFT/SMD Study of the Ga^{3+}/ Fe^{3+} Competition for Binding Bacterial Iron Acquisition Systems

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The importance of discovering new antibacterial drugs, with diverse therapeutic mechanisms beyond antibiotics, has led to the identification of bacteria's iron acquisition systems (siderophores) as a promising target. Siderophores are secreted by bacteria to capture iron(III) from their environment by binding the essential metal with high affinity. Gallium, an "abiogenic" ion known for its anticancer, antibacterial, and anti-inflammatory properties, is intriguing due to its ability to closely resemble the ferric ion. This similarity raises questions about whether gallium can effectively compete with native ferric ions for binding to siderophores. Understanding the molecular characteristics that favor Ga^{3+} binding over Fe^{3+} binding is of particular interest.
Furthermore, it is observed that while gallium-based therapy is effective against certain bacteria, it is not equally successful against others. To decipher the reasons behind this discrepancy, the researchers are using computational chemistry tools at the DFT/SMD level to assess the free energy of the competition between Ga^{3+} and Fe^{3+} ions for various structures, denticities, and charge states of siderophore ligands. The results not only align with recent experimental data but also contribute to our understanding of "Trojan horse" gallium-based therapy.

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Fragment Dissolved Molecular Dynamics, Uncovering New Opportunities in Drug Design

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As a response to the popularization of fragment-based strategies in drug design, fragment dissolved Molecular Dynamics (fdMD), a systematic semi-automatic methodology based on molecular dynamics simulations of the target protein solvated with multiple copies of the same ligand, was developed [1]. As a result, better exploration of the system is achieved, thereby facilitating the identification of the most favorable binding sites for the system through the use of a set of descriptors.
To accelerate the identification of binding sites and reduce the effect of possible false positives, Gaussian accelerated Molecular Dynamics (GaMD) [2] has been introduced to the fdMD methodology. As a result, it has been possible to hasten the identification of possible drug candidates (hits), considerably mitigating the effect of possible false positives and thus enabling faster and more efficient identification of the most favorable binding sites without any previous knowledge of the experimental binding site. To validate the effectiveness of the methodology, a set of systems with crystallographic information available have been studied, obtaining promising results.

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Charge Transport Properties of Cytochrome b_{562} in Junctions between Metal Contacts

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Life-sustaining processes, including respiration, photosynthesis, and various enzymatic catalytic activities, rely on electron transfer reactions mediated by redox proteins. One such protein, cytochrome b_{562} (Cyt b_{562}) found in *Escherichia coli*, contains a redox-active heme ($Fe^{2+/3+}$) cofactor bonded to the protein matrix, coordinated by axial histidine (His102) and methionine (Met7) ligands (Fig. 1). The conductive properties of a single Cyt b_{562} adsorbed on gold surfaces were recently investigated using electrochemical scanning tunneling microscopy (EC-STM) [1]. Here, we examine the related adsorption structures by using computational techniques to elucidate the charge transport properties and mechanisms.

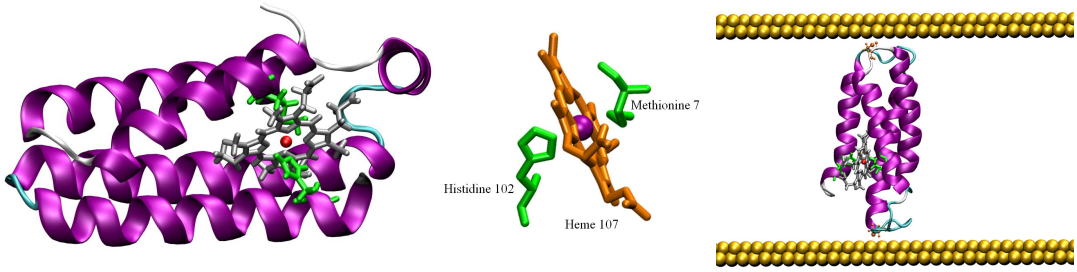

Fig. 1: Cytochrome b_{562}: (a) crystal structure (PDB id 2BC5); (b) detail of the heme (orange) redox site with the axial His102 and Met7 residues (green) coordinated to the central iron cation (purple sphere), (c) junction structure between the gold contacts.

We combine classical molecular dynamics (MD) and density functional theory (DFT) to investigate adsorption interactions and electronic states at the protein/metal interfaces and junctions [4]. We simulate the adsorption of mutated Cyt b_{562} on the flat gold (111) surface and use the obtained structures for the preparation of the cytochrome junctions between gold contacts. To predict the electronic-state alignment, we apply the DFT+Σ approach, followed by metal/protein coupling calculations using the projection operator-based diabatization (POD) method. Finally, the tunneling currents are evaluated within the Landauer formalism [2, 3], and the obtained conductance is compared with the experimental data. The results confirm the coherent tunneling as the charge-transfer mechanism in the Cyt b_{562} junction, in agreement with the previously investigated biomolecular junctions involving other proteins.

Acknowledgements: This project was supported by Czech Science Foundation (Project 20-02067Y). We are grateful for the computational resources provided by Metacentrum Vo and IT4Innovation National Supercomputing center of the Czech Republic.

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Design of Potent Cyclic Peptides for Lead Detoxification using Quantum Mechanics Methods

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We used DFT methods with COSMO/COSMO-RS implicit solvation to design a series of cyclic peptides that selectively bind toxic Pb(II) ion and eradicate its toxic effect on the cellular level, with superior potency than state-of-the-art drugs.

Using methodology developed in our previous work to calculate the binding constant of Pb(II), we computationally screened different variations of the scaffold and identified promising binders, five of which were subjected to *in vitro* testing, which revealed their enhanced Pb-detoxification capability due to high Pb-affinity and selectivity. The Pb-peptide complexes are strong and stable and was characterized experimentally and computationally. Accompanied by the lack of toxicity and enhanced stability of this peptide, these qualities indicate merit of these as a potential remedy for Pb poisoning.

Aiming to explore the advantages of noncanonical amino acids (ncAAs) of this nature, we studied the detoxification capabilities of peptides containing β-Mercaptoaspartic acid, each of which contains at least one ncAA. A thorough investigation that includes in vitro detoxification and mechanistic evaluations, metal-binding affinity, metal selectivity, and computational studies shows that these ncAAs are highly beneficial in additively enhancing Pb binding and reveals the importance of both high affinity and metal selectivity in synergistically reducing Pb toxicity in cells.

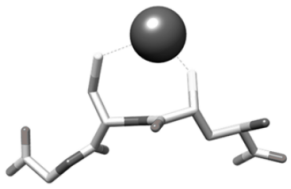

Fig. 1: Cyclic peptide with bound Pb(II) ion

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Catalytic Fields as a Tool to Compare Homologous Enzyme Variants and Reaction Mechanisms

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Static catalytic field Δs derived from the wavefunctions of transition state and reagent models represents the charge distribution of a molecular environment exerting optimal catalytic activity for any chemical reaction [1, 2]. It can be used to evaluate the catalytic role of specific amino acid residues, and the gradient of Δs was even used to discover the paths of concerted proton dislocation along the reaction pathway [3].

An analysis is presented for the reaction catalyzed by a family of homologous histydyl t-RNA synthetases, and despite very low sequence identity, the arrangement of the strictly conservative charged residues is complementary to the catalytic field Δs. In principle, it could even be used to validate alternative enzyme reaction mechanisms, as exemplified for three alternative reaction mechanisms proposed in the literature [4].

Keywords: catalytic field, differential transition state stabilization, enzymatic catalysis, reaction mechanism.

Acknowledgements: Research sponsored by NCN grant No 2017/27/B/ST4/01327.

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Monitoring Biomolecules by Chiral Raman Spectroscopy and Molecular Dynamics

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Biomolecular conformational flexibility affects their biological functions. The spectroscopy of Raman optical activity (ROA) is well suited to structural analyses in aqueous solutions, but the link between spectral shape and geometry is complicated. To advance the methodology, we studied we analyzed Raman and ROA spectra of model nucleotides [1] and glutathione peptide [2] forms.

The spectra were interpreted on the basis of molecular dynamics (MD) combined with density functional theory (DFT). The simulated spectra correlated well with the experimental data and enabled us to better understand dependence of the spectral shapes on conformational dynamics. Decomposition of the experimental spectra into calculated subspectra provided conformer populations that could be compared with MD modeling.

The combination of ROA with the computations has the potential to improve the force field and obtain more precise populations of the conformers. However, some spectral features could not be explained, and better computational techniques are needed in the future to spectroscopically determine conformation of peptides and nucleic acids.

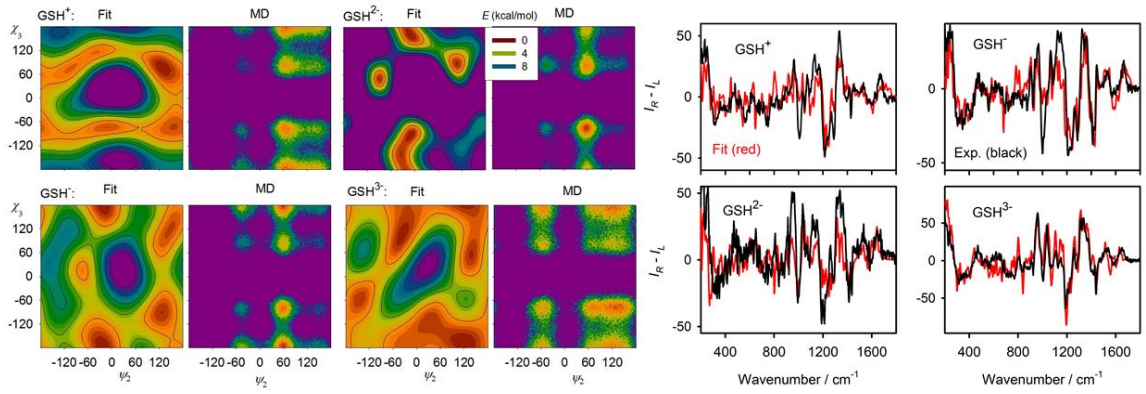

Fig. 1: Potential energies as functions of selected torsion angles obtained by the fit, and from free MD (left); experimental and fitted ROA spectra (right).

