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IV. SIMPOZIJ SUPRAMOLEKULSKE KEMIJE

Supramolecular Chemistry 2021

KNJIGA SAŽETAKA

Book of Abstracts

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IV. simpozij supramolekulske kemije – *Supramolecular Chemistry 2021*

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.

Ove godine održat će se IV. simpozij supramolekulske kemije (Supramolecular Chemistry 2021), kojim će biti nastavljen niz skupova iz tog područja. Sadržajem će pratiti prethodne. Sudionici će svoje znanstvene rezultate prezentirati u formi pozvanih predavanja, kratkih usmenih priopćenja te na posterskoj sekciji. Osim akademske zajednice, bit će uključeni i zapaženi rezultati iz privrede ostvareni primjenom načela supramolekulske kemije.

Simpozij će se baviti raznovrsnim temama iz područja supramolekulske kemije. Prezentirat će se različiti aspekti tekućih istraživanja iz područja makrocikličke kemije, molekuskog samoudruživanja, kemije funkcionalnih materijala, molekulske samoorganizacije, supramolekulskih vrsta u čvrstom stanju i sinteze kompleksnih supramolekulskih sustava te istraživanja u drugim srodnim temama.

Simpozij Supramolecular Chemistry 2021 održat će se u hibridnom obliku, uz poštivanje svih propisanih protuepidemijskih mjera. Radni jezici Simpozija su hrvatski i engleski.

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ZAHVALE



III. simpozij supramolekulske kemije (*Supramolecular Chemistry 2019*) organiziran je u okviru projekta Hrvatske zaklade za znanost IP-2018-01-6910, a potpomognut je sredstvima Zaklade hrvatske akademije znanosti i umjetnosti (Natječaj Zaklade HAZU za potpomaganje zakladnih namjena u 2021. godini) i Hrvatskog kemijskog društva.

PROGRAM

08:00 Registracija sudionika

09:00 Otvaranje konferencije – Uvodne riječi

Goran Pichler, tajnik Razreda za matematičke, fizičke i kemijske znanosti HAZU, David Matthew Smith ravnatelj IRB, Mirko Planinić, dekan PMF, Mladen Žinić, predsjednik Odbora za kemiju HAZU, Leo Frkanec, IRB

Predsjedavajući sekcije / Chairman: **Dražen Vikić Topić**

09:30 **Mirta Rubčić** (PMF) *Polioksomolibdati {Mo132} kao supramolekulski receptori*

10:00 **Ljiljana Fruk** (University of Cambridge) *Kontrastni sredstva i nosači lijekova*

STANKA ZA KAVU

Predsjedavajući sekcije / Chairman: **Vladislav Tomišić**

11:00 **Predrag Novak** (PMF) *Interactions of Macrolides as a Platform for Design of New Antibiotics*

11:30 **Jelena Parlov Vuković** (INA d.d.) *Asphaltene –structure and chemistry*

11:45 **Marija Alešković** (IRB) *Supramolecular Chemistry of Diamondoid Ammonium Salts*

12:00 **Andrea Usenik** (PMF) *Hydrophobic Effect and Beyond*

12:15 **Ines Topalović Piteša** (AlphaChrom) *AFM on a chip*

STANKA ZA RUČAK

Predsjedavajući sekcije / Chairman: **Leo Frkanec**

13:30 **Ognjen Miljanić** (University of Houston) *Greenhouse Gas Capture in Porous Molecular Crystals*

14:00 **Ivica Đilović** (PMF) *Molekulsko prepoznavanje – strategije samoudruživanja fleksibilnog receptora za anione*

14:30 **Tomislav Stolar** (IRB) *The Emergence of Prebiotic Molecular Recognition Patterns on a Nucleobase Level*

14:45 **Ivana Brekalo** (IRB) *Microporosity of a Guanidinium Organodisulfonate Framework*

15:00 **Nika Gazdek** (IRB) *Inclusion complexes of ferrocene uracil derivatives with cyclodextrins: solubility and binding ability*

STANKA ZA KAVU

Predsjedavajući sekcije / Chairman: **Dominik Cinčić**

15:45 **Filip Topić** (McGill University) *Understanding halogen-bonded cocrystallization through experimental and computational studies*

16:00 **Cristina Mottillo** (McGill University) *From greener synthesis to next-generation materials: Innovations in the production of metal-organic frameworks*

16:15 **Mihails Arhangelis** (University of Warsaw) *Periodic DFT calculation for understanding and predicting halogen bond transformations in solid state*

16:30 **Edi Topić** (PMF) *Symmetry Analysis of Layered Hybrid Halometallates(II)*

16:45 **Vinko Nemec** (PMF) *Halogenska veza u kokristalima iminskih metalnih kompleksa*

17:00 **Mladen Borovina** (PMF) *Investigating the Impact of Supramolecular Connectivity on Mechanical Properties of Crystals*

17:15 **Iva Zonjić** (IRB) *Interactions of benzothiazole ligands with DNA:RNA hybrids and triplex structures*

17:30 **Ernest Meštrović** (Xellia d.o.o.) *Non Covalent Interaction in Development of Innovative pharmaceutical product – current status and way forward*

17:00 **Posterska sekcija** (Predsjedavajući sekcije / Chairmen: Vladislav Tomišić, Leo Frkanec)

18:00 **Zatvaranje konferencije – završne riječi** Leo Frkanec, akademik Mladen Žinić

POSTERSKA SEKCIJAPredsjedavajući sekcije / Chairmen: **Vladislav Tomišić, Leo Frkanec**

1. **Matija Gredičak** (IRB), *Supramolecular substrate-catalyst complexes direct stereoselective arylations*
2. **Maria Kolympadi Markovic** (UniRi), *Catalytic Coupling of CO₂ with Propargyl Alcohol Substrates*
3. **Filip Vranješević** (UniRi), *Cyclic Carbamates Through Transition Metal-Catalyzed CO₂ Capture – an in Silico Approach*
4. **Lea Čolakić** (PMF), *Mehanička svojstva kristala kadmijevih(II) halogenida s 2,6-dibrompirazinskim ligandima*
5. **Ivan Petters** (PMF), *Cyclopentaphenylalanine as a Fluorescent Anion Sensor in Solution*
6. **Tea Babić** (PMF), *(A) Romantic Relationship Between Hydrophobic Cavities and Aromatic Alcohols*
7. **Iva Markuš** (PMF), *Diamantane Alcohols and Hydrophobic Cavities: The (not so) Perfect Match in Water and Structured Organic Solvents*
8. **Ruža Frkanec** (UniZg), *Adamantane in the Supramolecular Drug Delivery Systems*
9. **Magdalena Kralj** (IRB), *Supramolecular Control of Reactivity in the Solid State*

Polyoxomolybdates {Mo₁₃₂} as supramolecular receptors

Polioksomolibdati {Mo₁₃₂} kao supramolekulski receptori

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Polyoxomolybdates of the $\{((\text{Mo}^{\text{VI}})\text{Mo}^{\text{VI}}_5)_{12}\{\text{Mo}^{\text{V}}_2\}_{30} \equiv \text{Mo}_{132}\}$ type, also known as Keplerates, are anionic clusters of nanometer dimensions.¹ These systems are unique as they can be very easily synthesized and/or derivatized. Due to their specific structure, which includes 20 {Mo₉O₉} pores through which species of appropriate size can pass, these systems allow the study of various supramolecular phenomena, many of which are of interdisciplinary importance. For example, these anions can act as “nanochromatographs” for different cationic aqua complexes, depending on their size or radius.² On the other hand, the relatively simple exchange of coordinated anions, which bind on linker units of the Keplerate cluster, allows fine tuning of their properties such as hydrophilicity/hydrophobicity of their interior wall.^{3,4}

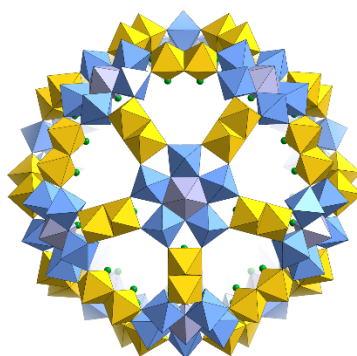


Figure 1. Keplerate {Mo₁₃₂}

¹ A. Müller, P. Gouzerh, *Chem. Soc. Rev.*, **2012**, *41*, 7431.

¹ M. Rubčić, V. S. Korenev, L. Toma, H. Bögge, V. P. Fedin, A. Müller, *Inorg. Chem. Front.*, **2014**, *1*, 740.

¹ S. Garai, M. Rubčić, H. Bögge, P. Gouzerh, A. Müller, *Chem. Eur. J.*, **2015**, *21*, 4321.

¹ S. Garai, M. Rubčić, H. Bögge, E. T. K. Haupt, P. Gouzerh, A. Müller, *Angew. Chem., Int. Ed.* **2015**, *54*, 5879.

