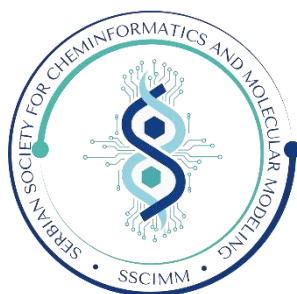




Book of Abstracts

**University of Kragujevac - Faculty of Science
Kragujevac, Serbia**

September 8-11, 2026



**1st International Computational Chemistry
Meeting - ICCM 2026**

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1st International Computational Chemistry Meeting, Kragujevac, September 08-11, 2026, Serbia.

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Foreword

Dear colleagues,

It was our great pleasure to welcome you to the 1st International Computational Chemistry Meeting, ICCM 2026.

ICCM 2026 was held at the Faculty of Science, University of Kragujevac, from 8 to 11 September 2026. The meeting was organized by the Serbian Society for Cheminformatics and Molecular Modelling and hosted at the Faculty of Science, University of Kragujevac.

ICCM 2026 brought together educators and researchers from across the diverse fields of computational chemistry. The participants applied computational chemistry and molecular modelling methods to gain deeper insight into chemical graph theory, molecular and quantum mechanics optimization, structure- and ligand-based drug design, and artificial intelligence algorithms for predicting molecular properties with industrial and medical applications.

ICCM 2026 also had a strong international character, with lecturers coming from China, Croatia, France, Germany, Italy and the United Kingdom. The lectures covered cutting-edge topics across theoretical chemistry, machine learning, and molecular modeling.

The main conference program was enriched by a practical hands-on workshop on the application of www.3d-qsar.com in medicinal chemistry. In addition, participants enjoyed a rich social program featuring a guided historical tour of Kragujevac, visits to the Šumarice Memorial Park and the 21st October Museum, an authentic Serbian gala dinner, and a farewell networking lunch.

We hope that you spent a useful and inspiring time with us, gained new perspectives, and were encouraged to develop new projects, discoveries, and collaborations.

The Organizing Committee

Program of the 1st International Computational Chemistry Meeting

Tuesday, September 8, 2026

- 09:00 Registration
- 09:45 Opening Ceremony
(A-I-25)
- 10:00 **We will dock you – accelerating Drug design with computational chemistry**
(A-I-25) Dr. Robert Vianello
Ruđer Bošković Institute, Zagreb, Croatia
- 10:50 **Steiner distance and related topological indices in chemical graph theory**
(A-I-25) Dr. Yaping Mao
Quinghai Normal University, China
- 11:25 Coffee Break
- 12:05 **Geometric influence on designing topological indices**
(A-I-25) Dr. Boris Furtula
University of Kragujevac, Kragujevac, Serbia
- 12:40 **Quantifying network similarity through structural features distributions**
(A-I-25) Dr. Izudin Redžepović
State University of Novi Pazar, Novi Pazar, Serbia
- 13:15 Lunch Break
Restaurant Klub 3
- 15:15 **Introduction and overview of the WorkShop**
(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy
- 15:30 **3-D QSAR: Ligand-Based 3-D QSARs**
(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy
- 16:00 **3-D QSAR: Structure-Based 3-D QSARs**
(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia
- 16:30 Coffee Break
- 17:00 **Build 3-D QSAR model: The www.3d-qsar.com portal**

(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy

17:30 **Registration of users to www.3d-qsar.com portal**

(A-I-21)

17:45 www.3d-qsar.com: **Generation of bioactive molecules with Py_MolEdit**

(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy

at 20:00 Social Dinner
Restaurant Stara Srbija

Wednesday, September 9, 2026

09:00 **Oriented electric fields - Universal catalysts**

(A-I-25) Dr. Sason Shaik
The Hebrew University, Jerusalem, Israel

09:50 **Understanding and modelling catalytic reactions with valence bond diagrams**

(A-I-25) Dr. Benoît Braïda
University of Sorbonne, Paris, France

10:25 Coffee Break

10:55 **Rethinking electron counting rules for σ -aromaticity**

(A-I-25) Dr. Slavko Radenković
University of Kragujevac, Kragujevac, Serbia

11:30 **Application of comparative binding energy (COMBINE) analysis in the design of BioActive molecules**