Acknowledgements: The work was supported by the Grant Agency (22-04669S).

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Protein Fragments as Modular Parts for Metalloprotein Design

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Metal ions are present in many proteins and enzymes. They are an invaluable asset in enzymatic catalysis, but also have structural function in some proteins. Multiple ways to design artificial metalloenzymes have been presented, including protein redesign based on known metalloenzymes, insertion of metal binding sites into stable folds, *de novo* design of metal-binding scaffolds, and machine learning approaches based on predetermined geometry of binding site. In our contribution, we approach metalloprotein and metalloenzyme design from a new standpoint. We take fragments from known protein structures and piecing them together to achieve desired geometries to achieve selective metal binding. The ideal binding site for a particular metal is selected based on systematic density functional theory (DFT) screening of possible binding sites. According to this ideal geometry, the fragments are connected to form a single short peptide (less than 60 amino acids) based purely on geometrical criteria. These short peptides are then ranked using molecular mechanics (MM) and DFT methods to find the best candidates for experimental verification of metal binding properties and potential catalytic activity.

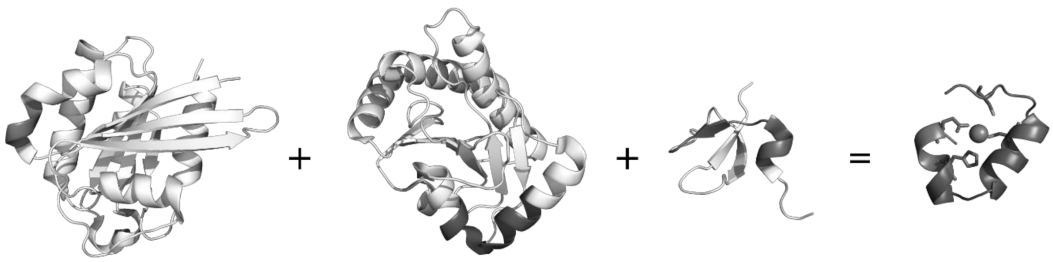

Fig. 1: Basic idea behind the concept of using protein fragments to design metallopeptides.

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Base-Pair Opening in Biased Molecular Dynamics Simulations

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Mismatched base pairs alter the flexibility and intrinsic curvature of DNA. The role of such DNA features is not fully understood in the mismatch repair pathway. MutS/DNA complexes exhibit DNA bending, PHE intercalation, and changes in base-pair parameters near the mismatch. Recently, we have shown that base-pair opening in the absence of MutS can discriminate mismatches from canonical base pairs better than DNA bending [1, 2].

We performed biased molecular dynamics simulations employing the Adaptive Biasing Force method to obtain free energy dependence on two collective variables (CVs). These were simple base-pair Opening and Shear. Opening was necessary to capture the mismatch discrimination properly. The inclusion of Shear into the calculations was a technical issue because the rearrangement of hydrogen bonding was found to be a rare event on the timescale of our simulations (~ 1 μs). While these two CVs worked nicely for *anti-anti* base-pair conformation, they were not too efficient for less common conformations, such as *syn-anti* and *anti-syn.*

This contribution will present an extension to our previous work, which addresses this problem. We will show the impact of different flavours of base-pair parameters, such as local and various extensions to simple variants compatible with 3DNA definitions, on the calculated free energy surfaces.

Acknowledgements:

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Coordinated Water as Hydrogen Bond Acceptor: Crystallographic and Quantum Chemical Study

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Among the rich variety of noncovalent interactions, hydrogen bond is probably the most famous one. Several studies have shown that metal coordination strengthens hydrogen bonds of water. [1] Most of these studies treated coordinated water as hydrogen bond donor. In this work, we have addressed the possibility of coordinated water as hydrogen bond acceptor.
A total of 1229 hydrogen bonds between coordinated water as hydrogen bond acceptor and uncoordinated water as hydrogen bond donor were found in the crystal structures deposited in the Cambridge Structural Database. These hydrogen bonds are somewhat longer and have lower tendency toward linear geometries than hydrogen bonds of donor coordinated water. Due to the close proximity of uncoordinated water to neighboring ligands, the observed hydrogen bonds are in most cases found together with additional interactions, which have a strong influence on the overall strength of the interactions. The B97D/def2-TZVP calculations show wide range of energies of observed hydrogen bonds (Figure 1), that depend on the charge of metal complexes and on additional interactions.

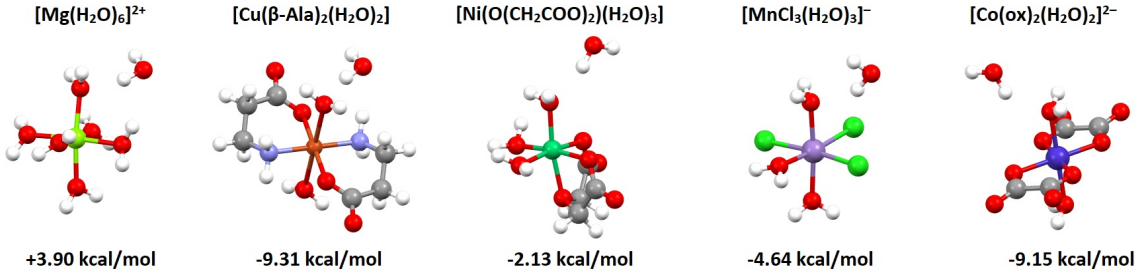

Fig. 1: Hydrogen bonds between coordinated and uncoordinated water and their B97D/def2-TZVP interaction energies.

This study suggests that hydrogen bonds of acceptor coordinated water are important contributors to the overall stability of supramolecular systems, even though they are weaker than hydrogen bonds of donor coordinated water.

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Conformational Classes, Conformational Preferences, and Conformational Transitions of Various DNA Dinucleotide Steps. Molecular Dynamics of Drew-Dickerson Dodecamer Revisited.

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The first atom-resolution results for duplex DNA structure [1] demonstrated variability of duplex 3D conformation, its dependence on nucleotide sequence and important contribution of its surroundings. More precise subsequent X-ray study [2] and Molecular Dynamics simulation during previous decades [3] supported these suggestions and demonstrated new features of DNA 3D structure formation. Extensive study of various DNA fragments and their complexes demonstrates extreme conformational variability of each dinucleotide step. Various local conformers, depending on their torsional angles and some other geometry characteristics, have been classified as the Conformational Alphabet of Nucleic Acids (CANA). [4]
We performed Molecular Dynamics simulation of the dodecamer with NDB ID 4C64 ns (NPT ensemble, 30°C, 1 atm), solvated with 4885 water molecules. We present the analysis of pathways of changes in the conformational parameters and conformation classes (CC) of dinucleotide steps along the trajectory. The results demonstrate differences in population of various conformational classes for each dinucleotide step of dodecamer. The main CC for all steps are BB00; BB01, BB07, BB04, while CC with one nucleoside of B family and other one of A family exist as well. Consideration of details of selected trajectory fragments for several steps demonstrates transition pathways between CC. Majority of such transitions include simultaneous change of the regions for two torsions. The results of population analysis of CC for various steps obtained in the MD study will be compared with the analysis for NDB and with computation results for isolated dinucleotide monophosphates.

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Computational Analysis of Zinc Binding Groups for Carbonic Anhydrase Inhibition

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Carbonic Anhydrases (CAs) are zinc based metalloenzymes which are an attractive drug target for the treatment of many diseases including cancer. Accurate prediction of relative binding affinities of CA inhibitors is key to accelerating the design and screening of improved drugs. High-level quantum chemical calculations are performed on a reduced active site model to gain a deeper understanding of the effect of the ligand structure on its binding affinity. A collection of thirty-three inhibitor molecules with systematic variations in their structures were studied where trends in binding energy is analyzed in terms of the deprotonation energy of the ligand and the donor atom-Zn (II) bond energy.

Acknowledgements: Support from the Research Training Program (RTP) scholarship is acknowledged. Calculations were performed at the NCI Gadi and UNSW Katana supercomputing centres.

