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Book of Abstracts

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Foreword

The 3rd European NECTAR Conference is a three-days meeting, held in Ljubljana, organized within the activities of COST Action CA18202 (NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research).

After the success of the 1st and 2nd editions, held in Belgrade and Lisbon, respectively, we decided to go on with the format of our annual NECTAR meeting, joining the Management Committee (MC), Core Group (CG) and Working Group (WG) meetings, together with a classical conference. This format allows NECTAR's WG members and other eminent scientists to share and disseminate latest results within the scopes of our COST Action while, simultaneously, discussing about the management and development of the Action itself.

The growing interest in NECTAR Activities and the results achieved by the Action, together with the high level of scientific discussion, made the European NECTAR Conference, in just three editions, a reference Conference for the most valuable European research groups working in the fields of Equilibria and Chemical Thermodynamics at all levels. This year's edition is particularly intense, registering the participation of researchers from academy, research centers and industrial stakeholders, with about one hundred of attendees coming from 22 different Countries, who contribute with 4 keynote lectures, 15 oral communications and 31 posters. Worth of mention is the significant involvement of early-stage researchers and attendants from International Target Countries (ITC).

This book collects the abstracts of the communications from attendees, hoping that it can serve as stimulus for fruitful scientific discussion and future collaborations.

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3rd NECTAR Conference Programme					
August 24th, Wed		August 25th, Thu		August 26th, Fri	
		8:30 - 9:00	Registration	8:30 - 9:00	Registration
		9:00 - 9:30	KN2 (WG4) P. VIKEGARD	9:00 - 9:45	SO/AO Communications
		9:30 - 9:50	OC6 S. BERTO	9:45 - 10:30	Individual WGs Meetings
		9:50 - 10:10	OC7 J. KLADNIK		
		10:10 - 10:30	OC8 T. BOROVIĆ		
		10:30 - 11:00	Coffee Break	10:30 - 11:00	Coffee Break
		11:00 - 11:30	KN3 (WG3) J. TELLINGHUISEN	11:00 - 13:00	Individual WGs Meetings
		11:30 - 11:50	OC9 M. SANADAR		
		11:50 - 12:10	OC10 C. KVARNSTRÖM		
		12:10 - 12:30	OC11 J. MUŠOVIĆ		
		12:30 - 12:50	OC12 Ž. MEDOŠ		
12:00 - 15:00	Registration	12:50 - 15:00	Lunch Break	13:00 - 15:00	Lunch Break
15:00 - 15:20	Opening Ceremony	15:00 - 15:30	KN4 (WG1) J. GALCERAN	15:00 -16:00	WGs Summary Managers Summary Core Group Meeting
15:20 -15:50	KN1 (WG2) P. RAPTA	15:30 -15:50	OC13 L. KNEŽEVIĆ		
15:50 -16:10	OC1 N. RIBEIRO	15:50 -16:10	OC14 E. ZANDA		
16:10 -16:30	OC2 K. STOKOWA-SOŁTYS	16:10 -16:30	OC15 E. BURA-NAKIĆ	16:00 - 16:30	Coffee Break
16:30 - 17:00	Coffee Break	16:30 - 17:00	Coffee Break	16:30 - 18:00	MC Meeting and Closing Ceremony
17:00 - 17:20	OC3 L. ANTONOV	17:00 - 18:00	Poster Session		
17:20 - 17:40	OC4 J. KUBINEC				
17:40 - 18:00	OC5 G. SANTONOCETA				

CONFERENCE PROGRAMME

Wednesday 24th

15:00 - 15:20	**Opening Ceremony**
Chairperson:	Maria Amelia SANTOS - *University of Lisbon, Portugal*
15:20 - 15:50	**KN1 (WG2)** - *In situ* EPR and UV–visible–NIR spectroelectrochemistry as a unique tool for redox mechanism and equilibria studies of biologically active ligands and their metal complexes Peter RAPTA - *Slovak University of Technology in Bratislava, Slovakia*
15:50 - 16:10	**OC1** - Spectroscopic studies on the ethidium bromide/DNA system: a golden standard that still needs information Nádia RIBEIRO – *University of Lisbon, Portugal*
16:10 - 16:30	**OC2** - Interactions of neurokinin B with copper(II) ions and their potential biological consequences Kamila STOKOWA-SOŁTYS - *University of Wroclaw, Poland*
16:30 - 17:00	Coffee Break
Chairperson:	Petr HERMANN - *Charles University in Prague, Czech Republic*
17:00 - 17:20	**OC3** - Favipiravir – tautomeric and complexation properties Liudmil ANTONOV - *Bulgarian Academy of Science, University of Chemical Technology and Metallurgy, Bulgaria*
17:20 - 17:40	**OC4** - Structural and solution study of scandium(III) complexes with phosphonate derivatives of H_4DOTA Jan KUBINEC - *Charles University in Prague, Czech Republic*
17:40 - 18:00	**OC5** - Water-soluble prismarene hosts: molecular recognition of ammonium cations in aqueous solution Giuseppina D. G. SANTONOCETA – *University of Catania, Italy*

Thursday 25th

Chairperson:	Winfried PLASS - *Friedrich Schiller University Jena, Germany*
9:00 - 9:30	**KN2 (WG4)** - A combined microcalorimetric cell for quantifying sorption phenomena followed by dissolution into liquid solvents Peter VIKEGARD - *Waters Sverige AB, Sweden*
9:30 - 9:50	**OC6** - Comparative study on the current tools for optimization of stability constants from potentiometric data Silvia BERTO – *University of Turin, Italy*
9:50 - 10:10	**OC7** - Solution chemical properties and biological activity of organoruthenium(II) complexes with *O*,*O*-, *N*,*O*- and *O*,*S*-ligands Jerneja KLADNIK - *University of Ljubljana, Slovenia*
10:10 - 10:30	**OC8** - The effect of salicylate on the solubility and self-aggregation of caffeine - a thermodynamic and computational approach Teona Teodora BOROVIĆ - *University of Novi Sad, Serbia*
10:30 - 11:00	Coffee Break
Chairperson:	Slobodan GADŽURIĆ - *University of Novi Sad, Serbia*
11:00 - 11:30	**KN3 (WG3)** - A (partial) resolution of binding enthalpy discrepancies in ITC studies of Ba^{2+}/crown ether complexation: the importance of calibration Joel TELLINGHUISEN - *Vanderbilt University, USA*
11:30 - 11:50	**OC9** - Cobalt extraction from chloride/nitrate/sulfate media with phosphonium-based ionic liquids Martina SANADAR - *University of Udine, Italy*
11:50 - 12:10	**OC10** - *In situ* FTIR and Raman spectroelectrochemistry on organic semiconductors in room-temperature ionic liquids Carita KVARNSTRÖM - *University of Turku, Finland*
12:10 - 12:30	**OC11** - Spectrophotometric study of stability constant of 1-butyl-3-methylimidazolium 2-mercaptobenzothiazole and cadmium(II) Jasmina MUŠOVIĆ - *University of Belgrade, Serbia*
12:30 - 12:50	**OC12** - Aggregation of metallacarboranes in aqueous solutions Žiga MEDOŠ - *University of Ljubljana, Slovenia*
12:50 - 15:00	Lunch Break

Chairperson:	Olga IRANZO, *CNRS, University of Aix-Marseille, France*
15:00 - 15:30	**KN4 (WG1)** - Thermodynamics and kinetics of the dissolution of In_2O_3 nanoparticles Josep GALCERAN – *University of Lleida and AGROTECNIO-CERCA, Spain*
15:30 - 15:50	**OC13** - Vanadium(IV) and vanadium(V) complexation with succinic acid by affinity capillary electrophoresis Lucija KNEŽEVIĆ - *Ruđer Bošković Institute, Croatia*
15:50 - 16:10	**OC14** - Complexation studies of U(IV) with hydroxamic acid ligands Emanuele ZANDA - *University of Paris-Saclay, France*
16:10 - 16:30	**OC15** - Study of bathocuproine and Cu(I) electrochemical behavior on Hg electrode surface Elvira BURA-NAKIĆ - *Ruđer Bošković Institute, Croatia*
16:30 - 17:00	Coffee Break
17:00 - 18:00	**Poster Session**
19:30 - 22:30	**Conference Dinner, Ljubljana Castle**

Friday 26th

9:00 - 9:45	**SO/AO Communications**
9:45 - 10:30	**Individual WGs Meetings**
10:30 - 11:00	Coffee Break
11:00 - 13:00	**Individual WGs Meetings**
13:00 - 15:00	Lunch Break
Chairperson:	*Demetrio MILEA – University of Messina, Italy*
15:00 - 16:00	**WGs Summary** **Managers Summary** **Core Group Meeting**
16:00 - 16:30	Coffee Break
16:30 - 18:00	**MC Meeting** **Closing Ceremony**

Keynote Lectures

In situ EPR and UV–visible–NIR spectroelectrochemistry as a unique tool for redox mechanism and equilibria studies of biologically active ligands and their metal complexes

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In this contribution the redox behavior and solution equilibrium studies of a variety of metal complexes with biologically active ligands are presented. The complexes and corresponding ligands have been studied by cyclic voltammetry, optical spectroscopy, electron paramagnetic resonance (EPR), *in situ* EPR/UV-visible-NIR (EPR/UV-Vis-NIR) spectroelectrochemistry and theoretical calculations. The experimental techniques such as cyclic voltammetry (CV) and EPR/UV-Vis-NIR spectroscopy provide important information on the changes in the electronic structure of solvated molecules in solution after electron and proton transfer. The combination of electrochemical and spectroscopic methods led to the development of *in situ* EPR/UV-Vis-NIR spectroelectrochemistry, which allows detailed studies of primary redox processes, as well as the consecutive reactions that take place after the electron transfer from the electrode to the molecules studied under the same experimental conditions (Figure 1). Thus, a various oxidation states of a molecule can be identified.

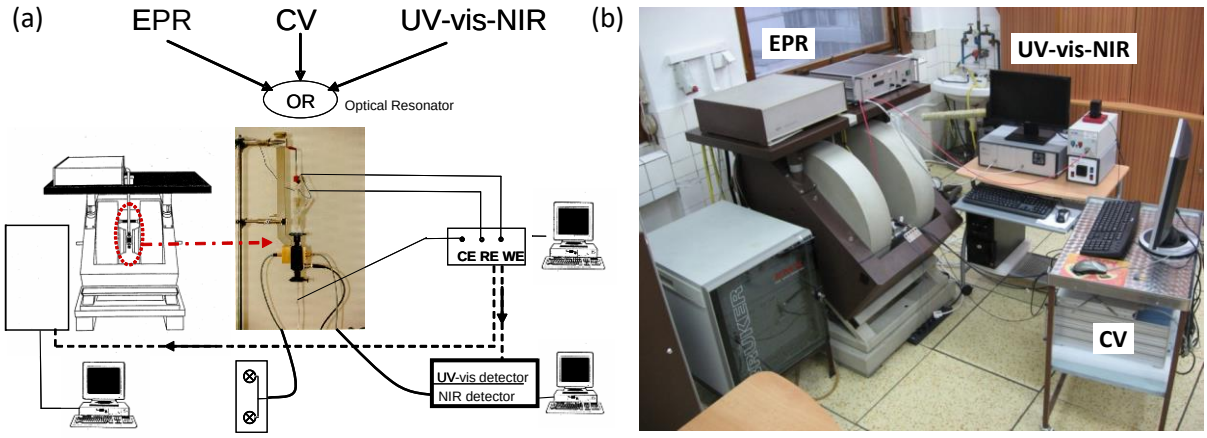

Figure 1. (a) Simplified scheme of the triple *in situ* EPR/UV-Vis-NIR spectroelectrochemical setup. (b) *In situ* EPR/UV-Vis-NIR spectroelectrochemical setup at the Slovak University of Technology in Bratislava.

Electrochemical and spectroelectrochemical studies of copper complexes with new thiosemicarbazones (TSCs) as triapine analogues bearing a redox-active phenolic moiety at the terminal nitrogen atom were performed and confirmed their redox activity in both the cathodic and the anodic region of potentials [1]. The one-electron reduction was identified as metal-centered by EPR spectroelectrochemistry. An electrochemical oxidation pointed out the ligand-centered oxidation, while chemical oxidations of proligands and their complexes afforded several two-electron and four-electron oxidation products, which were isolated and comprehensively characterized. The UV-Vis and EPR spectroelectrochemical measurements revealed that newly prepared Cu(II) complexes with triapine derivatives underwent irreversible reduction of Cu(II) with subsequent ligand release, while Fe(III) analogue showed an almost reversible electrochemical reduction in dimethyl sulfoxide (DMSO) [2]. Aqueous solution behavior of the ligands and their complexes were studied as well.

A series of water-soluble salicylaldehyde thiosemicarbazones with a positively charged trimethylammonium moiety and their Cu(II) complexes were studied concerning their redox activity [3]. The ability of Cu(II) complexes to be reduced by glutathione was investigated in solution by UV-Vis-NIR and EPR spectroscopy. It was confirmed that under the anaerobic conditions at physiological pH, the complexes are reduced to copper(I) species. The reduction reaction followed by EPR spectroscopy resulted in the formation of EPR silent Cu(I) species. These species can be reoxidized in the presence of oxygen to original Cu(II) complexes. Thus, investigated Cu(II) complexes were found to be redox-active at physiological pH and might react with intracellular reductants. In agreement with these data, the electrochemical and spectroelectrochemical studies of proligands and the Cu(II) complexes in DMSO, acetonitrile and aqueous solution, showed that only the complexes underwent a reduction in biological accessible window (–0.4 to +0.8V *vs.* NHE), while the proligands remained intact. Thus, the reduction is metal-centered, as described for other Cu(II) complexes developed as anticancer agents.

Acknowledgement. This work was supported by the Slovak Grant Agencies APVV (contract Nos. APVV-19-0024 and DS-FR-19-0035) and VEGA (contract No. 1/0504/20). This contribution is also based upon work from COST Action CA18202, NECTAR.

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A combined microcalorimetric cell for quantifying sorption phenomena followed by dissolution into liquid solvents

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Isothermal calorimetric sorption and dissolution techniques have gained attention over the years in fundamental thermodynamic studies and as analytical tools in industry, particularly in pharmaceutical activities dealing with drugs and excipients in the solid state. Sorption studies include enthalpic sorption isotherms, investigation of solvate or hydrate formations, and analysis of crystallinity levels of mixed crystalline/amorphous phases. Calorimetric dissolution techniques are often used to study different solid structures of the same compound by bringing them into a common equilibrium solvation state. Hence the enthalpy-change of a dissolution process constitute the break-up the solid structure and solvation of the molecules.

Since sorption to a certain solvent activity can be viewed as partial solvation it appears that sorption and dissolution measurements are interconnected. A common problem associated with calorimetric dissolution measurements is to have a well-defined initial hydration or solvation state of the specimen to be studied. Even small deviations and random variations of the hydration state may have impact on the precision and accuracy of the resulting solution enthalpy. This is of course more serious for hygroscopic materials such as amorphous organic solids, and proteins.

A combined sorption/dissolution cell is thought to provide significant advantage to the current techniques for analysis of kinetic and thermodynamic aspects of sorption and dissolution due to the close connection between the hydration state of a solid phase and dissolution behavior. The cell that will be presented has a dual function, i) equilibrating the solvent activity on the solid phase to a defined state for better accuracy and precision of dissolution measurements, and ii) provide increased understanding of the solid phase by analyzing its sorption behavior, with possible intermediate states prior to obtaining dissolution enthalpies.

In the presentation, a discussion of the technical difficulties, advancement thus far, and results on some selected test systems will be presented.

A (partial) resolution of binding enthalpy discrepancies in ITC studies of Ba^{2+}/crown ether complexation: The importance of calibration

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By conducting binding experiments at a range of temperatures T using isothermal titration calorimetry (ITC), one can obtain two estimates of the binding enthalpy — calorimetric ($\Delta H°_{cal}$) from the experiments at each T, and van't Hoff ($\Delta H°_{vH}$) from the T dependence of the binding constant $K°$. From thermodynamics it is clear that these two must be identical, but early efforts to demonstrate this for ITC data indicated significant inconsistency. In an extensive 2004 study of the Ba^{2+} + 18-crown-6 ether complexation used in prior comparisons, Mizoue and Tellinghuisen found modest (10-20%) but statistically significant differences, which were tentatively attributed to problems converting the calorimetric estimates to their standard state values, as implied by the superscript ° in the notation [1]. In the present work the 2004 results are reanalyzed using results obtained since then from temperature, heat, and volume calibration of the instrument [2] and a better determination of the data variance function required for the weighted least-squares fitting of the data [3]. The new results show consistency for temperatures 5-30 °C but persistent statistically significant differences from 35-46 °C. Several possible explanations for the remaining discrepancies are examined, with methods that include fitting the K and ΔH_{cal} data together [4].

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Thermodynamics and kinetics of the dissolution of In_2O_3 nanoparticles

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Many electronic devices contain indium, a Technology Critical Element. In some products (such as sensors for detecting volatile organic compounds), indium appears as In_2O_3 nanoparticles. So, the equilibrium and kinetics behaviour of the dissolution of In_2O_3 nanoparticles should be analyzed to evaluate possible environmental impacts. Given its high amalgam solubility and moderately negative redox potential, indium (III) is a suitable analyte for the electroanalytical technique AGNES (Absence of Gradients and Nernstian Equilibrium Stripping) [1-4]. As a result, AGNES can robustly determine free indium concentrations, $[In^{3+}]$, in dispersions of nanoparticles (without the need of a previous separation).

A relatively large amount of In_2O_3 nanoparticles (so that they are not all eventually dissolved) was dispersed either in KNO_3 0.1 mol L^{-1} (at pH 2, 3, 4, 5, 6, 7 and 8) or in synthetic seawater (pH 8). Dispersions were constantly stirred at 25°C. Aliquots from the dispersion were taken at different times during a period up to 6 months, and $[In^{3+}]$ was obtained with AGNES using a Thin Mercury Film Rotating Disc Electrode

The work will discuss the $[In^{3+}]$ found in the dispersions after various contact days, from trajectories (i.e. measured charges corresponding to increasingly longer deposition times, so as to check the attainment of the required equilibrium). In the case of seawater, a free concentration of 1.17 attomol L^{-1} was determined. At pH below 6, dissolution kinetics lasted around 90 days, while in seawater less than 18 days. Labile complexes in seawater critically help to reach huge gains in short times with AGNES. The solubility products of $In(OH)_3$ and In_2O_3 will be compared and discussed.

Acknowledgements: Support from the Spanish Ministry of Science and Innovation (Projects PID2019-107033GB-C21 and PID2020-117910GB-C21) and from FISDUR-Generalitat de Catalunya (KRS) is acknowledged.