Interactions of Macrolides as a Platform for Design of New Antibiotics

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Macrolide antibiotics belong to a class of macrolide molecules consisting of a central 12-16 membered macrolactone ring and one or more sugar units attached to it. The main representatives include erythromycin, azithromycin, clarithromycin and telithromycin. They have been widely used to treat infections caused by both gram-positive and gram-negative bacteria.¹ Macrolides bind to ribosomal 23S rRNA at or near the peptidyl transferase center and inhibit bacterial protein biosynthesis. However, the emerging multi-drug resistant microbial pathogens present serious and challenging problems which demand novel and more potent antimicrobial agents to be discovered. Despite of modern tools and approaches developed lately in medicine, biology and chemistry, there are still no new macrolide antibiotics on the market.

In order to discover and design more effective macrolide compounds, it is important to explore the interactions with ribosome and other biological targets and characterize free and bound conformations in solution.

NMR spectroscopy is one of the most powerful and valuable methods to study structure and binding of ligands to their biological receptors. A combination of NMR techniques such as transferred nuclear Overhauser effect spectroscopy (trNOESY), saturation transfer difference (STD), diffusion and solvent paramagnetic relaxation experiments (PRE) and molecular modelling can provide a wealth of information on macrolide binding epitopes and mode of action. Examples will be demonstrated in this talk.

The data so obtained can serve as a platform for discovery of novel compounds with an improved biological profile.

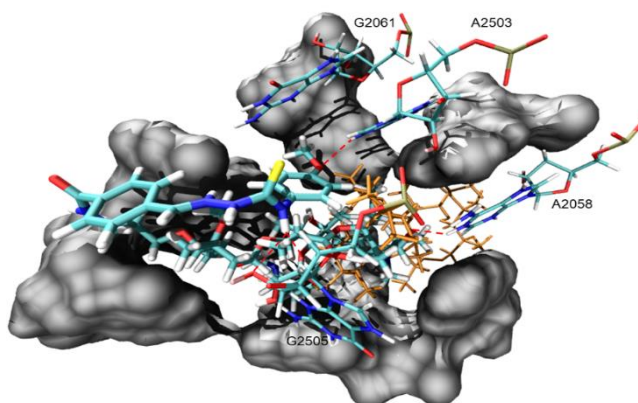


Figure 1. *E. coli* ribosome binding mode of a macrozone, an azithromycin-thiosemicarbazone conjugate.²

Part of the work presented in this talk has been supported by the Croatian Science Foundation (Project: Macrozones, IP-2018-01-8098)

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Asphaltene –structure and chemistry

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A common feature of crude oil samples is an extremely complex chemical composition.^{1,2} They consist of thousands of individual components, mainly hydrocarbons, ranging in size and structure. Exact molecular composition of crude components is still a matter of scientific studies. An understanding of composition and properties is crucial for the right application of appropriate processing facilities and the quality evaluation of crude oil and its final products. Asphaltenes are the most polar and the most problematic crude oil components and critical to all aspects of crude oil use.¹⁻⁵ Asphaltenes are complex organic macromolecules consisting of condensed aromatic and saturated rings, aliphatic moieties, some heteroatoms, including nitrogen, oxygen and sulfur and traces of metals, such as nickel, vanadium and iron. Several models of the asphaltene structure have been proposed and the most frequently elaborated are the continental and the archipelago model. Asphaltene can polymerize and convert into coke or asphaltic residue at high temperature. Also, they may aggregate and precipitate during crude oil processing and form aggregates, causing serious problems including reduction in oil flow, blocking of production pipes and some drawbacks during the processing of heavy ends, such as coke formation, corrosion, catalyst deactivation and poisoning. All these problems can cause huge production losses. Over the past few decades the chemistry and structure of asphaltene has become one of the most interesting field in crude oil research. In this presentation the structure and aggregation process of asphaltenes isolated from different origin will be discussed.

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- [2] O. C. Mullins, *Energy Fuels* **2010**, 24, 2179–2207. <https://doi.org/10.1021/ef900975e>
- [3] J. Parlov Vuković, P. Novak, J. Plavec, M. Friedrich, Lj. Marinić Pajc, T. Hrenar, *Croat. Chem. Acta* **2015**, 88, 89–95. <https://doi.org/10.5562/cca2612>
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Supramolecular Chemistry of Diamondoid Ammonium Salts

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Research on macrocyclic host molecules capable of encapsulating small guest molecules can inspire supramolecular architectures that mimic biological systems and can have useful technological applications.¹ We have recently shown that functionalized diamondoid ammonium salts are suitable guests for cucurbituril (CB[n]) hosts in aqueous environment. Especially strong binding was found for the complex of 4,9-diammonium diamondane derivative with CB[7], having an attomolar dissociation constant that rivals the interaction between avidin-biotin.²

As a continuation of our work, we explored complexation of diamondoid ammonium salts with β and γ cyclodextrins (CDs) in water (Figure 1). The key step in the synthesis of these permethylated diamondoid ammonium salts was selective functionalization of diamondane scaffold *via* nitroxylation and subsequent hydrolysis³ that was optimized in detail in the scope of this study.

When assessing the binding strength, we considered the size of the diamondoid salts, substitution type and number of functional groups as well as the cyclodextrin cavity size. Equilibrium constants and other thermodynamic parameters for the complexation of diamondoid ammonium salts with CDs were determined by ITC, conductometric and/or ¹H NMR titrations. Additional NMR spectroscopic techniques (¹H-¹H NOESY, ¹H DOSY) were employed to elucidate specific interactions of guest encapsulated within host molecules, along with the corresponding computational analysis.

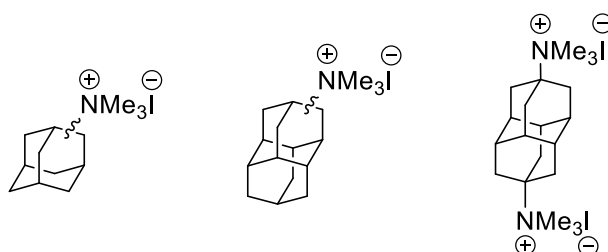


Figure 1. Diamondoid ammonium salts studied as CD guests.

Acknowledgements: This work was funded by the Croatian Science Foundation (UIP-2017-05-9653 (DiamMat), IP-2019-04-9560 (MacroSol)).

¹ J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley-VCH, New York, 2009.; F. Schibilla, J. Voskuhl, N. A. Fokina, J. E. P. Dahl, P. R. Schreiner, B. J. Ravoo, *Chem. Eur. J.* **2017**, *23*, 16059.

² L. Cao, M. Šekutor, P. Y. Zavalij, K. Mlinarić-Majerski, R. Glaser, L. Isaacs, *Angew. Chem. Int. Ed.* **2014**, *53*, 988; M. Šekutor, K. Molčanov, L. Cao, L. Isaacs, R. Glaser, K. Mlinarić-Majerski, *Eur. J. Org. Chem.* **2014**, 2533; J. Hostaš, D. Sigwalt, M. Šekutor, H. Ajani, M. Dubecký, J. Řezáč, P. Y. Zavalij, L. Cao, C. Wohlschlager, K. Mlinarić-Majerski, L. Isaacs, R. Glaser, P. Hobza, *Chem. Eur. J.* **2016**, *22*, 17226; D. Sigwalt, M. Šekutor, L. Cao, P. Y. Zavalij, J. Hostaš, H. Ajani, P. Hobza, K. Mlinarić-Majerski, R. Glaser, L. Isaacs, *J. Am. Chem. Soc.* **2017**, *139*, 3249.

³ N. A. Fokina, B. A. Tkachenko, A. Merz, M. Serafin, J. E. P. Dahl, R. M. K. Carlson, A. A. Fokin, P. R. Schreiner, *Eur. J. Org. Chem.* **2007**, 4738.

Hydrophobic Effect and Beyond

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Cyclodextrins (CDs) are the best known and most frequently investigated supramolecular hosts for hydrophobic species in aqueous solutions, characterized by their high water solubility and solubilizing ability. The latter is found to be of great interest in pharmaceutical industry and formulation development, implying the importance of thermodynamic investigations of the guest(CD) complex formation, particularly in storage conditions. During the recent years, cucurbit[n]urils (CB n) were recognized as outstanding receptors for non-polar species characterized by significantly higher affinity and selectivity, with complex stabilities even surpassing the one of biotin-avidin pair ($\log K > 15$).¹ The cyclodextrin and cucurbituril inclusion complex formation is attributed to favorable desolvation of the guest and the host cavity. In order to investigate the thermodynamical background of hydrophobically driven complexation in detail, the binding of a variety of hydrophobic and amphiphilic guests with α -, β -, γ -CD and CB7 was explored in several structured solvents (water, formamide, ethylene glycol) in a wide temperature range by means of isothermal microcalorimetry. The complex structure was investigated by NMR spectroscopy which revealed interesting information concerning/regarding the inclusion kinetics. Thus obtained results provided valuable insights into solvent and structural factors governing the complexation process, as well as its temperature dependence. For most of the explored systems, the temperature dependence of $\Delta_r G^\circ$ was weak (or negligible), which was the consequence of the enthalpy-entropy compensation. The finding is in line with the classical rationale of the hydrophobic effect at lower temperatures, and the non-classical explanation at higher ones.^{2,3}



Figure 1. Schematic representation of hydrophobically driven complexation

This research was fully supported by the Croatian Science Foundation (project MacroSol, IP-2019-04-9560) and European Regional Development Fund (project CluK, KK.01.1.1.02.0016).