Paramagnetic Host-Guest Complexes of Ruthenium(III) Compounds and Cyclodextrines

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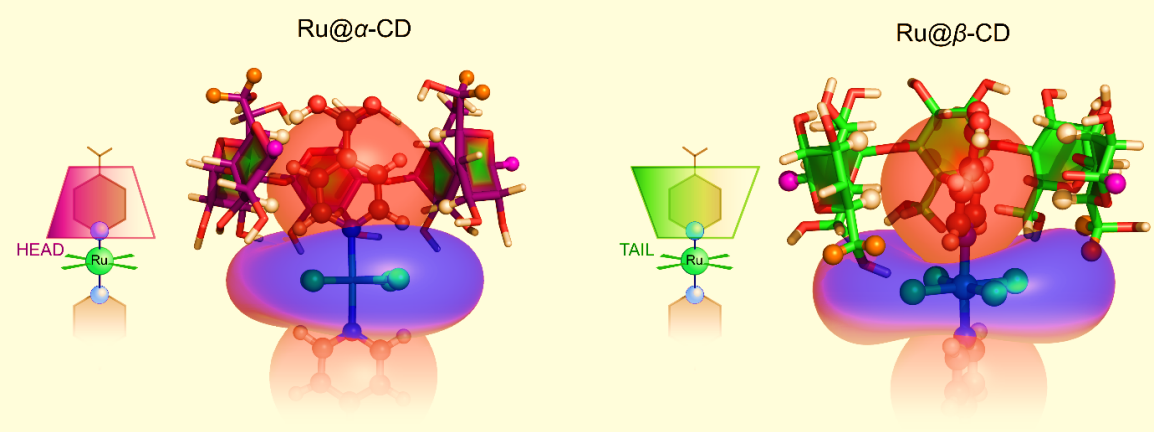
In this account, we utilize the hyperfine field intrinsic to ruthenium(III) coordination compounds to uncover details of their supramolecular host-guest binding with cyclodextrins. We interpret perturbations of the 1H NMR shifts of the host to suggest the binding mode of the interaction. We demonstrate how the size of the cyclodextrin cavity, methylation of cyclodextrin portal and the structural modification of the guest affect whether the binding occurs through a head or tail portal of the cyclodextrin and attempt to explain the observed differences in terms of molecular shapes and the charge-distribution complementarity between the host and guest. The study is complemented with calculations of hyperfine shift using point-dipole approximations. Paramagnetic NMR spectroscopy of host-guest systems is demonstrated to be a useful tool for investigating modes of molecular encapsulation [1].



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Computational Study of Conformational Possibilities of Separate Deoxynucleosides to the Formation of Various Conformational Classes of Minimal Fragments of DNA Chain

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This study is focused on the contribution of conformational possibilities of individual nucleosides to the formation of various conformational classes (CC) of minimal single-stranded DNA fragments, NtCs. [1] Several local minimum energy structures were obtained, using both quantum mechanics methods (DFT and MP2) and molecular mechanics simulations (AMBER force fields), for the four natural deoxynucleosides (deoxyadenosine, deoxyguanosine, deoxythymidine and deoxycytidine). The conformations studied correspond to BB00 (classical B-form), AA00 (classical A-form), and BB02 CC.

For purine nucleosides and deoxythymidine, the most favorable conformation obtained by both groups of methods corresponds to the BB00 class. However, in the case of deoxycytidine, quantum mechanics calculations identified the AA00-like conformation as the most energetically favorable minimum, whereas use of the AMBER force fields results in the BB00-like conformation as the global minimum, like the case of deoxythymidine.

To elucidate the difference observed in the minimum deoxycytidine structures, additional calculations were performed using the CHARMM force field, as well as calculations considering water as an implicit solvent using both force fields. The qualitative results obtained with the CHARMM force field are consistent with the quantum mechanics findings. The inclusion of water as an implicit solvent yields minor changes in the results.

To evaluate the contribution of details of molecular structure to conformational preferences of pyrimidine deoxynucleosides, a search of energy minima, corresponding to BB00 and AA00 classes, has been performed, using quantum mechanics methods, for pyrimidine nucleosides with modified bases related to alterations in the extra-ring functional groups. The results revealed that to favor the AA00-like conformation over the BB00 one in pyrimidine deoxynucleosides, the base must possess oxo group at position 2, and the N3 atom of the ring with a double bond, serving as a hydrogen bond acceptor.

Acknowledgements: The authors thankfully acknowledge computer resources, technical advice and support provided by Laboratorio Nacional de Supercómputo del Sureste de México (LNS), a member of the CONACYT national laboratories.

Funding: This research was funded by CONACYT, grant number CF-2023-G-1051 and by VIEP-BUAP.

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Halloysite as Suitable Adsorbent of Atrazine and Diuron

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Halloysite belongs to the kaolinite group of clay material and is characterized by its morphology with spiral nanotube shape. Due to this morphology and their unique properties such as large specific surface area, porosity, high adsorption capacity, different charge distribution on the inner and outer surfaces, and colloidal behaviour, halloysite nanotubes can act as suitable absorbers for various species [1]. In this work we tested halloysite as a suitable absorbent of two herbicides (atrazine and diuron), which have harmful effects on the environment, fauna and, of course, humans.

Mutual interactions of both herbicides with the halloysite nanotubes were calculated [2]. The preparation of minimum energy herbicide conformations was performed in the Conformers module and the geometry optimization and subsequent molecular dynamics of the whole halloysite models with herbicides were performed in the Forcite module of Materials Studio [3] using COMPASS force field [4]. A set of different amounts of herbicide were tested on the inner and outer surfaces of halloysite to find the most realistic model possible. Calculations show that both surfaces can interact with herbicides, and the loading and arrangement of herbicides on halloysite surfaces depends on their abundance and mutual interactions. Despite of this, the inner surface of halloysite showed stronger interactions with both herbicides than the outer surface, and especially with diuron (e.g., binding energies for atrazine and diuron were –115 ± 2 and –130 ± 3 kJ· mol^{-1}, respectively).

The simulations showed that atrazine and diuron molecules form a planar arrangement that is parallel to the surface, but only if free space is available. Higher herbicide concentrations show the arrangement that is more perpendicular to the surface due to mutual herbicide repulsive interactions. Furthermore, herbicides preferentially interact with the inner octahedral surface. The diuron molecule showed higher stability on the inner surface of the halloysite due to its higher polarity, which favours a better interaction with the polar OH groups from the octahedral surface of the halloysite structure.

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Theoretical Description of Peptide Bonds in Selected Systems Based on ETS-NOCV Method

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The ETS-NOCV approach allows for a comprehensive analysis of chemical bonds within one theoretical framework by combining the NOCV (Natural Orbitals for Chemical Valence) method of deformation-density decomposition with the ETS (Extended Transition State) bond-energy decomposition scheme. The ETS-NOCV approach has been utilized for a vast array of chemical structures and bonds. Hitherto no such analysis of peptide bonds, which are an invaluable element of many biomolecules, has been performed. This work endeavors to utilize the ETS-NOCV approach to qualitatively and quantitatively asses peptide bonds between proteinogenic amino acids and construct a prediction model of peptide bond strength. Six model dipeptides (Ala-Ala, Gly-Gly, Gly-Ala, Ala-Gly, Gly-Ile, Ile-Gly) were used in order to choose the most suitable partitioning scheme for NOCV description. The systematic analysis was performed on two dipeptide series (Ala-X and X-Ala, where X denotes one of 20 amino acids). Their respective energy minima were found by molecular dynamics and further quantum-mechanical optimization. The NOCV results for two dipeptide series in the chosen cation-anion partitioning was found to exhibit a clear σ/π donation/back-donation picture characteristic of the Dewar-Chatt-Duncanson model. This, in turn, allowed to construct the prediction model of the peptide bond strength between any amino acid pair. To verify model's predictions His-Thr and Tyr-Thr, predicted to exhibit the strongest, and Gly-Val, Trp-Val – the weakest bonds were analyzed. The results show an agreement of the qualitative trend between predicted and computed values.

Acknowledgements: I would like to thank the Academic Computing Center Cyfronet AGH for the opportunity to use the computing resources of PLGRID infrastructure.

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Quest for Compounds that Selectively Activate the Pro-apoptotic Bax Protein

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The Bcl-2 protein family is key in the regulation of apoptosis, a process that triggers cell death and is essential in diseases such as cancer. Studies have shown that the overexpression of anti-apoptotic proteins, a subfamily of Bcl-2 proteins responsible for ensuring cell survival, promotes the resistance of cancer cells to chemotherapy treatments. [1] On the other hand, a pathway has been discovered that allows for the regulation of this process by directly activating the pro-apoptotic protein Bax, a member of the Bcl-2 family that promotes cell death, in its alternative active center. [2]

The objective of this research is to find a compound that binds to the Bax protein in its alternative active center and activates it, triggering a cascade of reactions that result in the death of cancer cells without affecting healthy tissue. By following two different in silico perspectives and utilizing ligand databases available in the literature, 20 ligands have been found that could fulfil this function, of which 5 are already in experimental phase.

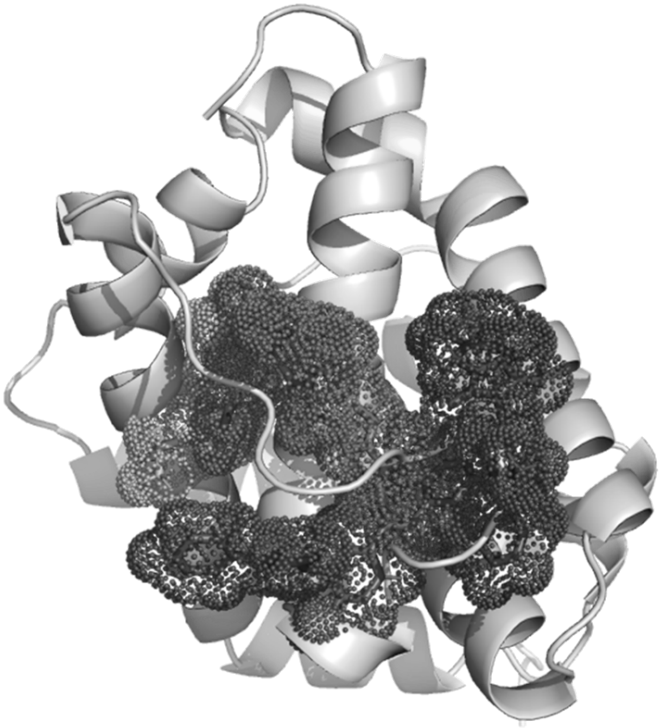

Fig. 1: Bax protein with final candidates

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Factors Influencing Charge Separation in Azurin Protein Mutants with Trp Residues. QM/MM/MD Simulation.

