SupramolChem2025

VII. SIMPOZIJ SUPRAMOLEKULSKE KEMIJE

Supramolecular Chemistry 2025

KNJIGA SAŽETAKA

Book of Abstracts

Knjižnica HAZU
Strossmayerov trg 14, Zagreb
9. prosinca 2025.

ACADEMIA SCIENTIARUM ET ARTIUM CROATICA MDCCCLXI

SECTIO CHEMICA ·1876· FAC·SCIENT·NAT·ET MATH·

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IMPRESSUM

ORGANIZATORI

Razred za matematičke, fizičke i kemijske znanosti Hrvatske akademije znanosti i umjetnosti

Kemijski odsjek Prirodoslovno-matematičkog fakulteta Sveučilišta u Zagrebu

Institut Ruđer Bošković

Hrvatsko kemijsko društvo

IZDAVAČ

Institut Ruđer Bošković, Zagreb

UREDNICI

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ISBN: xxx-xxx-xxxx-xx-x

supramolchem.org

Zagreb, 2025.

VII. simpozij supramolekulske kemije – *Supramolecular Chemistry 2025*

VII. simpozij supramolekulske kemije (*Supramolecular Chemistry 2025*) održat će se 9. prosinca 2025. godine u predavaonici Knjižnice HAZU s početkom u 9 h (do 17 h), u organizaciji Razreda za matematičke, fizičke i kemijske znanosti Hrvatske akademije znanosti i umjetnosti, Sekcije za supramolekulsku kemiju Hrvatskog kemijskog društva, Kemijskog odsjeka Prirodoslovno-matematičkog fakulteta Sveučilišta u Zagrebu i Instituta Ruđer Bošković.

Prvi simpozij „Supramolekulska kemija u Hrvatskoj – dosezi i pogled u budućnost", posvećen supramolekulskoj kemiji u Hrvatskoj, održan je 2017. godine kao minisimpozij koji je obilježio 50. godišnjicu otkrića krunastih etera, 30. godišnjicu dodjele Nobelove nagrade za supramolekulsku kemiju i četiri desetljeća sustavnog istraživanja u području supramolekulske kemije u Hrvatskoj.

Područje i znanstveni program simpozija

Ovogodišnji VII. simpozij supramolekulske kemije sadržajem će pratiti prethodne. Bit će posvećen aktualnim istraživanjima iz područja makrocikličke kemije, molekulskog samoudruživanja, kemije funkcionalnih materijala, molekulske samoorganizacije, supramolekulskih vrsta u čvrstom stanju i sinteze kompleksnih supramolekulskih sustava, kao i istraživanjima u drugim područjima povezanim sa supramolekulskom kemijom.

ORGANIZATORI

ZNANSTVENO-ORGANIZACIJSKI ODBOR

Leo Frkanec (IRB), predsjednik
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PROGRAM

8:00 – 9:00	**Registracija sudionika**
9:00 – 9:15	**Otvaranje konferencije**
	Predsjedavajući sekcije: **Leo Frkanec**
9:15 – 9:45	**Davor Margetić** (IRB), Self-Assembly of Bis-Porphyrin-Fullerene Systems
9:45 – 10:15	**Krunoslav Užarević** (IRB), Mechanochemistry of supramolecules for enhanced chemical and enzymatic reactivity
10:15 – 10:45	**Stanka za kavu**
	Predsjedavajući sekcije: **Vladimir Stilinović**
10:45 – 11:15	**Darko Vušak** (PMF), A Rare Case of Martensitic Phase Transition with Self-Healing Effect in Nickel Glycinamide Single-Crystals
11:15 – 11:45	**Leo Frkanec** (IRB), Amino-acid self-assembled nanofibre hydrogel as a minimal hydrolase mimic
11:45 – 12:00	**Luka Klemen** (PMF), Exploring Cation Binding using the Intrinsic Fluorescence of Calixarenes
12:00 – 12:15	**Ivica Cvrtila** (IRB), 2-Formylpyridine Blue Out of the Blue
12:15 – 14:00	**Stanka za ručak**
	Predsjedavajući sekcije: **Vladislav Tomišić**
14:00 – 14:30	**Ivana Brekalo** (IRB), Control of Zeolitic Imidazolate Framework Topology *via* Supramolecular Interactions
14:30 – 15:00	**Jana Pisk** (PMF), Next-Generation Room-Temperature Sensors: Mo Coordination Complexes in Action
15:00 – 15:15	**Marin Liović** (PMF), Calorimetry and Periodic DFT: Sublimation Reactions and a Solid-State Reaction
15:15 – 15:45	**Stanka za kavu**
	Predsjedavajući sekcije: **Dominik Cinčić**
15:45 – 16:15	***Tomislav Piteša*** (IRB), How to Efficiently Calculate Supramolecules?
16:15 – 16:45	**Marina Juribašić Kulcsár** (IRB), Supramolecular Catalysis Meets Photomechanochemistry: A New Route to Template-Assisted Olefin [2+2] Cycloaddition
16:45 – 17:00	**Lucija Vrban Đerek** (IRB), Computationally Guided Mechanochemical Design of Cyclodextrin – Dasatinib Inclusion Complexes for Controlled Drug Release
10:30 – 17:00	**Posterska sekcija**
17:00	**Zatvaranje konferencije**

POSTERSKA PRIOPĆENJA

PP1 **I. Nikšić-Franjić, A. Usenik, M. Belovari, M. Jurković, L. Klemen, N. Cindro, N. Došlić, I. Piantanida, and V. Tomišić**, *Intrinsic Fluorescence of Calixarenes: the Origin and Applications*

PP2 **M. Modrušan, J. Borovec, A. Usenik, G. Horvat, J. Požar, T. Hrenar, and V. Tomišić**, *Computational Study of Cation Binding by Tetra-O-2-oxopropyl-substituted Calix[4]arene Isomers*

PP3 **R. Kerep, D. Klarić, A. Budimir, and N. Galić**, *Thermodynamic Insights into Nabumetone–β-Cyclodextrin Encapsulation from Temperature-Dependent ITC Analysis*

PP4 **M. Modrušan, N. Vidović, N. Cindro, P. Jukić, A. Jurčević, G. Speranza, V. Tomišić, and G. Horvat**, *Alkaline Earth Metal Cation Binding by Leucine and Phenylalanine Penta and Hexa Cyclopeptides in Acetonitrile*

PP5 **K. Ribičić, M. Belovari, I. Piantanida, I. Jerić, and I. Đapić**, *Synthesis of fluorophore and peptide conjugates with dual activity for suppressing MDM2 protein and imaging cancer cells*

PP6 **M. Pajić, S. Muratović, and M. Juribašić Kulcsár**, *Kinetics of a Supramolecularly Templated Photomechanochemical [2+2] Cycloaddition*