(A-I-25) Dr. Rino Ragno
Sapienza University, Rome, Italy

12:05 Lunch Break
Restaurant Klub 3

14:30 www.3d-qsar.com: **Conformational search with Py_ConfSearch**

(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy

15:00 www.3d-qsar.com: **LB alignment with Py_Align**

(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia

15:30 www.3d-qsar.com: **Build LB 3-D QSAR model: (Rino Ragno)**

(A-I-21) Dr. Rino Ragno
Sapienza University, Rome, Italy

16:00 Coffee Break

16:30 www.3d-qsar.com: **Py-PDB**

(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia

17:00 www.3d-qsar.com: **Build SB 3-D QSAR model**

(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia

18:00 Guide City Tour

at 20:00 Social Dinner
Restaurant Panorama

Thursday, September 10, 2025

09:00 **Why are the excited states of heterocycles still challenging for theory?**

(A-I-25) Dr. Antonio Prlj
Ruđer Bošković Institute, Zagreb, Croatia

09:50 **How excited-state antiaromaticity drives ring-puckering and isomerization in benzene**

(A-I-25) Dr. Slađana Đorđević
Ruđer Bošković Institute, Zagreb, Croatia
University of Kragujevac, Kragujevac, Serbia

10:25 Coffee Break

10:55 **Optoelectronic properties of new porous metal halide semiconductors**

(A-I-25) Dr. Nourdine Zibouche
Lancaster University, Lancaster, UK

11:30 **Cryptands & computer chemistry – learning about selective ion complexation**

(A-I-25) Dr. Ralph Puchta
University of Erlangen-Nürnberg, Erlangen, Germany

12:05 Lunch Break
Restaurant Klub 3

- 14:30 Visit to Šumarice Memorial Park
- 16:00 www.3d-qsar.com: **Molecular Docking with Py-Docking**
(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia
- 16:30 Evolution of 3-D QSAR: **Comparative Binding Energy Analysis**
(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia
- 17:00 www.3d-qsar.com: **Build SB ComBinE model with Py_ComBine**
(A-I-21) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia
- 17:00 Coffee Break
- 18:00 www.3d-qsar.com: **Practical sessions on Py-MolEdit, Py-ConfSearch, and Py-**
(A-I-21) **Align**
Participants
- 18:30 www.3d-qsar.com: **Practical sessions on Py-PDB, and Py-Docking**
(A-I-21) Participants
- at 20:00 Social Dinner
Pizzeria Mali Napulj

Friday, September 11, 2025

- 09:00 **Do pnictogen onium cations and aromatic rings form only cation- π**
(A-I-25) **interactions? Answers from quantum chemical perspective**
Dr. Dušan Malenov
University of Belgrade, Belgrade, Serbia
- 09:50 **Melissa Officinalis l. as a potential source of natural agents for the**
(A-I-25) **prevention of gingivitis**
Dr. Svetlana Jeremić
State University of Novi Pazar, Novi Pazar, Serbia
- 10:25 Coffee Break
- 10:55 **Computational design of PROTACs and their ternary complexes**
(A-I-25) Dr. Milan Mladenović
University of Kragujevac, Kragujevac, Serbia

11:30 www.3d-qsar.com: **Practical sessions on Py-CoMFA**
(A-I-21) Participants

12:00 Lunch Break
 Restaurant Klub 3

14:00 www.3d-qsar.com: **Practical sessions on Py-ComBinE**
(A-I-21) Participants

14:30 www.3d-qsar.com: **Discussions of the results**
(A-I-21) Participants

15:30 Closing words
(A-I-25)

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Invited lectures

WE WILL DOCK YOU – ACCELERATING DRUG DESIGN WITH COMPUTATIONAL CHEMISTRY

Robert Vianello

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Computational chemistry has become an indispensable tool in modern drug discovery, enabling the rational design of biologically active molecules based on the three-dimensional structures of their targets. By integrating these techniques with experimental approaches, it is possible to gain detailed insights into binding mechanisms, facilitating efficient identification and optimization of new therapeutic agents. These strategies reduce the time and cost of drug development while improving our understanding of structure-activity relationships.