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Oral Communications

Spectroscopic studies on the ethidium bromide/DNA system: a golden standard that still needs information

Nádia RIBEIRO, [a] Orsolya DÖMÖTÖR, [b] Pedro PAULO, [a] Vanda Vaz SERRA, [a] Tarita BIVER, [c] João COSTA PESSOA, [a] Isabel CORREIA [a]

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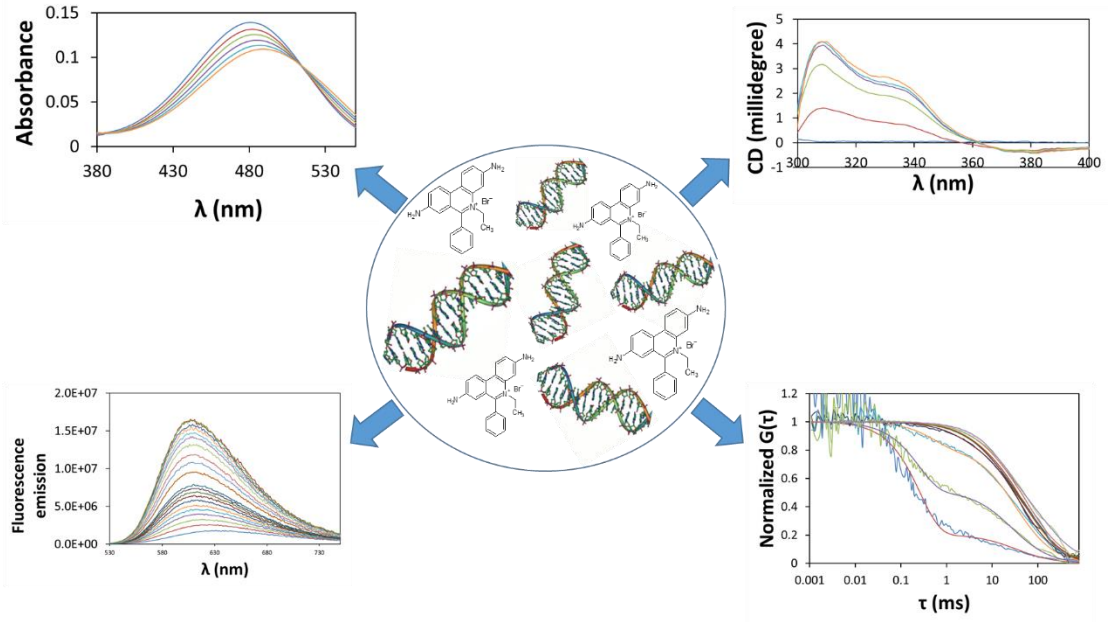
Intercalation is a common process of interaction of large aromatic systems with the base pairs of the genetic material, DNA [1]. Ethidium bromide (EB) is a well-known classical intercalator consisting of fused aromatic cycles, one of which bearing a nitrogen atom, with a positive charge. Several mechanistic studies show that EB slots between the base pairs and interacts through π stacking, thereby enhancing both fluorescence quantum yield (Φ_f) and lifetime (τ_f), and decreasing extinction coefficient (ε) [2, 3]. This molecule, despite its toxicity, is still nowadays commonly used as a DNA stain in many experiments and is readily accessible at high purity and relatively low cost at almost every supplier. Spectroscopic methods based both on the absorption and on the emission of light, are the most used to evaluate the dye/DNA interactions [4]. The Working Group 2 – Task Group 2 (WG2TG2) of Nectar (Network for Equilibria and Chemical Thermodynamics Advanced Research) COST CA18202 action, aims at providing robust protocols and good practices to optimize the experiments setup and data treatment of different type of researchers. The WG2TG2 has chosen as the standard the EB/DNA system, known since pioneer studies, providing new data and information to try to shed light on the sometimes-inhomogeneous literature data. While attempting to give a closer look into this system, several spectroscopic tools were used to re-analyze it and the results of different techniques will be presented and discussed. The intercalation process was confirmed by the characteristic hypochromic and bathochromic effects in the titration, followed by UV-Vis absorption, and the appearance of induced circular dichroism (CD) bands in the absorption region of the non-chiral EB molecule. Titration of an EB solution with DNA followed by steady-state fluorescence emission provided data to the determination of the binding constant and binding site size. Binding parameters were calculated using different models and procedures. Finally, fluorescence correlation spectroscopy (FCS) gave us the opportunity to characterize and analyze this interaction using a technique with single DNA chain detection sensitivity. Recognizing the strong interest of the community in this system, and inspired by WG2TG2 we give an overview of the results obtained using several spectroscopic techniques, focusing particularly on FCS and aiming to contribute to a deeper understanding of the relevant processes involved.



Scheme 1. Results obtained through different spectroscopic techniques on the interaction of ethidium bromide with DNA.

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Interactions of neurokinin B with copper(II) ions and their potential biological consequences

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Neurokinin B (NKB, Asp-Met-His Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2) is a member of tachykinin neuropeptide family which plays key roles in the proper functioning of female reproductive system, especially during sexual maturation and pregnancy [1]. The physiological level of NKB in blood grows continuously during pregnancy, reaching up to 0.08 nM [2]. Notably, a much higher level of NKB, 0.53–0.92 nM in peripheral blood and 1.42–2.35 nM in umbilical cord blood was found in pregnant women with preeclampsia (PE) [3], a multifactorial condition affecting 8–10 % pregnant women and contributing to estimated 50,000–60,000 globally every year [4]. The elevated blood plasma copper (29–56 μM) was observed in PE [5]. NKB secreted from the placenta enters both the maternal and fetal circulatory systems and is essential for the regulation of blood flow to the placenta. A possible coincidence of elevated blood serum copper and NKB is one reason to study the Cu(II)/NKB complexes.

In our studies we re-investigated the Cu(II) complexation by NKB using potentiometry, spectroscopic methods, and DFT calculations. NKB is very poorly soluble in water and its biological actions are associated with membranes. Therefore, the NKB/Cu(II) interactions were studied in sodium lauryl sulfate (SDS) micelles, as a membrane-mimicking medium compatible with potentiometric and spectroscopic experiments. In order to assist the data interpretation, the parallel potentiometric and spectroscopic experiments in water and SDS solutions were also performed for the DMHD-NH_2 tetrapeptide amide as a well-soluble model of the Cu(II) binding site of NKB.

The stability constants determined for NKB and its N-terminal tetrapeptide empower us to ask whether NKB might be able to bind Cu(II) ions *in vivo*. The actual speciation of Cu(II) ions in blood serum remains a debated issue, but we can make an estimate based on the data available for human serum albumin (HSA). HSA comprises about 15% of total blood serum copper, which is 17.6 ± 4.2 μM in healthy adults. Considering the average HSA concentration of 630 μM, one obtains the HSA saturation with Cu(II) ions as 0.42%. The dissociation constant for this complex is 100 fM. The normal level of NKB is less than 100 pM, but in PE it can be elevated to nM levels [2], accompanied by total blood serum Cu(II) elevation to 29–56 μM [5].

The NKB affinity for Cu(II) under blood serum conditions can be probably best represented by that of DMHD-NH2 in the presence of SDS (3.5 fM). The results of calculations of Cu(II) competition between HSA and NKB are presented in Table 5. In these calculations it is assumed that half of excess Cu(II) present in PE goes to the HSA/NKB system, that is between 5.7 and 21.8 μM. This estimate is based on the fact that HSA comprises about 50% of non-ceruloplasmin blood copper, and that ceruloplasmin elevation in PE is between 10% in mild and 70% in severe cases. These very preliminary estimates clearly indicate that the total level of Cu(II)NKB in blood serum may grow more than 100-fold during PE, making it a serious object of further research with respect to this dangerous condition.

The obtained results also pertain to previous studies which suggested that NKB may affect the copper transport in the central nervous system (CNS) [6]. First, we can suggest that the presumable stability of Cu(II)NKB in solution, ca. 3.5 fM is more than sufficient to stand the CNS conditions, as demonstrated by the presence in the cerebrospinal fluid of Cu(II) complexes of Aβ4-40/42 peptides, whose Kd values are ca. 30 fM [7]. The significant loss of Cu(II) affinity of NKB upon its binding to SDS makes NKB a potentially good Cu(II) delivery agent for the hCtr1 membrane receptor. At a distance from the membrane its affinity is very high, which may protect it from the adventitious Cu(II) loss, e.g. to Aβ peptides, but at the membrane its affinity drops to 3 pM, well below that of the N-terminus of hCtr1 copper receptor, 100 fM, thus facilitating the Cu(II) transfer to the receptor. It seems that the negatively charged phospholipid membrane may act as a switch for biological copper delivery.

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Favipiravir – tautomeric and complexation properties

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The appearance of the SARS-CoV-2 virus was crucial for our global society, causing a widespread pandemic with devastating health, social and economic challenges for the communities worldwide. This has posed a need for vital scientific breakthroughs, which include innovative approach in developing vaccines and antiviral drugs. The Japanese anti influenza drug Favipiravir has shown promising results in the treatment of the disease in China, India and Russia [1].

Favipiravir belongs to the 2-hydroxy pyrazine family and that is the reason why it is expected to have tautomeric abilities [2,3]. Therefore, for the first time an investigation has been conducted concerning its properties by using molecular spectroscopy (UV–Vis absorption, fluorescence and NMR) as well as quantum-chemical calculations. According to the obtained results, the enol tautomer is substantially more stable in the neutral Favipiravir form. Partially it is due to the hydrogen bonding between the hydrogen atom from the hydroxyl group and the oxygen atom from the amide group, which additionally stabilizes this structural form (Figure 1A).

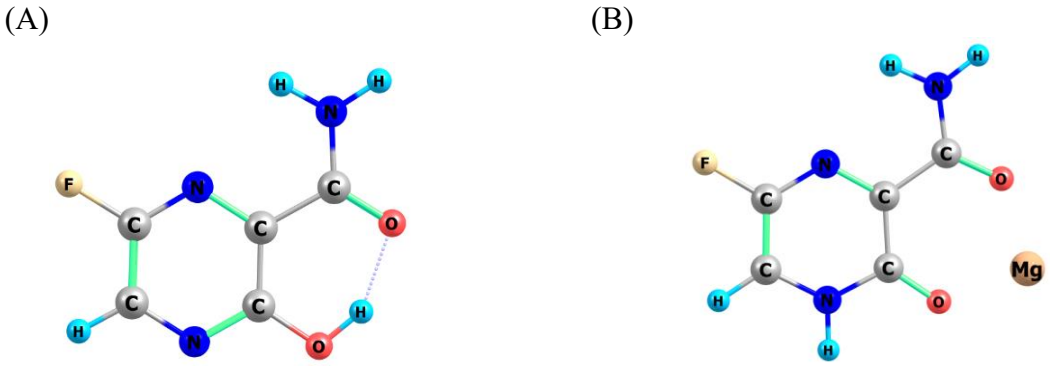

Figure 1. (A) Optimized structure of the enol tautomer; (B) Optimized structure of the magnesium-favipiravir complex.

The experimental results in solution show that the tautomeric equilibrium could be affected by changing the solvent environment (Figure 2) – the increased dielectric constant of the solvent, from toluene to water, leads to relative stabilization of the more polar keto form.

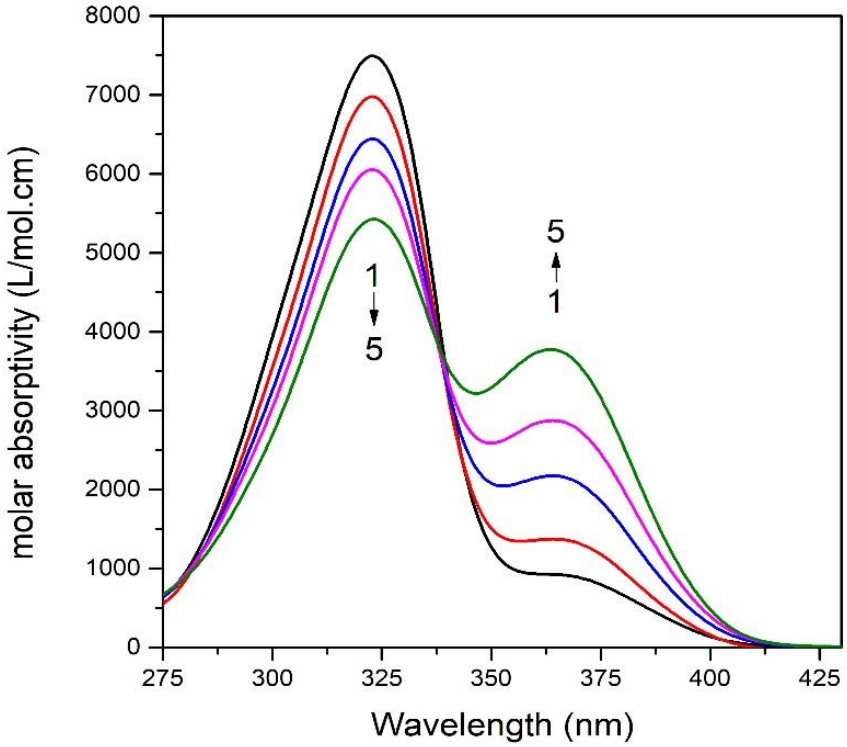

Figure 2. Favipiravir in acetonitrile/water binary mixture in %: 1 (black) – pure acetonitrile, 2 (red) – 80:20, 3 (blue) – 60:40, 4 (magenta) – 40:60, 5 (green) – 20:80.

In addition, a controlled shift of the tautomeric equilibrium can be achieved by complex formation in acetonitrile with alkaline earth metal ions. It is determined that stabilization of the keto tautomer is caused by structural re-arrangement – relocation of the proton from oxygen to nitrogen and capturing of the metal ion by the carbonyl groups (Figure 1B).

Acknowledgements:
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Structural and solution study of scandium(III) complexes with phosphonate derivatives of H_4DOTA

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Metal radioisotopes are used as a key component of metal-based radiopharmaceuticals. Among the metal radioisotopes, scandium ones are emerging and have potential be used in medicine. The radioisotopes emitting positrons (^{43}Sc $t_{1/2}$ = 3.9 h and ^{44}Sc $t_{1/2}$ = 4.0 h) can be used for imaging by positron emission tomography (PET)[1] and that with β^- emission (^{47}Sc $t_{1/2}$ = 80 h) therapeutic applications [2]. Combination of the radioisotopes leads to single-element theranostic pair. The Sc(III) ion cannot be applied as aqua-complex due to its non-specific biodistribution and must be bound in a stable and inert complexes. Despite of favorable properties and increasing availability of Sc-radioisotopes, fully suitable ligands for Sc(III) for *in vivo* applications have not been published [3].

Commonly used chelators for metal ions in radiopharmaceuticals are polyazamacrocycles and their derivatives. Very hard Sc(III) ion forms the most stable/inert complexes with DOTA-like ligands[4] and phosphorus(V) oxoacids are considered as very hard ligands. Phosphonate pendant arms increase basicity of DOTA-like ligands and, thus, thermodynamic stability of their complexes, and should be suitable for good coordination of the hard Sc(III) ion.

In this contribution, we present series of cyclen-based ligands (**Figure 1**) containing phosphonate and acetate pendant arms to investigate influence of their number on properties if Sc(III) complexes. They were synthetized by multi-step syntheses. Their Sc(III) complexes were prepared and fully characterized by spectral methods. Solid-state structures of some of them were determined by X-ray diffraction. Structural parameters were evaluated and compared with solution properties to determine the most suitable ratio of phosphonate and acetate pendant arms for good complexation. Dissociation kinetics of the prepared Sc(III) complexes was studied as well.

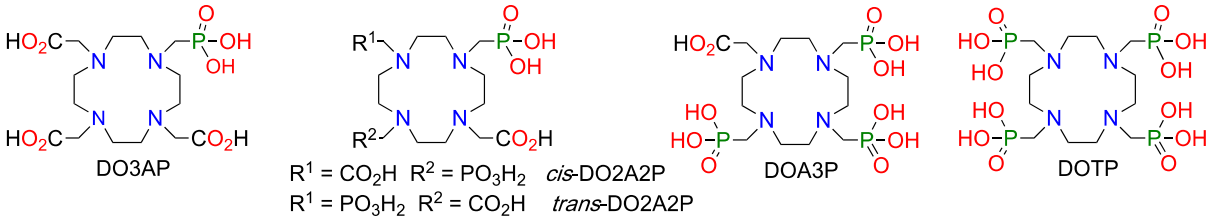

Figure 1: Structure of investigated phosphonate derivatives of H_4DOTA

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Water-soluble prismarene hosts: molecular recognition of ammonium cations in aqueous solution

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Naphthalene-based macrocycles have recently attracted a great deal of attention in supramolecular chemistry because of their structural and conformational features. Recently, a new class of deep-cavity macrocycles, named prism[*n*]arenes (n = 5 and 6) [1], and their water-soluble homologous bearing carboxylato groups on both upper and lower rim (PrS[*n*]^{carboxy}), have been synthesized and characterized [2].

As the structural and conformational features of water-soluble hosts play a crucial role in determining their binding affinity for charged guests [3], the complexation properties of this novel class of receptors toward singly and doubly charged ammonium cations have been investigated in aqueous solution at 25 °C and pH 7.6 by combining nuclear magnetic resonance (NMR) and isothermal titration calorimetry (ITC) measurements.

NMR experiments revealed that PrS[*n*]^{carboxy} hosts form 1:1 complexes with all the charged guests regardless of the macrocycle size (**Figure 1**).

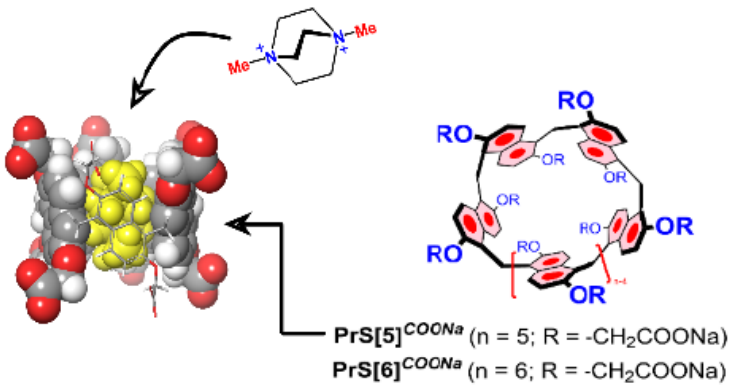

Figure 1. Example of host-guest inclusion complexes for PrS [5]^{carboxy}

ITC calorimetric measurements provided key information on both the binding affinities and the energetics of the recognition processes occurring in solution towards guests having different charge, size and shape. The stability of the host-guest complexes formed by PrS[5]^{carboxy} with the ammonium cations is significantly affected by the structural features of the differently charged guests, while the affinity values determined for PrS[6]^{carboxy} are quite comparable for all the cations investigated regardless of the properties of the guests [4].

The determination of the enthalpic and entropic contribution to the Gibbs free energy revealed striking features on the forces driving the encapsulation equilibria in solution. The inclusion of ammonium cations into PrS[5]^{carboxy} is driven by enthalpically favorable attractive forces. The complexation of the monocation guests in PrS[6]^{carboxy} is an entropically favored and driven process, whilst enthalpy drives the inclusion of the doubly charged guests.

