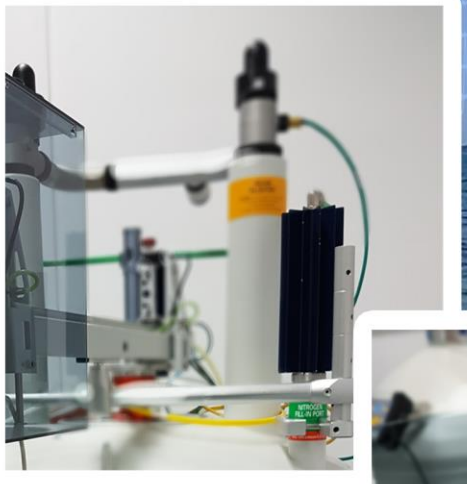
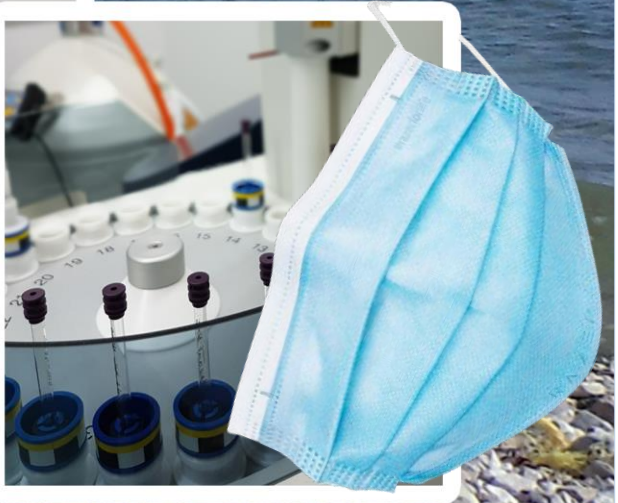
ADRIATIC NMR

September 22–24, 2020, Peroj, Croatia

BOOK OF ABSTRACTS

The Adriatic NMR Conference is organised by
the Department of Chemistry, Faculty of Science, University of Zagreb, Croatia





ADRIATIC NMR

September 22–24, 2020, Peroj, Croatia

ADRIATIC NMR CONFERENCE

Peroj, Croatia, 22–24 September 2020.

BOOK OF ABSTRACTS

IMPRESSUM

ORGANIZER

Department of Chemistry
Faculty of Science, University of Zagreb, Croatia

PUBLISHED BY

Department of Chemistry
Faculty of Science, University of Zagreb, Croatia

EDITORS

Nikola Bregović, Danijel Namjesnik, Predrag Novak, Jelena Parlov Vuković

DESIGN, WEB, AND LAYOUT

Danijel Namjesnik

TEXT PREPARED BY

AUTHORS, who are fully responsible for the abstracts

CONFERENCE VENUE

Hotel "Villa Letan"
Peroj 450
52215 Vodnjan
info@hotel-letan.hr
www.hotel-letan.hr
Tel: +385 52 521 006 ; 009

https://adriatic-nmr-conference.chem.pmf.hr/

ISBN 978-953-6076-58-1

Zagreb, 2020

ORGANIZER

DIAMOND SPONSOR

AlphaChrom

GOLD SPONSORS

xellia PHARMACEUTICALS

BRUKER

Aparatura
Analitička oprema i sustavi – Analytical equipment and systems

INA

magritek

Asolutic
a member of AlphaChrom Group

SILVER SPONSORS

JEOL
Solutions for Innovation

SCAN

KEFO
SINCE 1949

METTLER TOLEDO

Fidelta
A Galápagos Company

KOBIS

DONAU LAB

BELUPO

DONORS

LKB

Ru-Ve

MESSER
Gases for Life

SUPPORTED BY

ACADEMIA SCIENTIARUM ET ARTIUM CROATICA MDCCCLXX

Ministry of Science and Education
of the Republic of Croatia

Dear Participants,

It is our great pleasure to inform you that the organisation of Adriatic NMR conference will be continued in 2020. The Adriatic NMR 2020 will this time take place in the northern part of Adriatic, in Hotel Villa Letan, Peroj (Istria).

We kindly welcome colleagues sharing interest in NMR to attend the Adriatic NMR 2020 which will serve as a platform allowing participants to gain insight in recent developments of NMR spectroscopy, get acquainted with diverse applications of state of the art NMR techniques, and expand their knowledge of NMR theory. We strongly encourage all participants to share their scientific experience with the gathered NMR enthusiasts resulting in fruitful dialogues and new collaborations. The wide scope of the conference includes but is not limited to topics regarding the theoretical basis of NMR, method development, Bio-NMR, spectral data interpretation and simulation, metabolomics, NMR characterization of supramolecular systems and industrial applications of NMR spectroscopy. A section of the conference will be dedicated to solid state NMR, including theory and applications.

With strong hope that the Adriatic NMR 2020 will foster the exchange of important information, serve as an extensive networking opportunity, and with confidence that it will be a memorable experience, we cordially invite you to join us in Peroj in September 2020.

Organizing Committee

ORGANIZING COMMITTEE

PREDRAG NOVAK (chair)
Department of Chemistry, Faculty of Science, University of Zagreb, Croatia

DRAŽEN VIKIĆ-TOPIĆ (co-chair)
Ruđer Bošković Institute, Zagreb, Croatia

VLADISLAV TOMIŠIĆ
Department of Chemistry, Faculty of Science, University of Zagreb, Croatia

NIKOLA BREGOVIĆ
Department of Chemistry, Faculty of Science, University of Zagreb, Croatia

JELENA PARLOV VUKOVIĆ
INA – Industrija nafte d. d., Croatia

DANIJEL NAMJESNIK
Department of Chemistry, Faculty of Science, University of Zagreb, Croatia

KATARINA PIČULJAN
Department of Chemistry, Faculty of Science, University of Zagreb, Croatia

LARA JURKOVIĆ
Ruđer Bošković Institute, Zagreb, Croatia

JANEZ PLAVEC
National Institute of Chemistry, Ljubljana, Slovenia

KLAUS ZANGGER
Institute of Chemistry, Karl-Franzens-Universität Graz, Austria

ADRIATIC NMR

September 22–24, 2020, Peroj, Croatia

PROGRAMME

TUESDAY, SEPTEMBER 22	
9:00 – 9:50	**REGISTRATION**
9:50 – 10:00	**OPENING**
10:00 – 10:30	**Norbert Müller:** *NMR – What Else?*
10:30 – 11:00	**Tomislav Jednačak:** *Structure Characterisation of Bioactive Compounds and Their Interactions*
11:00 – 11:30	**COFFEE BREAK**
11:30 – 12:00	**Georgios Spyroulias:** *NMR Conformational Dynamics of RNA- and Nucleotide-Binding Proteins*
12:00 – 12:30	**Mario Gabričević:** *Use of ^{1}H-NMR in Investigation of Inclusion Complexes With Cyclodextrins*
12:30 – 14:00	**LUNCH BREAK**
16:00 – 16:30	**Francesca Benevelli:** *Smart scale NMR*
16:30 – 17:00	**Wiktor Koźmiński:** *High dimensionality and high resolution NMR experiments for IDPs*
17:00 – 17:30	**COFFEE BREAK**
17:30 – 18:00	**Mirta Rubčić:** *Carbohydrazides and Dihydrazones: the Aspects of Their Solid-state and Solution Chemistry*
18:00 – 18:30	**Andrea Usenik:** *Melting Down the Iceberg Model: Hydrophobic Cavities and (Sweetened) Alcohols*

WEDNESDAY, SEPTEMBER 23	
10:00 – 10:30	**Marco Geppi:** *Solid-state NMR: From Main Concepts to Applications*
10:30 – 11:00	**Svetlana Simova:** *NMR Metabolomics – Plants, Honey and Wine*
11:00 – 11:30	**COFFEE BREAK**
11:30 – 12:00	**Dajana Barišić:** *Palladium-mediated Regioselective C–H Bond Halogenation of Azobenzene Substrates by Mechanochemistry*
12:00 – 12:30	**Fabio Faraguna:** *Use of NMR in Biodiesel Synthesis*
15:00 – …	**CONFERENCE LUNCH**

THURSDAY, SEPTEMBER 24	
9:30 – 10:00	**Boban Anđelković:** *NMR metabolomics insight into phytochemistry*
10:00 – 10:30	**Mirna Petković Didović:** *^{13}C Solid-state NMR Study of Polyphthalamides for Use in Automotive Industry*
10:30 – 11:00	**COFFEE BREAK**
11:00 – 11:30	**Ljubodrag Vujisić:** *Natural products from Flora, Fauna and Fungi: NMR perspective*
11:30 – 12:00	**Mirjana Bukvić:** *Design, Synthesis and Characterization of Macrozones, New Antimicrobial Thiosemicarbazone-based Azithromycin Conjugates*
12:00 – 12:30	**POSTERS & SPONSOR PRESENTATIONS**
12:30 – 12:40	**CLOSING**
12:40 – 15:00	**LUNCH**