Tubulin polymerization inhibitors represent a cornerstone of anticancer therapy, as they disrupt microtubule dynamics essential for cancer cell growth. This lecture highlights our recent research efforts in the design, synthesis, and evaluation of benzazole-based compounds as potent tubulin-targeting agents (Figure 1). These chemically versatile scaffolds play an important role in medicinal chemistry,¹ offering a platform for the development of innovative bioactive molecules.

Using classical and microwave-assisted synthesis, we prepared *N*-derived benzimidazole acrylonitriles (Figure 1, X = C–H) with submicromolar antiproliferative activity (IC₅₀ 0.2–0.6 μM) and favorable selectivity.² Mechanistic studies confirmed inhibition of tubulin assembly and induction of mitotic arrest. Computational analyses identified critical protein-ligand interactions, guiding the design of improved analogues. In particular, replacement of the benzimidazole phenyl ring with pyridine led to imidazo[4,5-*b*]pyridines (Figure 1, X = N) with enhanced potency (IC₅₀ ~0.04 μM), reduced toxicity, and cell migration inhibition.³ Advanced computations revealed multiple binding modes at the colchicine site and alternative tubulin regions (Figure 2), underlining the versatility of these ligands. Since microtubule anomalies are, beyond oncology, linked to neuropsychiatric disorders, future perspectives, including repurposing for post-COVID neurological sequelae, will also be discussed.⁴

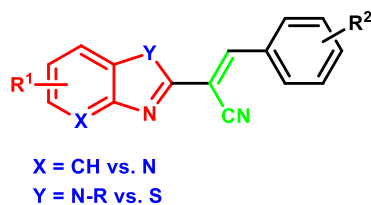


Figure 1. General chemical structure of studied ligands that interfere with the tubulin polymerization.

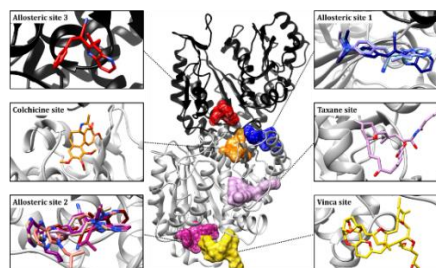


Figure 2. Various ligand binding sites on the α - (in black) and β -subunits (in gray) in the tubulin dimer, as identified through the docking and molecular dynamics simulations.

Keywords: Computational chemistry, Drug design, Tubulin inhibitors, Anticancer drugs

Acknowledgement: This work was supported by Croatian Science Foundation (grant number IP-2024-05-3953)

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STEINER DISTANCE AND RELATED TOPOLOGICAL INDICES IN CHEMICAL GRAPH THEORY

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Steiner distance is a natural generalization of the classical distance between two vertices in a graph. Let G be a connected graph and let $S \subset V(G)$ with $|S| \geq 2$. The Steiner distance $d_G(S)$ is defined as the minimum number of edges in a connected subgraph of G containing all vertices of S . When S consists of two vertices, the Steiner distance reduces to the usual graph distance. It therefore provides a unified framework for describing the collective connectivity of several vertices and for constructing multi-vertex distance-based topological indices. In this talk, we first introduce the basic concepts of Steiner trees, Steiner distance, and the Steiner k -Wiener index, together with their connections to classical graph distances and the Wiener index. We then present several topological descriptors derived from Steiner distance that are relevant to chemical graph theory, including the Steiner Wiener index, Steiner degree distance, Steiner Harary index, Steiner Gutman index, Steiner hyper-Wiener index, and Steiner Hosoya polynomial. Their fundamental properties, mutual relationships, and methods of computation for several important classes of graphs will be discussed. Finally, we review selected extremal and computational problems, conjectures, and open questions, and indicate possible directions for further research on Steiner-distance-based invariants in chemical graph theory and network analysis.

Keywords: Steiner distance, Steiner Wiener index, Steiner degree distance, Steiner Gutman index.

GEOMETRIC INFLUENCE ON DESIGNING TOPOLOGICAL INDICES

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Molecular descriptors are inevitable tools for modeling chemical phenomena and, as such, they govern the direction of investigations across many facets of chemistry. That's why the number of molecular descriptors is enormous, and a new descriptor appears almost every day. There is a real concern that introducing yet another index next to an already overflowing pool of descriptors will cause harm to molecular modeling, but this, by no means, should hinder the pursuit of "better" molecular descriptors.