The synthesis of water-soluble prismarenes and the thermodynamic fingerprints of their binding processes in aqueous medium can help the construction of new prismarene-based supramolecular systems with fascinating properties.

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Comparative study on the current tools for optimization of stability constants from potentiometric data

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Among the participants of COST Action CA18202 NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, a survey was conducted regarding what software is used daily and what problems the users are facing. The results show a high fragmentation in the software used, associated with a common dissatisfaction concerning the user experience, highlighting the need of the development of new IT tools for the management of chemical equilibria in solution by the NECTAR community. Following this line, WG4 is working to meet this need developing a free, multi-platform and open-source software, dedicated to the analysis of potentiometric data, with the aim of making it become the reference software for in solution speciation studies. Towards that goal, we have also undertaken a critical evaluation of the software actually available for the analysis of potentiometric data, in order to identify the strengths and weaknesses of each and to use this knowledge for the development of the new IT products. With this aim, the software Hyperquad [1,2], SUPERQUAD [3], PSEQUAD [4], BSTAC [5], OPIUM [6], Reactlab™ suite [7] and KEV, were tested on an

artificial dataset of six different titrations conducted on a hypothetic hexaprotic acid, in order to optimize the six protonation constants. The results obtained with the different software were analyzed and discussed. Moreover, the data analysis was carried out including some systematic errors in the calculation, quite common in the experimental procedures, in order to stress the impact of systematic errors arising in potentiometry on the refined parameters, and check the sensitivity of the different software in relation to these errors. The systematic errors considered were: carbonation of the base used as titrant, impurity of the solution components (partial salification of the titrated acid, for example), disregarding of the junction potential, the use of a not correct formal potential, changes on the ionic strength during the titration. The discussion of the results was also used to highlight the extent of the effects of systematic errors on the final results and to propose guidelines for the obtention of reliable formation constants.

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Solution chemical properties and biological activity of organoruthenium(II) complexes with *O,O*-, *N,O*- and *O,S*-ligands

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Ruthenium complexes represent an important field of research due to their promising biological effects for various therapeutic areas. Organoruthenium(II) chlorido **1a**–**d** and pta complexes **2a**–**d** bearing pyrithionato *O,S*-ligands (**a**, **b**), 8-hydroxyquinoline *N,O*-ligand (**c**) and *β*-diketone *O,O*-ligand (**d**) were synthesized (**Figure 1**) and tested for their anticancer and antimicrobial properties. Various complexes showed *in vitro* cytotoxicity to the multidrug-resistant cancer cell lines Colo 205 and Colo 320 and inhibitory activity to Gram-positive bacterial strains including resistant *S. aureus* (MRSA) and the Gram-negative bacterium *Chlamydia trachomatis*. In addition, one ruthenium complex also showed antiviral activity and decreased herpes simplex virus-2 growth. [1]

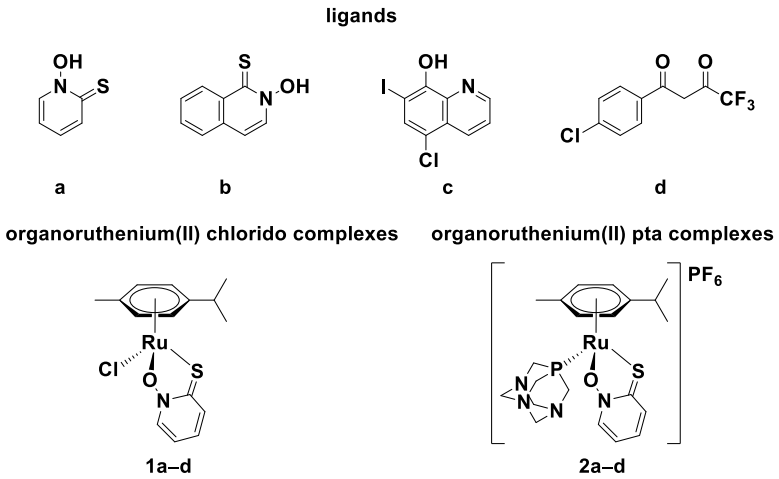

Figure 1: Structures of the ligands **a**–**d** and organoruthenium(II) complexes **1a**–**d** studied for their biological and solution chemical properties.

However, not only the biological activity but also the aqueous stability of the complexes needs to be studied to better understand the chemical properties of the complexes in solution, which may help in understanding certain biological effects. Therefore, we have performed an in-depth study on the solution speciation of complexes **1a**–**d** (Scheme 1), since among them **1a** and **1b** proved to have remarkable anticancer activity and antibacterial effect on Gram-positive bacteria. pK_a values of the selected compounds were also determined (Table 1). The solution speciation studies of complexes **1a**–**d** were performed using UV-vis spectrophotometry and pH-potentiometry. [1]

Table 1: pK_a values determined for the ligands **a** and **b** and their corresponding organoruthenium(II) chlorido complexes **1a**–**b** (pure water containing 200 mM Cl^-, T = 25.0 °C, I = 0.2 M KCl).

Compound	pK_a	Methode	Concentration
a	4.52 ± 0.04	pH-potentiometry	1.3 mM
b	4.63 ± 0.08	UV-vis	27 µM
1a	10.37 ± 0.06	pH-potentiometry	1.30 mM
	10.34 ± 0.03	UV-vis	250 µM
1b	10.29 ± 0.09	pH-potentiometry 2	0.6 mM
	10.25 ± 0.03	UV-vis	250 µM

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The effect of salicylate on the solubility and self-aggregation of caffeine - a thermodynamic and computational approach

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Caffeine (1,3,7-trimethylxanthine) belongs to the group of xanthine alkaloids together with theophylline and theobromine [1]. As an ingredient in coffee, black and green tea, soft and energy drinks, caffeine is the most widely used psychoactive substance [2]. Pure caffeine is a solid substance, odorless and slightly bitter-tasting. The solubility of caffeine in water is relatively low (approximately 16 $mg \cdot mL^{-1}$ at room temperature), which is one of the crucial problems, especially in preparations consumed or stored at low temperatures [3]. The prevalence of hydrophobic in water poorly soluble drugs and supplements is a major problem in drug design, food science, delivery, drug effect and bioavailability [4].

Caffeine is considered limitedly soluble in water due to self-association and aggregation of caffeine molecules by hydrophobic interactions [5]. A common solution for increasing solubility and limiting aggregation is to add some biocompatible molecules, excipients or hydrotropes. The effect of benzoic acid derivatives (sodium benzoate, sodium salicylate, salicylic acid, acetylsalicylic acid, etc.) on the influence of caffeine self-aggregation to increase the solubility of caffeine in water is specially investigated. Caffeine in combination with sodium salicylate can be found in various drugs or preparations such as Algopirin (used for acute low back pain), Acetaminophen (used for temporary relief of pain), Excedrin (used for Migraine headache) or Ephedrine-Caffeine-Acetylsalicylate stack (drug combination used in weight loss), *etc*. However, the mechanism by which these compounds increase the solubility of caffeine in water has remained unknown.

The present study analyzed experimental data from volumetric, viscosimetric measurements and computational simulations to understand caffeine hydration and aggregation properties in 0.1 $mol \cdot kg^{-1}$ sodium salicylate aqueous solution. Sodium salicylate reduces the bitter taste and increases the solubility of caffeine in water, which is the main reason for their combination in food products. The results noted in volumetric and viscometric measurements indicate that sodium salicylate promotes the self-aggregation of caffeine in water. After self-aggregation, the hydration number of caffeine increases significantly. Molecular simulations have allowed us to hypothesise how salicylate increases caffeine solubility. At the molecular

level, relocating salicylate moiety from the parallel stacking (π-π) aromatic complex with caffeine and its hydration could be the main reason for increasing the solubility of caffeine in water. The presented study provides clear guidelines on the choice of additives to increase caffeine's solubility in aqueous media (Figure 1).

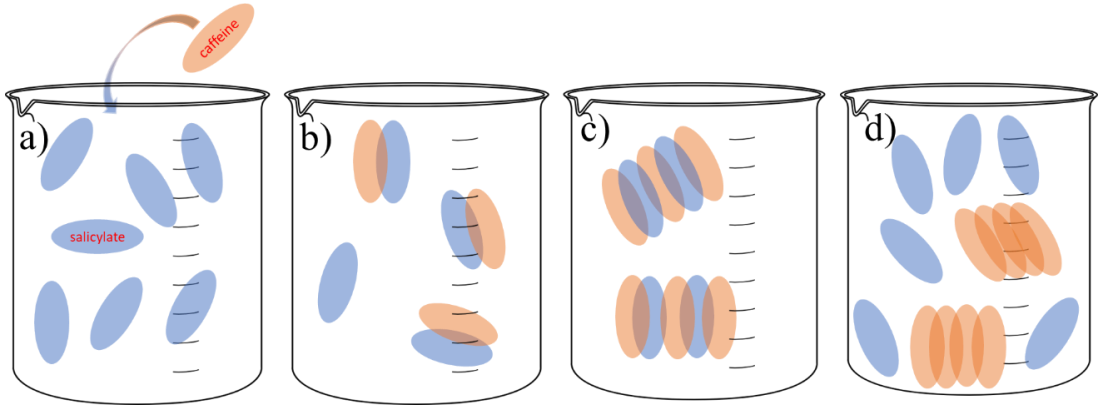

Figure 1. Visual representation of the potential role of salicylates in increasing the solubility of caffeine: a) adding of caffeine in sodium salicylate solution; b) forming of π-π interactions between caffeine and salicylate anions; c) caffeine and salicylate complexes that provide better solubility of caffeine monomers; d) forming of caffeine-caffeine complexes trough π-π interactions with salicylate anion release.

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Cobalt extraction from chloride/nitrate/sulfate media with phosphonium-based ionic liquids

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Room temperature ionic liquids (RTILs) have emerged and attracted increasing interest in the past few years in numerous applications. RTILs are salts generally composed by an organic cation and an inorganic anion in the liquid state at 25 °C. They present high thermal and chemical stability, non-flammability, wide electrochemical window, low volatility and low toxicity [1]. Moreover, these properties can be finely tuned by systematically altering the structure of cations and anions. Due to these attractive features, RTILs have been used as "green" substitutes of volatile organic solvents in a number of applications related to the energy and environmental fields (e.g. separations, extractions, electrochemistry and catalysis). Among these, the use of RTILs for the separation and recycling of “critical” metals deriving from mining or high-tech waste was proposed in the last decade [2].

The recycling of cobalt assumed a growing importance due to the growing demand related to his use in key technologies, such as Li-ion batteries or motors for electric mobility [3]. The current processes for cobalt recovery in the hydrometallurgical route from aqueous solutions have some advantages such as method flexibility, high purity and low energy consumption [4] and some works on the application of RTILs in such process have appeared in the last years [4,5].

Among the available RTILs, those based on phosphonium cation (Figure 1) have been studied for metal extractions in recent years [6]. However, only few works were focused on the nature of the dissolved metals and their speciation in RTILs [7], despite these are fundamental data to understand the separation processes.

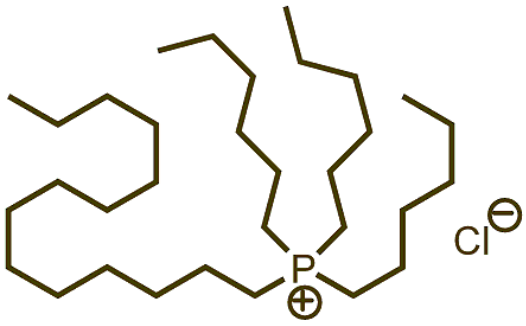

Figure 1. Structure of tri(hexyl)tetradecylphosphonium chloride ([P_{66614}][Cl])

In this communication, the results on Co(II) extraction in chloride/nitrate/sulfate media using [P_{66614}][Cl] (Figure 1), [P_{66614}][Decanoate] and [P_{66614}][Br] are reported, along with the extraction efficiency.

The interest in the Co^{2+} extraction with different media is due to the fact that the liquid samples containing the metal to be recovered usually can give extractions greater than 95%, with different Co(II) coordination. In addition, after stripping, the ionic liquid phase can be regenerated.

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In situ FTIR and Raman spectroelectrochemistry on organic semiconductors in room-temperature ionic liquids

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In situ FTIR and Raman spectroscopic studies of conducting polymers gives insight in the different processes taking place during electrochemical doping [1-6]. Due to the high absorbance properties of conducting polymers the Attenuated Total Reflection (ATR) technique combined with FTIR spectroscopy is a useful method for analysis of their structures. In situ Raman spectroscopic measurements give complementary information on charging induced changes in the carbon structure of the materials under study.

Generally, during charging of the polymer film, new bands in the spectral region of ca. 1600 to 600 cm^{-1} (low energy) are rising due to a strong electron-phonon coupling. Additionally, electronic transitions of formed charge carriers in the band gap enforce formation of broad absorption bands in the range from ca. 7000 to 1600 cm^{-1} (high energy).

In this study we focus on the ionic liquids induced changes in the properties of different conducting polymers.

The reason for the great interest in RTILs is their good properties such as: high ionic conductivity, high viscosity, low melting point (below 100 °C), sufficient thermal stability and a wide electrochemical window. An important discipline of science that benefits from the use of RTILs is electrochemistry. From an electrochemical point of view, RTILs open a field of new solvents with high conductance (additives not needed) and an extended electrochemical window combined with high stability.
Ionic liquids have been shown to act as good electropolymerization media for conducting polymers. The remarkable influence of polymerization conditions on the resulting polymer material is well known from experiments in organic solvents.

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Spectrophotometric study of stability constant of 1-butyl-3-methylimidazolium 2-mercaptobenzothiazole and cadmium(II)

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Ionic liquids (ILs) have been widely exploited in liquid-liquid extraction (LLE) because of the unique physicochemical properties that distinguish ILs from molecular solvents. Functionalized ILs (FILs) with a chelating functional group into organic anion are extractants and solvents at the same time [1]. Hydrophobic ILs with 2-mercaptobenzothiazole (or benzothiazoline-2-thione), [mbt] as anion have been designed as FILs and applied for the extraction of noble metals [2]. The $[mbt]^-$ is a bicyclic anion containing two heteroatoms sulfur and nitrogen, acting as a bidentate ligand in the reaction with metal ions. We synthesized hydrophilic ionic liquid 1-butyl-3-methylimidazolium 2-mercaptobenzothiazole [bmim][mbt] (Fig. 1) and successfully used for the formation of an aqueous biphasic system with potassium citrate and extraction of cadmium (II). The anion of the FIL is responsible for the formation of complexes with metals, while the cation is responsible for the formation of aqueous biphasic systems and the extraction of Cd(II). It was found that [bmim] MBT can be successfully used for Cd(II) extraction. Despite the extensive application of ILs in extraction, the influence of FIL on the formation of complexes between metal ions is still insufficiently investigated. This work aims to study stability complexes between [bmim][mbt] and Cd(II) in an aqueous solution by spectrophotometry.

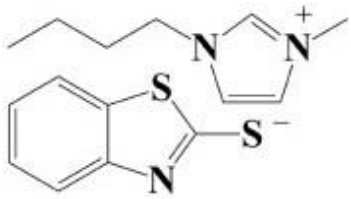

Figure 1. Chemical structures of [bmim][mbt]

Fig. 2(a) shows UV-VIS spectra of aqueous solution of [bmim][mbt], [bmim][mbt]+Cd(II), [bmim][Br], and spectra of Na[mbt] in methanol. Spectrum of [bmim][mbt] shows three peaks: at 205, 232 and 314 nm. Comparing absorption spectra of [bmim][mbt] with [bmim][Br] and Na[mbt], it can be seen that the absorption spectra of [bmim][mbt] mostly derive from anion [mbt], and there is a shifting of absorption peaks maximum from 321 nm in Na[mbt] to 309 nm in [bmim][mbt] due to the interaction between anion and cation of IL.

The formation of metal (Cd) complex with $[mbt]^-$ from FIL has been studied spectrophotometrically (Fig. 2(b)) at 25 °C. The ratio of Cd(II) and FILs was in a range from 1: 0.5 to 1: 8. The concentration of FIL was constant at 0.08mM. It can be seen that peak at 314 nm decrease with increasing ratio of Cd(II) : FIL and slightly move toward higher wavelength. These results indicate forming of Cd(II) and FIL complex. Based on obtained results, we will calculate the stability constants of Cd(II) and [bmim][mbt].

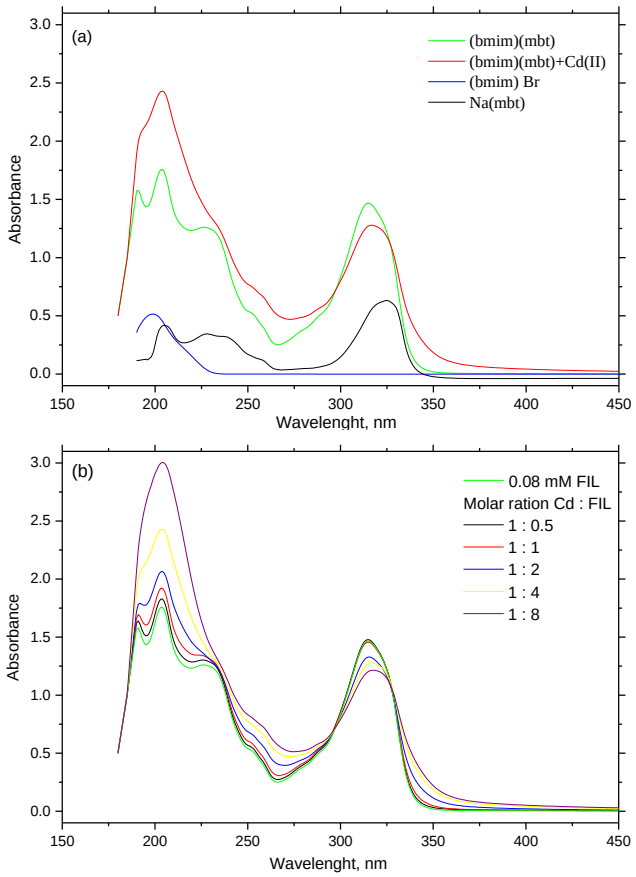

Figure 2.(a) UV spectra of [bmim][mbt], [bmim][mbt] + Cd(II), Na[mbt] and [bmim]Br; (b) UV spectra of building complexes of [bmim][mbt] and Cd(II) in aqueous solution. Concentration of FIL was constant (0.08 mM).

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Aggregation of metallacarboranes in aqueous solutions

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In recent decades, self-assembly of metallacarboranes has been extensively studied with the aim of understanding the unusual properties observed for aqueous solutions of these compounds. However, to this day the mechanism behind the aggregation process remains a subject of discussion.

In our recent study, isothermal titration calorimetry (ITC) measurements supported by NMR data analysis, dynamic light scattering (DLS), quantum chemistry calculations, and molecular dynamics simulations shed light on the complex aggregation behaviour of sodium bis(1,2-dicarbollide), commonly referred to as NaCOSAN (CObalt SANwich) [1]. The model of counterion-induced metallacarborane aggregation in water was introduced and verified. It entails the formation of stable pentamers of $COSAN^-$ around 2 sodium counterions via Coulombic-driven assembly.