POSTER SESSION	
P1	**Marija Aleško**vić, **Ruža Jozepović, Sunčica Roca, Nikola Bregović, Marina Šekutor** *Synthesis and Binding of Permethylated Diamondoid Ammonium Salts*
P2	**Lucia Ema Sekula, Iva Habinovec, Ivana Mikulandra, Jana Gašperov, Predrag Novak, Ivan Grgičević, Mirjana Bukvić** *Isolation and Structural Characterization of 9a- And 4''- Tetrahydrofurfuryl Macrozone Reaction Mixture Components Using the LC-SPE/NMR*
P3	**Tomislav Jednačak, Maja Majerić Elenkov, Tomica Hrenar, Karlo Sović, Jelena Parlov Vuković, Predrag Novak** *Structural Studies of Substituted Oxazolidinones by Spectroscopic and Quantum Chemical Methods*
P4	**Lara Jurković, Ivana Hazdovac, Nadica Maltar-Strmečki, Daniel Mark Lyons** *Dissolution Kinetics of Copper Nanoparticles in Model Physiological Fluids and Dynamics of Copper(II) Complexes with Chiral Amino Acids*
P5	**Jana Gašperov, Ivana Mikulandra, Tomislav Jednačak, Branimir Bertoša, Iva Habinovec, Predrag Novak** *Synthesis, Structure Characterization and Interactions Of 4''-Aminopropyl Derivative of Azithromycin*
P6	**Matija Modrušan, Nikola Cindro, Katarina Leko, Vladislav Tomišić** *Synthesis of Phenanthridine-Based Calix[4]arene Glycoconjugate and Physicochemical Characterization of its Complexation Reactions with Alkali Metal Cations*
P7	**Edi Topić, Katarina Pičuljan, Višnja Vrdoljak, Mirta Rubčić** *Solid-state and Solution Behaviour of Aryl Dihydrazones*
P8	**Alma Ramić, Ines Primožič, Tomica Hrenar** *Characterization of Cinchona Alkaloids with NMR Spectroscopy*

CONTENTS

INVITED LECTURES

POSTERS

AUTHORS AND PARTICIPANTS

INVITED LECTURES

NMR – WHAT ELSE?

Norbert Mueller

Johannes Kepler University Linz, Linz, Austria
norbert.mueller@jku.at

In this motivational lectures an overview of less common aspects of NMR are brought up in a narrative and - hopefully - entertaining way.

Relationships between mainstream applications of NMR in imaging and spectroscopy and the “exotic” applications are explained.

A few, but by no means exhaustive list of key words of topics covered includes:

“NMR imaging and spectroscopy of food and drinks”, “SAR by NMR”, “NMR-directed mutagenesis”, “Functional MRI”, “ex-situ NMR”, “Oilfield NMR”, “NMR of batteries”, “Nano-scale NMR”, “NMR in COVID-19 research”, “MR-Imaging and -Spectroscopy of bottled wine”, as well as technical concepts like “Hyperpolisation”, “Spin Noise”, “Magnet Technology”, “NV-centres”, “3D structure determination”, “Solid state NMR”….

STRUCTURE CHARACTERISATION OF BIOACTIVE COMPOUNDS AND THEIR INTERACTIONS

Tomislav Jednačak

Department of Chemistry, Faculty of Science, University of Zagreb,
Horvatovac 102a, HR-10000 Zagreb, Croatia
tjednacak@chem.pmf.hr

Biomolecular interactions play essential roles in all cellular processes, such as protein synthesis, gene regulation, molecular organisation and recognition events. Determining the three-dimensional structure of ligands, their receptors and complexes is crucial for understanding molecular mechanisms and dynamics involved in these interactions.[1]

The first step to achieve this goal is the synthesis of small molecules, which can act as ligands for biomolecular receptors and thus regulate their function. In order to obtain bioactive ligands with the desired physico-chemical properties and to optimize product yields, the syntheses can be monitored in real time by employing *in-line* techniques.[2] Further analysis of complex reaction mixtures is carried out *on-line* using a hyphenated system which combines HPLC and SPE with cryo-NMR detection (HPLC-SPE/cryo-NMR). This methodology is applied to monitor the reaction progress, explain the side-reaction mechanisms and unambiguously characterize the reaction components.[3]

In the next stage, binding of the prepared ligands to their biological targets is studied by a combined use of cryo-electron microscopy, X-ray diffraction and NMR techniques based on saturation transfer difference (STD), paramagnetic relaxation enhancements (PREs), transferred nuclear Overhauser effect (trNOESY), translational diffusion (DOSY) and chemical shift perturbations (CSP). The results obtained for free and bound ligands can provide valuable data on the groups responsible for binding, ligand conformation, orientation, immersion depth, binding modes and epitopes.[4] Structural information is further complemented with biochemical assays and molecular dynamics simulations to assess the structure-activity relationships and design the compounds with enhanced biological properties.

ACKNOWLEDGMENTS
This research was funded by HRZZ, grant number IP-2018-01-8098 ”Macrozones“ and by EMBO Short-Term Fellowship, grant number 8451

REFERENCES

[1] I. M. A. Nooren, J. M. Thornton, *EMBO J.* **2003**, *22*, 3486.
[2] P. Novak, A. Kišić, T. Hrenar, T. Jednačak, S. Miljanić, G. Vrbanec, *J. Pharm. Biomed. Anal.* **2011**, *54*, 660.
[3] I. Habinovec, T. Jednačak, P. Novak, *ADMET & DMPK* **2015**, *3*, 352.
[4] P. Novak, T. Jednačak, *NMR Spectroscopy for Studying Interactions of Bioactive Molecules*. In *Physico-Chemical Methods in Drug Discovery and Development*, Z. Mandić, Ed., IAPC Publishing: Zagreb, Croatia, **2011**, pp. 1–62.

NMR CONFORMATIONAL DYNAMICS OF RNA- AND NUCLEOTIDE-BINDING PROTEINS

Georgios A. Spyroulias

University of Patras, Department of Pharmacy, Patras, Greece
G.A.Spyroulias@upatras.gr

Lupus antigen protein is a multi-domain RNA binding protein. It was first described as an auto-antigen in patients suffering from rheumatic systematic lupus erythematosus and Sjogren's syndrome. La protein plays a key-role in the tRNA biogenesis by binding to UUU-3'-OH terminal motif of nascent RNA polymerase III transcripts. It guides accurate 5'end maturation of pre-tRNAs by RNase P, while protects their 3'ends from exonucleolytic digestion and prevents their misfolding through its chaperone activity. Although La is located in the nucleus, it also facilitates translation of certain cellular and viral-encoded mRNAs, involved to subcellular trafficking and antiviral defense. The protein consists of four distinct domains, namely La motif (LaM), two RNA recognition motifs (RRM1 and RRM2α) and a C-terminus region. So far, the structural data of the La and RRM motifs from few eukaryotes (including human) that exist are bound to synthetic oligonucleotides providing inadequate information on the possible roles of the full-length La protein, in a more dynamic tRNA – dependent cellular network.

To elucidate the structural phenomena occurring during the interaction of the protein, from *Dictyostelium discoideum*, with RNA substrates, as well as the stability of the protein, we initiated an extensive structural and functional characterization of a "domain library" of La. Our research focuses on the NMR-driven structure determination of each domain, their pairwise combinations and the study of the whole protein in free state via 2D/3D NMR. Along with the structural investigation, the dynamical properties of the above constructs are studied through ^{15}N-relaxation measurements. The final goal is the functional analysis of those domains and the elucidation of the role of each one of them in RNA recognition and binding using natural and synthetic RNA substrates. Interaction studies are carried out through NMR-driven titration experiments. Results will be discussed and compared with the corresponding ones from human La.