Due to their low complexity and the amount of information they carry, topological indices have become a prominent class of molecular descriptors, applied in diverse fields of molecular sciences. They have exhibited full potential in QSPR/QSAR investigations, in which portions of chemical space are investigated in a reasonable time. Among topological indices, a largely employed and investigated class is degree-based topological indices. Their information-carrying potential, compared to short computational time, attracts interest and widens their application scope.

Recently, a new approach for designing topological indices, based on simple Cartesian geometry, was proposed. It was immediately recognized in the science community and applied for the design of many, mostly degree-based topological indices. In this lecture, some aspects of this method will be outlined, and a couple of novel degree-based indices, such as the elliptic Sombor index¹, the complementary second Zagreb index², and the diminished Sombor index^{3,4} will be presented.

Keywords: Degree-based topological indices, Elliptic Sombor index, Complementary second Zagreb index, Diminished Sombor index.

References:

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QUANTIFYING NETWORK SIMILARITY THROUGH STRUCTURAL FEATURES DISTRIBUTIONS

Izudin Redžepović

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Assessing structural similarity among complex systems represented as networks remains a central challenge across science and engineering. Existing methods span exact and approximate techniques, each constrained by limitations in scalability and interpretability. In this talk, we present a recently introduced distribution-based framework for network comparison. The approach characterizes each network through its degree and distance distributions, offering a probabilistic representation of key structural features. Similarity is quantified using Jensen–Shannon and Hellinger measures, and by integrating degree- and distance-based perspectives, we derive a unified similarity score that captures complementary aspects of network structures. We demonstrate the method’s performance on structured network families and highlight its applicability to random and real-world networks, including molecular similarity analysis. This flexible framework provides an adaptable tool for comparing networks, opening new directions for the study of complex systems across diverse domains.

Keywords: Structural similarity, Degree and distance distribution, Random networks, Real-world networks, Molecular similarity.

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ORIENTED ELECTRIC FIELDS - UNIVERSAL CATALYSTS

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I will describe principles of electric-field mediated-chemistry, whereby oriented-external electric fields (OEFs) function as universal catalysts and symmetry elements that control reactivity and selectivity.^{1,2} The Talk highlights the rate-enhancing reactivity by OEFs for a variety of reactions in the gas phase and in solution (solvent screening of the OEF is imperfect, and hence, chemical reactions can occur in solution and are not limited to gas- or solid-phases).

The rate-controlling effects are uni-dimensional and coinciding with the direction of charge-transfer, which serves as a reaction axis (RA). As such, the OEF act as tweezers that orients molecular species along the respective RAs, and accelerates their transformation to unique products that differ from those produced in the commonly used thermal conditions. Thus, for example, we show that a Diels-Alder reaction which cannot occur thermally, transpires easily in the presence of OEFs. Similarly, experimentally non-reactive reaction mixtures give rise to novel products in the presence of the OEF.

The talk discusses experimental support of the theoretical predictions. Some of the applications also use continuous-flow setups, which will eventually scale-up product-yields to Molar concentrations, and render OEFs as practical tools in chemistry. Evidence is presented for existence of (OEF/thermal)-dichotomy, wherein the OEF-induced products differ from those which are produced by the corresponding thermal-only reactions.

The talk concludes with a vision that in the near future, OEF usage will change chemical-education, chemical-practice, and the art of making molecules.

References:

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2. S. Shaik et al, *Acc. Chem. Res.* **2025**, 58, 3071.

UNDERSTANDING AND MODELLING CATALYTIC REACTIONS WITH VALENCE BOND DIAGRAMS

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The Valence Bond diagram approach, first introduced in the early 1980's by Sason S. Shaik,¹ is a very powerful conceptual tool to rationalize trends in reactivity. It has been successfully applied along the years to many families of chemical reactions, up to enzymology.^{2,3}

In this contribution, we will show that Valence Bond Diagrams reveal the decisive role for secondary coordination sphere nucleophiles on methane C–H activation. *Ab initio* DFT calculations indicate that nucleophiles can significantly reduce enthalpic barriers to methane C–H bond activation, and following Valence bond diagram analysis suggests the formation of a two-center three electron bond as the origin of the catalytic nucleophile effect. A predictive model for methane activation catalysis follows, leading to the proposition that proteins with hydrophobic active sites, available strong nucleophiles, and hydrogen bond donors can be attractive targets for engineering novel methane functionalizing enzymes.⁴ If time remains, a second original application of Valence Bond diagrams on Frustrated Lewis Pairs systems, which have emerged as a new type of metal-free catalysts for reversible H₂ activation, will also be presented.