PP7 **K. Leko, B. Šijić, N. Cindro, A. Usenik, V. Stilinović, G. Talajić, and V. Tomišić**, *Thermodynamic and Structural Studies of Complexation of Alkali, Alkaline Earth, and Soft Metal Cations by a Thioamide Calix[4]arene Derivative*

PP8 **D. Barišić, M. Cvetnić, N. Bregović, and V. Tomišić**, *Synthesis and Characterization of Calix[4]arene Comprising Urea and Carboxylate Complementary Moieties*

LECTURES

Self-Assembly of Bis-Porphyrin-Fullerene Systems

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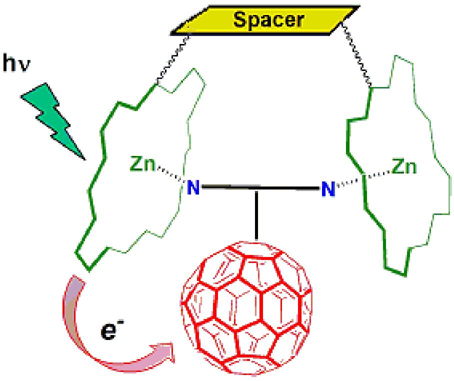
Electron donor-acceptor (D-A) interactions within fullerene-porphyrin architectures are important for multi-component model systems designed to transmit and process solar energy.[1] These organic photocurrent-generating constructs are often based on covalently linked fullerene and porphyrin components. The alternative construction approach employs self-assembly of components by axial coordination.[2,3] Here, synthesis and complexation studies of a bis-porphyrin-fullerene supramolecular complexes designed for organic photovoltaic devices[4] will be presented.[5,6]



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Mechanochemistry of supramolecules for enhanced chemical and enzymatic reactivity

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Supramolecular chemistry, or chemistry beyond molecules, is a field of research of chemical systems formed by the recognition and self-assembly of molecules through weaker intermolecular interactions, such as hydrogen bonding and van der Waals forces. It is crucial in biological systems, where fundamental processes in cell biology, such as enzyme-substrate binding, DNA replication, and protein folding, rely on these same non-covalent interactions to create complex structures with specific functions. Although commonly associated with solution processes, supramolecular self-assembly in the solid state can be readily achieved through mechanochemical processing. Mechanochemical screening of pharmaceutical cocrystals was responsible for the rise of interest in preparative mechanochemistry in the 1990s, demonstrating that mechanochemistry can lead to the stoichiometric and controllable formation of polymorphic cocrystal forms.

This lecture will show how supramolecular recognition in a mechanochemical reactor can be also exploited for solid-state recognition and separation of isomeric carboxylic acids[1], facilitate the prebiotic covalent bond formation in nucleobases[2], or steer photochemical reactions.[3] Finally, it will be shown here how mechanochemically formed supramolecular framework composite materials can protect enzymes in harsh environments and enhance their reactivity.[4]

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A Rare Case of Martensitic Phase Transition with Self-Healing Effect in Nickel Glycinamide Single-Crystals

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Supramolecular interactions direct how molecules recognize each other and assemble into different architectures. In crystals, non-covalent interactions direct the crystal packing and polymorphism, which features applications in pharmaceutical science, functional materials and crystal engineering.[1] There are two common types of polymorphic transitions: a reconstructive and martensitic type of transition.[2] Reconstructive transition often leads to the breaking of a crystal, due to the random movement and orientation of domains. On the other hand, in martensitic transitions, cooperative atomic, molecular, or ionic movements lead to the preservation of the crystal integrity.[2] Martensitic transitions, coupled with self-healing effect, are extremely rare in molecular compounds and usually discovered serendipitously.[3]

In this work, we report a thermally-induced martensitic type of polymorphic transition in a coordination compound of nickel(II) and glycinamide (Glyam), $[Ni(H_2O)_2(Glyam)_2]I_2$ (**1**). When the room-temperature polymorph, $\mathbf{1}_{\mathbf{RT}}$, is cooled below the transition temperature (approx. 210 K), it transforms into a twinned crystal of a low-temperature polymorph, $\mathbf{1}_{\mathbf{LT(twinned)}}$. If $\mathbf{1}_{\mathbf{LT(twinned)}}$ is heated above the transition temperature, it transforms and heals into a single-crystal of $\mathbf{1}_{\mathbf{RT}}$. Single-crystal X-ray diffraction, thermal and optical analyses of crystals revealed the complex cooperative molecular movements and the involvement of intermolecular interactions.[4]

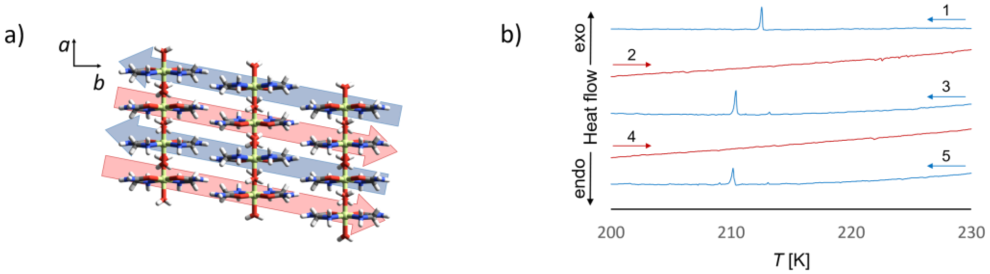

Figure 1. a) Molecular movements during polymorphic transition; b) DSC measurements during cooling (blue lines) and heating (red lines) cycles of a single crystal of 1.

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Amino-acid self-assembled nanofibre hydrogel as a minimal hydrolase mimic

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Recent advances in supramolecular gels have accelerated progress in materials chemistry, particularly in the development of self-organizing soft matter. Such materials offer broad opportunities for application in pharmaceuticals, food and cosmetic formulations, and in tissue engineering and regenerative medicine.[1] Natural enzymes are exceptionally efficient biocatalysts, and decades of work have focused on strategies to mimic their function. Recent studies have shown that fibrous nanoparticle matrices formed by the self-assembly of peptide-based hydrogels can act as efficient catalysts for ester hydrolysis.[2-5] To probe the origin of this activity and the role of supramolecular structure in catalysis, we designed a series of lipopeptides (**1**–**6**) (Fig. 1).

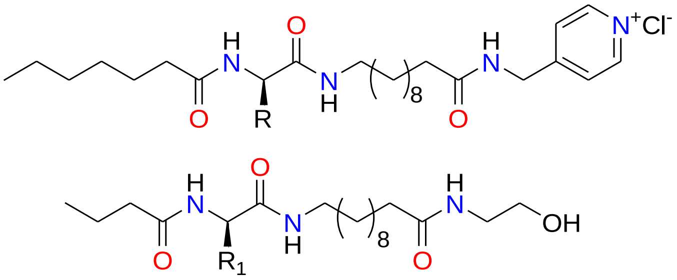

Figure 1. Structural formulas of low-molecular-weight hydrogelators **1**–**6** (R = benzyl, phenyl, imidazole, or indole; R¹ = phenyl or isopropyl).