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Electron transfer (ET) between protein redox centers or a redox center and a protein surface is often facilitated/accelerated by chains of aromatic amino acids (Trp, Tyr) [1] and understanding of its mechanism can lead to efficient artificial long-range charge separation. A convenient system for studying such a process is represented by artificial tryptophan pathways in azurin mutants. Investigated ET is triggered by near UV excitation of a Re^{I} sensitizer, $Re(His)(CO)_3(dmp)^+$ (dmp = 4,7-Me_2-1,10-phenanthroline), and a created hole is subsequently transferred through tryptophans (W124, W122) to the Cu^{I} center, unless recombination occurs (Fig. 1). [2, 3]

Individual ET steps are simulated using a multiscale model starting from a sequence of classical MM dynamics followed by hybrid QM/MM/MD simulations of the lowest-lying triplet states to imitate the entire process. The QM part is propagated at the PBE0-D3(BJ)/6-31G(d) level and contains the Re sensitizer, both tryptophans and amino acids connecting them. The rest of the protein and solvent form the MM part. Generated trajectories are utilized for characterization of charge separated CS1 and CS2 states with the hole localized at W124 and W122, respectively, and of dynamical factors leading to their crossing. Calculated data stress a significant effect of reduced Re complex orientation together with protein motions and changes in solvent distribution around W122, which are analyzed through electronic couplings, electrostatic potentials, and water radial distribution functions.

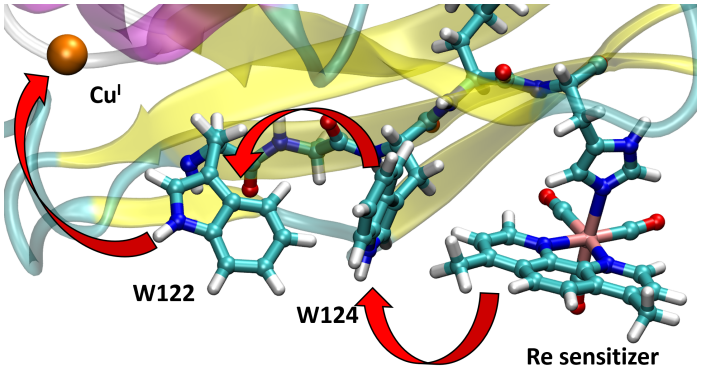

Fig. 1: Hole hopping pathway in the studied azurin mutant

Acknowledgements: Support from the Czech Science Foundation (GAČR) Grant No. 21-05180S is acknowledged. Calculations were performed at the Czech IT4-Innovations National Supercomputing Center (project OPEN-20-8).

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Discovery of a Potent Broad-Spectrum Metallo Beta Lactamase Inhibitor for Rescuing Beta Lactam Antibiotic Resistance

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Metallo-beta lactamases (MBLs) are zinc containing carbapenemases that inactivate nearly all beta lactam antibiotics. We have employed fragment-based screening of non-specific metal chelator library to identify novel classes of MBLi's with nanomolar inhibitory activity against metallo beta lactamases. Molecular simulation, spectroscopic study, X-ray structure characterization have further shed light into its exact mode of binding and keys molecular interactions required for binding. We have demonstrated their broad-spectrum activity against NDM variants and established its ability to rescue beta lactam antibiotic activity *in-vitro* and *in-vivo* against clinical strains of ESKAPE pathogens expressing MBLs. Finally, it possesses low cytotoxicity making it a promising lead candidate for further combination antibacterial therapy development.

8-substituted Adenine Derivatives as Potential Radiosensitizers. A Computational Study

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Radiation therapy (RT) is one of the three most commonly used methods of cancer treatment, but unfortunately, it is not always effective [1]. To increase the effectiveness of RT, so-called radiosensitizers (RSs) are used. RSs are chemical compounds that are able to sensitize cancer cells to ionizing radiation (IR). Modified nucleosides (MNs) belong to one of the groups of RSs, which, after incorporation into DNA, can ultimately lead to cancer cell death through a series of reactions induced by the dissociative electron attachment (DEA) process. There are many MNs of uracil known to have radiosensitizing properties. It seems that purine derivatives should exhibit radiosensitizing properties as well. It has been shown that 8-substituted derivatives of adenine or guanine can easily undergo the DEA process and potentially may act as RSs.

Derivatives of adenine substituted in position 8 with a benzylamine group were recently synthesized (see Figure 1). The dissociative electron attachment (DEA) profiles calculated at the B3LYP/6-31++G(d,p)/PCM level for 118 derivatives showed that depending on the substituent introduced into the aromatic ring of the benzylamine group, the activation barriers and thermodynamic stimulus span a range of 0-33 and from -30 to -60 kcal/mol, respectively. These data indicate thus the most efficient radiosensitizers for which synthesis will be attempted and the obtained computational results will be employed for the construction of a QSPR model predicting the radiosensitizing properties of the studied compounds. The QSPR model, with an acceptable predictive power, will help to understand the impact of the functional groups on the DEA process as well as enable the rational design of the purine-based radiosensitizers.

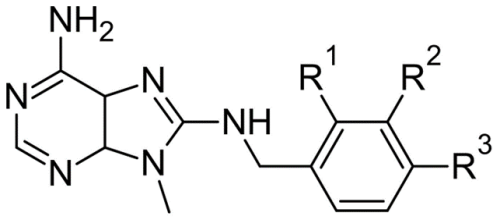

Fig. 1: Structural representation of newly synthesized adenine derivatives substituted at position 8. Functional groups introduced into the aromatic ring can be placed in R^1, R^2 or R^3 position

Keywords: Radiotherapy, Radiosensitizers, DEA, QM, DFT, DNA

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QM/MM Study of the Electron Hopping Processes of the Two Lowest Singlet Excited States of Cytosine, Its Aza-Derivatives and Carotenoids

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The electron hopping of selected heterocyclic compounds and selected carotenoids was studied using QM/MM simulations of excited states dynamics. Tully electron hopping and semiempirical methods OMx in combination with MRCISD method was used in the simulations [1]. Calculations were performed using Newton-X, MNDO99, MNDO2020 and Gromacs. The lifetimes of the excited states were estimated based on the simulations. The results showed that used methods correctly describes the time evolution of excited states of heterocyclic compounds. Deexcitation from S_2 state was ultrafast with femtosecond calculated lifetimes. Following deexcitation to ground state were longer, with 0.83 ps lifetime for Cytosine and with ∼1 ps and tens of picosecond lifetimes for Aza-Derivatives. This is great progress compared with the previous study [2] as the lifetimes were too long studying the dynamics in gas phase. The results also strongly suggest that electronic structures are very sensitive to the substitution on the triazine ring and that the photophysical properties of nucleic acid analogues depend highly on their molecular structures. In case of carotenoids only deexcitation from first excited state was described correctly. The results also suggest that the length of the pi conjugated system correlates with lifetime (the longer the chain the shorter the lifetime).

Acknowledgements: Computational resources were provided by the e-INFRA CZ project (ID:90254), supported by the Ministry of Education, Youth and Sports of the Czech Republic.

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[2] Tichý, O.; J., Burda, J. V. *J. Mol. Struct.* **2022**, *1250*, 131863.

Efficient Pipe Interface Between the Amsterdam Modeling Suite and External Software

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Multiscale modelling often requires coupling multiple components from different software packages to evaluate different levels of theory or to drive the calculation. This is typically implemented by passing input and output files around. However, the associated overhead of I/O operations and process start-ups is significant and becomes a major bottleneck when fast approximate potentials are used. The ideal alternative would be to directly link the necessary software libraries into a single program. Unfortunately, this is frequently infeasible due to technical incompatibilities or licensing restrictions.

To resolve this issue, we have designed an efficient communication protocol to connect two separate processes through a pair of data pipes. One of these processes then repeatedly calls routines exported by the other process, for example to evaluate a potential, perform a geometry optimization, or run a molecular dynamics simulation. Either role can be served by the Amsterdam Modeling Suite or external software. This setup makes it easy to combine the AMS driver with various external potentials or to couple fast potentials such as ReaxFF or GFN-xTB with external drivers. This approach avoids all the pitfalls of direct linking while introducing negligible overhead.

The communication protocol [1] is extensible, future-proof, portable and fully open, providing a reliable mechanism to connect independently developed components without potential compatibility issues. The interface can be easily accessed from Python code based on the libraries ASE and PLAMS. Additionally, a permissively licensed open-source library [2] with interfaces for C, C++, and Fortran further simplifies the integration of the pipe interface into other software packages.

[1] AMSPipe protocol specification, `https://www.scm.com/doc/AMS/Pipe_protocol.html`
[2] AMSPipe worker library, `https://github.com/SCM-NV/amspipe`

QM/MM Study of the Electron Hopping Processes of Conjugated Systems

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Mean lifetimes of the two lowest singlet excited states of linear conjugated polyenes from ethene to docosaundecaene were explored. The semiempirical OM2/MNDO method using MRCISD computational level was combined with Gromacs description of environment to perform QM/MM dynamics [1] of these molecules in *n*-hexane. In each step the time-dependent Schrödinger equation was solved and the transitions between states were carried out by the Tully's fewest switches algorithm. Mean lifetimes were determined by fitting the time dependent occupancies of the excited states according to the exponential decay law. The lifetimes of the S_2 state are very short: from hexatriene (7 fs) to octatetraene (51 fs). As for the S_1 state lifetime, ethene has the shortest one, 89 fs, in contrast to octatetraene, whose S_1 state lifetime is 1275 fs. The lifetimes are significantly shorter in comparison with the previous gas-phase simulations [2].