Keywords: Valence bond diagrams, Chemical reactivity, Methane C–H activation, Catalysis, Frustrated Lewis pairs

References:

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RETHINKING ELECTRON COUNTING RULES FOR σ -AROMATICITY

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Electron-counting rules of aromaticity, such as the Hückel and Baird rules, have long been used to predict both aromatic character and the tropicity of magnetically induced current density (MICD) in conjugated cyclic molecules.^{1,2} Originally formulated for annulenes, these rules were later extended to a broader class of monocyclic π -conjugated systems. More recently, it has been shown that Hückel and related aromaticity rules can also be successfully applied to σ -conjugated cyclic systems. In this work, we demonstrate a fundamental limitation of these electron-counting rules in cyclic systems containing tangentially oriented p atomic orbitals engaged in σ -type bonding. While the rules correctly predict MICD tropicity for systems with an even number of atoms in the ring, they fail for odd-membered rings, yielding incorrect predictions of aromatic and antiaromatic behavior. To illustrate this limitation, magnetically induced current densities were calculated for a series of *periodo*-annulenes at the B3LYP/def2-TZVP level of theory.³

Keywords: Aromaticity, Aromaticity rules, Ring currents.

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2. E. Steiner, P. W. Fowler, *J. Phys. Chem. A* **2001**, 105 (41), 9553.
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APPLICATION OF COMPARATIVE MOLECULAR BINDING ENERGY ANALYSIS IN THE DESIGN OF BIOACTIVE MOLECULES

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The Comparative Binding Energy (COMBINE) analysis is a structure-based (SB) quantitative structure-activity relationship (QSAR) method that derives predictive models by correlating experimental binding affinities with specific, weighted components of ligand-receptor interaction energies¹. Unlike ligand-based (LB) methods (e.g., CoMFA), which rely on superimposed ligands and probe fields, COMBINE uses the three-dimensional structures of ligand-receptor complexes to break down total interaction energy into residue-based descriptors. These descriptors usually include van der Waals and electrostatic terms, which are often supplemented by desolvation energies. PLS regression the method identifies critical amino acid residues that drive binding affinity. This approach enables the identification of key interactions, the prediction of binding modes, the assessment of protein mutations, and the rational design of inhibitors with improved potency and selectivity across diverse targets, including enzymes, protein-protein complexes, and nucleic acid binders. Nevertheless, the COMBINE approach was not as successful as the related method CoMFA. This is likely due to the lack of a user-friendly graphical interface for developing COMBINE-based models.

In 2012, a revised approach called COMBINER was first published¹, representing an improved and streamlined version of the original COMBINE analysis. In its initial application, COMBINER was employed to develop comprehensive SB 3-D QSAR models for wild-type and mutant enzymes, integrating ligand- and structure-based alignment procedures. This updated approach is now available as Python scripts (Py-ComBinE) on the computational medicinal chemistry platform www.3d-qsar.com². The Py-ComBinE methodology has been successfully applied to diverse therapeutic targets, including HIV-1 reverse transcriptase^{1,3,4}, zinc-based histone deacetylases⁵, DOT1L⁶, SARS-CoV-2 main protease⁷, bovine serum amine oxidase⁸, and the mycobacterial transporter⁹. Within the www.3d-qsar.com the Py-ComBinE approach represent a robust framework for generating predictive SB 3-D QSAR models. It optimizes field combinations and integrates them with LB data, facilitates the identification of critical protein residues, rationalizes binding modes, and guides the design of next-generation inhibitors for complex biological targets.

Keywords: Comparative binding energy, Structure based drug design, Molecular docking, 3-D QSAR, Prediction of drug binding affinities.

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WHY ARE THE EXCITED STATES OF HETEROCYCLES STILL CHALLENGING FOR THEORY?