Catalytically active hydrogelators were synthesized by attaching fatty chains to amino acids (L-Phe, L-Phg, L-His and L-Trp) at both the C- and N-terminal positions. Polar end groups, either hydroxyl or picolyl, imparted amphiphilicity and promoted self-assembly. Histidine and tryptophan were incorporated to introduce organocatalytic functionality. Self-assembly was confirmed by determining the critical aggregation concentrations and by characterizing the resulting aggregates using spectroscopic and microscopic techniques. Differences in amino-acid composition, chirality and hydrophobicity led to distinct supramolecular architectures, ranging from globular assemblies to extended fibres. Selected binary mixtures of hydrogelators were also evaluated. Histidine-containing derivatives catalysed the hydrolysis of *p*-nitrophenyl acetate in aqueous solution. The influence of supramolecular organization on catalysis is evident from the contrasting behaviour of the monomeric species and their assembled structures.

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Exploring Cation Binding using the Intrinsic Fluorescence of Calixarenes

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Calixarenes are commonly explored as fluorescent sensors,[1] yet their luminescent properties have been attributed primarily to derivatives bearing externally introduced fluorophores.[2] In contrast to this prevailing view, the present study investigates the intrinsic fluorescence of several calix[4]- and calix[6]arenes without additional fluorophores (Figure 1) and evaluates their fluorescence responses upon complexation with alkali and alkaline earth metal cations in water, methanol, and acetonitrile.[3] Although the examined macrocycles exhibit only weak to moderate emission, a pronounced fluorescence enhancement occurs upon cation binding. Notably, the monomeric tertiary-amide calixarene analogue displays the opposite trend, highlighting the distinct excited-state behaviour of macrocyclic versus monomeric architectures. Time-resolved fluorescence measurements combined with quantum chemical calculations elucidated the underlying emission mechanisms and accounted for the observed differences in photophysical properties between free ligands and their metal complexes. Overall, these findings demonstrate that intrinsic fluorescence can serve as a sensitive, quantitative probe for monitoring cation-complexation processes. The pronounced emission changes enable fluorimetric titrations at low ligand concentrations and allow reliable determination of rather high stability constants, thereby establishing intrinsic fluorescence as a valuable tool in the study of calixarene host–guest chemistry.

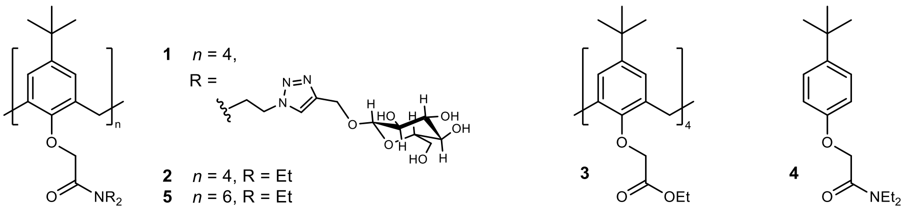

Figure 1. Structures of investigated calixarenes.

Acknowledgements. This research was funded by Croatian Science Foundation projects CalixCORE (IP-2024-05-3012), POC-Sens-Bioact (IP-2022-10-9829), PhInMol (IP-2022-10-4658), MicroSynTotal (IP-2024-05-5352), NextGenerationEU program (NPOO.C3.2.R2-I1.06.0043), and the European Regional Develop-ment Fund infrastructural project CIuK (KK.01.1.1.02.0016).

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2-Formylpyridine Blue Out of the Blue

Ivica Cvrtila,*[a] Vedran Kojić,[a] Darija Domazet Jurašin,[a] Sara Marijan,[a] Luka Pavić,[a] Branka Bilić,[a] Ana Šimatović,[a] Ivan Halasz[a]

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In the course of research in photochemistry of hydrazones[1] it was noted that solutions of 2-formylpyridine in acidic ammonium acetate buffer gradually turn blue, with faint colour visible already after two days of standing at room temperature. Upon longer standing, aside from deeper blue colour, macroscopic aggregates appear in the form of threads and globules, ultimately forming dark-blue webs (Figure 1). As such behavior has never been reported (except, possibly, as "black and insoluble tar side products"[2]) despite the existence of a solid body of related literature, including even the same starting materials,[3] we explored how to obtain that material in larger quantities, and further studied its formation and properties, including elucidation of its structure. Herein we present the current knowledge on its structure and possible formation routes, as well as its electric, optical, and supramolecular, in particular gelating properties.

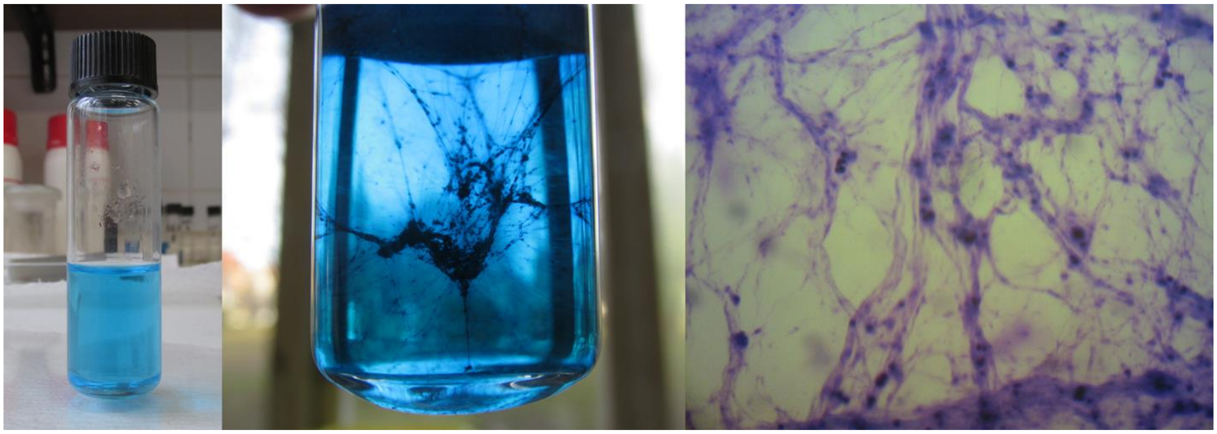

Figure 1. Blue color in of 2-formylpyridine acidic ammonium acetate buffer (left); dark-blue threads and globules in the same solution after one month of standing at room temperature (center); aggregates as seen under optical microscope (right).