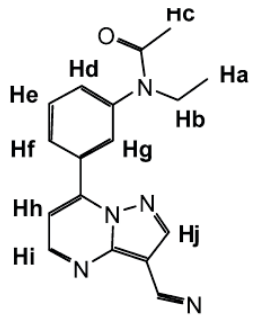
ACKNOWLEDGMENTS
We acknowledge partial support from EU FP7-REGPOT-2011 "SEE-DRUG" (nr. 285950) and NSRF 2014–2020 program of National Greek RIs "INSPIRED" (MIS 5002550) co-financed by Greece and the EU

USE OF ^{1}H-NMR IN INVESTIGATION OF INCLUSION COMPLEXES WITH CYCLODEXTRINS

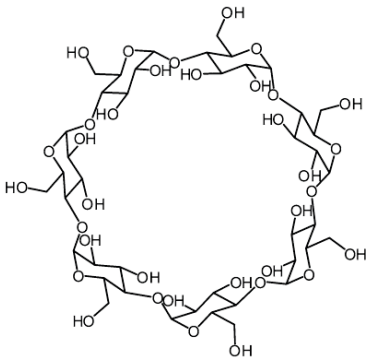
Mario Gabričević

Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, HR-10000 Zagreb, Croatia
mgabricevic@pharma.hr

The thermodynamics and stoichiometry of zaleplon (ZAL) complexation with different cyclodextrin derivatives [β-CD, hydroxypropyl-β-cyclodextrin (HP-β-CD), randomly methylated-β-cyclodextrin (RAMEB), sulphobutylether-β-cyclodextrin (SBE-β-CD)] in aqueous solution was studied by spectrofluorimetry and ^{1}H NMR spectroscopy in order to obtain a more general understanding of the driving forces behind the inclusion phenomena. Furthermore, thermodynamic parameters obtained by both techniques gave similar and negative values of ΔG for all complexes, indicating spontaneous inclusion of drug into CDs. From a thermodynamic point of view, two types of inclusions were determined. One is enthalpy driven ZAL complexation with β-CD, HP-β-CD and RAMEB, while the other is entropy driven complexation observed in the case of SBE-β-CD.



ZALEPLON



β-CD

BRUKER

Big performance, small package

The compact AVANCE NEO NanoBay extends the successful line of NEO consoles with dual-channel transmit & dual receive capabilities to routine 300 and 400 MHz NMR. With the novel NEO 'transceiver' architecture, each NMR channel in the AVANCE NEO is a functional spectrometer, enabling a new generation of multi-receive experiments. The small footprint NEO NanoBay supports a wide range of applications, including chemistry research and analysis, high-throughput screening for applied markets and quality control, and to structure verification in drug discovery.

For more information please visit: www.bruker.com/neo

NMR

Innovation with Integrity

SMART SCALE NMR

Francesca Benevelli,[a] Barbara Czarniecki,[b] Venita Decker,[c] Benjamin Goerling[c]

[a] Bruker Italia, via Lancetti 43, Milano, Italy
[b] Bruker Switzerland AG, Industriestrasse 26, Fällanden, Switzerland
[c] Bruker BioSpin GmbH, Silberstreifen, 76287 Rheinstetten, Germany
Francesca.Benevelli@bruker.com

Many novel NMR methods have been developed in the last years to allow extending the capabilities and the area of application of NMR. One of the main focus is to try to match the need of the scientists with a solution and in this direction stays the development of benchtop NMR system.

In this presentation we wish to show how NMR on a smart scale can provide useful answers both for traditional and novel application.

HIGH DIMENSIONALITY AND HIGH RESOLUTION NMR EXPERIMENTS FOR IDPS

Wiktor Koźmiński

Faculty of Chemistry, Biological and Chemical Research Centre, University of Warsaw, Warsaw, Żwirki i Wigury 101, 02-089 Warsaw, Poland
kozmin@chem.uw.edu.pl

Studies of biomolecular structure and dynamics by NMR spectroscopy at atomic resolution require acquisition of multidimensional spectra. However, the recording time of sufficiently resolved multidimensional spectra is often very long due to the sampling limitations. A variety of different methods, mostly based on non-uniform sampling, were proposed to overcome this limitation in multidimensional NMR spectroscopy. They could be utilized in two different ways, either to shorten the experiment duration without loss of resolution, or to perform experiments that are not obtainable conventionally, i.e. with significantly improved resolution and/or of high dimensionality. Most often first of these two, so called "Fast NMR" approach, is shown as the example of the utility of these methods, as it saves expensive spectrometer time. However, in many cases spectra which are not possible to record conventionally, featuring extraordinary resolution and high number of dimensions may be more interesting from scientific point of view as they reveal effects that are hidden, when spectral lines are broad, or enable resolving spectral ambiguities when peaks are overlapped. This second approach we refer to as "Accurate NMR". Its full potential is manifested when the overall experiment time is less important than a new information available from spectra of high dimensionality (4-6D) or of high resolution approaching natural line-width. The new methods were applied for NMR studies of intrinsically disordered proteins, where the structural disorder in combination with highly repetitive amino-acid sequences causes severe peak overlap in the spectra. Several novel 4-7D pulse sequences are proposed. The new experiments employ non-uniform sampling that enables achieving high resolution in indirectly detected dimensions.

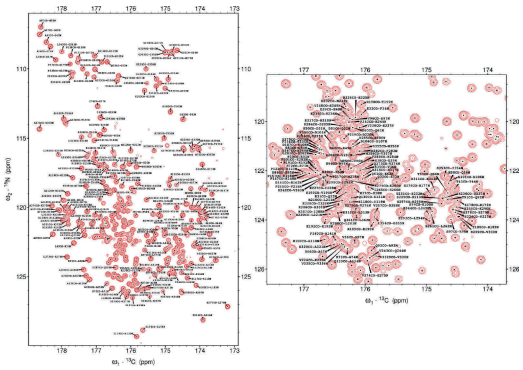


Figure 1. Resonance assignment of Tau3x (354 aa) shown on CON projection from 3D HNCO.[1]

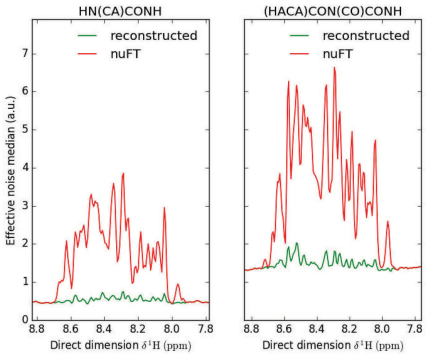


Figure 2 Noise median for 5D HN(CA)CONH (*left*) and 5D (HACA)CON(CO)CONH (*right*) SSA-reconstructed and nuFT spectra with respect to direct dimension δ^1H chemical shift.[2]

ACKNOWLEDGMENTS

Polish National Science Centre MAESTRO grant 2015/18/A/ST4/00270 is gratefully acknowledged.

REFERENCES

[1] S. Żerko, P. Byrski, P. Włodarczyk-Pruszyński, M. Górka, K. Ledolter, E. Masliah, R. Konrat, W. Koźmiński, J. Biomol. NMR. 65 (2016).
[2] K. Kosiński, J. Stanek, M.J. Górka, S. Żerko, W. Koźmiński, J. Biomol. NMR. 68 (2017) 129–138.
[3] K. Kazimierczuk, J. Stanek, A. Zawadzka-Kazimierczuk, W. Koźmiński, ChemPhysChem. 14 (2013) 3015–3025
[4] M. Nowakowski, S. Saxena, J. Stanek, S. Żerko, W. Koźmiński, Prog. Nucl. Magn. Reson. Spectrosc. 90–91 (2015) 49–73.

ULTRA Scientific is Now Agilent – and That's Good News for You

Ultra Scientific i Agilent od sada su jedno!
Sada možete na istom mjestu dobiti kvalitetne proizvode i stručne savjete iz svih područja rada u vašem laboratoriju – od kemijskih standarda, pripreme uzoraka, separacija, detekcije i analize, do savjeta i servisa.

Agilent ULTRA Chemical standardi vam pružaju:

- online pretragu, usporedbu i sve potrebne informacije za brzo i lako naručivanje
- brzu dostavu za 99.9% narudžbi koje se šalju unutar 48h
- personalizirana rješenja prema potrebama vašeg laboratorija
- pripremu uzoraka, kolone, potrošni materijal i dijelove, instrumentaciju i referentne materijale iz jednog izvora
- proizvode koji su rigorozno testirani i proizvedeni po ISO 9001, ISO 170252 te Guide 34 certifikatima

Sada su vaše kalibracije pouzdane s maksimalnom preciznošću.

Istražite naš novi portfolio!

Više od 7000 kemijskih standarda za vas na jednom mjestu.