¹ L. Cao et al., *Angew. Chem. Int. Ed.* **2014**, 53, 988–993; M. Šekutor et al., *Eur. J. Org. Chem.* **2014**, 2533; J. Hostaš et al., *Chem. Eur. J.* **2016**, 22, 17226; D. Sigwalt et al., *J. Am. Chem. Soc.* **2017**, 139, 3249.

² K. Leko, M. Hanževački, Z. Brkljača, K. Pičuljan, R. Ribić, J. Požar, *Chem. Eur. J.* **2020**, 26, 5208.

³ F. Biedermann, W. M. Nau, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2014**, 53, 2

AFM on a chip

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After nearly 10 years of research and development at the University of Waterloo, Canada, with funding from DARPA and the Ontario Research Fund, ICSPi commercialized the world's first single-chip atomic force microscope (AFM). ICSPi has integrated all the components of a normal AFM onto a single 1 mm x 1 mm silicon chip using their patented MEMS (micro-electro-mechanical systems) technology. Their chip features an integrated piezoresistive sensor, and vertical and lateral actuators, making it self-actuating and self-sensing. nGauge Atomic Force Microscope collects nanoscale data on your benchtop and extends your capabilities to 1,000,000x magnification.

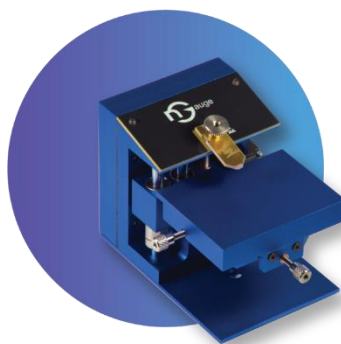


Figure 1. nGauge Atomic Force Microscope.

¹ <https://www.icspicorp.com/>

Greenhouse Gas Capture in Porous Molecular Crystals

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Porous molecular crystals are a class of porous solids that are built from discrete molecules rather than being extended polymeric structures. Their molecular nature makes them fundamentally interesting, as small molecules typically closely pack in the solid state, without leaving large voids. In addition, molecular crystals have higher solution and vapor phase processability, which allows their easier incorporation into thin films and devices. Our recent work has identified two new classes of porous molecular crystals. The first is based on rigid fluorinated aromatic compounds, which are terminated with pyrazole or tetrazole end-groups.¹ These termini are capable of hydrogen bonding and aromatic stacking and their solid-state assembly results in extrinsically porous structures with modular hexagonal pores. These pores are useful in the adsorption of Freons, hydrocarbons, and fluorinated anesthetics.² The second class of molecular precursors are produced by the benzoin condensation of rigid aromatic dialdehydes into cyclic oligomers known as cyclobenzoin. Cyclobenzoin self-assemble into porous solid-state structures and offer rich derivatization chemistry that either takes advantage of their esterification or condensation with 1,2-phenylenediamines. They are also solid-state hosts capable of capturing "thin" molecular guests, such as terminal alkynes, nitriles, or carbon dioxide.³ Their reduced derivatives bind small water clusters⁴ and are potential candidates for the binding and (de)stabilization of methane hydrates.

¹ T.-H. Chen, I. Popov, W. Kaveevivitchai, Y.-C. Chuang, Y.-S. Chen, O. Daugulis, A. J. Jacobson, O. Š. Miljanić, *Nat. Commun.* **2014**, *5*, doi: 10.1038/ncomms6131.

² T.-H. Chen, W. Kaveevivitchai, A. J. Jacobson, O. Š. Miljanić, *Chem. Commun.* **2015**, *51*, 14096.

³ Y.-T. Wang, C. McHale, X. Wang, C.-K. Chang, Y.-C. Chuang, W. Kaveevivitchai, O. Š. Miljanić, T.-H. Chen, *Angew. Chem. Int. Ed.* **2021**, *60*, 14931.

⁴ M. Alrayyani, X. Wang, O. Š. Miljanić, *Chem. Eur. J.* **2017**, *23*, 16476.

Molekulsko prepoznavanje – strategije samoudruživanja fleksibilnog receptora za anione

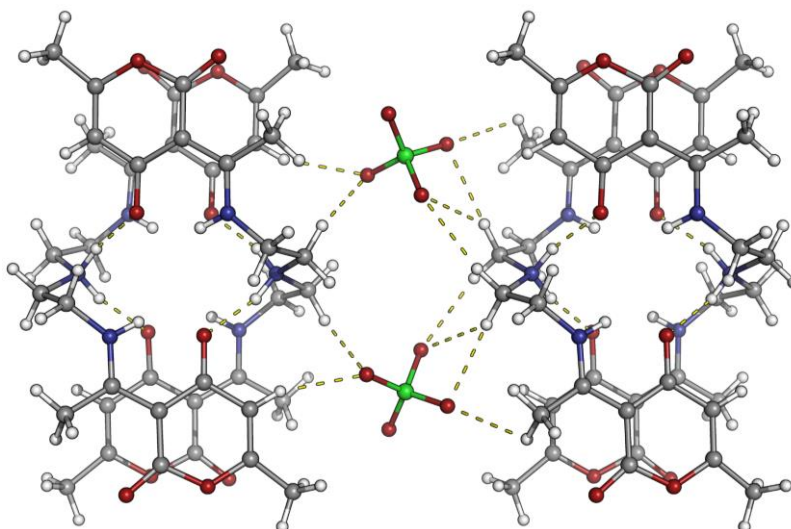
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Tijekom proteklih desetljeća proučavanje anionskih receptora postalo je sastavni dio brojnih istraživanja.¹ Sustavno proučavani rigidni receptori pokazali su veliku selektivnost prema anionima u otopini.² S druge pak strane, fleksibilniji receptori mogu prilagoditi svoju konformaciju kako bi ispunili specifične zahtjeve aniona (geometrija, gustoća naboja itd.).³ Takvi fleksibilni receptori često imaju niže afinitete od svojih rigidnih analoga, ali imaju veliki potencijal u razvoju različitih funkcionalnih supramolekulskih sustava.⁴

U istraživanjima vezanja aniona relevantnima za okoliš i industriju, fleksibilni poliaminski receptor (derivat dehidracetne kiseline) pokazao je izuzetnu prilagodljivost različitim anorganskim ili organskim anionima. Izrazita selektivnost za nitratne ili sulfatne ione, čak i u prisutnosti visokih koncentracija kompetitivnih aniona, postignuta je tek kristalizacijom iz otopine (slika 1). Predavanje će pokriti strukturne aspekte načina vezanja receptora u kompleksima s anionima. Također, sudnos koordinacijskog potencijala aniona i plastičnosti receptora će se raspraviti u okviru strategije samoudruživanja koje omogućuju najpovoljnije okruženje za izolaciju aniona, kako u otopini tako i u čvrstom stanju.⁵ Osim toga, prikazat će se kako se prepoznavanje aniona i odvajanje izomernih dikarboksilnih kiselina može učinkovito izvesti u čvrstom stanju.



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The Emergence of Prebiotic Molecular Recognition Patterns on a Nucleobase Level

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Nucleobases act as DNA recognition units and their specific base-pairing interactions are the most famous example of molecular recognition found in nature. On the prebiotic Earth, there was likely a pool of structurally similar nitrogen-bearing heterocyclic compounds that could have acted as nucleobases.¹ Such a hypothesis is corroborated by many synthetic experiments that produce other purines and pyrimidines besides the canonical nucleobases.^{2,3} Furthermore, the discovery of the presence of extraterrestrial nucleobases in carbonaceous meteorites,^{4,5} as well as nucleobase synthesis in interstellar ice analogs,⁶ strongly points to a pool of nucleobases that may have been present throughout the solar system before life emerged. Following these lines of thought, it becomes unclear as to how did nature know which nucleobases to incorporate into nucleic acids, if they were previously unable to base-pair and select between themselves.⁷ In this regard, the inability of canonical nucleobases to base-pair via Watson-Crick hydrogen-bonding in water is a long-standing bottleneck.⁸ This has led to the idea that other base-pairing combinations might have preceded canonical base-pairing that we observe today. In this work, we study molecular recognition properties in a pool of plausibly prebiotic nucleobases under a variety of prebiotic conditions. We demonstrate that some of them selectively self-assemble by hydrogen-bonding interactions in water or solid-state. We monitored supramolecular interactions in situ by synchrotron powder X-ray diffraction at variable temperatures, solved crystal structures of self-assembled base-pairs from X-ray diffraction data, and probed hydrogen-bonding interactions by solid-state nuclear magnetic resonance techniques. Furthermore, we used periodic DFT to determine the interaction energies of base pairs. Finally, to place them in a prebiotic context, we performed in situ monitoring of base-pairs photochemical stabilities under UV irradiation by resonant Raman spectroscopy.