Acknowledgements: Computational resources were provided by the e-INFRA CZ project (ID:90254), supported by the Ministry of Education, Youth and Sports of the Czech Republic.

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Establishing a Binding Model for Bombesin to Bombesin Receptors

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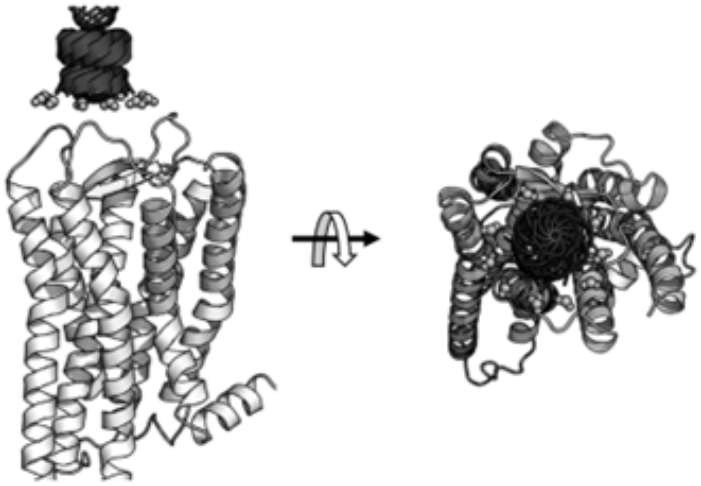
Bombesin receptors (BnR) belong to the class A G-Protein Coupled Receptors (GPCR), playing a crucial role in a wide range of biological activities. Notably, these receptors are involved in tumor growth, differentiation and are found overexpressed in multiple tumor types. [1, 2] Despite the significant biological interest in BnRs, our knowledge regarding the stereochemical features that contribute to their activity remains limited.

Bombesin (Bn) is a tetradecapeptide that has been extensively studied. It exhibits high affinity towards BnR subtypes 1 and 2 (BB1 and BB2), with the latter showing an affinity two orders of magnitude higher. Although certain key residues have been identified, the specific stereochemical features responsible for Bn's activity have not been elucidated. To shed light on this, we have developed a model of the peptide-receptor complex to identify the key interactions in this binding. Receptor structures were constructed through homology modelling, while the conformation of Bn peptide was determined by our research group. [3]



To achieve our aim, we employed a Steered Molecular Dynamics (SMD) study followed by Molecular Dynamics simulations to investigate the binding of Bn peptide to BB1 and BB2. Our study aims to decipher the binding mode of Bn to each receptor subtype and elucidate any differences in binding affinity.

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ETS-NOCV and Molecular Electrostatic Potential-Based Picture of Chemical Bonding

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The primary objective of our research [1] was to compare the depiction of chemical bonding using the ETS-NOCV method with the picture based on the deformation of Molecular Electrostatic Potential (MEP) within a similar perspective (molecule vs promolecule).

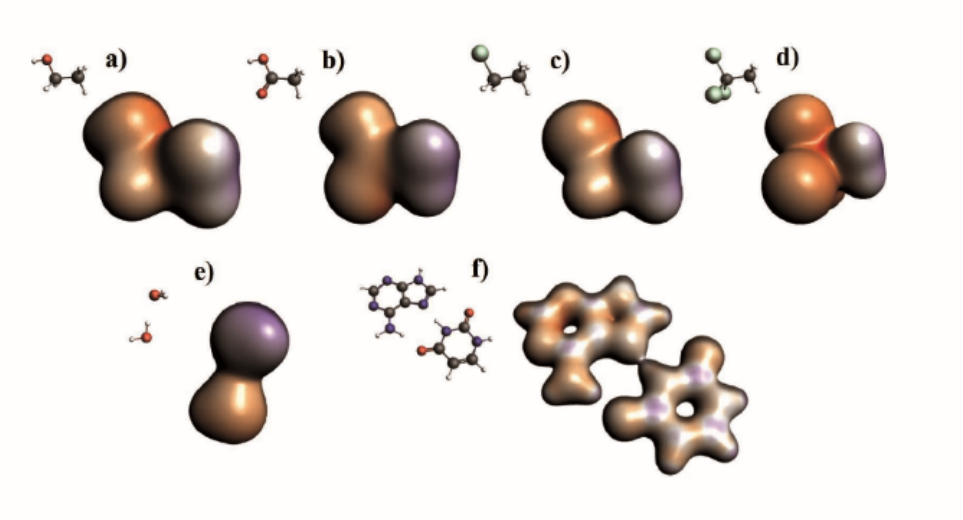

Fig. 1: Examples of the deformation in MEP, ΔV, plots, color-coded on the electron density isosurface for ethanol (A), acetic acid (B), chloroethane (C), 1,1,1-trichloroethane (D), water dimer (E), adenine-thymine complex (F). The density isocontour value is 0.01 a.u.for (A–D), and 0.05 a.u. for (E, F).

The systems analyzed include: the nitrogen molecule, simple hydrocarbons, their derivatives, and model systems with hydrogen bonds. The results indicate the primary features of chemical bonding revealed by the ETS-NOCV analysis are accurately represented through MEP deformation. However, the deformation of MEP appears to indicate the shift in electron density (charge transfer) between the fragments more distinctly. Consequently, combining the MEP deformation analysis with the ETS-NOCV approach offers a more comprehensive and straightforward understanding.

Acknowledgements: We thank the PL-Grid Infrastructure and the Academic Computational Centre Cyfronet of the University of Science and Technology in Krakow for providing computational resources.

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2. Originator and organizer of annual Interdisciplinary Cancer Research Workshops, New Orleans, 1978-1995.

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4. Cancer Association of Greater New Orleans: Board of Directors, 1978-present; Research Advisory Committee, 1982-present; President, 1990-1991.

5. Cancer Review Panel, Louisiana Board of Regents.

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20. Co-organizer, Cancer Research Workshop, University of New Orleans, November 2004.

21. Co-Organizer, ACS/EHCL Workshop on Petrochemical Industry in Louisiana, March, 2005.

22. Organizer, Fifth Congress of the International Society of Theoretical Chemical Physics, New Orleans, July 2005.

23. Organizer, ACS/EHCL Workshop on Post-Katrina Toxicity in New Orleans, June, 2006.

24. Co-organizer, Computational Chemistry Symposium, Central Regional Meeting of the American Chemical Society, Cleveland, OH, May 2009.

25. Co-organizer, Computational Chemistry Symposium, Southeast/Southwest Regional Meeting of the American Chemical Society, New Orleans, December 2010.

SOCIETIES:

1. Phi Beta Kappa
2. Society of Sigma Xi
3. American Chemical Society
4. American Physical Society
5. New York Academy of Sciences
6. International Society of Quantum Biology and Pharmacology
7. Environment and Health Council of Louisiana
8. Pittsburgh Diffraction Society
9. Louisiana Academy of Sciences
10. New Orleans Academy of Sciences

RESEARCH INTERESTS:

1. Reactive properties of organic and biologically-active molecules; chemical toxicity and carcinogenicity; properties and behavior of energetic materials; calculation of energetics of reactions; substituent and interaction parameters; solute-solvent interactions.

2. Relationship of energy to electronic density and to electrostatic potentials at nuclei; states of atoms in molecules; electronegativity and chemical potential; fundamental aspects of molecular electrostatic potentials

EXTERNAL FUNDING:

TOTAL SINCE 1981: $6.0 million.
PRIMARY SOURCES:

Office of Naval Research, Ballistic Missile Defense Organization, Army Research Office, Air Force Office of Scientific Research, Environmental Protection Agency, Defense Advanced Research Projects Agency, Eglin Air Force Base, U.S. Army Research, Development and Engineering Center, Defense Threat Reduction Agency.