[1] I. Cvrtila, H. Fanlo-Virgós, G. Schaeffer, G. Monreal Santiago and S. Otto, *J. Am. Chem. Soc.* **2017**, *139*, 12459–12465.
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Control of Zeolitic Imidazolate Framework Topology via Supramolecular Interactions

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Zeolitic Imidazolate Frameworks (ZIFs) are framework materials built from tetrahedral metal centers and imidazolate linkers. They exhibit exceptional polymorphism and flexibility, so the simplest ZIF – unsubstituted zinc imidazolate – exists in at least 18 different topologies,[1] some of which have several distinct crystallographic forms. As the many potential applications of ZIFs such as separations, gas capture, and catalysis, depend highly on their solid form,[2] control of this polymorphism is paramount. Mechanochemistry – a fast, quantitative and sustainable synthetic method[3] – has recently been effectively applied to ZIF syntheses, and it was shown that the ZIF solid form outcome can be controlled by different additives, such as liquids or salts.[4]

We here demonstrate[5] the use of commercially available liquid templates as structure-directing agents in the mechanochemical synthesis of new solid forms of zinc imidazolate (Zn**Im**$_2$). We show that multiple Zn**Im**$_2$ forms can be prepared by screening using liquid assisted grinding, including new forms of the **crb** topology. Furthermore, we use previously validated periodic DFT modeling[6] to explain the observed synthetic results, and in some cases even predict the outcomes of screening.

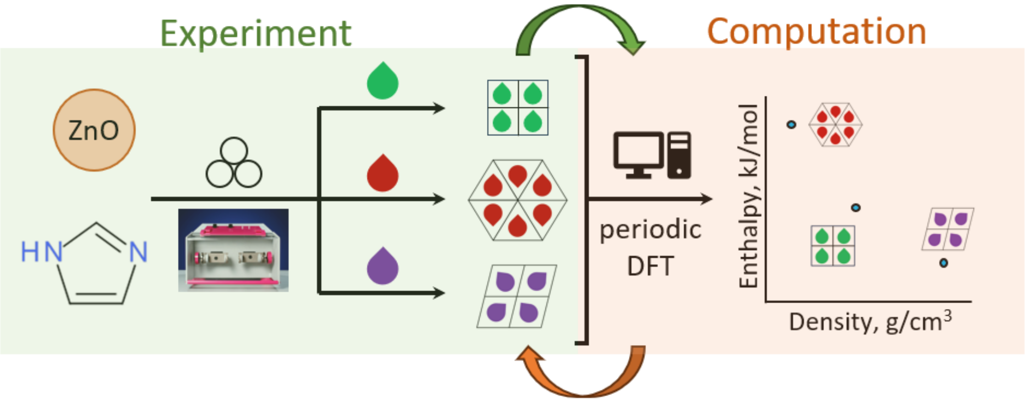

Figure 1. Schematic representation of the dependence of form outcome of the mechanochemical synthesis of ZnIm$_2$ on liquid additives, and the interplay of computation and experiment.

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Next-Generation Room-Temperature Sensors: Mo Coordination Complexes in Action

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Industry 4.0 leverages advanced technologies, including sensors, big data, artificial intelligence, and automated control systems, to transform traditional manufacturing into smart, data-driven processes.[1,2] Sensors play a pivotal role by converting physical stimuli, such as pressure, heat, and volatile compounds, into measurable electrical signals, enabling real-time monitoring and enhanced process control. Among sensor technologies, solid-state devices, particularly those based on transition metal (TM) complexes, are promising for detecting volatile organic compounds (VOCs) due to their tunable electronic properties. Here, we report the design, synthesis, and characterization of novel molybdenum coordination complexes derived from an oxalyldihydrazide ligand (H_4L).[3] Dinuclear $[Mo_2O_4(L)(MeOH)_2]\cdot 2H_2O$ and polynuclear $[Mo_2O_4(L)]_n$ complexes were obtained from different solvents and characterized by spectroscopic methods, elemental analysis, thermogravimetric analysis, single-crystal X-ray diffraction, and density functional theory calculations. Electrical measurements revealed moderate DC conductivities of 1.59×10^{-9} and 4.27×10^{-8} $\Omega^{-1}\cdot cm^{-1}$ at 200 °C for the dinuclear and polynuclear complexes, respectively. Notably, $[Mo_2O_4(L)(MeOH)_2]\cdot 2H_2O$ exhibited high room-temperature sensitivity to methanol, ethanol, propanol, and water vapours, with methanol exposure inducing a six-order-of-magnitude increase in conductivity. Optimized conditions allowed reproducible response cycles, with rapid response (40 s) and recovery (230 s) times for methanol detection. These findings demonstrate the potential of Mo-based coordination complexes as efficient room-temperature VOC sensors, advancing the development of smart sensing solutions.

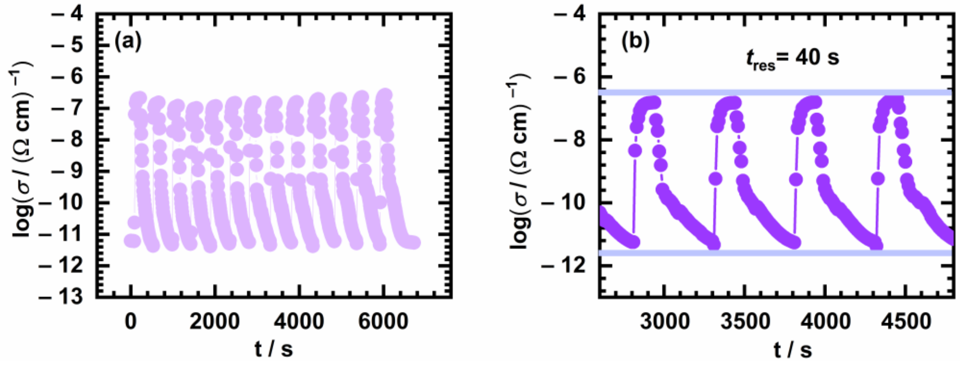

Figure 1. Conductivity for $[Mo_2O_4(L)(MeOH)_2]\cdot 2H_2O$ (1) in cyclisation experiments upon MeOH exposure (a) 13 cycles and (b) Inset: enlarged 4 cycles.