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Microporosity of a Guanidinium Organodisulfonate Framework

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With the recent emphasis on the importance of porous materials, so called porous hydrogen bonded organic frameworks (**HOFs**)¹ have started gaining attention. A well-known class of **HOFs** are bisguanidinium organodisulfonates (**GS**). **GS** have been extensively explored for the last 20 years due to their diverse host-guest chemistry, as well as their inclination towards architectural isomerism, a phenomenon in which a material can have the same composition and the same supramolecular bonding motive, but still differ in the overall crystal structure due to topological differences.²

Especially interesting is the persistence of the 2D hydrogen bonded sheet motif, which is so reliable that it can allow for targeted synthesis of a multitude of different pillared architectures, such as the bilayer or brick structure, where the type of architecture depends on the size of the guest and the pillar type. Most importantly, these materials have been shown to exchange guest molecules in a single crystal-to-single crystal fashion.³

Surprisingly, despite the stability of these frameworks, the desolvation of **GS** has not been extensively studied, and the structures of their empty forms—either 'collapsed' or 'open/porous'—have gone unreported. As a result, despite 20 years of prominence in the crystal engineering community, the formal existence of microporosity in the **GS** class of compounds has not yet been established.

In this work⁴ we study the desolvation of guanidinium 1,4-benzenedisulfonate (**G₂BDS**) and demonstrate that it is formally microporous. Furthermore, we study the absorption of gases into this material *via* Single Crystal-to-Single Crystal transformations.

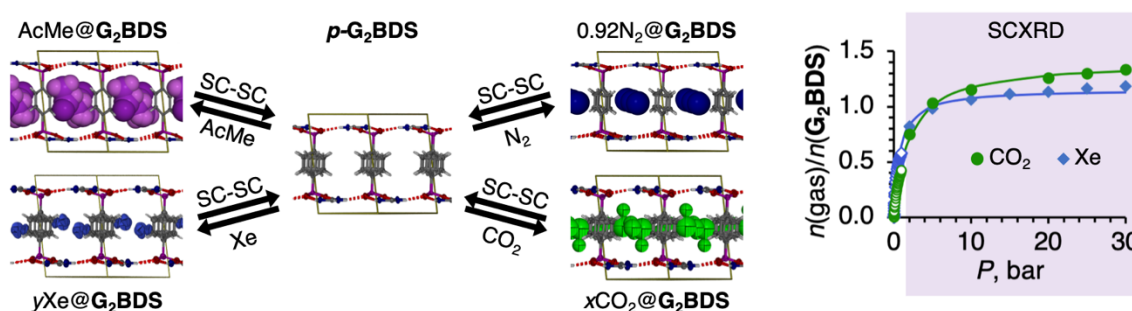


Figure 1. A summary of Single Crystal-to-Single Crystal transformations described here. Combined bulk (low pressure) and single crystal (high pressure) Xe and CO₂ sorption isotherms of G₂BDS.

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Inclusion complexes of ferrocene uracil derivatives with cyclodextrins: solubility and binding ability

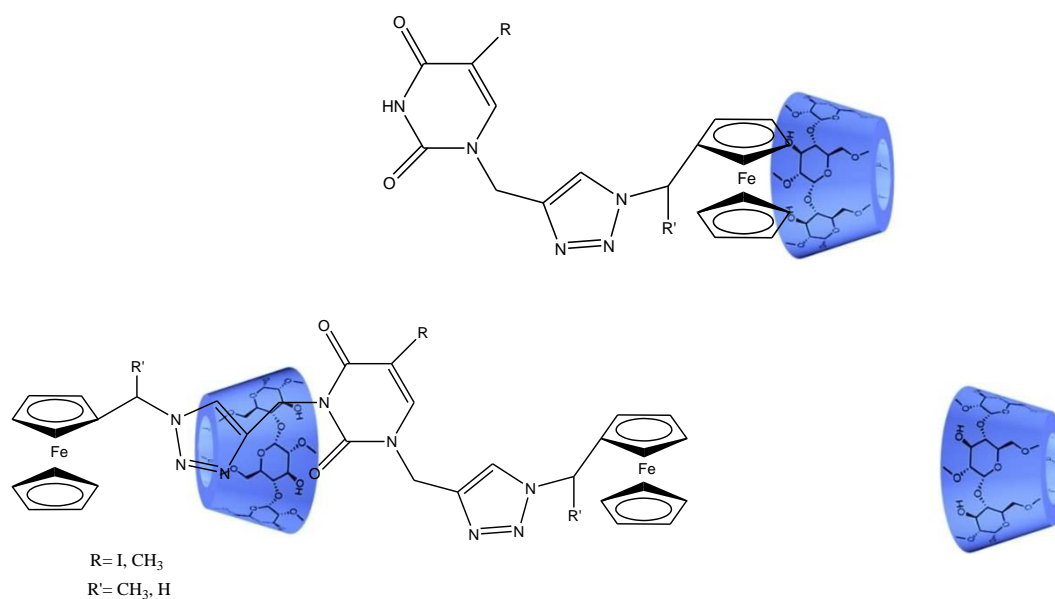
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Recent research shows that ferrocene uracil derivatives have biological activity.¹ However, their high lipophilicity limits the application. It is known that cyclodextrins show ability to improve drug water solubility by binding the hydrophobic moiety of the molecule inside of its cavity, such as ferrocene.² Ferrocene shows different binding orientations as well as binding constants for alpha, beta and gamma cyclodextrine in water.³ Environment of ferrocene can influence their binding to cyclodextrines.⁴

Therefore, we researched various ferrocene uracil derivatives with different R', R groups and studied their binding ability with α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin and modified (2-hydroxypropyl)- β -cyclodextrin in water (figure 1). Characterisation was performed using UV-Vis spectroscopy. Titrations were used to calculate binding constants that show range between 1-3.



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Understanding halogen-bonded cocrystallization through experimental and computational studies

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Halogen bonding (XB) has in the last two decades emerged as a useful addition to the toolbox of supramolecular interactions. Formed between the electropositive areas of halogen atoms as donors and electron rich atoms and moieties as acceptors, halogen bonding is conceptually similar to hydrogen bonding (HB). Solid-state studies have been key to the XB research, with cocrystallization providing an easy way to combine different donors and acceptors and study the structures and properties of resulting cocrystals.

Notwithstanding their similarity, through judicious choice of respective donors and acceptors, HB and XB can be used in an orthogonal manner to e.g. systematically afford three-component solids.¹ Similarly, orthogonality of HB and XB can give rise to polymorphism, with two different HB and two different XB motifs forming independently of each other and combining to give three distinct polymorphs of a two-component cocrystal.² Careful crystallization experiments were used to prepare samples of different polymorphs, with their relative stabilities established experimentally and confirmed computationally.

Next, starting from a known halogen-bonded cocrystal of naphthalene, a strategy could be established where the systematic exchange of the original crystal components with appropriate chromophores gave rise to pleochroic materials. Mechanochemical screening was used to discover new cocrystals and computational studies were used to rationalize the unexpected experimental results.³

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From greener synthesis to next-generation materials: Innovations in the production of metal-organic frameworks

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Metal-organic frameworks¹ are a class of highly porous materials that have been extensively studied over the past 25 years for applications in gas storage, hydrocarbon separation, and water harvesting². The recent development of a MOF-based system for the commercial storage of hazardous implant gases, as well as the continuous discovery of new promising MOF applications have established MOFs as advanced materials of the future.³ An amplified need for large-scale MOF production, coupled with the currently energy- and organic solvent-intensive methods for their synthesis, has called for the development of more efficient and economical methodologies for MOF manufacture⁴. Mechanochemical⁵ and accelerated aging⁶ methods are examples of recently developed methodologies that reduce the solvent, high temperatures, and corrosive reagents sometimes associated with traditional solvothermal MOF synthesis. Flow chemistry⁷ and spray drying⁸ have likewise been shown to afford multi-kilogram production of MOFs in relatively short timescales using greener solvent alternatives. Inspired by solid-state MOF synthesis as well as the search for less toxic solvents for MOF synthesis and activation, we now present a rapid and scalable methodology to produce high surface area MOFs using supercritical carbon dioxide (scCO₂). Activated, microporous MOFs are formed in short timescales (as little as 5 min) from readily available metal oxides in a process that is scalable to at least 0.5 Kg.⁹ Our work has also extended towards the development and commercialization of MOFs with unprecedented applications,¹⁰ as well as novel functional groups. This talk aims to present, from an industrial perspective, a versatile, environmentally friendly, and virtually solvent-free alternative for MOF synthesis, as well as new applications of functional MOFs.