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA:

1. National Computation Center Conference, National Research Council, Washington, D.C., April, 1970 (invited participant).
2. North American Meeting of the Catalysis Society, Houston, February, 1971 (invited speaker).
3. First International Congress of Quantum Chemistry, Menton (France), July, 1973 (invited participant).
4. Symposium in Theoretical Organic Chemistry, Southeast Regional Meeting of the American Chemical Society, El Paso, December, 1973 (invited speaker).
5. North American Meeting of the Catalysis Society, Toronto, February, 1975 (invited speaker).
6. Cancer Research Symposium, New Orleans, November, 1975 (invited speaker).
7. Second International Congress of Quantum Chemistry, New Orleans, April, 1976 (organizer).
8. Cancer Research Symposium, New Orleans, November, 1976 (invited speaker).
9. United States - Japan Cancer Research Conference, New Orleans, January, 1977 (invited participant).
10. Symposium on Excited States in Organic Chemistry and Biochemistry, Jerusalem, Israel, March, 1977 (invited speaker).
11. Sanibel Symposium in Quantum Biology, Palm Coast (FL), March, 1978 (invited Symposium Leader).
12. Photo-Oxidation Workshop, Texas Christian University, November, 1978 (invited speaker).
13. Cancer Research Symposium, New Orleans, November, 1978 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

14. Sanibel Symposium in Quantum Biology, Palm Coast (FL), March, 1979 (invited speaker).
15. Symposium on Catalysis in Chemistry and Biochemistry, Jerusalem, Israel, April, 1979 (invited speaker).
16. Third International Congress of Quantum Chemistry, Kyoto (Japan), October, 1979 (invited participant).
17. Symposium on The Role of the Electrostatic Potential in Chemistry, national meeting of the American Chemical Society, Houston, March, 1980 (invited speaker).
18. Symposium on Chemical Carcinogenesis, Jerusalem, Israel, April, 1980 (invited speaker).
19. Conference on Quantum Chemistry in Biomedical Science, New York Academy of Sciences, New York, June, 1980 (invited speaker).
20. Workshop on Fundamental Research Directions for the Decomposition of Energetic Materials, sponsored by Department of Defense, Berkeley, January, 1981 (invited participant).
21. Workshop on High Energy Molecules, sponsored by Army Research Office, Hilton Head, SC, April, 1981 (invited participant).
22. Sanibel Symposium in Quantum Biology, Palm Coast (FL), March, 1982, (invited Symposium Leader).
23. Seminar on High Density Energetic Materials, sponsored by U.S. Army Armament Research and Development Command, Dover, NJ, May, 1982 (invited speaker).
24. Symposium on Biological Structure/Activity Relations, American Chemical Society regional meeting, El Paso, Texas, December, 1982 (invited speaker).
25. Symposium on Theoretical Organic Chemistry, American Chemical Society regional meeting, El Paso, Texas, December, 1982 (invited speaker).
26. Workshop on High Energy Molecules, sponsored by Office of Naval Research, Chestertown, Maryland, August, 1983 (invited speaker).
27. Chemical Defense Research Conference, sponsored by the Chemical Research & Development Center, Aberdeen Proving Ground, MD, November, 1983 (invited speaker).
28. Sanibel Symposium in Quantum Biology, Palm Coast, FL, March, 1984 (invited speaker).
29. Working Group Meeting on Synthesis of High Density Energetic Materials, sponsored by U.S. Army Armament, Research and Development Center, Dover, NJ, May, 1984 (invited speaker).
30. Research Meeting, sponsored by Office of Naval Research, Arlington, VA, May, 1984 (invited speaker).
31. Conference on Molecular Basis of Cancer, Roswell Park Memorial Institute, Buffalo, NY, May-June, 1984 (invited speaker).
32. International Meeting on the Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis, International Agency for Research on Cancer, Lyon, France, September, 1984 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

33. Scientific Conference on Chemical Defense Research, sponsored by the Chemical Research & Development Center, Aberdeen Proving Ground, MD, November, 1984 (invited speaker).
34. Drug Information Association Workshop, Chicago, February, 1985 (invited speaker).
35. Research Meeting, sponsored by Office of Naval Research, Arlington, VA, May, 1985 (invited speaker).
36. Working Group Meeting on Synthesis of High Density Energetic Materials, U.S. Army Armament Research & Development Center, Dover, NJ, June 1985 (invited speaker).
37. Symposium on Structure-Activity Relationships, Division of Organic Chemistry, Central Regional Meeting of the American Chemical Society, Akron, Ohio, June, 1985 (invited speaker).
38. Working Group Meeting on Synthesis of High Energy Density Materials, U.S. Army Armament Research, Development and Engineering Center, Dover, NJ, May, 1986 (invited speaker).
39. Gordon Conference on Electron Distributions and Chemical Bonding, Plymouth, New Hampshire, July, 1986.
40. Workshop on Synthesis of High Energy Density Materials, Office of Naval Research, Chestertown, MD, November, 1986 (invited speaker).
41. Scientific Conference on Chemical Defense Research, sponsored by the Chemical Research, Development & Engineering Center, Aberdeen Proving Ground, MD, November, 1986.
42. Working Group Meeting on Sensitivity of Explosives, Army Research Office, Socorro, New Mexico, March, 1987 (invited speaker).
43. 17th Annual Conference on Toxicology, Wright-Patterson Air Force Base, Dayton, Ohio, November, 1987 (invited speaker).
44. Conference on High Energy Density Materials, sponsored by Air Force Office of Scientific Research, Newport Beach, CA, February, 1988 (invited speaker).
45. Mardi Gras Symposium in Theoretical Chemistry, New Orleans, February, 1988 (invited speaker).
46. Caged Nitramine Working Group Meeting, China Lake, CA, sponsored by Office of Naval Research, September, 1988 (invited speaker).
47. Energetic Materials Initiation Fundamentals Workshop, sponsored by Office of Naval Research, Livermore, CA, December, 1988 (invited speaker).
48. Conference on High Energy Density Materials, sponsored by Air Force Office of Scientific Research, New Orleans, LA, March, 1989 (invited speaker).
49. Symposium on Energetic Materials, Loker Hydrocarbon Research Institute, Los Angeles, CA, May, 1989 (invited speaker).
50. Symposium on Energetic Materials, American Chemical Society Northwest Regional Meeting, Reno, Nevada, June, 1989 (invited speaker).
51. NATO Advanced Study Institute on Chemistry and Physics of the Molecular Processes in Energetic Materials, Sicily, September, 1989 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

52. Scientific Conference on Chemical Defense Research, sponsored by the Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD, November, 1989.
53. Energetic-Oxidizers Synthesis Workshop, China Lake, CA, sponsored by Office of Naval Research, December, 1989 (invited speaker).
54. Conference on High Energy Density Materials, sponsored by Air Force Office of Scientific Research, Long Beach, CA, February, 1990 (invited speaker).
55. Symposium on Studies of Electron Distributions in Molecules and Crystals, American Crystallographic Association National Meeting, New Orleans, April, 1990 (invited speaker).
56. Sanibel Symposium in Quantum Biology, St. Augustine, FL, March, 1990 (invited Symposium Leader).
57. Working Group Institute on Synthesis of High Energy Density Materials, sponsored by the U. S. Army Armament Research, Development & Engineering Center, Monticello, NY, June, 1990 (invited speaker).
58. New Energetic Ingredients meeting, sponsored by Office of Naval Research, China Lake, CA, June, 1990 (invited speaker).
59. Conference on Chemical Defense Research, sponsored by the Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD, November, 1990.
60. Sanibel Symposium in Quantum Biology, St. Augustine, FL, March, 1991 (invited Symposium Leader).
61. Conference on Chemical Risk Assessment in the DoD: Science, Policy and Practice, Dayton, OH, April 1991 (invited speaker).
62. JANNAF CL-20 Symposium, China Lake, CA, April/May 1991 (invited speaker).
63. Meeting on Solute/Solvent Interactions, sponsored by the Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD, May, 1991 (invited speaker).
64. ISQBP 1991 President's Meeting on Prospects in Computer-Aided Drug Design, Palo Alto, CA, September, 1991 (invited Members' Session Leader).
65. Symposium on Molecular Charge Densities, 49th Annual Pittsburgh Diffraction Conference, Columbus, OH, November 1991 (invited speaker).
66. Conference on Chemical Defense Research, sponsored by the Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD, November 1991.
67. Workshop on Fundamental Physics and Chemistry of Combustion, Initiation and Detonation of Energetic Materials, Los Alamos, NM, March 1992 (invited speaker).
68. Sanibel Symposium in Quantum Biology, St. Augustine, FL, March, 1992 (invited Symposium Leader).
69. Meeting on Solute/Solvent Interactions sponsored by the Chemical Research Development and Engineering Center, Aberdeen Proving Ground, MD, May 1992 (invited speaker).
70. Gordon Conference on Energetic Materials, Bristol, New Hampshire, June 1992 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

71. Gordon Conference on Electron Distributions and Chemical Bonding, Plymouth, New Hampshire, July 1992.
72. Workshop on Current Trends in Computational Chemistry, Jackson, MS, November 1992 (invited speaker).
73. Conference on Chemical Defense Research, sponsored by the Army Edgewood Research, Development and Engineering Center, Aberdeen Proving Ground, MD, November, 1992.
74. Solute/Solvent Meeting, sponsored by the Chemical Research, Development and Engineering Center, Edgewood, MD, June 1993 (invited speaker).
75. ONR/LANL Joint Meeting on New Explosives and Oxidizers: Synthesis, Characterization and Prediction of Properties, Los Alamos, NM, June 1993 (invited speaker).
76. American Chemical Society Meeting, Division of Computational Chemistry, Chicago, IL, September 1993 (invited speaker).
77. Sterling-Winthrop Pharmaceuticals, Philadelphia, PA, November 1993 (invited speaker).
78. Office of Naval Research Meeting, Los Alamos, NM, November 1993 (invited speaker).
79. American Chemical Society Meeting, Division of Agrochemicals, San Diego, CA, March 1994 (invited speaker).
80. Solute/Solvent Meeting, sponsored by the Edgewood Research Development and Engineering Center, Edgewood, MD, June, 1994 (invited speaker).
81. Gordon Conference on Energetic Materials, New Hampton, NH, June 1994.
82. Sterling-Winthrop Pharmaceuticals, Philadelphia, PA, July 1994 (invited speaker).
83. Research Division, Kodak, Rochester, August 1994 (invited speaker).
84. American Chemical Society Meeting, Division of Physical Chemistry, Birmingham, AL, October 1994 (invited speaker).
85. Office of Naval Research Meeting, Chestertown, MD, October 1994 (invited speaker).
86. Research Division, Kodak, Rochester, January 1995 (invited speaker).
87. Energetic Materials Research Symposium, Sponsored by the American Institue of Aeronautics/Astronautics, Inyokern, CA, February 1995 (invited speaker).
88. Ballistic Missile Defense Organization Workshop on Combustion Instability in Interceptor Rocket Motors, Dallas, TX, February 1995.
89. Southeast Theoretical Chemistry Asociation (SETCA) Meeting, New Orleans, LA, May 1995 (invited speaker).
90. American Chemical Society Meeting, Chicago, IL, August 1995 (invited speaker).
91. Research Division, Kodak, Rochester, October 1995 (invited speaker).
92. Southeast/Southwest Joint Regional American Chemical Society Meeting, Memphis, TN, November 1995 (invited speaker).
93. Materials Research Society Meeting, Boston, MA, November 1995 (invited speaker).
94. MURI (Multi-University Research Initiative Meeting, Reno, NV, January 1996 (invited speaker).
95. American Chemical Society Meeting, New Orleans, LA, March 1996 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