Computer simulations demonstrate that the key prerequisite of the counterion binding to the aggregates is the strongly uneven charge distribution of $COSAN^-$ clusters. Simultaneously, the size of the counterion should fit into the void between the $COSAN^-$ clusters within the aggregate.

At low temperatures and/or high concentrations, metallacarboranes can (partly) form larger aggregates via the second aggregation mechanism which differs significantly from the pentamer formation. The second mechanism was revealed by applying the two-process model to fit ITC curves in wide temperature and concentration ranges [2]. Recent additional ITC measurements in the presence of NaCl and with improved three-process model of aggregation have revealed the presence of heptamers (in addition to pentamers) which are formed only due to favourable enthalpy contribution. Additionally, at concentrations above 0.5 M aggregates composed of more than 30 COSAN monomers form in a combined process of favourable enthalpy and entropy gains.

On Figure 1 some of the ITC results and the pentamer structure are presented.

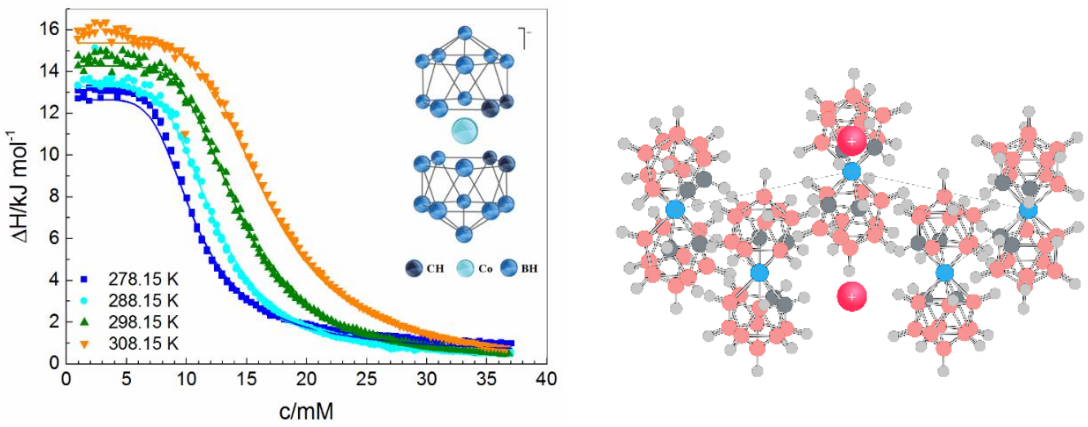

Figure 1. The enthalpograms and scheme of sodium bis(1,2-dicarbollide) - NaCOSAN - upon dilution of the 160 mM solution (left) and the pentamer structure as obtained by quantum chemistry calculations (right).

Acknowledgements:

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Vanadium(IV) and vanadium(V) complexation with succinic acid by affinity capillary electrophoresis

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Vanadium(V) speciation studies are vastly growing in the last decade after this subject was long neglected due to its complex chemistry and variety of oxidation states that it can take form of [1]. One of the main reasons for stated growing interest is a recent recognition of V as a potentially dangerous pollutant [2]. Various studies show concerning increase of V usage for industrial purposes as well [1–3]. Having in mind that toxic effect of V to surrounding biota is dependent on its speciation, it is of high importance to evaluate distribution of V species in various natural environments and recognize factors affecting it. Complex formation with natural organic matter (NOM) in the aqueous phase plays an important role in the biogeochemical cycle of V in natural aquatic environment [4]. However, this issue has not been often studied and important information on V interaction with organic ligands are still severely lacking [5]. Therefore, novel thermodynamic data on complex equilibria of V species with organic ligands are crucial in better understanding of the overall biogeochemical V cycle.

The complexation of different vanadium species (+IV and +V) with succinic acid was examined by affinity capillary electrophoresis (ACE) in aqueous acid solutions at different pH values (1.5, 2.0 and 2.5). In this study, succinic acid is chosen as a complexing agent for V(IV) and V(V) species as it can be used as a simple model of structurally more complex NOM [6]. ACE is based on the change in the electrophoretic mobility of detected species due to the interaction with other species present in the electrolyte. The injected sample contains a fixed amount of V species. A set of runs is performed using (H,Na)ClO_4 mixtures at constant pH and ionic strength (0,1 M), while the background electrolyte (BGE) contains varying amounts of succinic acid. The change in electrophoretic mobility with the increase of ligand concentration in the BGE is used to assess the speciation and equilibrium constants. Obtained data allow us to unravel the formation of protonated V(IV) and V(V) complex species and calculate their stability constant values.

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Complexation studies of U(IV) with hydroxamic acid ligands

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Uranium (U) is a significant contaminant for the environment because of its chemical toxicity and radiotoxicity affecting living organisms [1]. Human exposure is mainly derived from food chain contamination due to the spreading of Uranium in soils and water. Anthropogenic sources of Uranium are the most responsible for its spreading, and they mainly consist of mining, milling, fuel processing, weapon tests, or nuclear accidents [2].

The speciation and bioavailability of Uranium play a key role in its biogeochemical behavior in soils, reflecting on risk assessment and soil remediation studies [3]. The transfer of metal cations in soils and sediments is not only controlled by geological and physico-chemical parameters (clay and organic matter contents, pH, Eh, etc.), but also by microorganisms. The latter take part in the mobilization/immobilization of trace metals [4].

One of the main parameters determining the mobility of actinides in aquatic systems is their oxidation state which determines the different precipitation, complexation, sorption, and colloid formation behavior [5]. Under reducing conditions such as deep underground nuclear waste repositories and the depth of flooded uranium mines, anoxic sediments, and wetland soils, metal species occur on their lower oxidation state [6]. For instance, in contrast to U(VI), which is mobile, U(IV) is much less mobile due to the low solubility of U(IV) hydrous oxide ($UO_2 \cdot xH_2O(am)$) [7]. However, the migration of U(IV) is still possible due to the presence of inorganic or organic ligand. Consequently, the speciation of U(IV) in aqueous solution is of strong interest to predict its migration behavior. Nevertheless, data for the complexation of the tetravalent radiometal are scarce and inconsistent.

As natural iron-specific chelators, Siderophores have to be considered in this context [8]. These low molecular weight, water-soluble compounds are excreted by bacteria and fungi to overcome the limited bioavailability of iron under aerobic conditions by dissolving iron oxohydroxides present in the soils. Recently, they have also been recognized as effective actinide(IV) chelators and transporters, promoting the migration of plutonium in contaminated soils [9].

Because of the high affinity of actinides for hydroxamate ligands, their complexation study with U(IV) is of fundamental interest. However, the manipulation of the tetravalent metal cation in aqueous solution is not an easy task because of its instability to air and high tendency to hydrolyse. In fact, it is usually manipulated in glove boxes to keep inert conditions and it requires high acidity of the aqueous medium. On the contrary, an advantage of this metal species is its absorption in the visible region which allows U(IV) complexation studies through the classical technique UV-Vis spectroscopy.

This work is devoted to developing a method allowing complexation studies of the unstable U(IV) through UV-Vis spectroscopy using simple tools starting from a stable UO_2^{2+} solution. U(VI)aq in the presence of $HClO_4$ and in argon atmosphere was first studied through cyclic voltammetry to determine the best conditions for the electrochemical reduction. The electrolysis was then successfully performed, obtaining the complete conversion to U(IV) in a classical electrochemical cell. The completion of reduction was checked by UV-Vis spectroscopy. Finally, the reduced solution is transferred in a thermostated cell allowing the insertion of a quartz optic fibre for the registration of spectra; the entrance of argon to keep the inert conditions; and the addition of interacting species for complexation studies in a typical laboratory fume hood.

The interaction of U(IV) with some hydroxamic acids was then studied. The stability constant of the formed complex was determined through the software Hypspec and the obtained data were used to clarifying the speciation of Uranium in the presence of the ligands.

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The Centre National de la Recherche Scientifique (CNRS), the CNRS co-funded program NEEDS Environnement, the Agence Nationale de la Recherche (ANR project PLUTON, grant N° ANR-17-CE08-0053), the Conseil Régional de Bourgogne Franche-Comté, the European Regional Development Fund (FEDER), and the Ministère de l'Enseignement Supérieur de la Recherche et de l'Innovation are gratefully acknowledged for financial support.

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Study of bathocuproine and Cu(I) electrochemical behavior on Hg electrode surface

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Copper (Cu) is an essential trace element that is required by most aquatic organisms in a small amount. In larger amounts, however, it's free metal ion is toxic to most living species. Many organisms, including photosynthetic ones, can counteract the negative effects of high free copper concentrations by the production of ligands. These bind Cu, reducing the concentration of its free ionic form, and thereby its toxicity [e.g. 1]. Complexation also has an impact on the isotopic composition of Cu in oceans and rivers, conforming to theoretical predictions on the extent of fractionation between free ionic and complexed Cu(II) [2, 3].

Only a few studies have reported Cu redox speciation in nature. Detectable amounts of Cu(I) in rain and fog water, estuaries or ocean waters were reported [e.g. 4]. Although Cu(I) is, at least in an un-complexed form, not thermodynamically stable in the presence of oxygen and of other oxidants, an appreciable amount of Cu(I) present in the environment is assumed to be consequence of Cu(II) reduction with sulfite at high pH, by reduction with organic compounds, and by various radical and photochemical reactions in the presence of light [e.g. 5]. Nonetheless, speciation models usually assume that only the copper (II) oxidation state is significant based on the assumption that the system is at equilibrium and that the ε of seawater is controlled by the O_2/H_2O couple.

Although it represents a significant analytical challenge, we seek to develop analytical tools in order to measure copper redox speciation in a highly demanding matrix of seawater. Within the project two methods for Cu redox speciation will be further optimised. One is solid phase extraction involving selective Cu(II) vs Cu(I) chelation using bathocuproine (Cu(I) chelator) and EDTA (Cu(II) chelator) following the work of Buerge-Weirich and Sulzberger [4]. The method will be further optimised in order to get satisfactory recoveries of Cu(II) and Cu(I) in seawater matrix and in order to achieve preservation of the original Cu speciation with respect to the oxidation state. Other is electrochemical method which will be developed within the project. There fore¸ the results obtained within the project will enable use critical evaluation of the speciation results and the methods used. Here we represent progress on electrochemical analytical method development.

Figure 1. represent typical bathocuproine (BCP) cyclic voltammogram (CV) on Hg electrode (blue line) which is characterised with sharp peaks marked as C1/A1 and C2/A2 couples. Observed CV peak couples can be assigned to BCP adsorption and further reorientation of adsorbed BCP at the Hg electrode surface. Similar behavior is also reported and in the case

of phospholipid monolayer (PLM) where electrode potential induced reorientation of adsorbed PLM at the Hg electrode surface is observed causing changes in electrode capacitance [6]. Importantly, after Cu(I) addition in solution containing BCP changes in observed peak currents and position are occurring which are proportional to the Cu(I) added (Figure 1., orange and green line). Cu(I) detection limit is at the nmol dm^{-3} concentration range possibly enabling Cu redox speciation in coastal regions. The interference of Cu(II) with BCP was not observed if in solution together with PCP Cu(II) chelator (e.g. EDTA) was added preventing Cu(II)-BCP interaction.

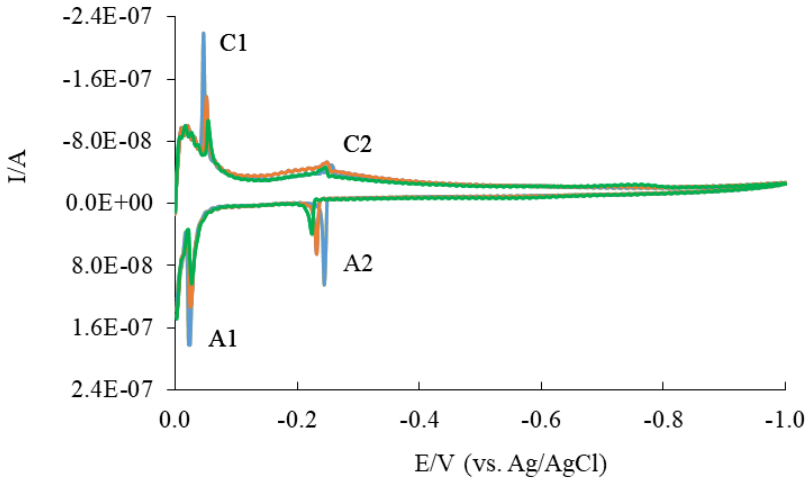

Figure 1. Blue line – CV of BCP (0.6 µmol dm^{-3}). Orange line – CV of BCP (0.6 µmol dm^{-3}) + Cu(I) (84 nmol dm^{-3}). Green line - CV of BCP (0.6 µmol dm^{-3}) + Cu(I) (168 nmol dm^{-3}). Supporting electrolyte composition: 0.55 mol dm^{-3} NaCl + 0.1 mol dm^{-3} borate buffer. Deposition potential: 0 V. Deposition time: 30 s.

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Poster Communications

Complexes of 18-membered hexaazamacrocyclic tetraacetate derivative for large ion coordination

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Polyazamacrocyclic ligands have been used in medicine for a long time [1]. Their complexes have been also studied as possible diagnostic and therapeutic agents in nuclear medicine. Recently, studies have highlighted promising properties of actinium-225. This radioisotope is suitable for a precise treatment of micrometastases as it decays via a cascade of four high-energy but short-range alpha particles [2].

This work deals with the preparation and characterisation of the 18-membered polyazamacrocycle H_4L^1 (**Figure 1**) and its complexes. Although the ligand is known for a long time, its studies are limited [3,4]. As its size should be suitable for complexation of large metal ions, pilot studies of complexes of the ligand with various large trivalent lanthanides and selected biogenic metal ions were carried out. Thus, kinetics of complexation and decomplexation via UV-VIS and paramagnetic NMR were performed as well as thermodynamic and structural characterization of the prepared complexes.

Kinetic studies suggest that Ln(III) complexation is a more complicated process than formation of complexes of DOTA-like ligands. The measurements showed an intermediate *in-cage* complex which slowly re-arranges to a final *in-cage* complex. Overall complexation of H_4L^1 is faster than that of DOTA. Based on the decomplexation studies, the Ln(III) complexes of H_4L^1 are more kinetically inert than those of DOTA. Equilibrium studies confirmed selectivity for large metal ions and formation of L:M 1:1 and 1:2 complexes. Solid-state structures of M(II) ion complexes in both metal-to-ligand ratios showed various coordination modes also involving the pyridine coordination.

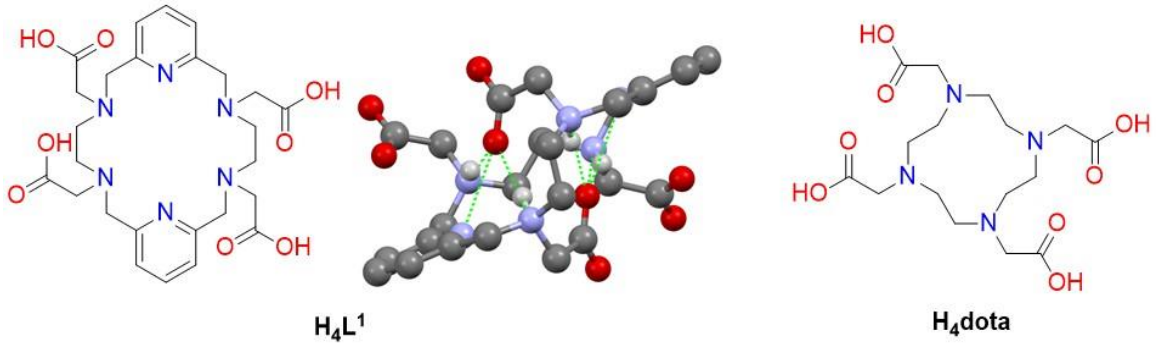

Figure 1. Structures of the 18-membered polyazamacrocyclic ligand and DOTA

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The new solid-contact ion-selective electrode based on dodecabenzylbambus[6]uril for perchlorate analysis

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Dodecabenzylbambus[6]uril ($Bn_{12}BU[6]$ – see Figure) is an anion receptor that binds the perchlorate ion the most tightly (stability constant ~10^{10} M^{-1}) of all anions due to the excellent match between the ion size in relation to the receptor cavity [1-3]. This new bambusuril compound was used as an ionophore in the ion-selective membrane (ISM) to develop ion selective electrodes (ISEs) for determination of perchlorate concentration utilizing the poly(3,4-ethylenedioxythiophene) (PEDOT) polymer film as a solid-contact material.

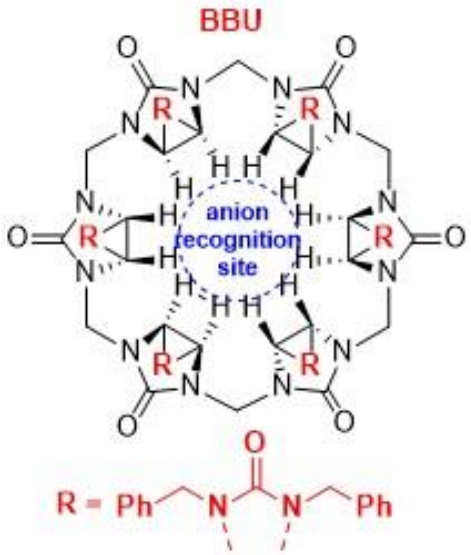

Figure: The chemical structure of dodecabenzylbambus[6]uril ($Bn_{12}BU[6]$ = ionophore)

Variation of the content of $Bn_{12}BU[6]$ and tridodecylmethylammonium chloride (TDMACl) in the plasticized poly(vinyl chloride)-based ISM was also tested. All the prepared solid-contact ISEs and their analytical performance were characterized by potentiometry, cyclic

voltammetry (CV), electrochemical impedance spectroscopy (EIS) and chronopotentiometry. The ISEs showed rapid response and a sub-Nernstian slope (~57 mV/decade) during potentiometric measurements in perchlorate solutions in the concentration range from 0.10 to 10^{-6} M simultaneously with their high stability and sufficient selectivity to other common inorganic anions like bromide, chloride, nitrate and sulphate. The function of the ISE was further verified by analysis of real water samples (lake, sea, and mineral water), which gave accurate and precise results. Other experimental details are given elsewhere [4].

Acknowledgement:

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Redox-active phenolate macrocyclic ligands for first-row transition metals complexation

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Molecular electronic is a perspective direction of temporary science. Downscaling of electronic devices at molecular level would allow for miniaturization or development of new technologies. Temporary molecular electronic research utilizes mainly organic conjugated systems or metal complexes. Among the later group, the first-row transition metal ions attract increasing attention for industrial applications due to the low price and good availability.

Construction of the molecular electronic devices requires stable metal ion binding without risk of relies of transmetalation. Macrocyclic ligands are promising building blocks as their complexes show often high thermodynamic stability and kinetic inertness and, thus, they may serve as intact construction units. The macrocyclic ligand of the first choice for complexation of the first-row transition metal ions are derivatives of 1,4,8,11-tetraazacyclotetradecane (Cyclam) due to the high thermodynamic stability. In addition, electrochemical properties of their complexes can be gently tuned by introducing of specific pendant arms at nitrogen atoms of the macrocycle which is easily synthetically accessible.