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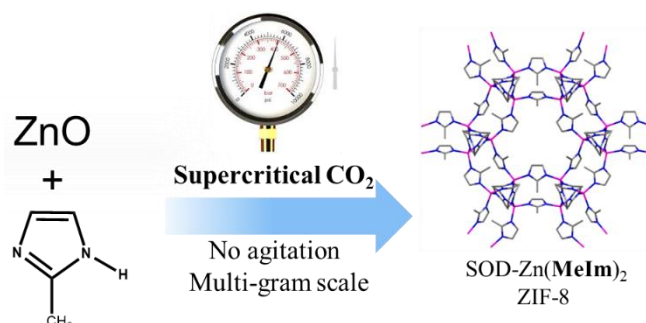


Figure 1. Multi-gram scale synthesis of ZIF-8 from ZnO in supercritical CO₂

Periodic DFT calculation for understanding and predicting halogen bond transformations in solid state

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Halogen bonding has gained prominence in crystal engineering as a new route to designing materials with unusual properties, yielding applications in luminescence,¹ magnetism² and data storage.³ Crystal structure prediction (CSP) calculations have played a major role in the design of molecular crystals based on light 2nd and 3rd row elements, while periodic density functional theory (DFT) has been used to predict solid-state properties. Yet, when it comes to halogen-bonded crystals, the success of CSP and periodic DFT has been more limited, owing to the difficulties in accurately describing the interactions formed by diffuse orbitals of heavy halogen atoms.

The key challenge for modelling halogen bonding in solid state as opposed to gas phase, lies in the presence of diverse supramolecular interactions (hydrogen bonding, π - π stacking etc.), which control the stability of the underlying crystal lattice as much as the actual halogen bond. Therefore, a reliable calculation must balance the contributions of all the interactions present in the crystal structure alongside the halogen bond. Selection of suitable DFT functionals for modelling halogen-bonded crystals is an open problem, which requires thorough consideration.

In this presentation we will demonstrate the use of periodic DFT calculations to explain and predict the solid state transformations of cocrystals with halogen bonding interactions with the heavy, increasingly metallic elements of the pnictogen group (I...P, I...As, I...Sb).⁴ The presentation will end with a demonstration of the prediction of stoichiometric interconversions of halogen-bonded cocrystals using periodic DFT, with subsequent experimental verification.⁵

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Symmetry Analysis of Layered Hybrid Halometallates(II)

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Layered hybrid halometallates(II) (LHHs) are double salts of general formula A_aBX_x , with A representing an organic cation, B representing a divalent metal cation and X representing a halogenide anion. LHHs represent a versatile platform for designing materials with the desired chemical, electric and magnetic properties,^{1,2} due to undemanding geometrical constraints on the organic part of the structure combined with relatively high coupling between inorganic building blocks.³

Structural characterization of these compounds, essential for modelling of the observed properties and improvement of their design, is hindered by the morphology of the samples (in case of single-crystal techniques) or ambiguities in cell and space group determination (for powder techniques). In order to facilitate the extraction of structural parameters from diffraction data, we propose a crystallographic symmetry analysis for these compounds. The analysis is done considering the allowed unit cell dimensions and settings, Wyckoff position combinations for cationic and anionic part of the structure and expected point group symmetry of the building blocks. Results of the analysis on some literature and in-house examples are discussed, as well as the implementation of analysis in the common crystallographic software.

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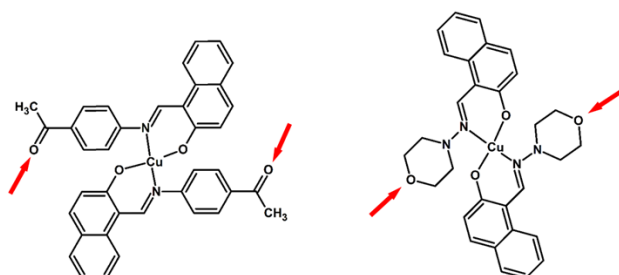
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Halogenska veza u kokristalima iminskih metalnih kompleksa

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Metalni kompleksi u kontekstu kristalnog inženjerstva materijala koji su povezani halogenskom vezom predstavljaju zanimljiv smjer istraživanja među ostalim i zato što su u zadnjih 70-ak godina dobro utvrđeni uobičajeni načini njihove pripreme, način koordinacije i razmještaja liganada oko metalnog centra, stabilnost i načini povezivanja međumolekulskim interakcijama (ponajviše vodikovim vezama).¹ Predvidiva koordinacija i geometrija takvih podjedinica mogu se tako iskoristiti kao polazna točka u izgradnji kokristala u kojima su podjedinice povezane vodikovom i halogenskom vezom, pri čemu se može dobiti i materijal željene supramolekulske dimenzionalnosti. Korištenje imina u metalnoj podjedinici kokristala jedan je smjer istraživanja u tom području.² Prednosti iminskih metalnih kompleksa su jednostavna priprema, predvidljiv način vezanja liganada na metalni centar, kao i robustnost dobivenog kompleksa u daljnjem postupku kokristalizacije. Funkcijske skupine, akceptori ili donori halogenske veze, nalaze se smještene na periferiji metalne podjedinice, čime su i dostupne za ostvarivanje supramolekulskih interakcija s poveznicama. Poznavanje ekvivalentnosti pojedinih metalnih centara ili poveznica omogućuje ciljanu izmjenu podjedinica sučinitelja u dobivenom materijalu tako da se očuva njegova kristalna struktura ali potencijalno izmijene željena makroskopska svojstva.^{1,2} Ipak, zasad su rijetka sustavna istraživanja ove vrste kokristala. Jedan primjer su dva niza ekvivalentnih kokristala iminskih niklovi(II) i bakrovi(II) kompleksa sa perhalogeniranim aromatskim spojevima.³ U tim kokristalima je prisutna halogenska veza između halogenog atoma donora i kisikovog atoma acetilne skupine iminskog liganada. Uz izostruktturnost kokristala niklova(II) i bakrova(II) kompleksa s istim donorom, opaženo je da se izmjenom bakrova(II) centra za niklov(II) centar kao i slabijeg donora za supramolekulski ekvivalentan jači donor dobivaju termički stabilniji kokristali. Drugi primjer je kokristal s iminskim bakrovim(II) kompleksom koji ima morfolinski kisikov atom smješten na periferiji.⁴ Pomalo neočekivano, u kokristalu je metalni kompleks tetraedarske geometrije, dok je ishodni metalni kompleks kvadratne.



Slika 1. Shematski prikazi istraživanih iminskih metalnih kompleksa. Crvenim strelicama označeni su periferno smješteni akceptori halogenske veze.

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Investigating the Impact of Supramolecular Connectivity on Mechanical Properties of Crystals

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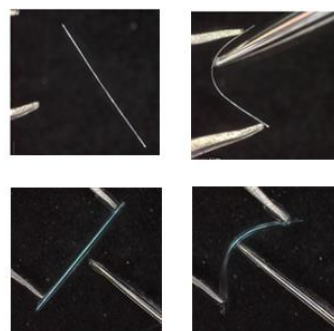
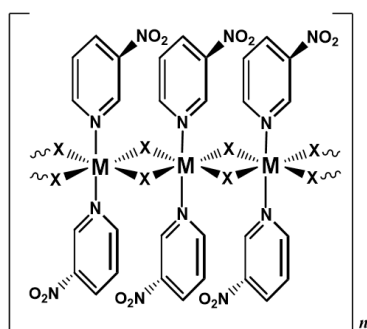
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Recent findings in the field of crystal engineering of molecular crystals have shifted the paradigm that crystals are brittle, rigid, and easily break when mechanical force is applied to them. There is a growing number of scientific papers which show that molecular crystals can also exhibit plastic and/or elastic deformation as a response to applied mechanical force. While these new phenomena are certainly interesting the mechanisms that lead to these extraordinary behaviors are not completely understood and require additional research.