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Calorimetry and Periodic DFT: Sublimation Reactions and a Solid-State Reaction

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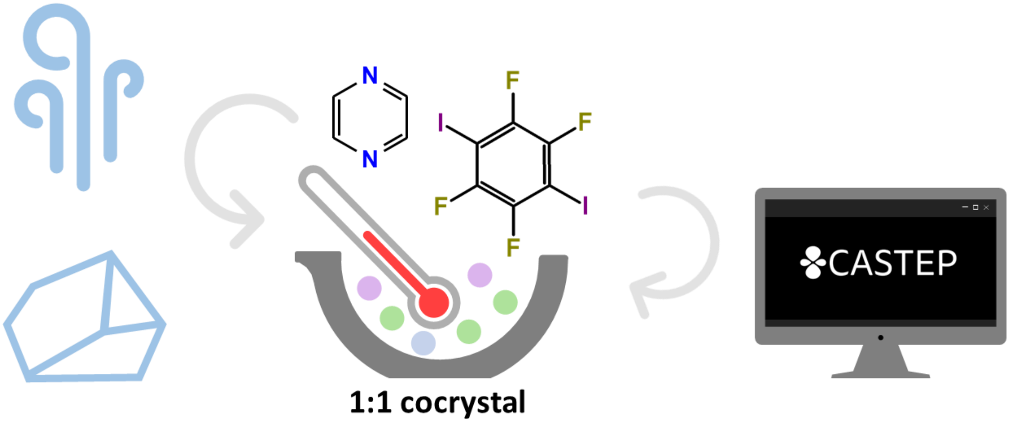
Reaction enthalpies for solid-state reactions are most often obtained via dissolution experiments using Hess's law[1] and in recent years were increasingly being complemented by periodic DFT calculations.[2] To the best of our knowledge, there is only one published report of solid-state reaction enthalpies being measured directly via isothermal calorimetry at room temperature.[3]

Here we extend this approach to a new reaction system, namely, pyrazine and 1,4-diiodotetrafluorobenzene. Neat powders were gently mixed in a Calvet calorimeter at 25 °C which quantitatively yielded their 1:1 cocrystal. This approach allowed for direct measurement of the solid-state reaction enthalpy. Further on, sublimation enthalpies of the reactants and the cocrystal were determined calorimetrically. Since all reaction components include only neutral molecules, sublimation enthalpies approximate their crystal structure enthalpies, providing an additional route to determine the solid-state reaction enthalpy applying Hess's law. In addition, all experimentally determined reaction enthalpies were supported by the dispersion-corrected periodic DFT calculations. Experimental and computational results were in reasonable agreement showcasing the model's ability to capture the thermodynamics of the reacting system both in gaseous and solid state.

Our finding that minimal mechanical input can trigger a solvent-free, room-temperature, solid-state reaction opens a practical route to systematic thermodynamic studies of such reactions using periodic DFT as a reliable compass in experimental design.



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How to Efficiently Calculate Supramolecules?

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Calculating the electronic states of molecules is the “zero-th” step in most computational-chemistry workflows. Unfortunately, the cost of conventional electronic-structure methods grows steeply with system size - typically with the fifth or sixth power - making such calculations impractical (and often entirely infeasible) for large molecular systems.

In this lecture, I will present the excitonic configuration interaction (ECI) method[1,2] - a supramolecular analogue of conventional CI method - that enables efficient computation of both ground and excited electronic states of molecular aggregates. The method treats each molecule in the aggregate at any conventional level of theory and then uses the resulting monomeric states as a basis for constructing the states of the full system. As a result, the overall computational effort scales nearly linearly with the number of molecules, allowing systems comprising up to several hundred medium-sized molecules to be treated efficiently.

In the end, I will briefly discuss the current state of ECI development and present the outlook on future directions.

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Supramolecular Catalysis Meets Photomechanochemistry: A New Route to Template-Assisted Olefin [2+2] Cycloaddition

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One of the most extensively studied reactions involving reactive supramolecular assemblies is the template-assisted olefin photodimerization.[1,2] This [2+2] cycloaddition typically requires a pre-formed co-crystal of the olefin with a template. Conventional methodologies rely on irradiating these photoactive co-crystals, often with periodic pauses to manually mix the sample which limits scalability and reproducibility of the reaction.[2-6]

Resorcinol (**res**) derivatives are efficient templates for olefin photodimerisation.[2-6] Until now, **res**-assisted cycloaddition of olefins has been carried out using manual[3,4] or vortex[5,6] mixing. The lowest reported template loading to achieve near-quantitative yield was 10 mol%, but it required 80 hours of irradiation with intermittent mixing.[3] More recently, 50 mol% of a **res** derivative enabled dimerisation in just 30 minutes in the vortex.[6] Despite these advances, application of ball milling that offers real-time Raman monitoring of the solid-state reaction is still not explored.

Here, we present the first template-assisted olefin [2+2] photocycloaddition performed in a ball mill.[7] Using catalytic amounts of template **res** (as low as 10 mol%) enables rapid, quantitative and stereoselective dimerisation of *trans*-1,2-bis(4-pyridyl)ethane (**bpe**). The described fully automated method, with real-time Raman monitoring, is the first to combine low loadings of the template (catalyst) with rapid, quantitative conversion and kinetic analysis. Together, these advances provide a sustainable and efficient solution to long-standing challenges in the solid-state photochemical dimerization of olefins.

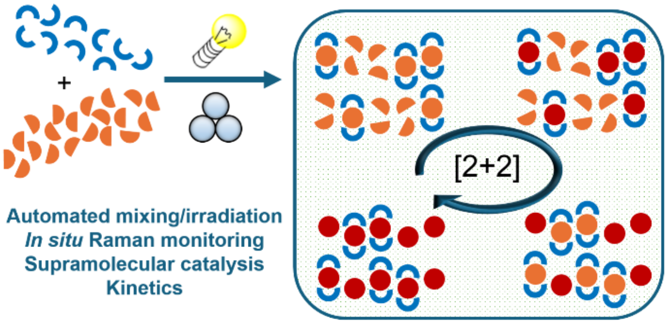

Figure 1. Photo-mechanochemical res-templated [2+2] cycloaddition of bpe in the ball mill.

Financial support was provided by Croatian Science Foundation (IP-2019-04-9951, IP-2020-02-1419 and DOK-2020-01-7515) and Ruđer Bošković Institute under NextGenerationEU NPOO KP1-25 program.

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Computationally Guided Mechanochemical Design of Cyclodextrin – Dasatinib Inclusion Complexes for Controlled Drug Release

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Dasatinib (DAS) is an effective tyrosine kinase inhibitor, but its poor solubility and low oral bioavailability continue to limit its therapeutic performance. To better understand how cyclodextrins can improve these properties, we combined mechanochemical co-grinding experiments with a set of targeted computational simulations. The three natural cyclodextrins (α-CD, β-CD, and γ-CD) were chosen as host systems, and their interactions with the two relevant protonation forms of DAS were explored through docking and molecular dynamics (MD) simulations carried out in the gas phase and in aqueous media.