Otkrijte kako možete iskoristiti široki izbor referentih materijala za analizu hrane, okoliša te elementarnu analizu.
Ovo je još jedan način na koji Agilent podupire vaš rad u laboratoriju u svakom dijelu procesa - od instrumenata, kolona, potrošnog materijala, do desetljeća aplikativnog iskustva.

www.agilent.com/chem/standards

ALPHACHROM

Science WITH CONFIDENCE

AlphaChrom d.o.o.
Karlovačka cesta 24, 10000 Zagreb
tel: +385 1 550 2200
www.alphachrom.hr

Agilent | Authorized Distributor

CARBOHYDRAZIDES AND DIHYDRAZONES: THE ASPECTS OF THEIR SOLID-STATE AND SOLUTION CHEMISTRY

Mirta Rubčić

Department of Chemistry, Faculty of Science, University of Zagreb,
Horvatovac 102a, 10000 Zagreb, Croatia
mirta@chem.pmf.hr

The hydrazone $R_1R_2C{=}N{-}NHR_3$ functional group is a universal building block, incorporated in a wide spectrum of organic and metal-organic compounds.[1] Its stability, acid-base behaviour, and structural modularity allow hydrazones to act as molecular switches, sensors, and/or as anion receptors.[2] On the other hand, the *E*/*Z* isomerization of hydrazones makes them suitable for the development of metal-organic architectures with stimuli-responsive properties.[3]

Within this large family of compounds especially intriguing are those derived from carbohydrazides and dihydrazides, as they allow the development of unsymmetrical or symmetrical derivatives. This in return offers a fruitful platform for the manipulation of the molecular geometry and conformation (*syn* or *anti*) of the material in a controllable way.

In this talk main synthetic approaches towards symmetrical and unsymmetrical carbohydrazides and dihydrazones will be considered. Selected examples of symmetrical and unsymmetrical carbohydrazides as well as dihydrazones will be given and discussed in terms of their solid-state and solution behaviour.[4,5]

ACKNOWLEDGMENTS
This work has been supported in part by the Croatian Science Foundation under the project IP-2016-06-4221.

REFERENCES

[1] L. A. Tatum, X. Su, I. Aprahamian, *Accounts Chem. Res.* **2014**, *47*, 2141.
[2] X. Su, I. Aprahamian, *Chem. Soc. Rev.* **2014**, *43*, 1963.
[3] M. Ruben, J.-M. Lehn, G. Vaughan, *Chem. Commun.* **2003**, 1338.
[4] M. Rubčić, N. Galić, I. Halasz, T. Jednačak, N. Judaš, J. Plavec, P. Šket, P. Novak, *Cryst. Growth Des.* **2014**, *14*, 2900.
[5] E. Topić, I. Landripet, M. Duguin, J. Pisk, I. Đilović, V. Vrdoljak and M. Rubčić, *New J. Chem.*, **2020**, *44*, 13357.

MELTING DOWN THE ICEBERG MODEL: HYDROPHOBIC CAVITIES AND (SWEETENED) ALCOHOLS

Andrea Usenik,[a,*] Katarina Leko,[a] Marko Hanževački,[b,c] Zlatko Brkljača,[b] Katarina Pičuljan,[a] Vesna Petrović Peroković,[a] Željka Car,[a] Rosana Ribić,[a,d] Josip Požar[a]

[a] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, 10000 Zagreb, Croatia
[b] Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia
[c] Department of Chemical and Environmental Engineering, The University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom
[d] University Center Varaždin, University North, Varaždin, Jurja Križanića 31b, 42000 Varaždin, Croatia
*ausenik@chem.pmf.hr

The temperature and solvent effect on the complexation of various guests (Figure 1) with α-, β- and γ-cyclodextrin and cucurbit[7]uril was explored experimentally and by means of molecular dynamics simulations. The stability constants of all investigated complexes were by far the highest with cucurbit[7]uril in water. A pronounced temperature dependence of $\Delta_r H°$ and $\Delta_r S°$, resulting in almost complete enthalpy-entropy compensation was observed solely in water. The complexation thermodynamics was in line with classical rationale of the hydrophobic effect at lower temperatures, and the non-classical explanation at higher ones. Unlike in water, the hosting in formamide and ethylene glycol could be attributed to non-classical solvophobic effect. The optimized inclusion complex structures corresponded to those deduced by means of NMR spectroscopy and the experimentally obtained and calculated $\Delta_r G°$ were in very good agreement. The carried out research bridged the gap between the classical and non-classical rationale of hydrophobic effect and demonstrated that solvophobically driven formation of inclusion complexes is not a water-limited phenomenon.[1,2] However, among explored structured solvents, water stood out as unique solvation and complexation medium.

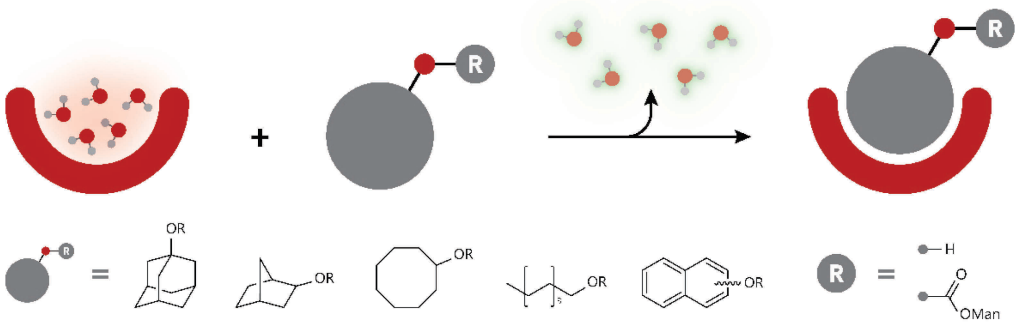


Figure 1. Schematic representation of the complexation process and guest structures

ACKNOWLEDGEMENTS
This research was fully supported by the Croatian Science Foundation (projects MacroSol; IP–2019–04–9560, SupraCAR; IP–2014–09–7309, PEPTGLYCOSAR; IP–2014–09–7899, CompSoLS–MolFlex; IP–2013–11–8238).

REFERENCES

[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*, 2−16.

Xellia Pharmaceuticals is a leading developer, manufacturer and supplier of life-saving anti-infectives. With over 100 years of industry experience in developing last resort treatments for infectious diseases, Xellia is focused on the supply of products which not only save lives, but also improve and enhance patients' quality of life. We are a specialty pharmaceutical company focused on fermented antibiotics and injectable finished products. Headquartered in Copenhagen, Denmark, and owned by Novo A/S, we are more than 1700 employees globally. From state-of-the-art manufacturing sites in the U.S, China, Denmark and Hungary to R&D sites in Norway and Croatia; Xellia Pharmaceuticals excels within innovative product development to deliver high quality products.

SOLID-STATE NMR: FROM MAIN CONCEPTS TO APPLICATIONS

Marco Geppi

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via G. Moruzzi 13, 56124 Pisa, Italy
marco.geppi@unipi.it

In this lecture the main concepts allowing to understand the applications of NMR to solid phases will be first presented. In particular, the anisotropic nature of all the internal nuclear interactions will be introduced, clarifying why they cause severe linebroadening in the spectra of solid powders. Inhomogeneous and homogeneous linebroadening mechanisms will be discussed with particular attention to the information that they potentially contain and the techniques that can be used to remove them. The different theoretical approaches used to describe solid state and solution state NMR, as well as the different effects of nuclear interactions on the spectra of solids and solutions will be discussed in detail.

Afterwards, the complementary approaches used to study solids by NMR will be presented: low- and high-resolution 1D techniques, and 2D experiments. Particular attention will be dedicated to the high-resolution solid state NMR techniques (Magic Angle Spinning, Cross Polarization, High Power Decoupling) and to their implementation on NMR spectrometers, discussing the state of the art of the instrumentation dedicated to solids.

Nuclear relaxation properties peculiar of solids and the important phenomenon of spin diffusion will be also dealt with.

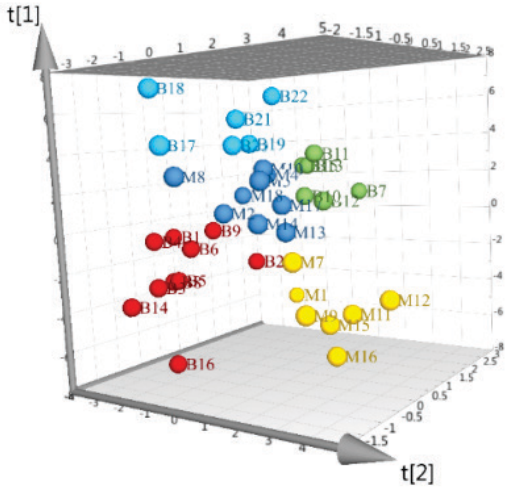
Examples of applications of solid state NMR spectroscopy to different classes of materials, ranging from pharmaceuticals to polymers, will be shown, highlighting the main structural and dynamic information that can be derived.