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Heterocyclic compounds are essential building blocks of biomolecules and systems that are highly relevant for optoelectronic applications. Surprisingly, even the lowest electronically excited states of heterocycles present a challenge for quantum chemical calculations. This is due to the difficulty of accurately providing a balanced description of excited states with very different characters, e.g., bright vs. dark, ionic vs. covalent, singly vs. doubly excited, etc. We analyse the origins of these different characters from both molecular orbital (MO) and valence bond (VB) theory perspectives, using pseudosymmetry arguments that connect the two viewpoints.[1] We discuss the importance of electronic correlation for achieving a balanced description of excited states and explain why it is difficult, or even impossible, to reach high accuracy with conventional density-functional theory approximations. Finally, we delve into the origins of less studied but occasionally relevant problems, such as valence–Rydberg mixing.

Keywords: Heterocycles, excited states, MO theory, VB theory, Pseudosymmetry.

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HOW EXCITED-STATE ANTIAROMATICITY DRIVES RING-PUCKERING AND ISOMERIZATION IN BENZENE

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This study investigates the ultrafast photodynamics of benzene following excitation to the S_2 state using non-adiabatic trajectory surface hopping (TSH) combined with XMS-CASPT2/cc-pVTZ electronic structure calculations. Our simulations reveal a rapid $S_2 \rightarrow S_1 \rightarrow S_0$ internal conversion cascade accompanied by pronounced out-of-plane geometric distortion. Detailed trajectory analysis demonstrates that out-of-plane ring-puckering accounts for 93% of the non-radiative decay events through the S_1/S_0 conical intersection seam. We interpret this structural evolution as a mechanism for relieving the excited-state antiaromatic character of the 6π -electron system, with out-of-plane deformation leading to electron localization.

Decay through the S_1/S_0 conical intersection seam leads to the formation of vibrationally hot ground-state molecules. Over the 500 fs simulation, the dynamics access structural motifs associated with potential photoproducts. In particular, we identify structures related to benzvalene and Dewar benzene, as well as a smaller fraction of ring-opened structures. These findings provide a first step toward a dynamical perspective on excited-state aromaticity.

Keywords: Excited-state, Aromaticity, Nonadiabatic molecular dynamics.

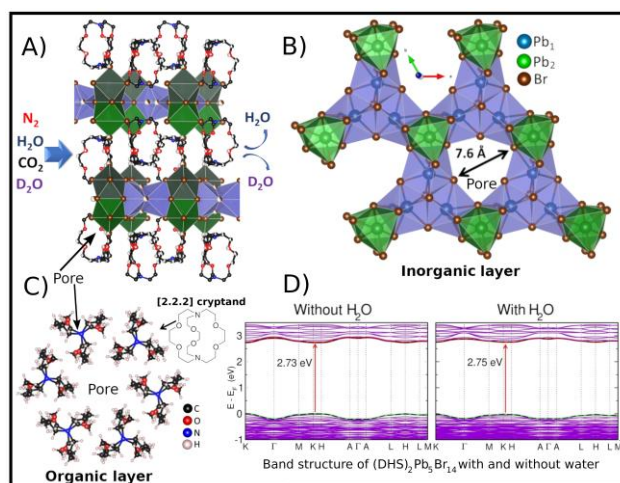
OPTOELECTRONIC PROPERTIES OF NEW POROUS METAL HALIDE SEMICONDUCTORS

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Recent advancements in the field of metal halide perovskites and related materials has led to the development of porous metal halide semiconductors presented in Figure 1.¹⁻³ These novel materials possess a unique porous structure with interconnected nanoscale pores, offering high surface area-to-volume ratios and tunable optoelectronic properties. They exhibit unprecedented water stability and promising characteristics such as efficient photoluminescence and antibacterial properties, making them attractive candidates for a wide range of applications including sensing, photocatalysis, water treatment, biomedical, and energy conversion.^{1,4} Additionally, their dielectric and quantum confinement effects at the nanoscale present opportunities for photonics and optoelectronic devices. In this talk, I will present the structural characteristics of these porous metal-halide materials and provide first-principles simulation insights into their electronic structure and optical properties.



Keywords: Metal-halides, Pervoskites, Porous materials, DFT.