Gas-phase MD simulations were used deliberately to reflect the solvent-free conditions of planetary ball milling and to observe how DAS behaves when confined within the cyclodextrin cavity in the absence of competing solvent interactions. These simulations provided a clear picture of the early steps of inclusion and helped explain the drug's tendency to amorphize during co-grinding. Additional MD simulations in explicit water offered insight into complex stability under physiological conditions and enabled us to directly compare the behavior of the two cyclodextrin hosts. The computational results showed stable host–guest assemblies and energetically favorable orientations that closely matched trends observed experimentally. The simulated interaction patterns supported the DSC and FT-IR findings, which indicated reduced crystallinity and noticeable spectral changes consistent with complex formation. In line with these observations, dissolution studies showed a clear improvement in DAS solubility and release rate from the co-ground systems.

Overall, the computational analysis provided a mechanistic explanation for the experimentally observed benefits of cyclodextrin complexation. By linking molecular-level behavior with solid-state and dissolution data, this work highlights how simulations can guide the design of improved DAS formulations with better solubility and more predictable release characteristics.[1]

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POSTERS

Intrinsic Fluorescence of Calixarenes: the Origin and Applications

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Calixarene derivatives have been widely recognized as promising fluorescent sensors when suitably functionalized with fluorophoric groups, as it has been believed that these compounds are not enough intrinsically fluorescent.[1, 2] We investigated the intrinsic fluorescence of three calix[4]arenes lacking additional fluorescent moieties and explored the possibility of quantitative fluorimetric examination of their cation-binding processes taking place in different solvents (water, methanol, and acetonitrile). The fluorescence of free calixarenes substantially increased, and was blue shifted to some extent, upon alkali and alkaline earth metal cation binding. Insights into the emission mechanisms were gained by time resolved fluorescence measurements and quantum chemical calculations. Computational results revealed that calixarene *cone* rigidification plays an important role in enhancing receptor fluorescence upon cation binding (Fig. 1.).[2] Spectrofluorimetry has shown to be as an effective and sensitive technique for the quantitative monitoring of complexation reactions involving calixarene derivatives and related compounds, regardless of whether additional fluorophores are present in their structures. That enables cation sensing at low concentrations in various solvents and large binding constants are measurable by direct instead of competitive titrations.[4]

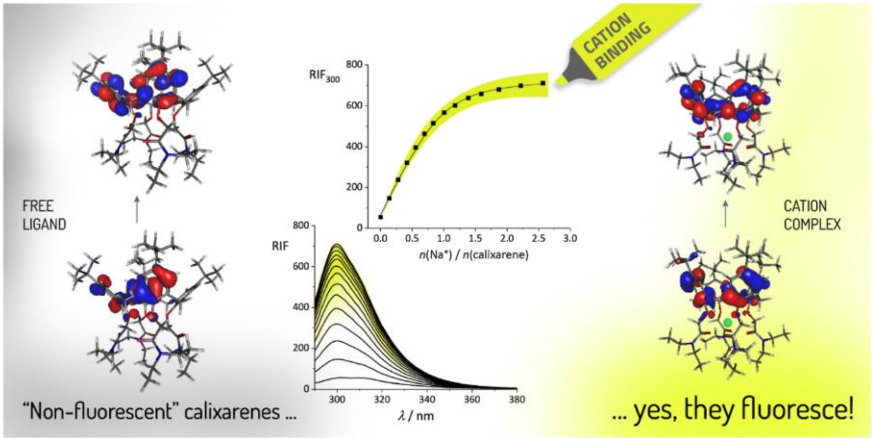

Figure 1. Intrinsic fluorescence of calixarenes substantially increases upon cation binding.

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Computational Study of Cation Binding by Tetra-*O*-2-oxopropyl-substituted Calix[4]arene Isomers

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Due to rotation around methylene bridges, calix[4]arenes can adopt four conformations: *cone*, partial *cone*, 1,2-alternate, and 1,3-alternate. Cone conformers bearing electron-donor functional groups were shown to be excellent cation receptors.[1] One of the simplest among them, ketone derivative in *cone* conformation, exhibits high affinity towards alkali metal cations in various solvents, with acetonitrile and methanol being the most favorable for cation binding.[2] Recently, we experimentally and computationally investigated binding of first- and second-group metal cations by partial *cone* calix[4]arene ketone derivative.[3] The significant reduction of its complexation affinity relative to the regular *cone* isomer was attributed to the "missing link": the lack of coordination by the inverted pendant arm as well as the absence of solvent inclusion in the calixarene hydrophobic cavity.

In this work, we computationally examined the binding of alkali and alkaline earth metal cations with all atropisomers of tetra-*O*-2-oxopropyl-substituted calix[4]arene (Figure 1), both *in vacuo* and in acetonitrile and methanol solutions. For that purpose, classical molecular dynamics simulations and quantum chemical calculations were employed. The results provided an insight into the structural diversity of complexes formed by different calixarene isomers and the energetics behind the complexation processes *in vacuo* and in solution. Particular attention was given to the solvent effects, including solvent molecule inclusion and its orientation within the calixarene *basket*.

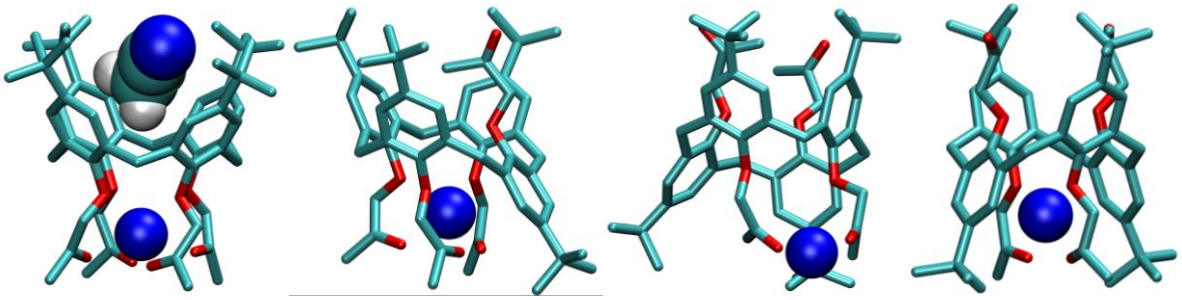

Figure 1. Structures of sodium complexes of calixarene ketone derivative isomers in acetonitrile.

ACKNOWLEDGEMENTS

This work was supported by the Croatian Science Foundation under project IP-2024-05-2012 (CalixCORE) and European Regional Development Fund (project CIuK, KK.01.1.1.02.0016).