NMR METABOLOMICS – PLANTS, HONEY AND WINE

Svetlana Simova, Dessislava Gerginova, Yavor Mitrev, Kalina Alipieva

Bulgarian NMR Centre, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bontchev Str. Bl 9, 1113 Sofia, Bulgaria
*sds@orgchm.bas.bg

Metabolomics approach has as objective a comprehensive analysis of the set of metabolites, which are the final products of biochemical processes and a result of environmental and genetic interactions in a given biological system. It allows detailed investigation of qualitative and quantitative characteristics of complex chemical and biological samples.[1] The resulting NMR data provide a wealth of information about the samples.



Some of the challenges, problems, and advantages of extracting quantitative information from NMR data by chemometric methods will be presented. Examples of NMR spectra of wine, honey and plant extract will be discussed and will illustrate the potential of the combination of NMR and chemometrics for chemical profiling and biomarker identification.

ACKNOWLEDGMENTS
The financial support of the Bulgarian National Science Fund (UNA-17/2005, DRNF-02-13/2009) and Ministry of Education and Science - Bulgaria (INFRAMAT project, contracts D01-155 and D01-284) is gratefully acknowledged.

REFERENCES
[1] P. Ebrahimi, N. Viereck, R. Bro, S. Engelsen, *Modern Magnetic Resonance* **2018**, 1649.

PALLADIUM-MEDIATED REGIOSELECTIVE C–H BOND HALOGENATION OF AZOBENZENE SUBSTRATES BY MECHANOCHEMISTRY

Dajana Barišić* and Manda Ćurić

Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia
*Dajana.Barisic@irb.hr

Development of methods for the direct and selective replacement of inert C–H bond by C–X, C–N, C–S, C–O, or C–C bonds is of immense importance for organic synthesis.[1a] The transition metal-catalyzed direct transformations of inactive C–H bond into other functional groups has emerged as a superior approach, which significantly simplifies the synthesis and reduces the generation of byproducts.[1b] Currently, these processes still rely predominantly on solvent-based protocols. During the past decade, chemical transformations in the solid-state have become increasingly popular among chemists due to the unique benefits which the solid-state methods provide in terms of sustainability, reaction times, yields, solubility, selectivity, and chemical reactivity.[1c]

As a continuation of our previous comparative mechanistic study of the mechano-chemical C–H bond activation in an unsymmetrical azobenzene by common Pd(II) catalysts,[2] here we present results for palladium-mediated regioselective mechano-chemical C–H bond halogenation of azobenzene and its substrates containing electron-donating and electron-withdrawing groups in 4,4'-positions of azobenzene. Careful selection of liquid and/or solid additives can direct the reaction towards different halogenated products which depend on the electronic properties of substituents, and utilization of *ex situ* ^{1}H NMR spectroscopy provided detailed insight into the monitored reactions and revealed possible intermediates.

ACKNOWLEDGMENTS
This work has been supported by Croatian Science Foundation under the project IP- 2019-04-9951 (MECHEMFUN).

REFERENCES

[1] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.; b) P. Gandeepan, L. Ackermann, *Chem*. **2018**, 199.; c) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs et al., *Chem. Rev.* **2012**, *41*, 413.
[2] A. Bjelopetrović, S. Lukin, I. Halasz, K. Užarević, I. Đilović, D. Barišić, A. Budimir, M. Juribašić Kulcsár, M. Ćurić, *Chem. - A Eur. J.* **2018**, *24*, 10672.

USE OF NMR IN BIODIESEL SYNTHESIS

Fabio Faraguna

Faculty of Chemical Engineering and Technology, University of Zagreb, Marulićev trg 19, Zagreb, Croatia
ffaragun@fkit.hr

The oil industry is increasingly preoccupied with the topic of biofuels, due to the regulatory and general social pressures. In 2016, the share of the transport sector in the total emissions of greenhouse gases in the European Union (EU) was 27%, of which nearly 72% is from the road transport. To reduce the impact of the transport sector on the global warming and climate changes, the EU targets prescribe the reduction of greenhouse gas emissions by 30% by 2030 compared to the level in 2005. Therefore, it is necessary to use non-fossil fuels and biofuels are currently being considered as the most plausible alternative fuel. One of the most commonly used biofuels in the transport sector is biodiesel. It can be used as a pure biodiesel (B100) in internal combustion engines, but it is commonly used as a blend with diesel fuel (up to 7 vol%). The cost of raw materials contributes the most in the total price of biofuels, so the use of waste oils and animal fats as a starting material is highly desirable. The main advantage of the aforementioned raw materials is that their use reduces waste from one industry and turns it into the raw material (profit) for the other, which reduces the expenses.

In our studies we synthesize alternative biodiesels from different feedstock (fresh and used oil) and study the influence of reaction parameters on reaction conversion to determine optimal conditions for their synthesis. We employ 1H NMR as a fast and versatile technique to determine the conversion and initial purity of synthetized biodiesels. In this lecture results form our studies with an emphasis on 1H NMR analysis will be presented.

ACKNOWLEDGMENTS
The research was funded by “Development of functional biofuels and (bio)additives and characterization of blends with mineral fuels” (FunBioFA, UIP-2019-04-5242), Croatian Science Foundation.

NMR METABOLOMICS INSIGHT INTO PHYTOCHEMISTRY

Boban Anđelković,[a]* Ivana Sofrenić,[b] Iris Đorđević,[c] Stefan Ivanović,[b] Mirjana Cvetković,[b]Dejan Gođevac,[b] Slobodan Milosavljević[a,d]

[a] Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia
[b] Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia
[c] Faculty of Veterinary Medicine, University of Belgrade, Bulevar oslobođenja 18, 11000 Belgrade, Serbia
[d] Serbian Academy of Sciences and Arts, Knez Mihailova 35, 11000 Belgrade, Serbia
*aboban@chem.bg.ac.rs

Metabolomics has emerged in recent years as an indispensable tool for the analysis of thousands of metabolites from crude natural extracts, leading to a paradigm shift in natural products drug research. Many of the technologies used in metabolomics have method-specific advantages and drawbacks in terms of diversity of metabolites detected, sensitivity, or resolution.

We will describe the use of metabolomic methods for:

- Correlation of propolis composition to altitude of collection and revealing its major botanical origin.
- revealing cytotoxic metabolites from *Mahonia aquifolium* stem-bark
- application for differentiation of the ambiguous taxonomy of the genus *Amphoricarpos* Vis.

In order to correlate variability in *Populus* type propolis composition with the altitude of its collection, NMR spectroscopy followed by OPLS was conducted. The botanical origin of propolis was established by comparing propolis spectral data to those of buds of various Populus species. An O2PLS method was utilized to integrate two blocks of data. The utilization of various NMR experiments, in combination with sophisticated multivariate analysis methods, was demonstrated to be a powerful tool to correlate propolis composition to altitude of collection and reveal its major botanical origin. OPLS methods were used to identify changes in the chemical composition of propolis, while O2PLS methods enabled the identification of the botanical origin of propolis.[1]

A ^{1}H NMR-based metabolomics method was used to reveal cytotoxic metabolites from *Mahonia aquifolium* stem-bark. Primary and secondary metabolites in the *Mahonia aquifolium* extracts were identified by thorough analysis of ^{1}H and 2D NMR spectra, without prior isolation. An OPLS multivariate analysis method was used to correlate the chemical composition of the plant extracts with the results of cytotoxic activity against Human cervical adenocarcinoma cell line.[2]

Metabolomic methods were used to get more insight into the ambiguous taxonomy of the genus *Amphoricarpos* Vis. The ^{1}H NMR spectroscopy combined with multivariate data analysis has been applied. OPLS-DA has been shown to be the best method for clear discrimination of these samples based on the metabolites present in the extracts. ^{1}H NMR fingerprinting in combination with PCA and OPLS-DA showed a clear separation between the species resulting in two groups according to metabolomic similarities.[3]

ACKNOWLEDGMENTS

This study's were financially supported by the Serbian Ministry of Education and Science, Project No. 172053. The authors thank Dr. Vele Tešević, Faculty of Chemistry, University of Belgrade and Dr Vlatka Vajs, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, for support and consulting.

REFERENCES

[1] B. Anđelković, Lj. Vujisić, I. Vucković, V. Tešević, V. Vajs, D. Gođevac, *J Pharmaceut Biomed*, **2017**, *135*, 217–226.
[2] D. Godjevac, A. Damjanovic, T. Stanojkovic, B. Andjelkovic, G. Zdunic, *J Pharmaceut Biomed*, **2018,** *150*, 9–14.
[3] M. Cvetkovic, B. Andjelkovic, V. Stevanovic, M. Jadranin, I. Djordjevic, V. Tesevic, S. Milosavljevic, D. Godjevac, *Phytochem Lett*, **2018,** *25*, 1–5.