Here we report synthesis of cyclam derivatives bearing carboxylate, phosphonate or phenolate coordinating pendant arms and structural and electrochemical characterization of their complexes. For further applications and investigation of electrochemical effects of the metal ions on the surrounding structures, we have decorated the complexes with redox-active nitrophenolic group (Figure 1). The nitro group serves as a sensor which allows evaluation of the mutual effect of the two redox centers. The mutual effect is closely related to the conductivity of the studied structure which is the key property for the application as building units in the molecular electronic devices.

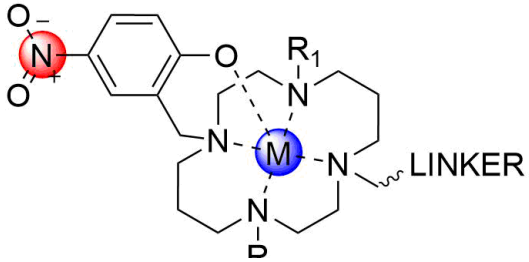

Figure 1. Schematic structure of nitrophenolic derivative

Complexes of ditopic macrocyclic ligand with a bis(phosphinate) spacer

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The "free" Ln^{III} ions are toxic but have several unique properties useful for biological imaging (such as MRI or luminescence imaging). Thus, thermodynamically stable and kinetically inert complexes of these ions are used in medicine. Typically, these complexes contain ligands based on H_4dota (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). However, the currently used MRI contrast agents have suboptimal properties because of technological advancements in MRI (mainly higher magnetic fields of MRI scanners). For these higher fields, complexes of Gd^{III} with multitopic ligands weighing about up to 6 kg mol^{-1} [1] are more suitable. Moreover, the multitopic ligands may facilitate energy transfer between different Ln^{III} ions, i. e., the lanthanide-sensitized lanthanide luminescence. Furthermore, the Ln^{III} complexes of phosphinate derivatives of H_4dota have multiple desirable properties in comparison with complexes of other H_4dota derivatives, such as fast coordinated water molecule exchange, high hydrophilicity and high extent of second-sphere hydration. However, the studies on multitopic ligands, especially of those linked by phosphinate group, are limited.

For these reasons, we prepared and studied Ln^{III} complexes of ditopic methylene-bis(phosphinate)-bridged ligand $(DO3AP)_2CH_2$ and its Ln^{III} complexes (**Figure 1**). First, we studied the isomeric composition and dynamics of solutions of these complexes as these solutions contain multiple stereoisomers in equilibrium. Next, we determined the relaxivity of the Gd^{III} homodinuclear complex of the studied ligand at low magnetic field and luminescence properties of the Eu^{III} and Tb^{III}-containing complexes. Then, inertness of Ce^{III} homodicomplex was studied by UV-vis spectroscopy. Finally, all of the studied properties were compared with properties of analogous complexes of monotopic ligand containing methylene-bis(phosphinic) acid on one pendant arm, $DO3AP^{PIN}$ [2] (**Figure 1**) which we also studied. This approach was used to determine the effect of ditopicity on the studied properties.

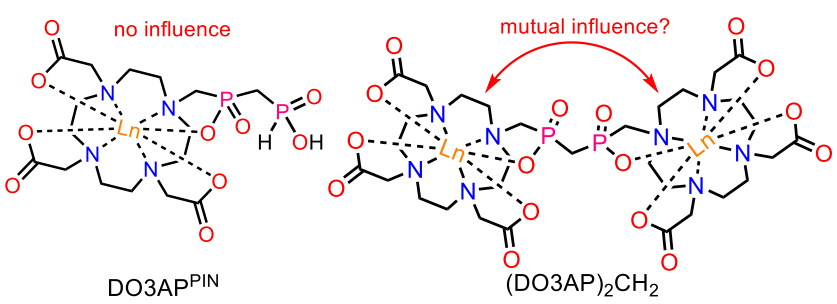

Figure 1. The Ln^{III} complexes of ditopic ligand $(DO3AP)_2CH_2$ where the mutual influence of Ln^{III} ions was evaluated, and those of monotopic ligand $DO3AP^{PIN}$, used as reference complexes.

The determined relaxivity of the Gd^{III} homodicomplex of $(DO3AP)_2CH_2$ was significantly larger than the relaxivity of Gd^{III} complex of $DO3AP^{PIN}$ confirming the importance of ditopicity of complexes at higher magnetic fields of MRI scanners. However, the equilibrium composition in solutions of Ln^{III} complexes of ditopic $(DO3AP)_2CH_2$ was analogous to the equilibrium composition in solutions of Ln^{III} complexes of $DO3AP^{PIN}$. In summary, while relaxivity of the complex is highly affected by ligand ditopicity, the thermodynamic stability of isomers of these complexes are affected insignificantly.

Acknowledgements:

We thank the COST Nectar Action and Ministry of Education of the Czechia (no. LTC20044), and the Grant Agency of Charles University (No. 68122) for financial support.

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Versatility of (aminomethyl)phosphinic acid pendant arm in complexes of DOTA-like ligands

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Molecular imaging is a powerful non-invasive diagnostic tool to localize abnormalities *in vivo* [1]. To increase contrast of selected area, contrast agents (CAs) are utilized. CAs are generally based on metal complexes and, thus, must be stable and inert *in vivo* to prevent leaching of free metal ion (commonly, Ln(III) or first-row transition metal M(II) ions). Hence, polyazamacrocycles with proper pendant arms are used as ligands and cyclen with four acetate pendant arms, *i.e.*, DOTA (**Figure 1**) stands out as "the golden standard" for coordination of Ln(III) ions. Substitution of one pendant arm of DOTA with a methylphosphinate group leads to ligands suitable for further derivatization and for fine tuning of properties of their complexes [2]. Commonly, stability / inertness of formed metal complexes *in vivo* remains unchanged upon such substitution and is sufficiently high, and, thus, the ligands are good adepts for further studies.

In this work, one (aminomethyl)phosphinic pendant arm on DOTA moiety is introduced (forming a bifunctional ligand DO3AP^{AM}, **Figure 1**). Influence of the pendant amine (de)protonation on properties of its complexes, and differences in properties after acetylation of the pendant amine (DO3AP^{AcAM}, a model for conjugates of DO3AP^{AM}, **Figure 1**) were investigated. The change of relaxation properties were evaluated over Ln(III) series as the ions alter ^{31}P NMR parameters (usable in ^{31}P magnetic resonance spectroscopy)[3] as well as relaxation properties of bulk water (MRI and PARACEST imaging[4]). Moreover, syntheses, solid-state structures and speciation in solution of ligands and their Ln(III) complexes will be presented.

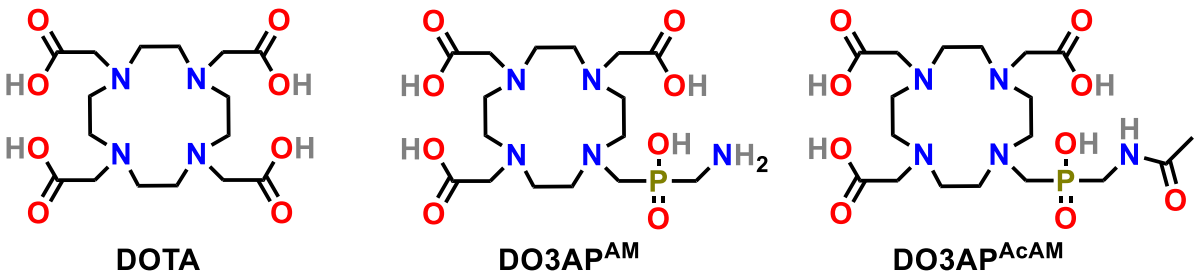

Figure 1. Structures of ligands mentioned in the text above.

Acknowledgements:

The work was supported by COST Nectar Action and Ministry of Education of the Czechia (no. LTC20044).

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Development of supramolecular hybrid materials based on metallacages

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Hybrid materials for drug delivery covers a broad range of hybrid nanomaterials and nanocomposites used in drug delivery systems. The combination of polymer scaffolds and drug nanocarriers and the association of controlled drug release properties provide novel materials, considered hybrid as they gather two therapeutic effects: scaffolding and drug delivery. Many drug carriers are also often associated with stability issues, drug leaking or considerable interaction with undesirable cells, hindering their clinical function. Hence, for topical application, drug nanocarriers are often introduced in conventional secondary vehicles in order to provide the desired properties necessary for the administration route.

Here, inspired by previous studies [1], we report on a new class of synthetic hydrogels integrating self-assembled supramolecular 3D-coordination complexes, namely metallacages. To this aim, a family of Pd_2L_4 metallacages (Fig. 1A) has been selected, previously shown to be able to encapsulate and deliver cisplatin to cancer cells [2,3]. As polymer scaffold, different lengths of modified polyethylene glycol molecules (PEG) were used to be tethered to the cage scaffold to provide the desired hydrogel (Fig. 1B).

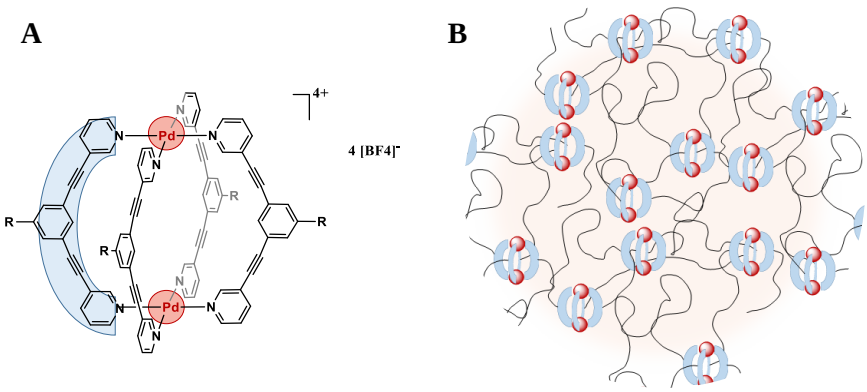

Figure 1. A) Metallacage scaffold used in this study; B) Schematic representation of the desired hydrogel-containing metallacages.

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Identification the protonated complex species of metal ions by affinity capillary electrophoresis

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The protonated complex species of metal ions with different ligands are difficult to identify by physical methods. Generally, these species have been postulated to improve the fitting of potentiometric or spectrophotometric data. In this work the advantages of affinity capillary electrophoresis (ACE) are demonstrated for identification of protonated complex species. The cases of U(VI) complexes with oxalic and succinic acids are investigated.

The mobilities of U(VI) are measured in aqueous acid solutions containing ligand at different concentrations (from 0 up to 0,5 M) in the range of pH 1,5 - 2,5. The observed U(VI) mobility was found to decrease with increasing ligand concentration added to the background electrolyte solution. Since the changes of metal-ion mobilities at different pH values reflect the chemical equilibria occurring in solution [1], the ACE data enabled us to unravel the complex species forms.

References:

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Antiproliferative indolo[2,3-*d*]benzazepine and indolo[2,3-*c*]quinoline derivatives and their copper(II) complexes: solution studies and interaction with DNA

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Paullones are small molecule cyclin-dependent kinase (CDK) inhibitors developed in the early 1990's (Fig. 1) [1]. CDKs are a group of serine/threonine kinases which control the transmission between successive stages of the cell cycle, therefore CDKs are considered as potential targets for anti-cancer medication [2]. Indolo[3,2-*c*]quinolines are known to induce apoptosis in cancer cells. These planar molecules most probably intercalate into DNA and inhibit topoisomerase I/II [3]. The ligands **HL^1**−**HL^8** shown in Fig. 1 are related structurally with paullone and indolo[3,2-*c*]quinoline. Limited aqueous solubility of the basic structure of these molecules is a main obstacle in development of effective and bioavailable agents. This issue can be addressed by the introduction of metal chelating sites into the molecule. Complex formation with metal ions fundamentally affects the charge, solubility and lipophilicity of a ligand. The attachment of morpholine, known as a pharmacophore moiety, can improve the pharmacological profile of a drug candidate. The copper(II) complexes of the ligands shown in Fig. 1 revealed low micro- to sub-micromolar IC_{50} values with promising selectivity toward human colon adenocarcinoma doxorubicin-resistant Colo320 cancer cells as compared to the doxorubicin-sensitive Colo205 cell line.

Hereby, we present the comprehensive solution chemical characterization of a series of indolobenzazepine and indoloquinoline derivatives **HL^1**−**HL^8** and their copper(II) complexes (**1**−**8**). Aqueous stability, solubility and lipophilicity of the presented ligands and copper(II) complexes were studied. Furthermore, stability in human blood serum and DNA binding of selected compounds were assayed as well. Studies were implemented by UV-vis spectrophotometry, steady-state and time-domain fluorescence spectroscopy.

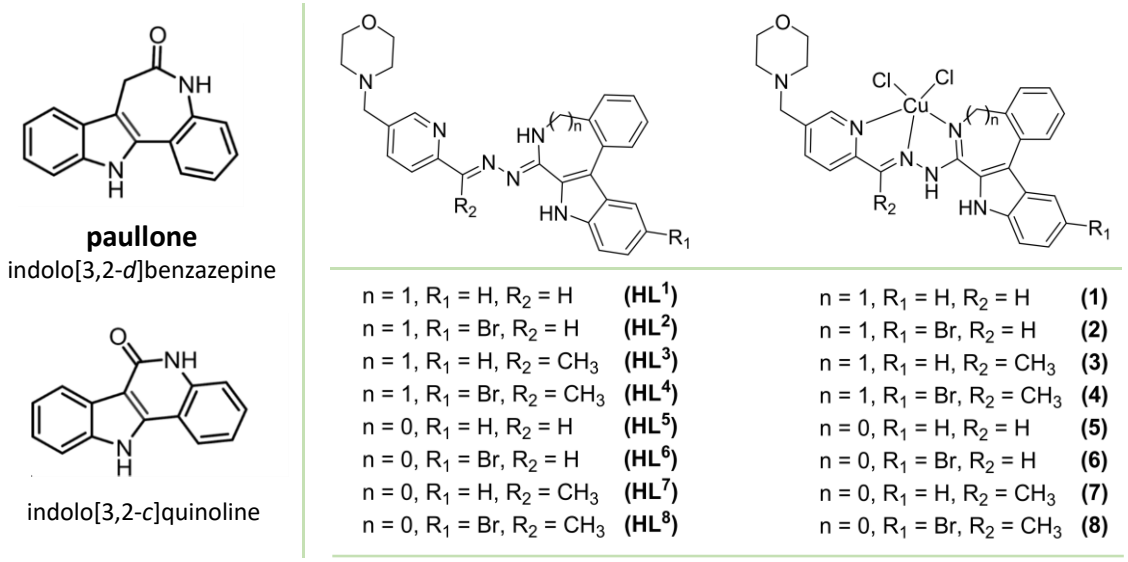

Figure 1. The structure of paullone and indolo[3,2-*c*]quinoline together with the synthesized metal free ligands **HL^1**–**HL^8** and their copper(II) complexes **1**–**8**.

Acknowledgements:

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Anticancer methylenetrimethylammonium-thiosemicarbazonates and their copper(II) complexes: solution chemistry, redox properties and cytotoxicity

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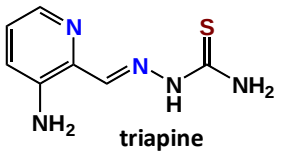
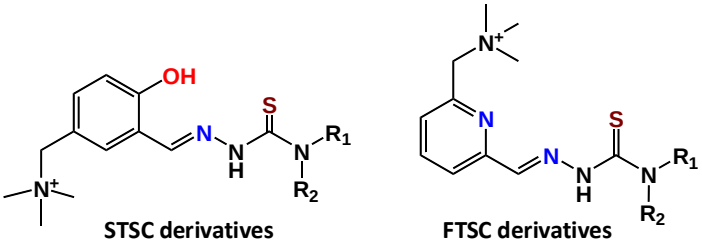
Thiosemicarbazones (TSCs) are important class of compounds due to their wide spectrum of pharmacological effect including activity against cancer, bacterial and viral infections [1,2]. α-*N*-pyridyl and salicylaldehyde tridentate derivatives contain a pyridine-nitrogen or a phenolato-oxygen at chelating position, respectively, in addition to the (N,S) donor set of the TSC moiety. Among the α-*N*-pyridyl TSCs the 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (triapine) is the most prominent representative. Following several phase I and II trials [1,3], currently a phase III trial is recruiting patients to test the combination of triapine, cisplatin and radiation therapy. The mechanisms of action of TSCs are often connected with their ability to form stable and redox active complexes with endogenous metal ions such as iron or copper. On the other hand, numerous copper(II) complexes of TSCs exhibit significantly higher anticancer activity than the corresponding ligands and it is suggested that their redox properties may have an impact on the cytotoxicity [1,4]. The copper(II) binding ability of both the α-*N*-pyridyl and salicylaldehyde tridentate TSCs is fairly strong, although it can be fine-tuned by the substituents on the TSC scaffold.



triapine

TSCs have generally limited water solubility, although the well-balanced lipo-, hydrophilic character of a drug candidate molecule is an important feature, however tuning the hydrophilic/lipophilic character in order to achieve an optimal aqueous solubility and high cytotoxicity is a challenge in the development of more effective anticancer drugs. Herein, the salicyladehyde (STSC) and 2-formylpyridine (FTSC) thiosemicarbazone families were expanded with the positively charged trimethylammonium group -NMe_3^+, which can provide

increased water-solubility, cytotoxicity via the possible interaction with organic cation transporters playing role in the uptake of various positively charged drugs in cancer cells [5].



We have studied the proton dissociation processes of selected 5-methylenetrimethylammonium STSC [6] and 6-methylenetrimethyl-ammonium FTSC derivatives, the solution stability and redox properties of their copper(II) complexes in addition to their *in vitro* cytotoxicity against drug-sensitive (Colo-205), doxorubicin-resistant (Colo-320, overexpressing ABCB1) human colon adenocarcinoma cell lines and the non-cancerous human embryonal lung fibroblast cell line (MRC-5). For the characterization of the solution chemical properties pH-potentiometry and UV-visible spectrophotometry were applied, and the redox reaction of the copper(II) complexes with glutathione and ascorbic acid was monitored by UV-visible spectrophotometry, and spectroelectrochemical measurements were performed to determine the redox potentials and check the chemical reversibility. The compounds described in this work represented a sound basis for further development as antiproliferative agents.