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CRYPTANDS & COMPUTER CHEMISTRY – LEARNING ABOUT SELECTIVE ION COMPLEXATION

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Supramolecular chemistry is traditionally an experimental science, driven by serendipity and unexpected findings and therefore attractive for all sorts of chemical subfields. The application of quantum chemical methods has proven in the last decades to be a valuable tool to rationalize results and gain deeper insights. Computational chemistry, often dealing with one isolated (supra)molecule is an outstanding possibility to investigate molecular systems unhampered by solvent molecules, neighboring effects or counter ions.[1]

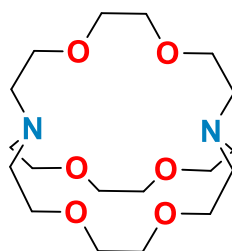


Figure: Lehn's original cryptand, best known by Lehn's notation [2.2.2] – system name 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane.

This lecture will report our results of the last two decades, mainly based on density functional theory (DFT) calculations, on selective cation complexation by the classical [2.2.2] cryptand of J.-M. Lehn and their corresponding metallo topomers. These studies allowed us to design and compare different types of cryptands, predict the favored and selected metal cations and understand the individual molecular mechanism to host the cations as good as possible.

While this approach is fascinating for supramolecular and computational chemists, it is additionally an excellent possibility to include learners of different levels of education into a scientific project. The chemistry can be understood based on the topics taught in school and undergraduate lectures and own investigations can be done at the computer with out any harm or danger.

Keywords: Cryptands, cryptates, Selective ion complexation, DFT.

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DO PNICTOGEN ONIUM CATIONS AND AROMATIC RINGS FORM ONLY CATION- π INTERACTIONS? ANSWERS FROM QUANTUM CHEMICAL PERSPECTIVE

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Cation- π interactions are among the strongest noncovalent interactions and are very important for numerous chemical and biological systems.[1] Very strong interactions of alkali and alkaline earth metal cations with aromatic rings [2] can be strengthened by transition metal coordination of the ring, which was demonstrated for cyclopentadienyl (Cp) sandwich compounds [3] and even more so for benzene sandwich compounds [4].

In this work we have studied interactions of pnictogen onium cations (ammonium, phosphonium, arsonium) with (uncoordinated) benzene, as well as with Cp (ferrocene, ruthenocene and osmocene) and benzene sandwich compounds (bis(benzene)chromium, bis(benzene)molybdenum and bis(benzene)tungsten). Similarly to interactions of alkali and alkaline earth cations,[4] the following increase in interaction strength was observed: benzene < Cp sandwich < benzene sandwich. It was shown that ammonium ion forms stronger interactions than phosphonium ion; however, no further weakening of interactions was observed for arsonium ion. Moreover, phosphonium and arsonium ions have the same orientation towards the aromatic moieties, while the orientation of ammonium ions is essentially different. Further analyses showed that ammonium ion forms solely cation- π interactions, while phosphonium and arsonium ions interact by combining cation- π and pnictogen binding, as evidenced by the σ -holes on corresponding electrostatic potential maps. The existence of this charge assisted pnictogen bonding in addition to cation- π interaction for systems with phosphonium and arsonium ions was confirmed by Atoms in Molecules (AIM), Natural Orbitals for Chemical Valence (NOCV) and Reduced Density Gradient (RDG) analyses.

Keywords: Sandwich compounds, Cation- π interactions, Pnictogen bonds, Ammonium, Phosphonium.

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MELISSA OFFICINALIS L. AS A POTENTIAL SOURCE OF NATURAL AGENTS FOR THE PREVENTION OF GINGIVITIS

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Melissa officinalis L. is an aromatic plant species that has been used in traditional medicine in Serbia for centuries. Its characteristic pleasant, lemon-like aroma makes beverages prepared from its aerial parts particularly refreshing, especially during periods of high temperatures. The aroma is primarily attributed to citral, a mixture of two geometric isomers: geranial (α -citral, *trans*-citral, or (2E)-3,7-dimethylocta-2,6-dienal) and neral (β -citral, *cis*-citral, or (2Z)-3,7-dimethylocta-2,6-dienal) [1, 2].

In the present study, molecular docking was employed to investigate the potential of these monoterpenes as inhibitors of hydrolases from four bacterial species associated with gingivitis, one of the most common inflammatory diseases affecting the gingival tissue: *Porphyromonas gingivalis* (PDB ID: 9FMA), *Aggregatibacter actinomycetemcomitans* (PDB ID: 4U10), *Fusobacterium nucleatum* (PDB ID: 7EP9), and *Streptococcus mutans* (PDB ID: 2W3Z) [3, 4]. The inhibitory potential of geranial and neral was compared with that of chlorhexidine, a standard agent used in conventional gingivitis treatment.