^{13}C SOLID-STATE NMR STUDY OF POLYPHTHALAMIDES FOR USE IN AUTOMOTIVE INDUSTRY

Mirna Petković Didović,[a,*] Cédric Lorthioir,[b] Paul Sotta[c]

[a] Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Faculty of Medicine, University of Rijeka, Braće Branchetta 20, 51000 Rijeka, Croatia
[b] Equipe Systèmes Polymères Complexes, Institut de Chimie et des Matériaux Paris-Est, UMR 7182 CNRS / Université Paris Est Créteil, 2-8 rue Henri Dunant, 94320 Thiais, France
[c] Solvay Axel'one, Laboratoire Polymères et Matériaux Avancés, 87 Rue Frères Perret, F-69192 St Fons, France
*mirnapd@uniri.hr

Polyphthalamides (PPA) are a subgroup of polyamides in which a portion of aliphatic segments of the polymer backbone is substituted by aromatic moieties. The substitution results in an increase of melting point, glass transition temperature, thermal stability, oil and antifreeze resistance, etc., making PPAs very successful as a metal replacement for automotive components. Depending on the type and amount of aromatic species used, PPAs can be amorphous or semi-crystalline. This research was focused on representatives of both categories. An amorphous sample PA66/6I was investigated using ^{13}C chemical shift anisotropy, ^{13}C T_2, and ^{1}H-^{13}C dipolar coupling measurements both in dry and wet state, in order to determine molecular origins of relaxation processes. This was of interest due to the extreme sensitivity of the material to moisture, i.e., a dramatic decrease of glass transition temperature upon water sorption [1]. On the other hand, semi-crystalline sample PA66/6T was investigated in regard to the phenomenon of co-crystallization. Traditionally, the ability of two copolymer components to co-crystallize is determined via melting point variations with copolymer composition [2]. This approach requires an array of samples with varying compositions, which is seldom obtainable. Here we show how solid-state NMR can provide several approaches to give required answers using a single sample.

REFERENCES

[1] M. Laurati, P. Sotta, D. R. Long, et al., *Macromolecules* **2012**, *45*, 1676.
[2] T. F. Novitsky, C. A. Lange, L. J. Mathias, et al., *Polymer* **2010**, *51*, 2417.

NATURAL PRODUCTS FROM FLORA, FAUNA AND FUNGI: NMR PERSPECTIVE

Ljubodrag Vujisić

Faculty of Chemistry, University of Belgrade, Serbia
ljubaw@chem.bg.ac.rs

DESIGN, SYNTHESIS AND CHARACTERIZATION OF MACROZONES, NEW ANTIMICROBIAL THIOSEMICARBAZONE-BASED AZITHROMYCIN CONJUGATES

Mirjana Bukvić

Fidelta Ltd., Zagreb, Croatia
Mirjana.Bukvic@fidelta.eu

In spite of a numerous existing macrolide antibiotics, such as azithromycin, the emerging multi-drug resistant microbial pathogens present serious and challenging problems in medical treatment which demand novel and more effective antimicrobial agents to be discovered. Unfortunately, the number of newly marketed antibiotics has decreased dramatically in recent years. Withdrawal of the macrolide antibiotic telithromycin has prompted our efforts to search for new anti-infective macrolide compounds. Design, synthesis, structure characterization by 1D and 2D NMR techniques and biological evaluation of a novel hybrid class of azithromycin conjugates, the macrozones, are presented. Evaluation of prepared compounds against a panel of pathogenic bacteria revealed that these molecules showed excellent activities against susceptible S. pneumoniae, S. pyogenes and E.faecalis strains, comparable to or better than azithromycin. Furthermore, prepared macrozones exhibited excellent activity against efflux resistant S.pneumoniae, 32 times better than that of azithromycin, and very good activity against efflux resistant S. aureus strain against which azithromycin is inactive. The results described here can serve as a good basis to guide further activities directed toward the discovery of more potent macrolide anti-infectives.

POSTERS

Fidelta
A Galápagos Company

Fidelta is your preclinical integrated drug discovery partner.

We offer a full range of in house capabilities including medicinal chemistry, pharmacology, ADME, pharmacokinetics and toxicology (AAALAC and OLAW accredited). We have expertise in inflammation, respiratory, infection, CNS and oncology. Our integrated drug discovery is driven by our determination to deliver efficacious, safe and differentiated preclinical candidates and a strong history with translational science, focusing on patients and disease-relevant test models and systems.

www.fidelta.eu

Automatsko doziranje

Quantos

Automatsko doziranje praha i tekućina

Smanjite broj pogrešaka pripremom savršene koncentracije. Poboljšajte sigurnost i uštedite vrijeme i novac. Dostupna razlučivost: 0,1 mg, 0,01 mg, 5 µg, 1 µg.

- Sigurno i točno doziranje
- Isplativost
- Automatsko dispenziranje praha
- Automatsko dispenziranje tekućina
- Kompaktnost i modularnost
- Jednostavno korištenje

▶Za više informacija: **www.mt.com/quantos**

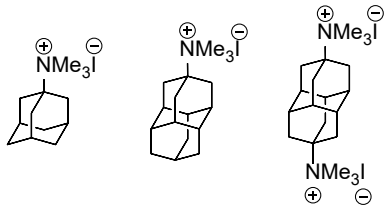
METTLER TOLEDO

SYNTHESIS AND BINDING OF PERMETHYLATED DIAMONDOID AMMONIUM SALTS

Marija Alešković,[a] Ruža Jozepović,[a] Sunčica Roca,[b] Nikola Bregović,[c] Marina Šekutor[a]

[a] Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia
[b] NMR Center, Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, Croatia
[c] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, 10000 Zagreb, Croatia
*marija.aleskovic@irb.hr

Supramolecular complexes are stabilized by non-covalent interactions between the host and the guest molecule. Molecular recognition studies can give insight into many processes occurring in nature and prove useful for technological applications.[1] It was recently demonstrated that functionalized adamantane and diamantane ammonium salts are suitable guests for cucurbituril hosts. Moreover, some diamantane derivatives are capable of extremely tight binding with cucurbiturils in water, forming complexes with attomolar dissociation constants.[2] Such ultrastable complexes rival the strength of binding processes acting in biomolecular receptors (*e.g.*, avidin-biotin).



As a continuation of our research, we explored complexation of selected adamantane and diamantane ammonium salts with cyclodextrin host molecules. The binding strength was assessed as a function of diamondoid salt size, functional group position and cyclodextrin cavity size. By changing these parameters, a structure-selectivity relationship can be determined and next generation of guests proposed. Various NMR spectroscopic techniques and ITC measurements were employed to determine the stability constants and explore host-guest interactions. Computation methods were used to gain further insight into structural features of formed complexes and to better understand the factors governing their stabilities.

ACKNOWLEDGMENTS

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

REFERENCES

[1] J. W. Steed, J. L. Atwood, Supramolecular Chemistry, Wiley-VCH, New York, **2009**.
[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.

ISOLATION AND STRUCTURAL CHARACTERIZATION OF 9a- AND 4''- TETRAHYDROFURFURYL MACROZONE REACTION MIXTURE COMPONENTS USING THE LC-SPE/NMR

Lucia Ema Sekula,[a] Iva Habinovec,[a,*] Ivana Mikulandra,[a] Jana Gašperov,[a] Predrag Novak,[a] Ivan Grgičević,[a] Mirjana Bukvić

[a] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, Zagreb, Croatia
[b] Fidelta d.o.o., Prilaz baruna Filipovića 29, Zagreb, Croatia
*ihabinovec@chem.pmf.hr

Due to a global problem of growing bacterial resistance, discovery of new antibiotics is of an outmost importance and various studies are in progress to overcome the resistance mechanisms.[1–3] Macrozones are novel bioactive conjugates of azithromycin and thiosemicarbazides that posses very good *in vitro* antibacterial activity against selected Gram-positive and Gram-negative bacteria.[4] Efficient and rapid purification and isolation of newly synthesized bioactive compounds is a crucial step prior to biological evaluation. Furthermore, isolation and identification of impurities is very important procedure during the drug development in pharmaceutical industry. Preparative and semipreparative HPLC techniques are classical purification methods, but they can be time and solvent consuming. In this study we have successfully used hyphenated LC-SPE/NMR approach for the isolation and structural characterization of main components and some impurities in 9a- and 4''-tetrahydrofurfuryl macrozone reaction mixtures. Structures of the isolated compounds were proposed on the basis of the analysed one- and two-dimensional NMR spectra and MS spectra, respectively.

ACKNOWLEDGMENTS
This work was supported by Croatian Science Foundation under the project IP-2018-01.8098.