Acknowledgements:

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Complexes formed with $[Ru(\eta^6\text{-}p\text{-cymene})(Cl)_2]_2$, $[Rh(\eta^5\text{-}C_5Me_5)(Cl)_2]_2$ and $[Re(Cl)(CO)_5]$ organometallic cations of sterane-based ligands bearing (N,N) donor set

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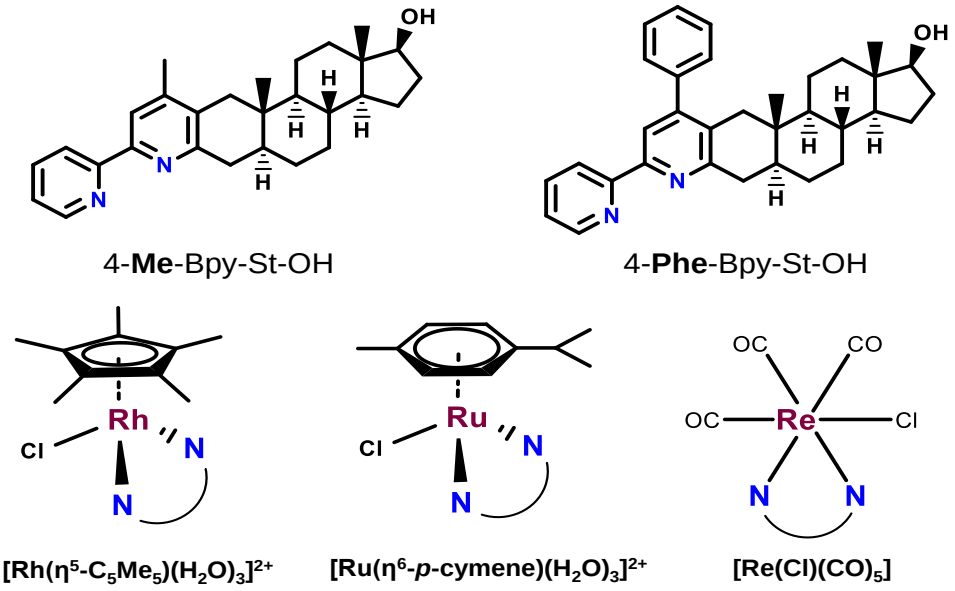
The often-caused noxious side effects of clinically used anticancer drugs forced the development of novel chemotherapeutic agents aiming to obtain more effective and selective candidates. Among the metal-based chemotherapeutics, platinum(II) complexes such as cisplatin are widely used for decades in cancer therapy against solid tumors due to their effectiveness. However, their use is also accompanied by the aforementioned drawbacks [1]. The development of complexes of other platinum group metal ions, such as the half-sandwich ruthenium(II) or rhodium(III) complexes may overcome these problems by showing significant potential in this field, with a wide-range of bioactivity.

The investigated piano-stool complexes are built up by a bidentate ligand, which contains a 2,2'-bipyridine chelating moiety with (N,N) donor atom set and a sterane backbone, as well as chlorido co-ligand as leaving group. These components affect the solution stability, solubility, lipophilicity and ultimately the pharmacokinetic properties and biological activity relative to the free bidentate ligand. Our previous results showed the formation of highly stable complexes with aromatic (N,N) donor atom in combination with organoruthenium and organorhodium cations [2]. Furthermore, the 2,2'-bipyridine unit is well-known of its strong chelating ability towards other metal ions such as $[Re(Cl/H_2O)(CO)_5]^{0/+}$, whose complex and its derivatives are also investigated owing to their antiviral effects [3]. In this work, two novel sterane-based ligands and their $[Ru(\eta^6\text{-}p\text{-cymene})(L)Cl]^+$ (RuCym(L)), $[Rh(\eta^5\text{-}C_5Me_5)(L)Cl]^+$ (RhCp*(L)) and $[Re(L)Cl(CO)_3]$ complexes were developed (Scheme 1). In addition to the synthesis, investigation of the ligands as well as the complexes in terms of solution equilibria and biological activity is also reported. The synthesis of the half-sandwich complexes was performed in dichloromethane, followed by the addition of *n*-hexane resulting in precipitation. In the case of Re(I)- complexes, the reaction was carried out in toluene in which the formed complexes were insoluble. All the compounds were isolated in a relatively good yield (70 – 90%), and were characterized by ^1H, ^{13}C NMR spectroscopy and high-resolution mass spectrometry. UV-visible spectrophotometry was used to investigate the solution speciation of



Scheme 1. Chemical structure of the ligands and the organometallic complexes

the ligands as well as the complexes in 30% (v/v) DMSO/water medium. The ligands are found in their neutral form at physiological pH based on the determined proton dissociation constants (pK_a). Both the two ligands form highly stable complexes with the half-sandwich RuCym and RhCp* triaqua cations; and they are present at 93-98 % in the used medium at pH = 7.40, however a slight decrease in the stability constants could be observed in the case of RuCym complexes compared to RhCp* ones.

Acknowledgements:

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Solution studies on the interaction of three new Schiff base 8-hydroxyquinolines with essential metal ions

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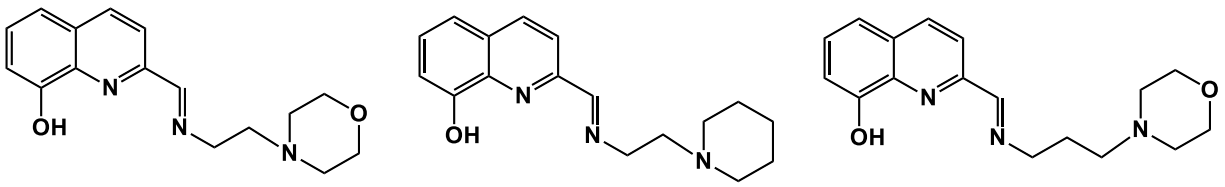
8-hydroxyquinoline (HQ) is considered a privileged scaffold in medicinal chemistry, having a myriad of potential pharmacological applications, due to its antimicrobial, antifungal and anticancer activities [1,2]. A possible synergistic effect between the HQ scaffold, chelated to a metal ion with potential for involvement in redox processes, is an interesting strategy, and several examples have already been reported [3,4]. In this work, three new Schiff base HQs substituted at position 2 with piperidine/morpholine type moieties were prepared in addition to their Cu(II) and Zn(II) complexes in order to obtain stable, efficient and selective compounds for cancer therapy. All metal complexes were characterized by elemental analysis, ESI mass spectrometry, FTIR and UV-visible absorption spectroscopies, as well as by single-crystal X-ray diffraction. The *in vitro* cytotoxic activity of the ligands and the complexes was also assayed in human pancreatic cancer and melanoma cancer cells (BxPC3 and A375, respectively). The Schiff base HQ derivatives showed moderate standalone activity and the metal complexes were always more cytotoxic than the corresponding ligands.



L[1] **L[2]** **L[3]**

Figure 1. Chemical structures of the HQ ligands.

In the anticancer effects of HQ derivatives, their interactions with endogenous metal ions play an important role, as their biological effects are related to the *in situ* formation of complexes with metal ions such as Cu(II) and Zn(II) ions. In our case, the isolated metal complexes were more active against the tested cell lines in comparison with the free ligand. In order to get a closer understanding of the mechanisms of action of the new ligands and the complexes, the proton dissociation constants of the ligands in pure aqueous medium, as well as the complex formation processes with the mentioned essential metal ions, using UV-visible spectrophotometric titrations, were determined. For the Cu(II) complexes, cyclic voltammetric measurements were performed to monitor the redox properties. The redox reactions were also followed with two natural reducing agents, namely ascorbic acid and glutathione with UV-visible spectrophotometric detection.

Acknowledgements:

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Effect of the amino acid environment of histidine on the copper(II) binding selectivity of Tau fragments

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder, its main symptom is dementia, and leads to the decline of motor and cognitive functions. Pathophysiological changes involving abnormal protein aggregation in the central nervous system characterise AD. These changes begin several years earlier before the first clinical symptoms appear. While aggregation of amyloid-β (Aβ) leads to the formation of extracellular amyloid plaques, aggregates of hyperphosphorylated Tau protein form intracellular neurofibrillary tangles [1-4]. Previous studies also justified that metal ions such as Cu(II), Zn(II), Fe(II), that are essential for normal brain function, are accumulated in the brain of AD patients and contribute to the hyperphosphorylation of Tau protein, leading to cell impairment. [5]. Tau protein contains 12 histidine amino acids in the sequence which provide high metal binding affinity to Tau and its various peptide fragments. These residues with metal binding ability are well-separated and several other coordinating side chains are also available close to the histidyl sites [6]. However, the characterisation of the metal binding sites of Tau protein have not adequately been clarified yet.

The systematic investigation of Tau fragments containing the possible metal binding sites began a few years ago in our research group [7-9]. As a first step we investigated the copper(II) complexes of histidyl containing fragments from the N-termini (Tau(9-16), Tau(26-33)) and R3 region (Tau(326-333). These studies reveal the outstanding copper(II) binding selectivity of Tau(26-33) containing –TMH– sequence. In the continuation of this work, different fragments and mutant peptides were studied that contain a seryl or threonyl residue close to the histidyl sites: Ac-ATMHQD-NH_2 (Tau(29-34) mutant), Ac-AQPHTEI-NH_2 (Tau(91-97)), Ac-KTDHGA-NH_2 (Tau(385-390)), Ac-SPRHLS-NH_2 (Tau(404-409)). Beside serine and threonine, proline amino acid could also play crucial role in the stability and structure of copper complexes of these fragments because the peptide binding formed from the secondary amine group does not allow its coordination. Therefore the coordination of copper(II) ions to the proline containing peptides is modified relative to those of fragments without proline.

Generally, the imidazolyl group of histidine is the anchoring site of Tau fragments, followed by deprotonation and coordination of peptide nitrogens preceding histidine at higher pH. The presence of threonyl side chain usually enhances the stability of complexes formed

around physiological pH and its participation in the coordination of copper(II) ion results in specific spectroscopic parameters.

On the other hand, the presence of proline in two Tau fragments, Tau(91-97) and Tau(404-409), results in the deprotonation and coordination of the peptide nitrogen atoms towards the C-termini and imidazole nitrogen is also replaced by an amide nitrogen resulting in the formation of [$CuLH_{-4}$] complexes.

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Nickel(II) and zinc(II) complexes of Tau(320-333) fragment

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The aggregation and hyperphosphorylation of tau protein play important role in the pathogenesis of neurodegenerative diseases. The conformational changes of proteins and subsequent aggregation are also affected by metal ions that accumulate in high concentrations, such as Cu(II), Ni(II) and Zn(II) ions [1,2]. The most important metal ion binding site for proteins are the thiolate group of cysteine and the imidazole ring of the histidine side chain.

The main goal of our work was to investigate the metal complexes of the Tau(320-330) fragments (Ac-SKCGSLGNIHHKPG-NH_2 and Ac-SKCGSLGNIHHHKPG-NH_2 peptides). These peptides contain the two potential metal binding sites of tau protein, Cys322 and His329,330.

Based on the potentiometric titration data, we can state that mono- and dinuclear complexes are also formed. In the neutral pH range (pH ≤ 7) histidyl and cysteinyl side chains serve as metal binding sites, while in alkaline solution (pH > 7), the neighbouring deprotonated amide nitrogens are also involved in the coordination of the nickel(II) ion. Spectroscopic data confirmed the formation of coordination isomers at 1:1 metal ion to ligand ratio. Evaluation of CD spectra made it possible to assess the ratio of the coordination isomers of mononuclear complexes. It was found that the nickel(II) ion is predominantly bound to the thiolate moiety (70%) although the metal ion can also be coordinated by histidyl residues (30%) On the other hand, at twofold metal ion excess (Ni(II):L = 2:1 ratio) one nickel(II) ion is bound to the 'SKCG' part of the peptide and the other metal ion is coordinated by the 'HH' or 'HHH' moieties.

The Zn(II) complexes have enhanced stability due to the macrochelate structure formed by the multidentate coordination of peptides. However, the presence of nickel(II) and zinc(II) ions results in the formation of mixed metal complexes, where the nickel(II) ion is mainly bound to the N-terminal part of the molecule, while the zinc(II) ion is coordinated by histidyl residues.

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Co(III) and Ga(III) complexes as antimicrobial drug candidates. Solution studies and synthesis

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There is an urgent need to develop novel antibiotics as antimicrobial resistance (AMR) is reported to be one of the leading causes of death worldwide. Multi-drug resistant pathogenic infections were associated with approximately 4.96 million deaths annually in 2019, with 4.95 million of these being directly associated with bacterial AMR. The antimicrobial properties of metals have been well known for centuries, with many metal-based compounds playing important clinical roles as therapeutics and diagnostic agents. We are interested in complexing bioactive ligands with Co(III) and Ga(III) and utilizing siderophores to enhance the uptake of Bi(III) and Ga(III).

The determination of pK_a values for ligands and stability constants for complexes and the generation of pH speciation distribution curves are invaluable for medicinal inorganic chemists focused on the development of metal complexes as antimicrobial drug candidates.

GSK1322322 is an N-formyl hydroxylamine-based potent and reversible inhibitor of PDF developed by GlaxoSmithKline (GSK). N-Formyl hydroxylamines are also known as reverse- or retro-hydroxamates and much like hydroxamic acids represent an important class of bidentate metal-chelating functional group. Proton dissociation processes of the peptide deformylase inhibitor GSK1322322 were determined using pH-potentiometric, UV–vis spectrophotometric and ^{1}H NMR titrations. Complex formation equilibrium processes of GSK1322322 with Ga(III) were studied by pH-potentiometry and ^{1}H NMR spectroscopy. The successful synthesis and characterisation of Co(III) and Ga(III) complexes of N-formyl hydroxylamines were subsequently undertaken and the antibacterial activity of a Co(III) peptide deformylase inhibitor complex investigated [1].

Bacteria have a high demand for Iron (Fe) as it plays a vital role in DNA synthesis and oxygen metabolism. To satisfy this high requirement pathogenic bacteria produce Fe-scavenging molecules known as siderophores, which sequester Fe from their extracellular

environment and the hosts innate Fe transporting proteins. Consequently, siderophore Fe uptake systems can therefore be targeted as an antibacterial strategy. Cefiderocol for example is a new class of antibiotics known as siderophore drug conjugate's (SDC's) that hijack the bacteria's own Fe acquisition system to internalize a cephalosporin antibiotic.

pK_a values were determined for the catechol based ligands, 2,3 DHBA, aminochelin and azotochelin and stability complexes for the corresponding Ga(III) complexes. A novel series of Ga(III) bipyridyl catecholate complexes has been successfully designed, synthesised and fully characterised. Preliminary toxicity studies have demonstrated $[Ga(bipy)_2(2,3Dhba_{-1H})][NO_3]$ exhibits promising activity against the pathogenic microbe Aspergillus fumigatus. The synthesis of Ga(III) aminochelin and azotochelin complexes are currently being undertaken and progress to date will be reported [2].

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[2] Unpublished results.

Synthesis and characterization of tryptophane metabolites metal complexes

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Tryptophan (Trp) is an essential amino acid with a large variety of physiological functions, and a fundamental role on the regulation of immune, central nervous and gastrointestinal nervous systems and with a significative influence on the intestinal microbiota [1,2]. Trp metabolic disorder can affect the balance of intestinal microbiota leading to inflammation that contributes to the progression of colorectal cancer (CRC), and vice-versa, *i.e.*, CRC development results in inflammation that changes the homeostasis of intestinal microbiota affecting Trp metabolism. From Trp metabolism, compounds like kynurenic acid (KynA), xanthurenic acid (XA) and 8-hydroxyquinoline-2-carboxilic acid (8-HQA) are formed and are known by their biological activity that results, mainly, from their sequestering ability towards specific metal cations (*e.g.*, Fe^{3+}, Cu^{2+}, Zn^{2+}) [3,4]. In our more recent work, we are trying to understand more about TrpM possible influence on metal homeostasis in the gut [5,6]. In the frame of that work, efficient strategies of synthesis for Fe^{3+}, Cu^{2+} and Zn^{2+} -TrpM complexes have been developed. Particularly, the optimization of synthetic procedures in terms of metal-ligand molar ratio, solvent, temperature, pH and reaction time. have been performed.

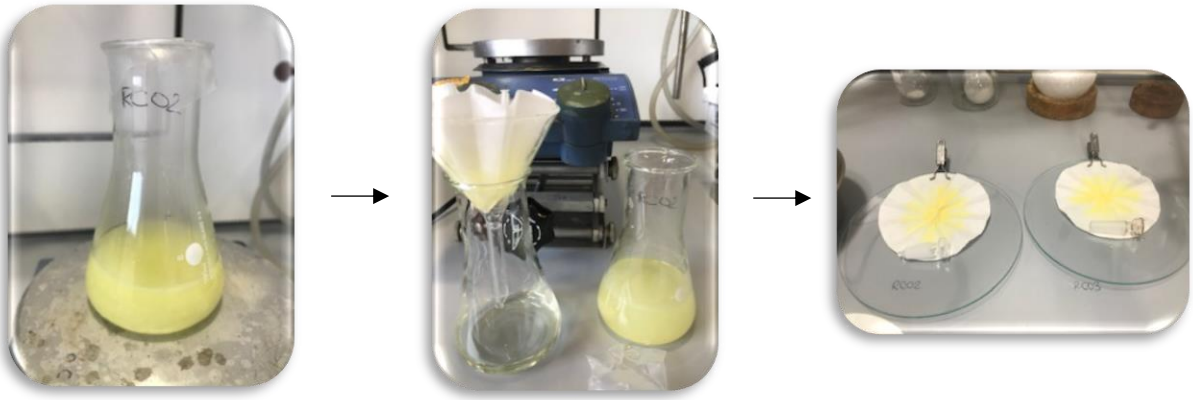

Figure 1: Representative steps of the synthetic procedure

In this work, details of the synthetic strategies developed will be presented. All the solid compounds obtained were analyzed by IR spectroscopy (ATR-IR) and mass spectrometry. Depending on the amount obtained, some of them have been characterized by thermogravimetric analysis and, in the case of Zn^{2+} complexes, ^{1}H NMR spectroscopy was also used.

Acknowledgments:

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Handling non-covalent drug delivery systems: optimization of hyaluronic acid – carnosine complexes

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The increasing interest in drug delivery as a method for administering pharmaceutical compounds to achieve a therapeutic effect in human diseases lies in the possibility to overcome many of the drawbacks when supplying a drug to the patient, i.e., degradation, interaction with other cells, incapacity to penetrate tissues as a result of the drug chemical nature. Macroscopically, conventional drug administration relies on pills, eye drops, ointments or intravenous solutions. At the molecular level, novel drug delivery approaches often include drug entrapment within polymeric materials that may reach the desired bodily compartments [1-3].

Hyaluronic acid (HA) is a linear polymer consisting of repeating disaccharide units of glucuronic acid and glycosaminoglycan. It is the major physiological constituent of the extracellular matrix and its chemical-physical properties are closely related to its molecular weight [4, 5]. Carnosine (Car) is a dipeptide made of alanine and histidine. It is known to have antioxidant and metal ion-chelating properties, i.e., towards Cu^{2+} ion [6]. Recently, a covalent conjugate HA-Car has been patented and showed unprecedented healing properties toward osteoarticular diseases [7, 8].