Our previous research has found that cadmium(II) halide coordination polymers with halogen substituted pyrazine ligands can exhibit bending deformation and revert to their original state as long they are not bent beyond a certain threshold (i.e. the critical radius).¹ It was also shown that halogen bonds formed between halide and halogen atoms could indeed play a crucial role in defining the mechanical properties of these crystals. Halogen substituted pyrazines are considered relatively weak halogen bond donors and the interactions that they form are comparable to weak hydrogen bonds.² Therefore replacing weak halogen bond donors with weak hydrogen bond donors could in theory produce similar mechanical responses in crystals. To investigate this venue, we opted to use nitropyridine ligands since they also have a conformationally rigid structure as well as nitro groups which can serve both as a potential hydrogen bond acceptor and due to their electron withdrawing nature have an activating effect on present C–H hydrogen bond donors. We also expanded our research to copper(II) halides (chloride and bromide) to investigate if findings for cadmium(II) halide compounds could be applied to different metal halides which possess similar structural features (i.e. form 1D coordination polymers). All four possible coordination polymers were successfully crystallized and gave needle like crystals which were of adequate quality for mechanical property measurements. Their crystal structures were also successfully determined and correlated with observed mechanical responses.

Acknowledgements: This work has been fully supported by the Croatian Science Foundation under project „From form to function: Mechanically flexible crystalline materials with controllable responses“ (IP-2019-04-1242).



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Interactions of benzothiazole ligands with DNA:RNA hybrids and triplex structures

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Nucleic acids are molecular targets for many drugs that are used in cancer therapy due to their essential functions in cells (replication, transcriptional and translational regulation, enzymatic reactions).¹ Nucleic acid structures present a wide variety of shapes with varying major and minor groove widths that can be recognized by small molecules using a non-specific (mainly electrostatic) binding along the nucleic acid exterior, a specific groove binding and intercalation (insertion of planar aromatic molecules between base pairs).²

Interactions of an array of nucleic acid structures with a small series of benzothiazole ligands were screened by competition dialysis. The main aim of this study was the detection of benzothiazole-based moieties with selective binding or spectroscopic response to DNA:RNA hybrids and ATT triplex in regard to regular (non-hybrid) DNA and RNA duplexes and single-stranded forms. Complexes of nucleic acids and benzothiazoles, screened by this method, were then characterised by UV/Vis, fluorescence, circular dichroism (CD) spectroscopy and isothermal titration calorimetry. Compound **6** could differentiate between B- (binding of **6** dimers inside minor groove) and A-type (intercalation) helices by mode of binding while both **5** and **6** selectively stabilized ATT triplex regarding AT duplex. Compound **3** induced strong condensation-like changes in CD spectra of AT-rich DNA sequences.

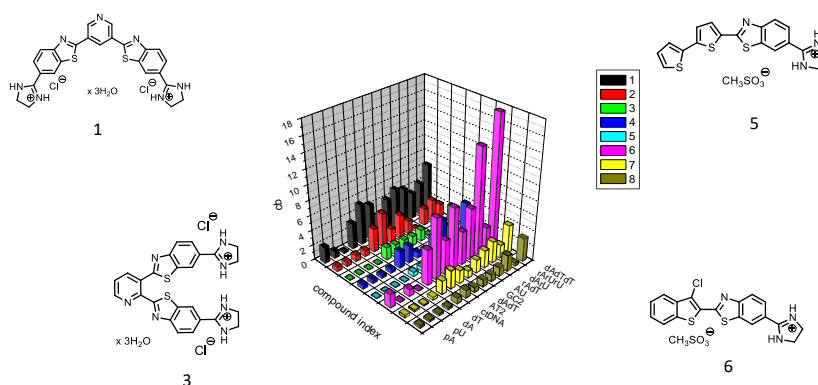


Figure 1. Benzothiazole ligand structures that gave the best results in the competition dialysis assay.

¹ L.H. Hurley, *Nature Reviews Cancer*, **2002**, *3*, 188-200.

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Non Covalent Interaction in Development of Innovative pharmaceutical product – current status and way forward

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It is well known that Non-covalent interactions are critical in maintaining the three-dimensional structure of large molecules, such as proteins and nucleic acids and this fact was and is used in the understanding drug – target interaction. This is basis for many New Chemical Entity discover program over Industrial and Academia. Beside this there is also space for utilization of non-covalent interaction in development or improvement of property of existing drug of to increase performance of drug product. Non covalent interaction can be connect with solid state property and with this one can start with design proper crystal property. From another aspect non covalent interaction is very important for understanding interaction in solution which open space for design of drug delivery system based on understanding interaction on molecular level in the drug product. The scope of this lecture is to present current trend and share vision about role of supramolecular chemistry in the future of drug discovery and development.

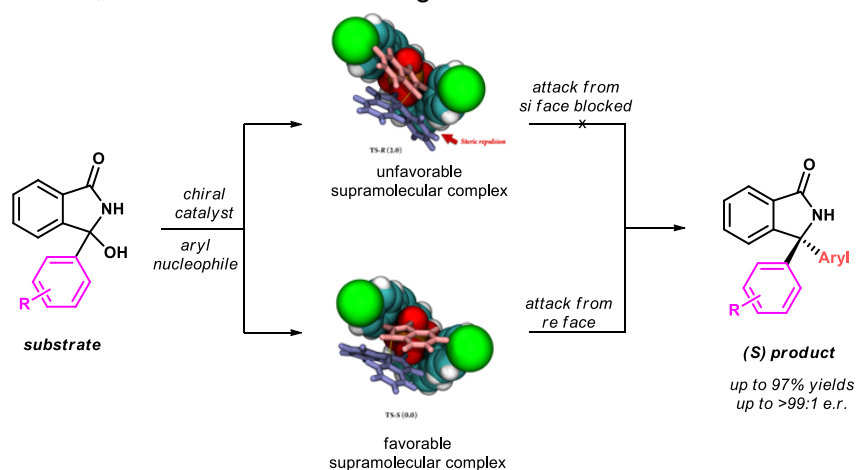
Supramolecular substrate-catalyst complexes direct stereoselective arylations

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The past fifteen years have seen remarkable advances in the use of non-covalent interactions as key activating and controlling elements in the field of asymmetric catalysis. The area of non-covalent asymmetric organocatalysis is now developing at a faster rate than the covalent variety as new arenas are explored for modes of catalysis which primarily employ hydrogen bonding and ion pairing interactions. This recent direction is in somewhat sharp contrast to earlier developments in asymmetric catalysis, which almost solely relied on dative covalent substrate–metal–ligand interactions. Whilst non-covalent interactions had been implicated in some key processes (i.e. Noyori transfer hydrogenation), they were generally regarded as of secondary importance. This contrasts with enzymatic catalysis, where non-covalent interactions are crucial to the mechanism of catalysis. Relatively recent developments in non-covalent organocatalysis have demonstrated that multiple non-covalent interactions orchestrated by small molecule chiral catalysts can be tremendously powerful tools for controlling enantioselectivity.

By employing this non-covalent interaction principle, we developed stereoselective Brønsted acid-catalyzed arylations of benzophenone-derived imines to afford chiral α -triarylmethanamines. The key to the success of this transformation is the *in situ* generation of reactive benzophenone iminium species, which forms a non-covalent supramolecular complex with the catalyst. The structure of the complex – due to steric hindrance – directs nucleophilic attack only from one side of the stereotopic face of the electrophile, thus generating arylation product in a stereoselective fashion. Structure of the complex, stereochemical induction, and mechanistic investigations will also be discussed.



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Catalytic Coupling of CO₂ with Propargyl Alcohol Substrates

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Carbon dioxide (CO₂) is an abundant and sustainable C1 building block for producing valuable synthetic intermediates and biologically active chemicals, such as carbonates and carbamates.¹

Based on density functional theory (DFT) calculations (using the B2PLYP/B3LYP), we have evaluated several propargyl alcohols as CO₂ trapping substrates by comparing the thermodynamic stability between starting materials and final carbonates. Exergonic reactions are predicted for conjugated propargyl alcohols when additional C-C bonds are formed *via* domino reactions.

We have therefore envisaged palladium-catalyzed intermolecular reactions on suitable propargylic alcohols bearing an aryl halide moiety to produce α -alkylidene cyclic carbonates.² The fixation of CO₂ can be accomplished by the alkoxide produced in the basic medium, and the cyclization can be mediated by the Pd catalyst which is expected to be inserted by oxidative addition to the aryl halide bond. Reductive elimination may afford the final product and regenerate the catalyst.

We present herein our recent computational and experimental results according to the reaction scheme shown in Figure 1.