REFERENCES

[1] M. Bukvić Krajačić, M. Dumić, P. Novak, M. Cindrić, S. Koštrun, A. Fajdetić, S. Alihodžić, K. Brajša and N. Kujundžić, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 853–856.
[2] Z. Zao, L. Jin, Y. Xu, D. Zhu, Y. Liu, C. Liu, P. Lei, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 480–484.
[3] B. Arsić, P. Novak, M. G. Rimoli, J. Barber, G. Kragol and F. Sodano, *Macrolides: Properties, Synthesis and Applications*, De Gruyter, Berlin, **2018**.
[4] P. Novak, I. Grgičević, I. Mikulandra, M. Bukvić, M. Banjanac, V. Radovanović, I. Habinovec, B. Bertoša, *Int. J. Antimicrob. Agents* **2020**, accepted for publishing.

STRUCTURAL STUDIES OF SUBSTITUTED OXAZOLIDINONES BY SPECTROSCOPIC AND QUANTUM CHEMICAL METHODS

Tomislav Jednačak,[a,*] Maja Majerić Elenkov,[b] Tomica Hrenar,[a] Karlo Sović,[a,*] Jelena Parlov Vuković,[c] Predrag Novak [a]

[a] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, HR-10000 Zagreb, Croatia
[b] Ruđer Bošković Institute, Bijenička cesta 54, HR-10000 Zagreb, Croatia
[c] Central testing laboratory, Refining & marketing business division, INA-Industrija nafte d.d., Lovinčićeva 4, HR-10000 Zagreb, Croatia
*tjednacak@chem.pmf.hr; karlo.sovic@chem.pmf.hr

Oxazolidinones belong to an important class of aliphatic heterocycles with interesting biological properties, such as antimicrobial, psychotropic, anticoagulant, anticancer, fungicidal and antithyroid activities.[1,2] Their solution- and solid-state structures are stabilized by intermolecular hydrogen bonds through NH and carboxyl moieties, which act as hydrogen bond donors and acceptors, respectively. Obtaining a detailed insight into the structure and dynamics of these interactions is a major prerequisite for the design of new drugs with enhanced biological properties.

In this research we applied a combination of 1D and 2D NMR techniques, vibrational spectroscopy and quantum chemical calculations to study the structure and hydrogen bonding of bioactive oxazolidinones. It has been observed that in low polarity solvents, such as chloroform, dimers are formed presumably by intermolecular hydrogen bonds between oxazolidinone molecules forming the most stable complexes, which has also been found in the solid state (Figure 1a). In more polar solvents, like dimethylsulfoxide and methanol, intermolecular interactions with solvent molecules prevail. Changing the solution concentration considerably affected oxazolidinone resonances only in chloroform, further confirming the dimer formation (Figure 1b).

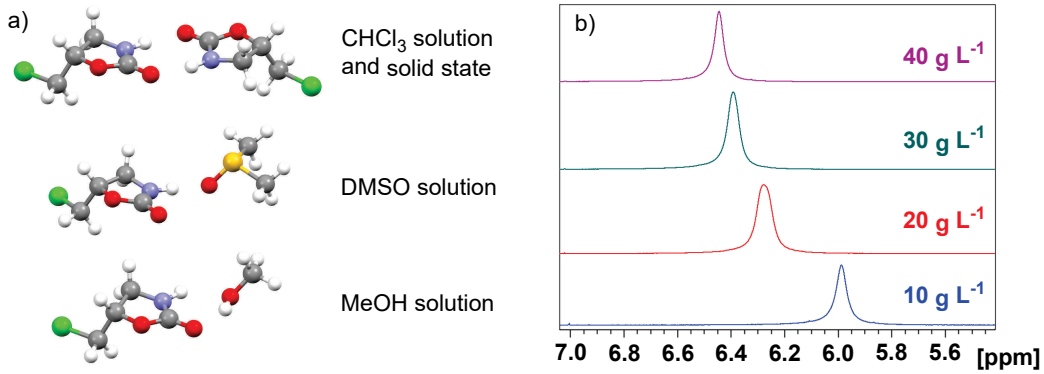


Figure 1. a) The most stable complexes of 5-chloromethyl-oxazolidin-2-one and b) concentration dependence of its amide proton signal in chloroform-d.

ACKNOWLEDGMENTS
This research was funded by HRZZ, grant number IP-2016-06-3775 "ADESIRE".

REFERENCES

[1] N. Pandit, R. K. Singla, B. Shrivastava, *Int. J. Med. Chem.* **2011**, *2012*, 1.
[2] B. Das, A. V. S. Rajarao, S. Rudra, A. Yadav, A. Ray, M. Pandya, A. Rattan, A. Mehta, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6424.

DISSOLUTION KINETICS OF COPPER NANOPARTICLES IN MODEL PHYSIOLOGICAL FLUIDS AND DYNAMICS OF COPPER(II) COMPLEXES WITH CHIRAL AMINO ACIDS

Lara Jurković,[a] Ivana Hazdovac,[a] Nadica Maltar-Strmečki,[b,*] Daniel Mark Lyons[a,*]

[a] Center for Marine Research, Ruđer Bošković Institute, G. Paliage 5, 52210 Rovinj, Croatia
[b] Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia
*nstrm@irb.hr; lyons@irb.hr

Metallic nanoparticles have attracted huge attention in biomedical applications due to their unique size-dependent properties, in particular copper nanoparticles because of their anti-bacterial, anti-fungal, anti-inflammatory and anti-proliferative properties.[1] However, the potential for interactions with non-targeted healthy cells, especially as copper nanoparticles may undergo a range of chemical transformations in the body, represents a still unresolved issue. In particular, the quantity and rate of copper nanoparticle dissolution in bodily fluids and tissue, with release of ionic Cu^{2+}, may represent a key step in the pharmacokinetics and potential toxicity of such nanomaterials. Thus, we report herein an analysis of the physicochemical properties and dissolution kinetics of copper nanoparticles in saline solution in the presence of bovine serum albumin as a simplified model for blood plasma. Further, as copper(II) complexes with amino acids serve as models for metalloproteins and transport in a wide range of important biological processes, we have subsequently investigated the nanoparticle-released Cu^{2+} in terms of the dynamical behavior of copper(II) bis-complexes with selected chiral amino acids (nonpolar, polar and electrically charged). The complexes were studied by electron paramagnetic resonance (EPR) spectroscopy with the presence of the *cis* and *trans* isomers determined for both L- and D- enantiomers.[2] The influence of this chirality on the rotational motion of the Cu(II)-amino acid complexes was also examined. These results will help in resolving transformation pathways, behaviour and safety of metallic nanoparticles in physiological fluids as their application in biomedicine becomes more widespread.

ACKNOWLEDGMENTS
This work has been supported by the Croatian Science Foundation [project numbers HRZZ-IP-2018-01-5351 and HRZZ-IP-2013-11-1108].

REFERENCES
[1] E. G. Halevas, A. A. Pantazaki, *Nanomed. Nanotechnol. J.* **2018**, *2*, 119.
[2] M. S. Bukharov *et. al.*, *Phys. Chem. Chem. Phys.* **2014**, *16*, 9411.

SYNTHESIS, STRUCTURE CHARACTERIZATION AND INTERACTIONS OF 4"-AMINOPROPYL DERIVATIVE OF AZITHROMYCIN

Jana Gašperov,[a] Ivana Mikulandra,[a] Tomislav Jednačak,[a] Branimir Bertoša,[a] Iva Habinovec,[a] Predrag Novak[a]

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

*ivana.mikulandra@chem.pmf.hr

Azithromycin belongs to macrolide class of antibiotics which exert its biological activity by binding to bacterial ribosome at or near the peptidyl transferase center thus inhibiting protein biosynthesis. They are effective in treating infections caused by Gram-positive and some Gram-negative bacteria. Due to the increased development of bacterial resistance much effort is directed towards the discovery of new more potent antibiotics. A series of bioactive azithromycin derivatives, the new class of macrozones have been prepared by coupling thiosemicarbazones to azithromycin at position 4" (Figure 1). Here we present their synthesis, characterization and interactions of macrozone precursor, 4"-aminopropyl azithromycin with the ribosome isolated from *E. Coli*. A combination of NMR experiments such as saturation transfer difference (STD) and transferred nuclear Overhauser effect spectroscopy (trNOESY) and molecular modeling were applied to determine binding epitopes and explore bound conformations.

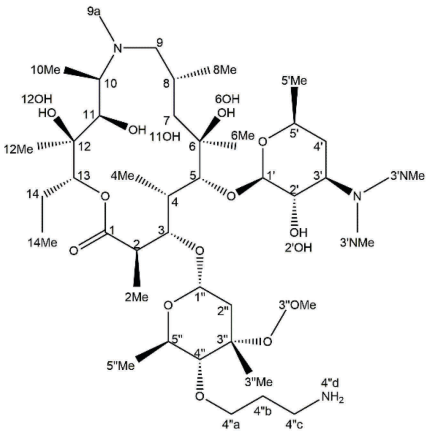


Figure 1. Structure of 4"-aminopropyl azithromycin.