The molecular docking results showed that chlorhexidine generally exhibited more favorable interactions with the investigated protein targets and a higher predicted inhibitory potential than the studied monoterpenes. The exception was the hydrolase from *Fusobacterium nucleatum*, against which chlorhexidine showed no inhibitory potential, whereas both geranial and neral interacted with the active site, suggesting a potential inhibitory effect.

Although citral showed lower inhibitory potential toward the other hydrolases than chlorhexidine, its activity was not negligible. Conventional Hydrogen Bonds were the most prevalent ligand–protein interactions, followed by hydrophobic Alkyl–Alkyl and π –Alkyl interactions, indicating that both polar and hydrophobic contacts contribute to stabilization of the citral–protein complexes.

Although these results cannot replace experimental antimicrobial studies, they provide a theoretical basis for considering constituents of *Melissa officinalis* L. extract as potential modulators of bacterial proteins associated with oral infections. In cases of established or severe gingival inflammation, appropriate conventional therapy remains essential. Nevertheless, the potential use of *Melissa officinalis* L. preparations and extracts as complementary agents for the prevention and maintenance of oral health warrants further investigation.

Beverages prepared from *Melissa officinalis* L. also offer a pleasant aroma and taste and contribute to fluid intake during periods of high temperatures. Thus, the traditional use of this plant, supported by scientific validation of its biological effects, may represent an interesting link between traditional herbal medicine and contemporary research on naturally occurring bioactive compounds.

Keywords: *Melissa officinalis* L., Geranial, Neral, Gingivitis, Molecular docking.

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COMPUTATIONAL DESIGN OF PROTACS AND THEIR TERNARY COMPLEXES

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PROteolysis TArgeting Chimeras (PROTACs) are heterobifunctional molecules that induce selective degradation of target proteins through the ubiquitin–proteasome system (UPS). They comprise a ligand that binds the protein of interest (POI) and an E3 ubiquitin ligase-recruiting ligand, connected by a linker. Simultaneous engagement of the POI and E3 ligase promotes the formation of a POI–PROTAC–E3 ternary complex (TC), facilitating target ubiquitination and subsequent proteasomal degradation. However, the formation of a stable and productive TC in vitro or in vivo remains one of the most challenging aspects of PROTAC design, as it depends on the intricate interplay among the POI, PROTAC, and E3 ligase. Accordingly, accurate prediction of TC formation represents a major challenge in computational PROTAC design. Although established computational approaches, such as PROsettaC, PROTAC-Model, and BOTCP, as well as more recent methods including DeepTernary and TERNIFY, have demonstrated a remarkable ability to reproduce experimentally resolved TCs and, to varying extents, predict previously unknown POI–E3 orientations, their performance generally benefits from known or reliably predicted binding modes of the PROTAC warhead and E3-ligase recruiter. Consequently, the de novo construction, refinement, and reliable ranking of previously unknown TCs remain challenging. To address this limitation, we present TERNARYON, an integrated in silico workflow for the de novo construction and assessment of structurally feasible PROTAC TCs in the absence of experimentally resolved ternary structures, using the design of HDAC4-targeting PROTACs with potential therapeutic relevance to spinal muscular atrophy (SMA) as a case study. TERNARYON combines structure-based alignment of available co-crystallized complexes with ambiguity-driven HADDOCK3 protein–protein docking to explicitly explore the POI–E3 interaction landscape and generate an ensemble of candidate POI–E3 binary complexes (BCs). Geometrically compatible BCs are subsequently subjected to geometry-guided pre-orientation of the complete PROTAC, followed by reversible or irreversible docking using AutoDock Vina and its derivatives to construct and refine candidate ternary complexes. By integrating protein–protein interaction sampling, geometry-guided PROTAC placement, and alternative docking strategies within a single structure-based framework, TERNARYON provides a complementary approach for modeling PROTAC ternary complexes when an experimentally resolved POI–PROTAC–E3 structure is unavailable.

Keywords: PROTACs; Ternary complexes; Ternary complex modeling; HADDOCK3; HDAC4.

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