For its versatility, physiological functions and healing properties, HA has potential applications in drug delivery as "host" system [5]. Nonetheless, simply mixing HA with the desired "guest" drug cannot itself built-up a suitable drug delivery system (DDS). In this work, we aim to develop HA-based non-covalent DDSs relevant for the cure of osteoarticular and/or ophthalmological diseases. In this context, isothermal titration calorimetry (ITC) offers the unique possibility to study not only thermodynamic properties of the resulting DDSs [9, 10, 11] but also to investigate their stability under conditions that simulate the *in vivo* ones [12].

Here, we report preliminary results on HA-Car based DDSs containing both high and low molecular weight HA. The thermodynamic parameters of the various complexes and species obtained as well as the driving forces of their formation are discussed with regards to the peculiar properties of the starting building blocks.

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Ferric and ferrous assimilation systems: diversity of equilibria & a source of potential applications

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Iron acquisition is one of the key steps for promoting microbial growth. Although Fe(III) has long been considered the nutritionally important oxidation state of Fe at the host-pathogen interface, Fe(II) can also be bioavailable particularly in anaerobic and/or acidic niches, both of which would enhance the solubility of Fe(II).

Under iron-deficient conditions most aerobic microorganisms secret low molecular-weight, highly specific Fe(III) chelating compounds – siderophores, which actively transport ferric ions into the cells via specific receptors in the microbial membranes [1].

The difficulties in synthesis of structurally complicated natural siderophores has directed the siderophore research towards biomimetic chemistry, aiming at mimicking or reproducing the function of the natural product rather than its detailed structure. This approach allowed us to diversify the arsenal of biologically active siderophore-type molecules, introduce additional desired chemical and/or physical properties, and provide means to identify general motifs governing an interplay between structure and function in biological activity [1-4].

Taking into account, that siderophores are absent in the host cells, they are tempting targets for microbial imaging; 68Ga and 89Zr are positron emitters that have recently become the subject of great interest for molecular imaging applications using positron emission tomography (PET). Of the evaluated siderophores, 68Ga-ferrioxamine E (FOXE) and its close biomimetic analogs were shown as the most promising for possible applications in PET imaging of S. aureus [4]. On the other hand, desferrioxamine B (DFO) is currently the most commonly used chelator to radiolabel biomolecules with 89Zr [5]. However, its *in vivo* stability has proven insufficient, and transchelation has been observed. Our Zr(IV) – DFO solution studies provided information on the actual chemical form of the complex in biological media, and this can

contribute to a better understanding of the in vivo speciation and differences in the biological activity of this and other chelators [6,7].

Overall, proposed derivatives may hold potential as inert and stable carrier agents for Fe(III), Ga(III) and Zr(IV) ions for diagnostic medical applications. They could also allow identifying critical microbial compartments in which siderophores accumulate and thus illuminate key targets for specific drugs against bacterial/fungal diseases.

The major bacterial system that transports Fe(II) across the cytoplasmic membrane is the Feo system, common in both pathogenic and non-pathogenic bacteria [8]. It may possibly transport other divalent metal cations, such as Mn(II) and Zn(II). In order to explore metal binding properties of Feo system, we select peptides derived from specific parts of this protein system and study their binding equilibria with Fe(II), Mn(II) and Zn(II) ions.

The studies of equilibria of the above systems and metal ions are rather difficult, as there are issues concerning hydrolysis and keeping appropriate oxidation state of metal ions. In this context, the studies fit well into the goals and were discussed within WG1 NECTAR for highly hydrolysable (HHC) and/or low-valence state (LVC) cations and WG2 NECTAR for strong and/or multifunctional ligands, macromolecules, polyelectrolytes.

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Interaction of cytotoxic ruthenium(III) containing bulky disubstituted triazolopyrimidines with DNA and proteins

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Over the past 30 years, researchers have received much attention from ruthenium complexes due to their interesting chemical and biological properties. Ruthenium complexes are particularly attractive in the anticancer field of three main properties: i) a rate of ligand exchange often comparable to that of platinum complexes which can be tuned by coordination of appropriate ancillary ligand; ii) the ability of ruthenium ion to mimic the behavior of iron in binding with specific biological molecules, including serum transferrin and albumin [1-4] **iii)** under physiological conditions these complexes are accessible in several oxidation states (Ru(II), Ru(III), Ru(IV)).

Following this research line in the design of compounds with antitumor activity, we have focused on syntheses of novel ruthenium(III) complexes with 5,7-ditertbutyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dbtp). All ruthenium(III) compounds have been characterized by IR, MS, UV-Vis, X-ray, magnetic and EPR studies. In our study, we proved the presence of octahedral ruthenium(III) complexes with monodentate 5,7-ditertbutyl-1,2,4-triazolo [1,5-*a*]pyrimidines in the solution, which is very important for the subsequent use of these compounds in antitumor therapy. In order to choose the compound(s) with the most promising therapeutic effectiveness, we estimated important biological parameters in a solution such as: the hydrolysis rate, lipophilicity (logP parameter), *in vitro* antiproliferative activity (A549 - non-small cell lung carcinoma, T47D - breast carcinoma, mice fibroblasts Balb/3t3) and interactions with CT-DNA and apotransferirin, whose determination is important in planning a selective and effective anticancer therapy.

We noticed that two studied lipophilic ruthenium(III) complexes display the most gratifying *in vitro* against two human tumor cell lines, A549 (non-small cell lung carcinoma) and T47D (breast carcinoma), and non-covalently bind to DNA. Finally, results obtained for two lipophilic ruthenium(III) with 5,7-ditertbutyl-1,2,4-triazolo[1,5-*a*]pyrimidine look promising and demonstrate that modification of the coordination sphere by bulky ligand is a good direction for the design of high cytotoxic ruthenium(III) complexes [5].

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C-terminal sequence of the bacterial FeoB protein- potential binding site for transition metal ions?

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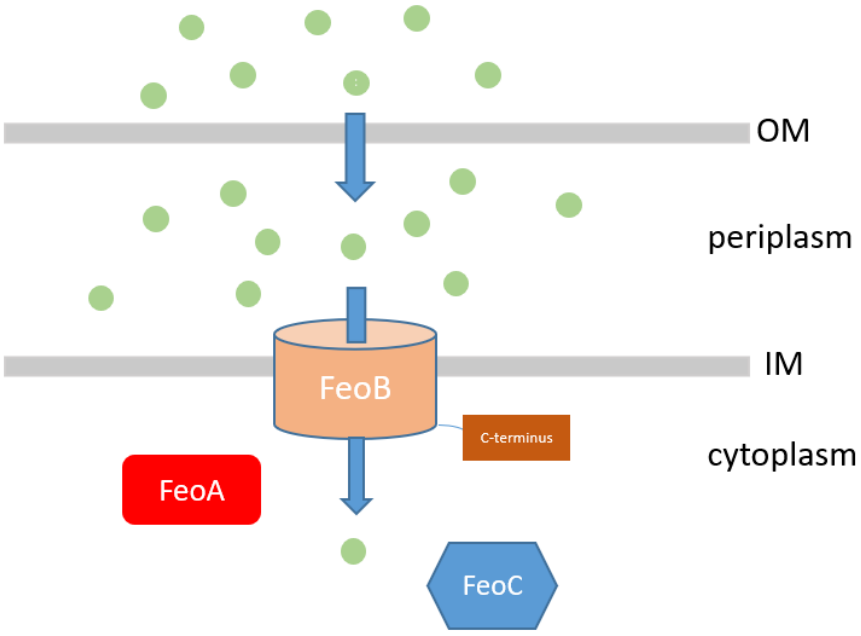
Bacterial resistance to antibiotics has been a growing problem worldwide [1], hence alternative methods of treating bacterial infections are sought. During infection, bacteria need to assimilate transition metal ions from the host environment, such as Fe(II), Mn(II) and Zn(II), which play a key role in pathogenicity and survival and are transported into bacterial cell by specific transporters located in the bacterial membrane. The Feo system, common in both pathogenic and non-pathogenic bacteria, is considered to be the most important bacterial transport system for Fe(II) ions, possibly transporting other divalent metal cations, such as Mn(II) and Zn(II), which are often transported by ferrous iron transporters [2]. Feo consists of three proteins, transmembrane FeoB and cytoplasmatic FeoA and FeoC proteins. The most important is the transmembrane FeoB protein, that transports metal ions to the bacterial cell from the periplasm. C- terminal end of FeoB protein located in the cytoplasm is rich in cysteine, histidine and glutamic and aspartic acids residues, that could potentially bind Fe(II), Mn(II) and Zn(II) cations after they have been transported through the membrane or act as an Fe(II) concentration sensor inside the cell. Scheme of the Feo system is shown below.



In order to explore metal binding properties of FeoB C-terminus, three peptides derived from the C-terminus of *E. coli* K12 strain FeoB protein were chosen and their complexes with Fe(II), Mn(II) and Zn(II) ions were studied with the use of methods such as potentiometry, mass spectrometry, EPR and NMR spectroscopies. We obtained peptides protonation constants, stability constants of complexes and propose geometries of complexes and metal binding residues. With that data we will discuss thermodynamic properties of the complexes.

The scope of this research fits well into the goals of COST NECTAR WG1 Low Valence Cations subgroup, as the results will provide an insight into the methodology of working with iron(II) and thermodynamics of iron(II) complexes, in this case with biological ligands.

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New 8-hydroxyquinoline benzohydrazones: solution behaviour, metal complexation (Cu^{II} and $V^{IV}O$) and anticancer properties

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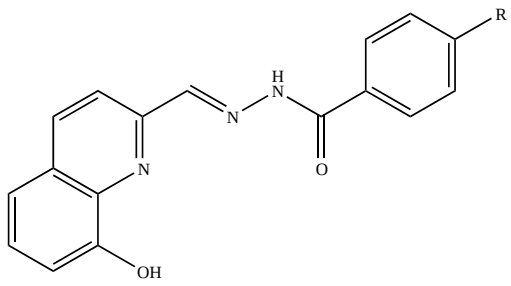
Cancer is a leading cause of death in developed countries, with a substantial burden on public health. In 2020, the estimated cancer incidence and mortality in the European Union was 4.0 million new cases (all cancer types, excluding non-melanoma skin cancer) and 1.9 million cancer deaths [1]. The development of new metallodrugs for cancer therapy has been a dynamic field of research since the serendipitous discovery of cisplatin's antiproliferative properties. Despite its efficacy in the treatment of many cancer types, severe toxicity and intrinsic or acquired resistance are the main drawbacks of Pt-based drugs, which prompted researchers to search for alternative metallodrugs with higher efficacy and selectivity.

Widely explored alternatives, regarding the metal core, are copper and vanadium. It has been established that tumor growth and metastasis in cancer cells have increased need for copper, since this metal ion is involved in cellular processes that include signaling, oxidative phosphorylation, cell growth, proliferation, angiogenesis and autophagy [2]. Vanadium, on the other hand, is a metal ion that has shown very interesting biological properties [3]. Vanadium complexes inhibit tyrosine phosphatases and/or activate tyrosine phosphorylases, impacting signal transduction pathways that may lead to cellular apoptosis and/or activation of tumor suppressor genes. Furthermore, both metals may be involved in reactive oxygen species (ROS) generation by Fenton-like reactions and may also induce cell-cycle arrest and cytotoxic effects through DNA interaction and lipid peroxidation.

All these effects depend not only on the metal ion but also on the organic ligand which will modulate steric and electronic effects and consequently the biological profile of the metal complex. In the hereby reported system, the choice fell on 8-hydroxyquinoline benzohydrazones derived from 2-carbaldehyde-8-hydroxyquinoline and benzylhydrazides containing different substituents in the *para* position (Fig. 1).



R = H, L^1
R = Cl, L^2
R = F, L^3
R = CH_3, L^4
R = OCH_3, L^5
R = OH, L^6
R = NH_2, L^7
R = pyridine, L^8

Figure 1. Structural formula of the ligand precursors prepared, and abbreviations used.

We report their synthesis and characterization as well as their complexes with Cu^{II} and $V^{IV}O$ metal ions. All compounds were characterized by elemental analyses and mass spectrometry as well as FTIR, UV-visible absorption, NMR (ligand-precursors) and EPR (complexes) spectroscopies, and by DFT computational methods. Proton dissociation constants, lipophilicity and solubility in aqueous media were determined for all ligand precursors. Complex formation was evaluated by spectrophotometry for selected ligands and corroborated by EPR spectroscopy. While with Cu^{II} only complexes with L:M = 1 stoichiometry were obtained in solution and solid state, with $V^{IV}O$ 1:1 and 2:1 complexes were obtained [4].

The antiproliferative activity of all compounds was evaluated in malignant melanoma (A-375) and lung (A-549) cancer cells. Overall, the metal complexes perform better (lower IC_{50} values) than their corresponding organic free ligands, and Cu^{II}-complexes are more cytotoxic than the $V^{IV}O$-complexes. Their cellular impact is explored and mechanisms of action involving ROS and apoptosis are proposed.

Overall, these are systems with very high potential for application in cancer therapy. Since selectivity towards cancer cells is usually a shortcoming in the development of anticancer drugs based on labile metal ions, nanoplatforms such as liposomes and polymeric nanoparticles are being developed for the targeted delivery of the metal complexes.

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Dual-active half-sandwich ruthenium complexes bearing tetrahydropyrimidines: Interaction with DNA and BSA

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A series of novel Biginelli hybrids (tetrahydropyrimidines-THPMs) and their ruthenium(II) complexes were synthesized to discover new dual-active agents. Ligands (THPMs) were synthesized via acid-catalyzed one-pot Biginelli reaction using aromatic aldehydes, *N*-methylthiourea, and methyl acetoacetate [1]. Ruthenium complexes were characterized by IR, NMR, and X-ray techniques and investigated for their cytotoxic effect on human cancer cell lines and normal fibroblasts [2]. The results of the flow cytometry analysis suggest that the proportion of cells in the G2/M phase decreased following the increase of subG1 phase in all treatments. These results confirmed that cells treated with selected complexes were induced to undergo apoptotic death. In addition, the ruthenium complexes display significant inhibitory potency against SARS-CoV-2 M_{pro}. Furthermore, molecules containing nitro or chloro fragment have the lowest values of ΔG_{bind} and K_i, comparable to cinanserin and hydroxychloroquine. We also studied the interactions between biomacromolecules (DNA or BSA) and ruthenium complexes to understand their suitability for potential use as dual-active medicaments. The results indicated that selected compounds have a great affinity to displace EB from the EB-DNA complex through intercalation. Also, obtained results of fluorescence titration of BSA with selected ones support that a significant amount of the tested compounds could be transported and distributed through the cells.

In addition, achieved results will open a new avenue in drug design for more research on the possible therapeutic applications of dual-active Biginelli-based drugs (anticancer-antiviral). Dual-active drugs based on the hybridization concept “one drug curing two diseases” could be a successful tactic in healing patients who have cancer and the virus SARS-CoV-2 at the same time.

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Spectrophotometric determination of stability constants cobalt (II) and cholinium-picolinate

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Heavy metal poisoning is a common health problem because of mining, smelting, industrial, agricultural and sewage waste. Also, cobalt intoxication has become more frequent due to the wide use of metal hip implants. Chelation therapy uses chelating agents (complexing agents) to detoxify poisonous metals by converting them into a chemically inert form that can be excreted without further interactions with the body [1]. Ionic liquids (ILs) with the ability to coordinate metal ions could be used to treat wastewater and metal intoxication. Although ILs have been applied to extract metal ions, the basic information about IL and metal ions' stability constant is still poor [2]. The picolinate anion has a free electron pair on the nitrogen atom and a deprotonated carboxyl group (Fig.1), acting as a chelating ligand. This paper aims to investigate the complex formation of Co(II) with cholinium picolinate ([Ch][Pic]) by UV/VIS spectrophotometry in the wavelength range of 400-800 nm.

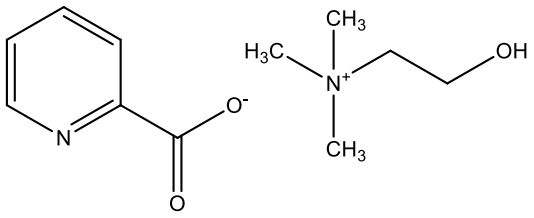

Figure 1. Structure of cholinium-picolinate, [Ch][Pic]

Fig. 2(a) shows spectra of Co(II) and a mixture of Co(II) and [Ch][Pic] in an aqueous solution. Spectra were recorded in the wavelength range of 400–800 nm using a UV-Vis Shimadzu spectrophotometer at 25°C. The concentration of Co(II) was constant (0.11 M), and the concentration of [Ch][Pic] varied in the range from 0.11 – 0.40 M. Complex of $Co(NO_3)_2$ x 6 H_2O shows a broad peak with a maximum at 512 nm. By adding [Ch][Pic] into the aqueous

solution Co(II), the maximum peak shifts to shorter wavelengths (from 512 to 481 nm), and the peak intensity increases. Also, the color of the complex changes from pink to orange (Fig. 2(b)). These preliminary results represent the basis for determining the stability constant(s) of the Co(II) and [Ch][Pic] complex, as well as the influence of ionic liquid on the formation of these complexes.

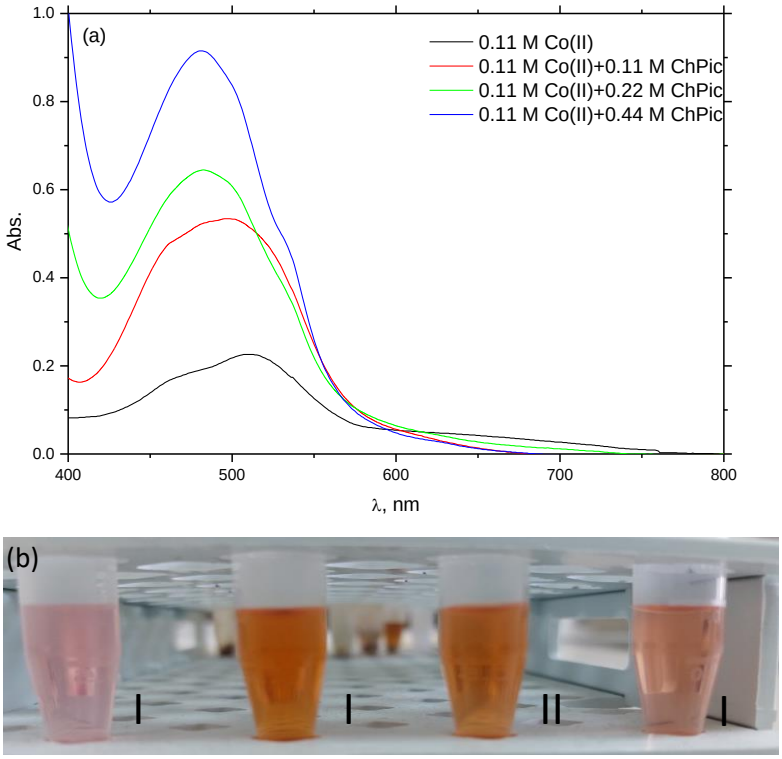

Figure 2. (a) Absorption spectra of $Co(NO_3)_2$ x 6 H_2O, and Co(II)+[Ch][Pic] at 25 °C; (b) picture of aqueous solution of (I) $Co(NO_3)_2$ x 6 H_2O; (II) – (IV) mixture of Co(II) and [Ch][Pic] in the molar ratio 1: 4, 1:2 and 1:1, respectively.