ACKNOWLEDGMENTS

This work has been supported by Croatian Science Foundation under the project IP-2018-01-8098.

REFERENCES

[1] B. Arsić, P. Novak, J. Barber, M. G. Rimoli, G. Kragol, F. Sodano, *Macrolides: properties, synthesis and applications*, Walter de Gruyter, Berlin/Boston, **2018**.

SYNTHESIS OF PHENANTHRIDINE-BASED CALIX[4]ARENE GLYCOCONJUGATE AND PHYSICOCHEMICAL CHARACTERIZATION OF ITS COMPLEXATION REACTIONS WITH ALKALI METAL CATIONS

Matija Modrušan,* Nikola Cindro, Katarina Leko, Vladislav Tomišić

Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, Zagreb, Croatia
*mmodrusan@chem.pmf.hr

Calixarenes are a class of supramolecular hosts consisted of phenolic residues linked by methylene bridges in the *ortho* position.[1] They can be easily functionalized to give receptors for various ionic and/or neutral species. Calixarene amide derivatives have very high affinities towards alkali metal cations,[2,3] and can be glycosylated to produce water-soluble compounds.[4] In the scope of this work, fluorescent, phenanthridine-based calix[4]arene glycoconjugate (Figure 1) was synthesized. The affinity of this ligand towards alkali metal cations was investigated by means of spectrophotometry, fluorimetry, microcalorimetry, and ^{1}H NMR spectroscopy. From the obtained results, stability constants of the complexes formed, as well as the corresponding standard Gibbs energies, enthalpies and entropies were calculated and discussed.

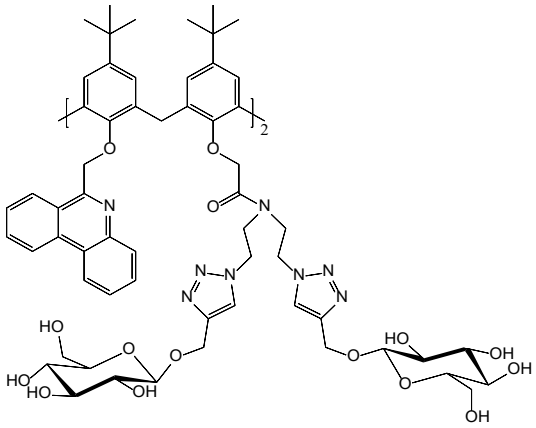


Figure 1. Structure of phenanthridine-based calix[4]arene glycoconjugate.

ACKNOWLEDGMENTS
This research was fully supported by the Croatian Science Foundation (project MacroSol, IP-2019-04-9560).

REFERENCES

[1] C. D. Gutsche, Calixarenes: An Introduction, 2nd edition, The Royal Society of Chemistry, Cambridge, **2008**.
[2] G. Horvat, L. Frkanec, N. Cindro, V. Tomišić, *Phys. Chem. Chem. Phys.* **2017**, *19*, 24316–24329.
[3] K. Leko, N. Bregović, M. Cvetnić, N. Cindro, M. Tranfić Bakić, J. Požar, V. Tomišić, *Croat. Chem. Acta* **2017**, *90*, 307–314.
[4] N. Cindro, J. Požar, D. Barišić, N. Bregović, K. Pičuljan, R. Tomaš, L. Frkanec, V. Tomišić, *Org. Biomol. Chem.* **2018**, *16*, 904–912.

SOLID-STATE AND SOLUTION BEHAVIOUR OF ARYL DIHYDRAZONES

Edi Topić,[a,*] Katarina Pičuljan,[a] Višnja Vrdoljak,[a] Mirta Rubčić[a]

[a] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, 10000 Zagreb, Croatia
*etopic@chem.pmf.hr

Hydrazones serve as a valuable platform for exploring fundamental aspects of soft material engineering, owing to their straightforward preparation and chemical robustness.[1] Naturally, insight into their behaviour propels the development of novel chemosensors, biologically active materials and catalysts.[2] Dihydrazones, while seldom explored, offer a plethora of compelling chemical and structural scenarios.[3]

Within this study, aryl dihydrazones derived from succinic and adipic acid dihydrazide were synthesized and thoroughly investigated in the solid-state and solution. The potential of the prepared ligands for the development of coordination polymers based on molybdenum(VI) species was investigated under various reaction conditions. The isolated compounds were characterized in the solid-state and solution by appropriate spectroscopic and diffraction methods and compared with the relevant data for neutral dihydrazones. The results unveil that while neutral dihydrazones demonstrate substantial conformational flexibility in solution, crystallization or chelation effectively lodges the dihydrazone framework in a robust *anti* conformation.

ACKNOWLEDGMENTS
This work has been fully supported by the Croatian Science Foundation under the project IP-2016-06-4221.

REFERENCES
[1] E. Topić, I. Landripet, M. Duguin, J. Pisk, I. Đilović, V. Vrdoljak and M. Rubčić, *New J. Chem.* **2020**, *44*, 13357.
[2] X. Su, I. Aprahamian, *Chem. Soc. Rev.* **2014**, *43*, 1963.
[3] S. D. Kurbah, A. Kumar, S. Shangpung, I. Syiemlieh, I. Khongjoh, R. A. Lal, *Z. Anorg. Allg. Chem.* **2017**, *643*, 794.

CHARACTERIZATION OF *CINCHONA* ALKALOIDS WITH NMR SPECTROSCOPY

Alma Ramić,* Ines Primožič, Tomica Hrenar

Department of Chemistry, Faculty of Science, University of Zagreb, Zagreb, Croatia
* aramic@chem.pmf.hr

Cinchona alkaloids are natural products isolated from the bark of the *Cinchona* tree and alkaloids isolated on industrial scale are quinine, quinidine, cinchonine and cinchonidine. They have interesting structure which includes bicyclic aliphatic quinuclidine ring and aromatic quinoline ring connected with a chiral carbon atom having hydroxyl group.[1] These alkaloids have diverse chemical applications, for example they are used as chiral resolving agents or chiral stationary phases for chromatographic separations as well as chiral catalysts or chiral ligands in asymmetric synthesis.[2,3] In this study, transfer hydrogenation of cinchonidine and cinchonine over a palladium on carbon catalyst using formic acid/ammonium formate as hydrogen donor was studied and the course of reaction was monitored by ^{1}H NMR spectroscopy. Since the peaks of NMR spectra of cinchona alkaloids are found in three distinct regions (aromatic, olefinic and aliphatic), monitoring of reaction was convenient to realize with ^{1}H NMR spectroscopy. The structure of products of hydrogenation reactions was completely verified with 2D NMR spectroscopy techniques such as COSY, HSQC and HMBC and compared with unmodified alkaloids.

ACKNOWLEDGMENTS
Supported by the Croatian Science Foundation, Project No. IP-2016-06-3775 ADESIRE.

REFERENCES

[1] Kacprzak, K. M., *Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes* **2013**, 605.
[2] Ilisz, I., Bajtai, A., Lindner, W. & Péter, A., *Journal of Pharmaceutical and Biomedical Analysis* **2018**, *159*, 127.
[3] Wang, H., *Catalysts* **2019**, *9*, 244.

INA

Više od pola stoljeća iskustva u naftnom i plinskom poslovanju širom svijeta.



AUTHORS AND PARTICIPANTS

AUTHORS

PARTICIPANTS

Alešković, Marija
Barišić, Dajana
Bobanac Marjanović, Marina
Bregović, Nikola
Bukvić, Mirjana
Cindro, Nikola
Faraguna, Fabio
Gabričević, Mario
Gašperov, Jana
Guzan, Zvonimir
Habinovec, Iva
Hošnjak, Ema
Jednačak, Tomislav
Jurković, Lara
Ladavac, Mila
Mikulandra, Ivana
Modrušan, Matija
Namjesnik, Danijel
Novak, Predrag
Parlov Vuković, Jelena
Petković Didović, Mirna
Pičuljan, Katarina
Pupić-Bakrač, Mirko
Ramić, Alma
Ripamonti, Angelo
Rubčić, Mirta
Sekula, Lucia Ema
Šeler Namjesnik, Martina
Tomišić, Vladislav
Topić, Edi
Usenik, Andrea
Vikić-Topić, Dražen

ADRIATIC NMR

September 22–24, 2020, Peroj, Croatia

ISBN 978-953-6076-58-1