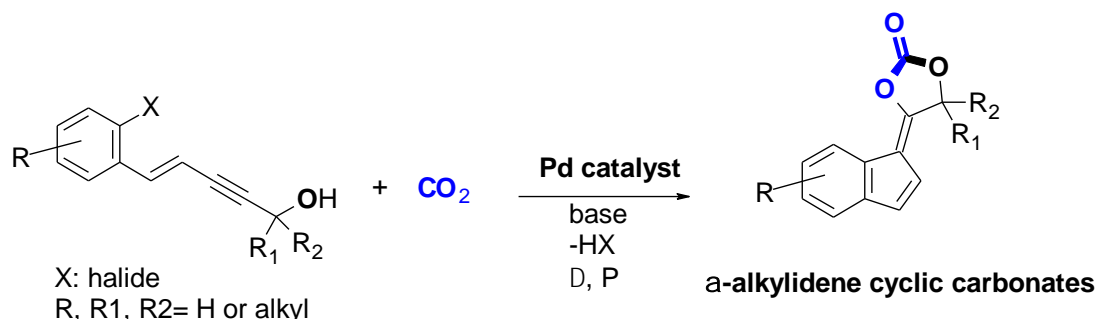


Figure 1. General reaction scheme of Pd-catalyzed domino reactions between suitable propargyl alcohols and CO₂

¹ Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933; S. Wang, C. Xi, *Chem. Soc. Rev.* **2019**, *48*, 382-404.

² K. Iritani, N. Yanagihara, K. Utimoto, *J. Org. Chem.* **1986**, *51*, 5499-5501; Y. Inoue, Y. Itoh, I.-F. Yen, S. Imaizumi, *J. Mol. Cat.* **1990**, *60*, L1-L3; S. Sun, B. Wang, N. Gu, J.-T. Yu, J. Cheng, *Org. Lett.* **2017**, *19*, 1088-1091.

Cyclic Carbamates Through Transition Metal-Catalyzed CO₂ Capture - an *in Silico* Approach

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Optimization of reaction conditions using *in silico* methods is a relatively novel approach to organic synthesis. We have evaluated potential substrates for a novel palladium-catalyzed CO₂ capture reaction that produces carbamates (Figure 1b) using DFT analysis of reaction thermodynamics and selected several amines that appeared promising. These substrates have been synthesized and are being tested for CO₂ capture under a range of experimental conditions and catalysts. If successful, our intramolecular cascade reaction will enable us to produce a complex cyclic carbamate motif in one step using a simple reaction under mild conditions and a very cheap, environmentally friendly reagent (CO₂). The mechanism of this reaction will also be studied to further optimize the reaction conditions. Finally, given that cyclic carbamate moieties are often present in small molecule therapeutics (e.g. Efavirenz and Linezolid), reaction products will also be tested for anti-cancer and antibacterial activity.

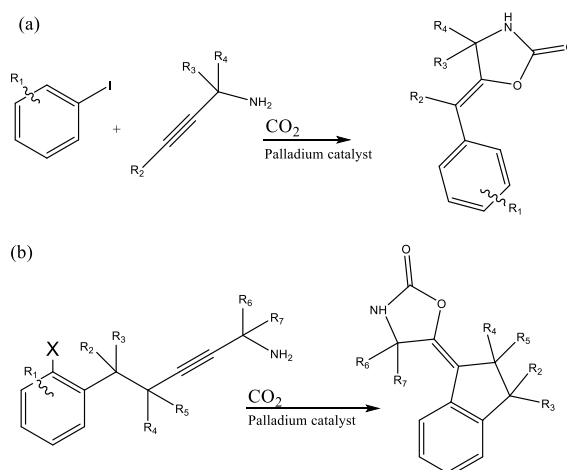


Figure 1. (a) The type of reaction reported by Nevado et al that yields carbamates with a tetrasubstituted alkene motif from CO₂ using a Pd catalyst¹; (b) Our (intramolecular) version of this cascade reaction.

¹ P. García-Domínguez, L. Fehr, G. Rusconi, C. Nevado, Chem. Sci. **2016**, 7, 3914.

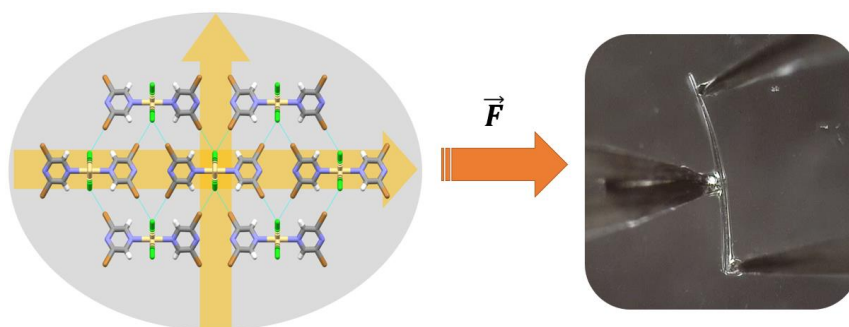
Mehanička svojstva kristala kadmijevih(II) halogenida s 2,6-dibrompirazinskim ligandima

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Fizikalna i kemijska svojstva čvrstih tvari ovise, ne samo o njihovoj molekularnoj strukturi, već i finom međuodnosu brojnih supramolekulskih interakcija. Iz tog razloga kristalno inženjerstvo doživljava svoj procvat jer omogućava razumijevanje i kontrolu faktora koji utječu na usmjeravanje supramolekulskog povezivanja prema željenom ishodu, a time i ostvarivanje ciljanih svojstava materijala.¹ Krutost i krtoost kristala često se postavljaju kao ograničavajući faktori kod njihove upotrebe u praksi. No, posljednjih je godina opažen rastući broj literaturnih navoda koji opisuju molekulske kristale s fleksibilnim odzivom na primjenu svjetlosnog, toplinskog ili mehaničkog podražaja.^{2,3} Dosadašnja istraživanja mehanički potaknute fleksibilnosti uglavnom su bila ograničena na organske molekulske kristale, dok su mehanička svojstva metalo-organskih kristalnih krutina mnogo manje istražena.

U dosadašnjim istraživanjima kristalnih jednodimenzijskih koordinacijskih polimera kadmijevih(II) halogenida pokazano je da su međumolekulske interakcije zajedno sa strukturnim zaključavanjem (engl. *interlocking*) odgovorne za elastični odziv kristala koordinacijskih polimera⁴, ali i da male razlike u jakosti i geometriji međumolekulskih interakcija mogu bitno promijeniti vrstu i stupanj mehaničkog odziva.^{5,6} Kako bi utjecaj različitih strukturnih parametara na fleksibilni odziv kristalnih koordinacijskih polimera bio dodatno razjašnjen, u ovom je radu korištena nova serija koordinacijskih polimera kadmija(II) sa 2,6-dibrompirazinskim ligandima, koji također pokazuju elastičan odziv na primjenu vanjske mehaničke sile. Priređenim spojevima određena je molekulska i kristalna struktura, a strukturne karakteristike u kristalima priređenih spojeva korelirane su sa stupnjem mehaničkog odziva. Ovaj je rad financirala Hrvatska zaklada za znanost projektom IP-2019-04-1242.



Slika 1. Kristalna struktura i elastičan odziv kristala $[\text{CdCl}_2(2,6\text{-di-Br-pz})_2]_n$.

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CYCLOPENTAPHENYLALANINE AS A FLUORESCENT ANION SENSOR IN SOLUTION

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In the last few years artificial ion transporters, which imitate natural systems in selective anion binding and are capable of passing the hydrophobic lipid barriers, have been intensively investigated.^{1,2} As such, cyclopeptides could be used for selective binding and membrane transport of predominant anions *in vivo* (Cl⁻, HCO₃⁻, and H₂PO₄⁻/HPO₄²⁻). These compounds generally exhibit improved metabolic stability and bioavailability as well as enhanced binding affinity and selectivity toward substrates compared to their more flexible linear analogs.²⁻⁴ Cyclopeptides derived from fluorescent amino acids, like phenylalanine, could potentially be very sensitive fluorimetric ion sensors due to the high sensitivity of fluorescence spectroscopy.

In the scope of this work, we conducted spectrophotometric and fluorimetric titrations to obtain stability constant of complexes of cyclopentaphenylalanine (Figure 1) with various anionic species in methanol and acetonitrile. Furthermore, we carried out classical molecular dynamics simulations in order to investigate conformational changes of the receptor upon anion complexation in solution.

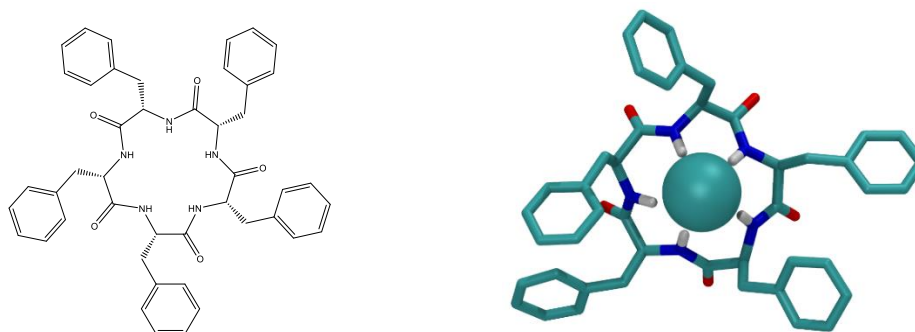


Figure 1. Structure of cyclopentaphenylalanine and its complex with chloride anion obtained by MD simulations.