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Improving ethylene glycol-based heat transfer fluids by biocompatible molecule caffeine

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Nowadays, energy demands are continually increasing, pointing out the importance of more efficient energy production and consumption. Therefore, intensifying heat transfer processes and reducing energy losses due to ineffective use have become increasingly essential tasks. The heat transfer fluids (HTF) have an important role in removing the excess heat from a system with various applications ranging from building heating, ventilation and air-conditioning (HVAC) systems, electronics or automotive [1]. The organic solvent with desirable thermal characteristics such as prominent heat capacity, low freezing point, high boiling point and good thermal stability is ethylene glycol (EG), popular antifreeze and HTF in numerous commercial and industrial applications [2].

As already stated, the ideal HTF enhancer substance must be environmentally friendly, cost-effective, high heat capacity and prominent thermal transfer performance. Therefore, the idea to use ethylene glycol and caffeine [3] mixture as a potential heat transfer media was established. The fluidity of the caffeine + ethylene glycol system is a consequence of the interactions that occur, as well as the changes in the structural organization of ethylene glycol, so it is necessary to understand their fundaments to apply this mixture as a potential heat transfer fluid. Moreover, the experimental values obtained in this presentation will be vital for the process design and operation of heat exchangers and thermal energy storage.

Detailed physicochemical characterization of ethylene glycol and caffeine + ethylene glycol mixtures is performed based on density, viscosity and refractive indices measurements in the temperature range from (288.15 to 343.15) K. The apparent molar volume, apparent molar volume at infinite dilution, *Masson*'s experimental slope, limiting apparent molar expansibility, viscosity *B*-coefficient, thermodynamical parameters of viscous flow and molar refractions have been evaluated from experimental measurements and results are additionally proven by molecular dynamic simulations.

According to these volumetric results at different temperatures, it was concluded that caffeine manifests structure-breaking properties in EG. Also, it was found that adding caffeine

reduces EG viscosity, while caffeine molecules have a high tendency to form self-aggregates due to weak interactions with EG. The rheological behavior indicates the Newtonian behaviour of this mixture. The applied Jones-Dole equation shows the structure-breaker properties of caffeine molecules in ethylene glycol. The structure-breaker properties, along with weak interactions between ethylene glycol and caffeine, induced a significant level of caffeine self-aggregation, which is proved by positive Sv coefficient values and supported by molecular dynamics simulation results.

The MD simulations were used as an additional tool to establish the solvation properties of caffeine in ethylene glycol. The computational simulations make it possible to understand interactions between caffeine and ethylene glycol, as well as a theoretical proof for caffeine self-aggregation (Figure 1).

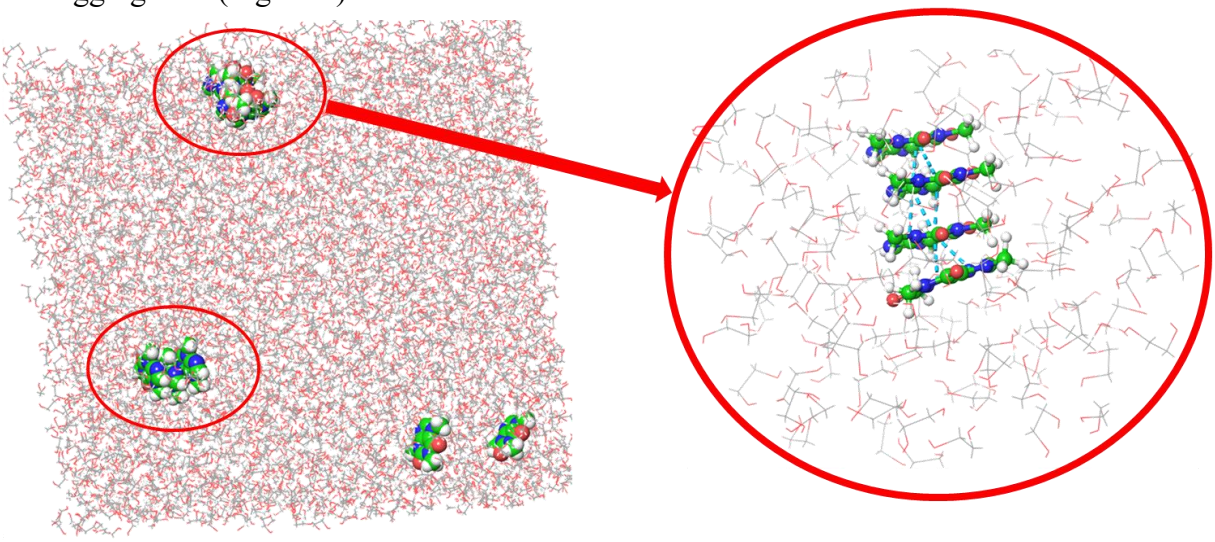

Figure 1. The snapshot of caffeine in ethylene glycol at temperature T = 298.15 K (the blue dotted line represents π-π interactions).

Based on the obtained results in this research, it can be concluded that caffeine addition in ethylene glycol improves its properties as a heat transporter, primarily due to increasing system fluidity and the possibility of heat storage in caffeine self-aggregates. The analysis of convective heat transfer parameters could confirm the benefit of applying caffeine + ethylene glycol systems as heat transporter.

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Enthalpy of mixing 1-butyl-3-methylimidazolium carboxylates with water

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Water is a unique, ubiquitous solvent in biology and occurs in various solutions, mixtures, and materials. Its behavior is highly dependent on conditions and its environment, mainly due to its strong orientation-dependent hydrogen bonding and intermolecular interactions. Its interactions with ions have been studied extensively in a wide range of concentrations [1]. However, due to the limited solubility of common salts in water, the interactions in systems with small amounts of water surrounded by ions – that is, in a confined space of – are still unclear. Room temperature ionic liquids (RTILs) could be excellent model systems for this purpose, allowing experiments at ambient conditions.

Three RTILs were synthesized from 1-methylimidazole in a three-step process using 1-bromobutane and corresponding carboxylic acid to produce 1-butyl-3methylimidazolium butanoate, 1-butyl-3-methylimidazolium hexanoate and 1-butyl-3-methylimidazolium octanoate. Water was titrated in small aliquots into the prepared RTILs in the TAM 2277 (ThermoMetrics, Sweden) calorimeter where the heat flow was measured and integrated to obtain the enthalpy of mixing as a function of the composition of the solution in the titration cell.

The experimental enthalpies were then fitted to the Redlich-Kister equations to allow calculation of the partial excess molar enthalpies and compared with values obtained from various thermodynamic models to gain further insight into the behavior of water in RTIL-based mixtures [2].

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Phase diagrams of rose and MB models of water

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When it comes to understanding of properties of a material, it is useful to know in which phases this material exists at different conditions. By constructing phase diagram of the material, knowledge about positions of phase transitions and structure of different phases can be obtained. Here, we used Nested Sampling (NS) algorithm to predict phase transitions and construct phase diagrams of Mercedes-Benz (MB) and rose water model. Nested Sampling is an algorithm that enables direct calculation of partition function, from which other thermodynamic quantities can be calculated. Using nested sampling no a priori knowledge about phases is needed in order to determine phase transitions, moreover all phase transitions regardless their type can be determined. Mercedes-Benz and rose water model are simple two-dimensional water models, in both models water molecules are modelled as Lennard-Jones disks, however orientationally dependent hydrogen bonding potential of the models is different. Using nested sampling we located multiple phase transitions and determined complete phase diagrams of both models.

Reactions between $NiX_2 \cdot 6H_2O$ (X= Cl, Br, NO_3) and 2-(hydroxymethyl)pyridine: complex solution equilibria and six novel crystalline products

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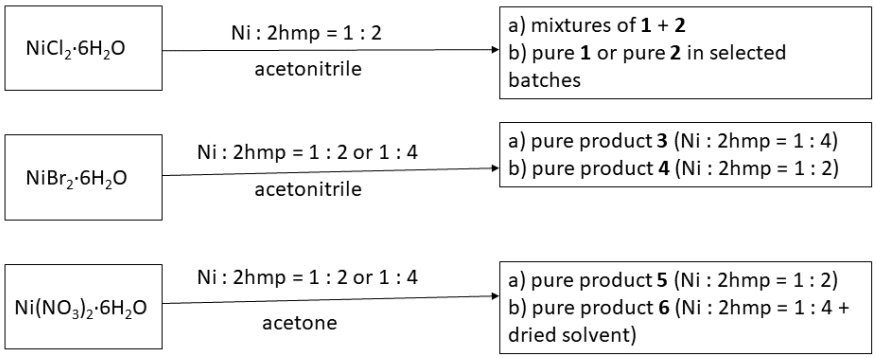
Simple pyridine-based alcohols have been frequently used in the synthesis of novel coordination compounds in the last decade [1]. On one hand, the reason for their use is their commercial availability and low cost. On the other hand, although very simple they possess the ability to coordinate to metal centers in different manners – mainly as neutral molecules via N,OH sites or as anionic ligands in highly basic environment via N,O^-. Usual bidentate chelating coordination modes lead to the formation of larger architectures with interesting physical characteristics and to the use of the products, especially as catalysts in oligomerization reactions [2, 3].

As my professional interest lies primarily in crystal structure determination, the decision was taken to perform simple reactions between 2-(hydroxymethyl)pyridine, 2hmp, and different nickel salts with formulae $NiX_2 \cdot 6H_2O$ (X= Cl, Br, NO_3) in selected solvents (acetone or acetonitrile, optionally dried over Na_2SO_4 and 4 Å molecular sieves) to obtain and characterize the solid crystalline products. However, despite of the simplicity of synthetic work, the structural analysis of the obtained products has shown that the equilibria in solutions at ambient conditions are not straightforward. Subtle (and often uncontrollable) changes in synthetic and/or crystallization conditions lead to six different products:

1 $[Ni(2hmp)_3]Cl_2 \cdot H_2O$,
2 $[Ni(2hmp)_2(OH_2)_2]Cl_2$ with water molecules in *cis* positions,
3 $[Ni(2hmp)_3]Br_2$,
4 $[Ni(2hmp)_3]Br_2 \cdot CH_3CN$,
5 $[Ni(2hmp)_3](NO_3)_2$ and
6 $[Ni(2hmp)_2(OH_2)_2](NO_3)_2$ with water molecules in *trans* positions.

The results of preliminary studies will be discussed, with emphasis on synthetic procedures (Scheme 1). Furthermore, the comparisons amongst the crystal structures will be given, together with the following Hirshfeld surface analysis (Figure 1).



Scheme 1. Synthetic procedures leading to six novel coordination compounds of Ni(II) with 2hmp.

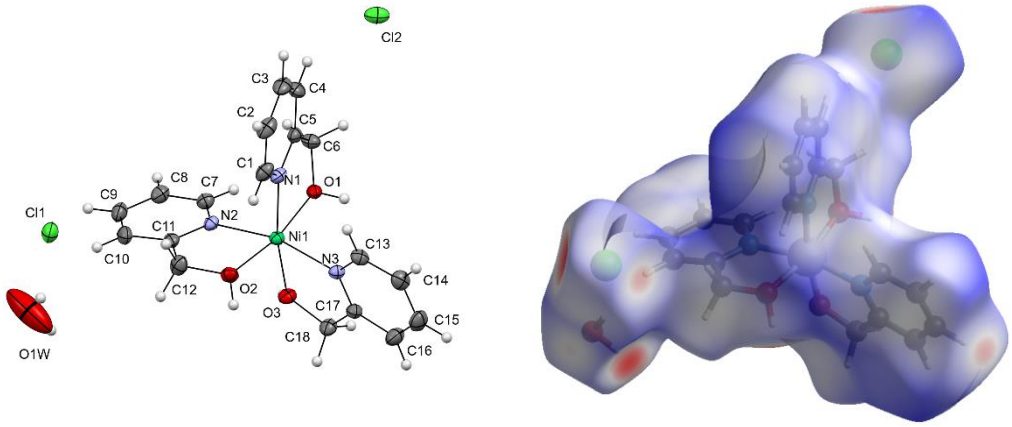


Figure 1. ORTEP representation of compound **1** (left) and its Hirshfeld surface depicted over d_{norm} (right).

References:

[1] C. R. Groom, I. J. Bruno, M. P. Lightfoot, S. C. Ward, *Acta Crystallogr.* **2016**, B72 (2), 171-179.
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Anatase to rutile phase-transformation kinetics: A high-temperature XRD study

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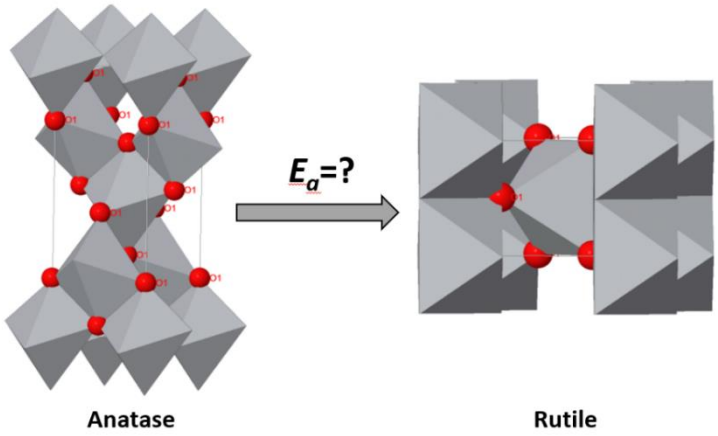
TiO_2 is used in a variety of applications, each requiring a specific crystal structure. A detailed study of the kinetics in the calcination phase would provide information about the activation energies. In this way, the further process could be carried out in a more environmentally friendly, efficient, and consequently economical way. In this work, we have investigated the phase transformation kinetics during calcination process in titanium white production of three different TiO_2 samples, which have a predominantly anatase crystal structure in the initial composition.

High temperature X-ray diffraction curves were recorded for the samples calcined at 750 °C, 800 °C, 850 °C, and 900 °C and thermostated at listed temperature for 0 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, and 70 min. Quantitative analysis of phase composition was performed using Rietveld refinement. The conversion ratio of anatase to rutile was calculated using the John-Mehl-Avrami-Kolmogovor (JMAK) equation. This equation resulted in the coefficients *n* and *k*, which were used to calculate the activation energy via the Arrhenius equation.



Scheme: Crystal structure transformation from anatase to rutile.

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Inversion Theory Levelling as new method with improved accuracy for thermodynamic parameter prediction on antioxidants

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Theoretical methods have so far proved successful in predicting both thermodynamic and kinetic parameters in general chemistry [1]. Since the beginning of their development in the early 1920s, theoretical methods have been used as an alternative to standard experimental methods, offering promising insights into something that is more difficult to achieve experimentally - the prediction and evaluation of transition states.

Based on various theoretical approaches, theoretical chemistry to this day has numerous methods that account for various effects and phenomena (e.g., short- and long-range interactions, nonlocal treatment of electron order, kinetic densities, etc.) [2-4], which has allowed chemists to gain greater insight into the ionic and covalent nature of many different systems.

Our approach is based on the so-called Inversion Theory Levelling method, which is new in computational science and involves the use of carefully selected levels of theory in an inverse manner to achieve higher accuracy in the calculation and estimation of thermodynamic parameters. In the current context, "inverse mode" should refer to the DFT type methods, which correspond to the Jacob-Ladder scheme [5] and would therefore cause larger wall times for the computation of frequencies and optimization paths of the given system. Our approach is illustrated using phenol, the best known reference for oxygenated antioxidants, focusing on bond dissociation enthalpies (BDEs) and proton affinities (PAs), the most important parameters related to antioxidant activity [1]. Our local benchmarks were guided by the use of ωB97X-V, the nonlocal version of ωB97XD, mixed with Grimme's GGA composites (PBEh-3c, r^{2}SCAN-3c, and B97-3c), whose BDE and PA were to be compared with M062X/6-311+G(d,p) in gas and condensed phases. As a basis set for the nonlocal ωB97X-V functional, pcseg-1 (basis set with double-ζ quality in agreement with the polarization phenomenon benchmark) was chosen [6]. With respect to the meta-GGA and triple-ζ basis set combination (i.e., 6-311+G(d,p)) at the theory level as a reference, these few method combinations could reduce the relative absolute error deviation (RAED) to only 1-3% and even achieve chemical accuracy in BDEs and PAs compared to experimental values [7].

The improvement of the above thermodynamic properties would be evaluated based on RAED, wall time estimation and measurement, and theory level.

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Anomalous regions and phase transitions in core-softened models

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We determined hierarchy of anomalous regions in the core-softened system. Core-softened disks have two length scales of interaction, a hard core with one diameter and a soft corona with a larger diameter. One model has pure repulsion other has small attraction. The study was done by molecular dynamics, Monte Carlo simulation and integral equation theory. We determined regions of density, diffusivity and structural anomalies and their hierarchy.

We also checked the possibility that fluids with core-softened potential has the critical points and we could not determine them. Regarding integral equation theory, some versions failed to get the correct structure and thermodynamics of the system depending on the position in phase space while others are working rather well like modified Verlet closure for example.

An electric field changes water's phase transitions

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We have modelled influence of the electric field on water properties. We use the MB model of water, a simple two-dimensional statistical mechanical model in which waters are represented as Lennard-Jones disks having Gaussian hydrogen-bonding arms, modified to interact with electric field. We perform Monte Carlo simulations to explore how water molecules are organized in the electric field of different strengths. The small strength of the electric field does not affect properties of water and position of phase transitions, while the strong strengths shift boiling and melting points as well as position of the density anomaly. From certain strength on the density anomaly disappears.

Complexing properties of amino acids and N, O-donor heterocycles with silver(I) and zinc(II) central atoms and their biological properties

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As the healthcare industry has focused on dealing with the pandemic situation in the last two years, many other treatment processes have been delayed. It is therefore natural that after two years, patients with various advanced infectious and tumor diseases begin to appear in hospitals and clinics. This fact leads to the requirement that scientists work intensively on the development of effective and selective antimicrobial and anticancer drugs. All organisms, from bacteria to mammals, produce substances that defend against pathogens [1]. The vast majority of them are antimicrobial peptides (AMP) with short amino acid sequences, which primarily act as a defence against a wide range of pathogens [2].

One of the ideas to help the immune system in acute infectious conditions is to combine antimicrobial metal ions (Ag^{+}, Zn^{2+}, Cu^{2+}) with effective organic ligands that are similar in structure and properties to antimicrobial peptides. Based on this, we have recently focused on ligands such as amino acids or on N, O-donor heterocyclic bioligands.

The contribution will present the results obtained by potentiometric measurements of several Ag(I)/Zn(II)-ligands binary systems (ligands = amino acids, N, O-donor heterocycles). Moreover antimicrobial and anticancer properties of selected Ag(I) and Zn(II) complexes and their potential drug formulation will be shown [3].

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