96. Second International Congress on Theoretical Chemical Physics, New Orleans, LA, April 1996 (invited speaker).
97. Meeting of the Electrochemical Society, Los Angeles, CA, May 1996 (invited speaker).
98. American Chemical Society Meeting, Orlando, FL, September 1996 (invited speaker).
99. Research Division, Kodak, Rochester, NY, October 1996 (invited speaker).
100. JANNAF Meeting on Combustion, Monterey, CA, November 1996 (invited speaker).
101. Energetic Materials Workshop, Annapolis, MD, December 1996 (invited speaker).
102. First UNCW Mini-Symposium on Chemical and Biochemical Structure and Function, Wilmington, NC, January 1997 (invited speaker).
103. American Chemical Society Meeting, San Francisco, CA, April 1997 (invited speaker).
104. Basic Research in the National Defense Meeting, The Association of American Universities, Washington, DC, May, 1997.
105. Symposium on Density Functional Theory and Applications, Durham, North Carolina, June 1997.
106. UIUC MURI Review Meeting/JANNAF Meeting on Combustion, Seattle, WA, July 1997 (invited speaker).
107. 214th American Chemical Society National Meeting, Las Vegas, NV, September 1997 (invited speaker).
108. MURI Review Meeting, Palm Beach, FL, November 1997 (invited speaker).
109. 6th Annual Conference on Current Trends in Computational Chemistry, Vicksburg, MS, November 1997.
110. ADN Workshop, UIUC MURI Meeting, Reno, NV, January 1998 (invited speaker).
111. Energetic Materials Workshop, Office of Naval Research, Annapolis, MD, January 1998 (invited speaker).
112. Boron Combustion Workshop, UIUC MURI Meeting, Cleveland, OH, July 1998 (invited speaker).
113. First Southern Symposium on Computing, Hattiesburg, MS, December 1998 (invited speaker).
114. MURI Review Meeting, Tucson, AZ, December 1998.
115. JANNAF Conference, Cocoa Beach, FL, October 1999 (invited speaker).
116. ONR Initiation Workshop, Arlington, VA, June 2000 (invited speaker).
117. Boulder Meeting, Boulder, CO, June 2000 (invited speaker).
118. Bioinformatics on the Bayou, New Orleans, LA, November 2000 (invited speaker).
119. Sanibel Symposium in Quantum Biology, St. Augustine, FL, March, February 2001 (invited speaker).
120. First Southern School of Computational Chemistry, Orange Beach, AL, March 2001 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

121. Southeast Theoretical Chemistry Asociation (SETCA) Meeting, Auburn, AL, May 2001 (invited speaker).
122. 10th Annual Conference on Current Trends in Computational Chemistry, Jackson, MS, November 2001 (invited speaker).
123. Southeast Regional American Chemical Society Meeting (SERMACS), Symposium on Computational Chemistry, Charleston, SC, November 2002 (invited speaker).
124. ISQBP President's Conference, Snowbird, UT, December 2002 (invited speaker).
125. Third Southern School of Computational Chemistry, Orange Beach, AL, March 2003 (invited speaker).
126. Modeling Interactions in Biomolecules Workshop-I, Nove Hrady, Czech Republic, September 2003 (invited speaker).
127. Workshop on Energetic Materials, Karlsruhe, Germany, June 2005 (invited speaker).
128. Modeling Interactions in Biomolecules Workshop-II, Prague, Czech Republic, September 2005 (invited speaker).
129. Sixth Southern School of Computational Chemistry, Jackson, March 2006 (invited speaker).
130. New Trends in Energetic Materials Conference, Pardubice, Czech Republic, April 2006 (invited speaker).
131. Modelling and Design of Molecular Materials Workshop, Wroclaw, Poland, September 2006 (invited speaker).
132. Mini-Symposium in Theoretical and Computational Chemistry, Santiago, Chile, January 2007 (invited speaker).
133. Methods and Applications in Computational Chemistry-2 (MACC-2), Kiev, Ukraine, July 2007 (invited speaker).
134. Conference on Modeling Interactions in Biomolecules-III (MIB-III), Prague, Czech Republic, September 2007 (invited speaker).
135. Defense Threat Reduction Agency Contractors' Meeting, Alexandria, VA, January 2008 (invited speaker).
136. Modelling and Design of Molecular Materials Conference 2008, Piechowice, Poland, June 2008 (invited speaker).
137. Defense Threat Reduction Agency Contractors' Meeting, Alexandria, VA, November 2008 (invited speaker).
138. Ninth Southern School of Computational Chemistry and Materials Science, Jackson, MS, July 2009 (invited speaker).
139. Symposium on Halogen Bonding, National ACS Meeting, Washington, DC, August 2009 (invited speaker).
140. Model(l)ing 09, Erlangen, Germany, September 2009 (invited speaker).
141. Conference on Modeling Interactions in Biomolecules-IV (MIB-IV), Hruba Skala, Czech Republic, September 2009 (invited speaker).
142. Defense Threat Reduction Agency Contractors' Meeting, Alexandria, VA, October 2009 (invited speaker).

INVITED SPEAKER OR PARTICIPANT IN MEETINGS AND SYMPOSIA: (continued)

143. Mini-Symposium: Summer Talks in Santiago, Santiago, Chile, January 2010 (invited speaker).
144. Workshop on Halogen Bonding, Milano, Italy, May 2010 (invited speaker).
145. Workshop on Insensitive Munitions, NATO-MSIAC, Brussels, Belgium, May 2010 (invited speaker).
146. Modelling and Design of Molecular Materials Conference 2010, Wroclaw, Poland, July 2010 (invited speaker).
147. 20th Conference on Current Trends in Computational Chemistry, Jackson, MS, October 2011 (invited speaker).
148. Summer Talks in Santiago III (Politzer Conference), January 2012 (invited speaker).
149. Gordon Research Conference on Crystal Engineering, Waterville Valley, NH, June 2012 (invited speaker).
150. ONR Contractors' Meeting, Arlington, VA, August 2012 (invited speaker).
151. Modelling and Design of Molecular Materials Conference 2012, Wroclaw, Poland, September 2012 (invited speaker).
152. El Congreso del Futuro 2013, Santiago, Chile, January 2013 (invited speaker).
153. Tri-Services Contractors' Meeting, Roswell, VA, August 2013 (invited speaker).
154. Conference on Modeling Interactions in Biomolecules-VI (MIB-VI), Marianske Lazne, Czech Republic, September 2013 (invited speaker).
155. International Symposium on Halogen Bonding (ISXB1), Porto Cesareo, Italy, June 2014 (invited speaker).
156. Modelling and Design of Molecular Materials Conference 2014, Kudowa Zdröj, Poland, September 2014 (invited speaker).
157. Virtual Conference in Computational Chemistry (VCCC-2014), University of Mauritius, Mauritius, August 2014 (invited presentation).
158. WinterSchool in Computational Chemistry, February 2015 (invited presentation).
159. Virtual Conference in Computational Chemistry (VCCC-2015), University of Mauritius, Mauritius, August 2015 (invited presentation).
160. Conference on Modeling Interactions in Biomolecules-VII (MIB-VII), Praha-Průhonice, Czech Republic, September 2015 (invited speaker).
161. Conference on Current Trends in Computational Chemistry, Jackson, MS, October 2016 (invited speaker for joint talk with Jane Murray).
162. Faraday Discussions on Halogen Bonding, Ottawa, Canada, July 2017 (invited speaker).
163. IUPAC Workshop on Chalcogen, Pnicogen and Tetrel Bonding, Satellite Meeting to International Symposium on Halogen Bonding (ISXB3), Greenville, SC, June 2018 (invited speaker).