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Thermodynamic Insights into Nabumetone–β-Cyclodextrin Encapsulation from Temperature-Dependent ITC Analysis

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The supramolecular encapsulation of nabumetone (NAB) within β-cyclodextrin (β-CD) was studied using isothermal titration calorimetry (ITC) in 0.20 M phosphate buffer (pH 6.8) over the temperature range 293–313 K. Temperature-dependent ITC analysis provided the thermodynamic profile of the 1:1 NAB–β-CD inclusion complex, showing moderate binding affinities ($\log K = 3.27$–3.68) with a maximum at 298 K. Complexation was consistently exothermic and enthalpy-driven, with Gibbs free energies of –19 to –21 kJ mol^{-1}. Linear regression of $\Delta_r H^\circ$ versus temperature yielded a significantly negative heat-capacity change, $\Delta_r C_p = -456 \pm 158$ J mol^{-1} K^{-1}, indicating extensive desolvation and restructuring of confined water within the host cavity upon guest encapsulation. Complementary solubilization studies, using the shake-flask method in aqueous and biorelevant media, enabled quantitative determination of NAB concentration by validated UV/Vis spectrophotometry. These measurements confirmed a pronounced β-CD-induced enhancement of NAB solubility and supported the formation of NAB–β-CD inclusion complexes across a broad concentration range.

High-resolution mass spectrometry (LC-Q-TOF, FIA-ESI$^+$) studies on NAB–β-CD mixtures in aqueous solution revealed characteristic supramolecular ions corresponding to $[\text{NAB}+\beta\text{-CD}+\text{Na}+\text{H}]^{2+}$ and $[\text{NAB}+2\beta\text{-CD}+2\text{H}]^{2+}$. Optimization of ionization parameters enabled stable detection of singly and doubly charged host–guest assemblies, thereby directly verifying the complex stoichiometry in solution.

Overall, the combined ITC, solubility, and mass spectrometry results demonstrate that NAB encapsulation in β-cyclodextrin is a spontaneous, enthalpy–driven, and water–reorganization–regulated supramolecular process, governed by hydrophobic inclusion and desolvation effects that are strongly influenced by temperature.

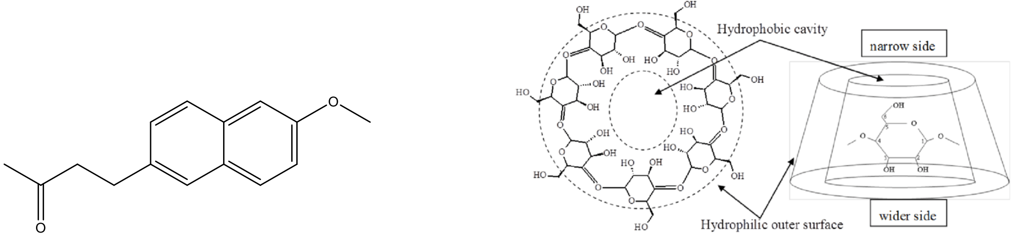

Figure 1. Chemical structure of nabumetone and β-cyclodextrin.

Acknowledgements. This work has been supported by the Croatian Science Foundation under the project IP-2022-10-6033.

Alkaline Earth Metal Cation Binding by Leucine and Phenylalanine Penta and Hexa Cyclopeptides in Acetonitrile

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In the past few decades, cyclopeptides have attracted interest as supramolecular receptors. Being efficient receptors for simple cations and, as shown in recent years, for anions makes them applicable in science as well as in technology. Our recent papers have shown that the type of amino acid and ring size have a strong influence on the binding of simple anions in various organic solvents.[1–3] In this work, cation binding properties in terms of stability constants, reaction enthalpy, and entropy of cyclopeptides comprised of five and six phenylalanine or leucine amino acids were studied using various methods in acetonitrile. To get insight into the structure of free cyclopeptides and their complexes, MD simulations with explicit solvent molecules were performed. Experimental and computational results were discussed in terms of sidechain type and cyclopeptide ring size.

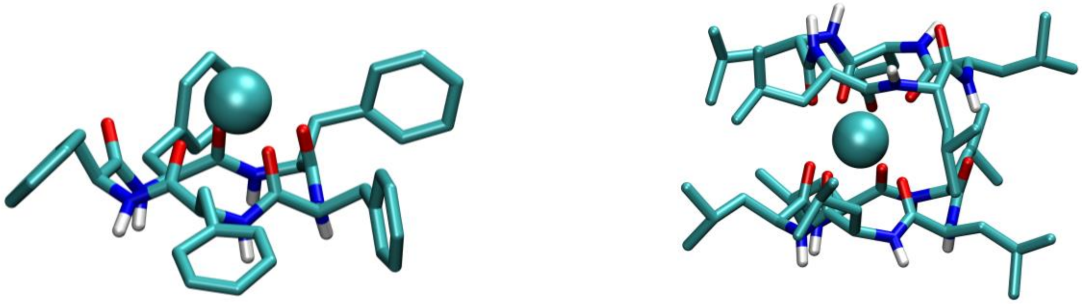

Figure 1. The representative structures of c(Phe$_4$)Ca^{2+} and c(Leu$_5$)$_2$Ca^{2+} in acetonitrile obtained by MD simulations at 25 °C. The hydrogen atoms of side chain are omitted for clarity.

ACKNOWLEDGEMENTS

This work was supported by the Croatian Science Foundation under project IP-2025-02-8238 (CPepFunxIon), IP-2024-05-2012 (CalixCORE), and European Regional Development Fund (project CIuK, KK.01.1.1.02.0016).

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Synthesis of fluorophore and peptide conjugates with dual activity for suppressing MDM2 protein and imaging cancer cells

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Intracellular reactions are fundamental to cell metabolism often involving interactions among small molecules, proteins, DNA and RNA. A promising approach to studying these molecular interactions within cells along with protein labeling includes using small molecule fluorophores that act as molecular probes and selecting the appropriate fluorophore is crucial for effectively targeting specific compounds. MDM2 is an E3 ubiquitin ligase enzyme and acts as the main antagonist of the tumor suppressor p53. While p53's tumor-suppressing activity is regulated through various mechanisms, preventing MDM2 from tagging p53 for degradation via ubiquitination and subsequently blocking its breakdown in the proteasome is considered the most crucial way to activate p53 in response to DNA damage or genotoxic stress.

Peptides and their derivative peptidomimetics are a significant class of molecules engineered to inhibit MDM2 activity and restore the tumor-suppressing function of p53. Compared to small molecules peptides offer the advantage of targeting additional regions of the p53/MDM2 interface especially those with relatively flat surfaces whereas small molecules typically require deep narrow grooves for effective binding. Therefore, in the current work we have focused on preparation of series of peptide-fluorophore conjugates for MDM2 inhibition. We used fluorophores such as coumarin to investigate for their ability to penetrate cells and spatially track MDM2 inhibition. Coumarin was coupled to p53-derived peptide sequence via conjugation with different dibenzocyclooctyne compounds using click chemistry. We believe that in this way by modulating cellular response with prepared conjugates we will be able to determine impact of regulation of MDM2 inhibition in tumour.