ACKNOWLEDGEMENTS

This work was supported by the Croatian Science Foundation under project IP-2019-04-9560 (MacroSol).

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(A) Romantic Relationship Between Hydrophobic Cavities and Aromatic Alcohols

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β -cyclodextrin and cucurbit[7]uril are known to be very good receptors for adamantane-like guests in water,¹ due to their perfect fit within the mentioned cavities. By contrast, the hosting of aromatic guests was far less frequently explored. The influence of various substituents on benzene inclusion remained almost unknown. Likewise, the binding thermodynamics of aromatic and structurally similar aliphatic guests was never systematically compared. We therefore studied the complexation of various aromatic alcohols and their hydrogenated analogues (Figure 1) with cucurbit[7]uril and β -cyclodextrin in water using several experimental techniques (isothermal titration microcalorimetry, fluorimetry, spectrophotometry and NMR spectroscopy). Considerable substituent impact on the complex stability was observed in the case of *p*-substituted phenols which can be explained by differences in electron density distributions of the hosts and guests. Substantial influence of guest aromaticity on complexation thermodynamics was observed in experiments with hydrogenated derivatives of 2-naphthol. The reactions involving the aliphatic guest were far more entropically favourable, leading to higher stability constants compared to complexes with aromatic analogues. For most of the examined host-guest systems an enthalpy-entropy compensation was observed, resulting in weak temperature dependence of $\Delta_r G^\circ$. The complexation thermodynamics was in agreement with the classical interpretation of the hydrophobic effect at lower temperatures and the non-classical explanation at higher ones.^{1,2}

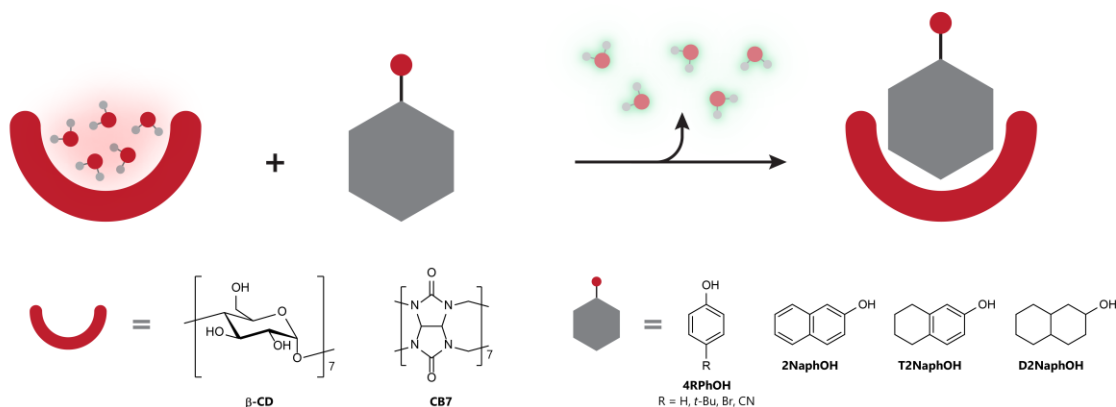


Figure 1. Schematic representation of the complexation process and guest structures.

This research was fully supported by the Croatian Science Foundation (project MacroSol, IP-2019-04-9560) and European Regional Development Fund (project CluK, KK.01.1.1.02.0016).

¹ K. Leko, M. Hanževački, Z. Brkljača, K. Pičuljan, R. Ribić, J. Požar, *Chem. Eur. J.* **2020**, *26*, 5208.

² F. Biedermann, W. M. Nau, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 2.

Diamantane Alcohols and Hydrophobic Cavities: The (not so) Perfect Match in Water and Structured Organic Solvents

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Diamantane derivatives combined with cucurbit[*n*]urils have received significant attention in the field of supramolecular chemistry due to their outstandingly high complex stability constants, reaching above petamolar values for positively charged diamantane diammonium salts and cucurbit[7]uril in water.¹ On the other hand, their complexation with cyclodextrins has been rarely investigated.² We have therefore studied temperature and solvent effects on the complexation of diamantane alcohols (Figure 1) with cucurbit[7]uril and β -cyclodextrin in water and structured organic solvents (formamide, ethylene glycol) by means of isothermal titration calorimetry and NMR spectroscopy. The complexes of apical derivatives with CB7 in water were the most stable products ($\log K > 7$), whereas the complexation of 4-DiaOH with β -CD was the most favorable in formamide. For most of the studied host-guest systems a significant temperature dependence of $\Delta_r H^\circ$ and $\Delta_r S^\circ$ was observed, which resulted in an almost complete enthalpy-entropy compensation. For these systems complexation thermodynamics was in line with the classical rationale of the solvophobic effect at lower temperatures, and the non-classical explanation at higher ones.^{3,4} The results of ¹H NMR titrations were in accord with the thermodynamic studies and have revealed an interesting difference in complex formation kinetics between cucurbit[7]uril and β -cyclodextrin hosts.



Figure 1. Schematic representation of the investigated hosts and guests.

This research was fully supported by the Croatian Science Foundation (projects MacroSol, IP-2019-04-9560 and DiamMat, UIP-2017-05-9653) and European Regional Development Fund (project CluK, KK.01.1.1.02.0016).

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⁴ F. Biedermann, W. M. Nau, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2014**, 53, 2.

Adamantane in Supramolecular Drug Delivery Systems

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The design and synthesis of safe and highly specific drug delivery systems with improved properties is a priority research in the growing area of nanomedicine. Nanomedicine offers a new platform for drug delivery development, from minimizing the toxicity of pharmaceuticals to improving their efficacy. The unique structural and chemical properties of adamantane are well known and recognized in the organic chemistry and pharmaceutical chemistry. They provide exceptional opportunities in the design of various adamantane based scaffolds or carrier systems for drug delivery. The unique structural and chemical properties of adamantane are well known and recognized in the organic chemistry and pharmaceutical chemistry. They provide exceptional opportunities in the design of various adamantane based scaffolds or carrier systems for drug delivery. Adamantane can be used in two ways, as a building block to which different functional group are covalently bonded (adamantane based dendrimers) or as a part of self-assembled supramolecular systems where the adamantane is accommodated on the basis of its lipophilicity (liposomes) and strong host-guest interaction (cyclodextrins). The results reported in literature encourage the development of novel adamantane-based structures and self-assembled supramolecular systems for basic chemical investigations as well as biomedical application.

Figure 1. Your figure caption may be placed here. Delete this text box if not used.

¹ References - Instructions to Authors CCA (https://hrcak.srce.hr/upute/upute_autorima_Croatica_chemica_acta.pdf)
²

Supramolecular Control of Reactivity in the Solid State

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Mechanochemistry has grown as a promising alternative method in the various areas of inorganic, organic, and metal-organic chemistry because it can promote solid-state reactions quickly and quantitatively, even on a large scale [1].

Multicomponent solids, like cocrystals have been recognized and used to execute solid state reactions selectively and efficiently. Building on these recent advances, herein we employ real-time in situ Raman spectroscopy monitoring [2,3] to explore the possibilities of manipulating the reaction kinetics and chemical reactivity of the Knoevenagel condensation in solid state. We emphasize in particular reaction paths and product selectivity that can be explored in the solid state by applying principles of crystal engineering [4,5] through the use of polymorphs, desmotropes, cocrystals, or salts.

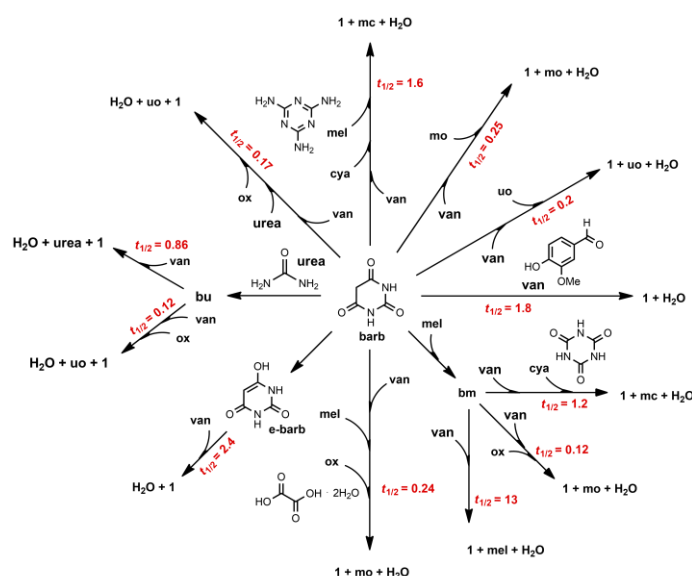


Figure 1. Modifications of barbituric acid and employed reaction conditions, with the approximate half-life for each reaction, $t_{1/2}$ (hours).

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