INVITED LECTURES:

1. University of Detroit, February, 1966.
2. Louisiana State University in New Orleans, February, 1966.
3. University of Texas (Austin), March, 1969.
4. University of Houston, March, 1969.
5. North Texas State University, March 1970.
6. Case Western Reserve University, April, 1970.
7. University of Waterloo (Canada), July, 1970.
8. University of Cincinnati, April, 1971.
9. University of Strasbourg (France), June, 1972.
10. Warwick University (England), July, 1972.
11. Princeton University, November, 1973.
12. Fairfield University, March, 1974.
13. Johns Hopkins University, March, 1974.
14. East Texas State University, November, 1974.
15. Mt. Sinai Medical School (New York), December, 1974.
16. University of Texas (El Paso), April, 1975.
17. Cleveland State University, October, 1975.
18. Southern University (Baton Rouge), February, 1977.
19. Northeastern Louisiana University, February, 1977.
20. Weizmann Institute (Israel), April, 1977.
21. Free University of Berlin (West Germany), April, 1977 (2 lectures).
22. Sloan-Kettering Cancer Research Center, New York, June, 1977.
23. Wichita State University, December, 1977.
24. East Texas State University, April, 1978.
25. Battelle Memorial Institute (Columbus), May, 1978.
26. Louisiana State University (Baton Rouge), July, 1978.
27. New Mexico State University, April, 1979.
28. University of Texas (El Paso), May, 1979.
29. Tulane University, September, 1979.
30. Tulane Medical School, May, 1980.
31. Energetic Materials Division, Armament Research & Development Center, Dover, New Jersey, June, 1980.
32. Dow Chemical Company, Plaquemine, Louisiana, September, 1980.
33. Case Western Reserve University (Chemistry Dept.), March, 1983.
34. Case Western Reserve University, School of Medicine, April, 1983.
35. Chemical Systems Laboratory, Aberdeen Proving Ground, MD, May, 1983.
36. Energetic Materials Division, Armament Research & Development Center, Dover, New Jersey, June, 1983.
37. Environmental Protection Agency, Washington, DC, February, 1984.
38. Wright State University (Dayton, Ohio), May, 1984.
39. New Jersey Institute of Technology, Newark, NJ, July, 1984.
40. Energetic Materials Division, Armament Research & Development Center, Dover, New Jersey, July, 1984 (series of three lectures).
41. Environmental Protection Agency, Washington, DC, May, 1985.

INVITED LECTURES: (continued)

42. Energetic Materials Division, Armament Research & Development Center, Dover, New Jersey, July and August, 1985 (2 lectures).
43. University of Florida, Gainesville, October, 1985.
44. University of Alabama in Birmingham, March, 1987.
45. University of Texas at Dallas, March, 1987.
46. Southern Methodist University, Dallas, January, 1988.
47. University of Southern California, Los Angeles, December, 1990.
48. Naval Research Laboratory, Washington, DC, February, 1993.
49. University of Houston, April, 1993.
50. Texas Tech University, Lubbock, March, 1994.
51. Skidmore University, New York, December, 1995.
52. University of Illinois at Chicago, Chicago, IL, March, 1996.
53. Jackson State University, Jackson, MS, April, 1999.
54. University of Mississippi, Oxford, MS, November, 1999.
55. Auburn University, Auburn, AL, December, 1999.
56. Rutgers University-Newark, Newark, NJ, October, 2000.
57. Florida Atlantic University, Boca Raton, FL, November, 2001.
58. University of South Carolina, Columbia, SC, January, 2002.
59. University of New Orleans, Physics Department, October, 2002.
60. Mississippi College, Clinton, MS, February, 2003.
61. Florida Atlantic University, Boca Raton, FL, November, 2003.
62. Pontificia Universidad Catolica de Chile, Santiago, Chile, December 2003.
63. Charles University, Prague, Czech Republic, January, 2004.
64. Universidad de Chile, Santiago, Chile, December, 2004.
65. Pontificia Universidad Catolica de Chile, Santiago, Chile, December, 2004.
66. Cleveland State University, February, 2006.
67. Michigan Technological University, Houghton, MI, October ,2006.
68. Southeast Pacific Advanced Research Institute (SEPARI), Valparaiso, Chile, September, 2008.
69. Calvin College, Grand Rapids, MI, October, 2008.
70. Ludwig-Maximilian Universität, Munich, Germany, October, 2008.
71. Marquette University, Milwaukee Wisconsin, November, 2011.
72. Jackson State University, Jackson, MS, July 2012.
73. Mississippi College, Clinton, MS, December, 2013.
74. Clark Atlanta University, Atlanta, GA, February 2018.
75. University of New Orleans, New Orleans, LA, November 2018.

RESEARCH PUBLICATIONS:

1. "The Electrostatic Forces Within the Carbon Monoxide Molecule"
   P. Politzer, J. Phys. Chem., 69, 2132 (1965).

2. "A Study of the Bonding in the Hydrogen Molecule"
   P. Politzer, J. Phys. Chem., 70, 1174 (1966).

3. "The Electronic Density Distribution in Lithium Hydride"
   P. Politzer and R. E. Brown, J. Chem. Phys., 45, 451 (1966).

4. "Polarization and Exchange Effects in Some Simple Molecular-Ions"
   P. Politzer, J. Chem. Phys., 45, 1856 (1966).

5. "Bond Lengths and Atomic Orbital Radii Among the Diatomic Hydrides and Their Ions"
   P. Politzer, J. Phys. Chem., 70, 4041, (1966).

6. "Bond Length Relationships Among the Diatomic Hydrides and Their Ions"
   P. Politzer, J. Phys. Chem., 71, 3068 (1967).

7. "Orbital Sizes and Dipole Moments in Diatomic Hydrides"
   P. Politzer, Chem. Phys. Letters, 1, 227 (1967).

8. "On the Problem of Defining the Charge on an Atom in a Molecule"
   L. C. Cusachs and P. Politzer, Chem. Phys. Letters, 1, 529 (1968).

9. "On the Electronic Density Distribution in Diborane"
   P. Politzer and L. C. Cusachs, Chem. Phys. Letters, 2, 1, (1968).

10. "A Charge-Transfer Interpretation of the Interactions of Hemoglobin with Oxygen and Carbon Monoxide"
    P. Politzer, Biochim. Biophys. Acta, 153, 799 (1968).

11. "Electron Affinities of Atoms"
    P. Politzer, Trans. Faraday Soc., 64, 2241 (1968).

12. "An Investigation of Definitions of the Charge on an Atom in a Molecule"
    E. W. Stout, Jr. and P. Politzer, Theoret. Chim. Acta, 12, 379 (1968).

13. "The Electronic Structures of Carbon Monoxide, Carbon Dioxide, and Carbonyl Sulfide"
    M. J. Hazelrigg, Jr. and P. Politzer, J. Phys. Chem., 73, 1008 (1969).

14. "Bond Orders of Homonuclear Diatomic Molecules"
    P. Politzer, J. Chem. Phys., 50, 2780 (1969).

15. "Bond Orders of Heteronuclear Diatomic Molecules"
P. Politzer, J. Chem. Phys., 51, 459 (1969).

16. "Molecular-Orbital Theory of Electron Donor-Acceptor Complexes. III. The Relationship of State Energies and Stabilization Energies to the Charge-Transfer Transition Energy"
R. L. Flurry, Jr. and P. Politzer, J. Phys. Chem., 73, 2787 (1967).

17. "Anomalous Properties of Fluorine"
P. Politzer, J. Amer. Chem. Soc., 91, 6235 (1969).

18. "Atom Promotion and Bond Properties in the Hydrogen and the Lithium Molecules"
P. Politzer, Theoret. Chim. Acta, 16, 120 (1970).

19. "The Constant Term in the Energy Function of a Point-Charge Model of Diatomic Molecules"
P. Politzer, J. Chem. Phys., 52, 2157 (1970).

20. "A Study of the Electronic Density Distribution in Nitric Oxide"
P. Politzer and R. R. Harris, J. Amer. Chem. Soc., 92, 1834 (1970).

21. "Properties of Atoms in Molecules. I. A Proposed Definition of the Charge on an Atom in a Molecule"
P. Politzer and R. R. Harris, J. Amer. Chem. Soc, 92, 6451-6454 (1970),

22. "Properties of Atoms in Molecules. II. The Position of the Center of Electronic Charge of an Atom in a Molecule"
P. Politzer and E. W. Stout, Jr., Chem. Phys. Letters, 8, 519 (1971).

23. "The Distribution of the Pi Electronic Charge of the Carbon-Carbon Triple Bond"
P. Politzer and R. R. Harris, Tetrahedron, 27, 1567 (1971).

24. "Comparison of Two Definitions of Atomic Charge, as Applied to Hydrogen Fluoride"
P. Politzer and R. S. Mulliken, J. Chem. Phys., 55, 5135 (1971).

25. "Properties of Atoms in Molecules. III. Atomic Charges and Centers of Electronic Charge in Some Heteronuclear Diatomic Molecules"
P. Politzer, Theoret. Chim. Acta, 23, 203 (1971).

26. "Energy Calculations with the Extended-Huckel Method"
P. Politzer, R. K. Smith and S. D. Kasten, Chem. Phys. Letters, 15, 226 (1972).

27. "Properties of Atoms in Molecules. IV. Atomic Charges in Some Linear Polyatomic Molecules"
P. Politzer and P. H. Reggio, J. Amer. Chem. Soc., 94, 8308 (1972).

28. "Anomalous Properties of Halogen Substituents"
P. Politzer and J. W. Timberlake, J. Org. Chem., 37, 3557 (1972).

29. "An Investigation of the High-Frequency Form of Carbon Monoxide Chemisorbed on Nickel Oxide"
P. Politzer and S. D. Kasten, Surf. Sci., 36, 186 (1973).

30. "On the Validity of the Core-Point-Charge Approximation for Inner Subshells of Atoms"
P. Politzer and K. C. Daiker, Chem. Phys. Letters, 20, 309 (1973).

31. "Properties of Atoms in Molecules. A Proposed Method for Calculating the Extent of Distortion of an Atom"
P. Politzer, J. D. Elliott and B. F. Meroney, Chem. Phys. Letters, 23, 331 (1973).

32. "Properties of Atoms in Molecules. V. An Easy Procedure for Estimating Atomic Charges from Calculated Core-Electron Energies"
P. Politzer and A. Politzer, J. Amer. Chem. Soc., 95, 5450 (1973).

33. "Molecular Electrostatic Potentials. Mechanistic Aspects of Electrophilic Attack on Furan"
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