Kinetics of a Supramolecularly Templated Photomechanochemical [2+2] Cycloaddition

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Combination of mechanochemistry with additional energy inputs, such as light, heat, or electric fields, has enabled new strategies for controlling chemical reactivity in the solid state.[1] By continuously supplying mechanical energy, vortex or ball milling can promote molecular mobility, facilitate the formation of transient supramolecular assemblies, and enable photoreactions that require strict spatial preorganization.[2,3] Understanding how these dynamic environments evolve over time is essential for elucidating mechanisms of solid-state reactions and identifying kinetic signatures associated with supramolecular control.

In this work, we employed *in situ* Raman monitoring to investigate the kinetics of the photomechanochemical [2+2] photocycloaddition of *trans*-1,2-bis(4-pyridyl)ethylene (**bpe**) templated by catalytic amounts of resorcinol (**res**).[4] Under ball milling combined with UV irradiation, the reaction displays characteristic conversion profiles that strongly depend on the template loading. To rationalize these trends, the reaction kinetics were analyzed using the Johnson–Mehl–Avrami–Kolmogorov (JMAK) and Finke–Watzky (FW) models.[5] Both approaches indicate that the nucleation step is influenced by supramolecular templation, whereas the subsequent growth phase remains relatively constant across conditions. The increase in the Avrami exponent at lower template concentrations suggests heterogeneous or higher-dimensional growth during the reaction. Overall, these results show that catalytic supramolecular templation primarily governs the onset of reactivity, while mechanochemical activation ensures rapid propagation once nucleation has occurred.

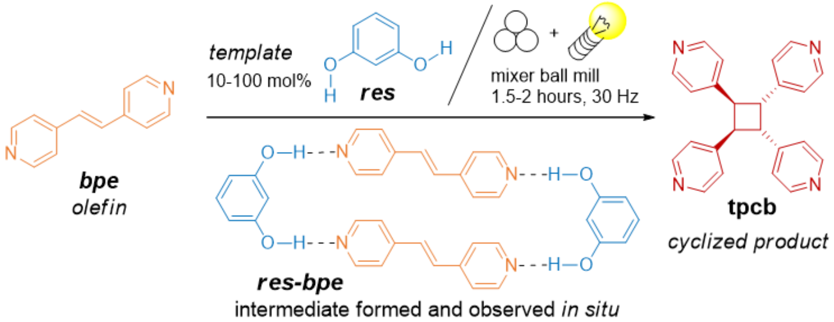

Figure 1. Photomechanochemical [2+2] Cycloaddition of bpe templated by res.

Acknowledgement This work has been supported by Croatian Science Foundation (IP-2019-04-9951, IP-2020-02-1419 and DOK-2020-01-7515) and Ruđer Bošković Institute under the project NextGenerationEU NPOO IRB KP1-25.

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Thermodynamic and Structural Studies of Complexation of Alkali, Alkaline Earth, and Soft Metal Cations by a Thioamide Calix[4]arene Derivative

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Calixarenes are macrocyclic oligomers composed of phenolic residues linked by methylene bridges in the *ortho* position.[1] Depending on the size and functionalization of upper and/or lower rim, these compounds can be very efficient or even selective receptors for various ionic and neutral chemical species.[1,2] Among them, those bearing sulfur-based functional groups form stabile complexes with low-charge density and soft metal cations.[3] In the scope of this work, binding affinity of thioamide calix[4]arene derivative **L** (Figure 1) towards alkali, alkaline earth, and soft metal cations in acetonitrile was investigated by means of spectrophotometry, NMR spectroscopy, isothermal titration calorimetry, and X-ray crystallography. The obtained results were discussed regarding the structural characteristics of the ligand, as well the size, charge density, and polarizing power of the cations.

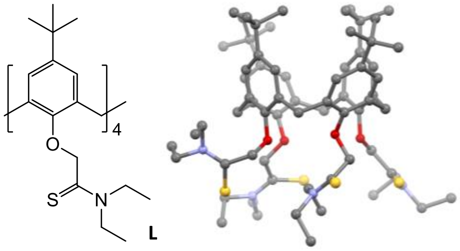

Figure 1. Molecular structure of thioamide calix[4]arene derivative **L**.

Acknowledgements. This work has been supported by Croatian Science Foundation (projects CalixCORE (IP-2024-05-3012) and MicroSynTotal (IP-2024-05-5352)) and the European Regional Development Fund (infrastructural project CIuK, grant number KK.01.1.1.02.0016).

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Synthesis and Characterization of Calix[4]arene Comprising Urea and Carboxylate Complementary Moieties

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Rational design of small molecules capable of controlled self-assembly remains a central objective in supramolecular chemistry, particularly for the development of responsive polymeric materials formed through non-covalent interactions.[1] Urea derivatives are often applied as receptors for oxyanions, due to the stable eight-membered ring formation upon binding. Recently, we reported a successful preparation of stable heterodimeric capsules in acetonitrile combining urea- and carboxylate-calix[4]arenes. In this work we demonstrated the reversible disruption and reassembly of these species triggered by simple external stimuli, specifically acid or base addition.[2]

Building on these concepts, the present work explores whether analogous host–guest design can be extended toward larger supramolecular polymers with potential to act as molecular tunnels imposing strict control over their assembly.

We report the synthesis and preliminary characterization of a calix[4]arene monomer bearing both urea and carboxylate moieties, designed to promote polymer-like aggregation via complementary binding patterns. Synthesis was performed in five-step convergent route designed to preserve the integrity of both functional moieties and mass spectrometry studies confirmed the successful preparation of the desired monomeric species. Preliminary studies using a combination of NMR spectroscopy, conductometry, and potentiometry indicate aggregation of the prepared ditopic receptor in DMSO, MeOH, and MeCN. Thermal and concentration-dependent experiments provided insight into the stability and reversibility of the assemblies, which are essential parameters providing the basis for future development of these systems.

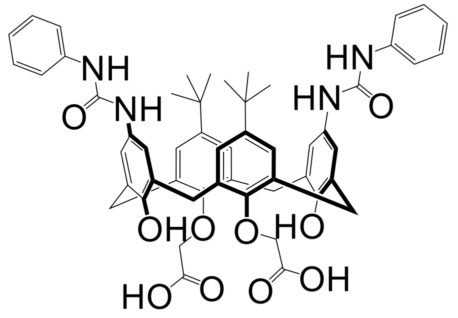

Figure 1. Structure of investigated calix[4]arene comprising urea and carboxylate moieties.

Acknowledgements. This work has been supported by the Croatian Science Foundation (CalixCORE: IP-2024-05-3012).

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VII. SIMPOZIJ SUPRAMOLEKULSKE KEMIJE
Supramolecular Chemistry 2025

Knjiga sažetaka – Book of Abstracts