OC1
Solution thermodynamics of tetravalent metal complexes: the yirconium challenge

Michel MEYER

Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), UMR 6302 CNRS, Université de Bourgogne Franche-Comté, 9 avenue A. Savary, 21078 DIJON, France.
michel.meyer@u-bourgogne.fr

Owing to their high charge density, tetravalent cations belonging to the d- (Ti, Zr, Hf) and f-blocks (Ce, Th, U, Np, Pu) show a strong tendency to undergo hydrolysis and polycondensation reactions even at low pH, eventually leading to the formation of insoluble oxo/hydroxo species.[1-5] Thus, the free aqua ions M^{4+} are only stable in very acidic solutions. Across the actinide series, the steady decrease of the ionic radius on going from Th^{4+} to Pu^{4+}, the An^{4+} cations become harder and thus more acidic and more prone to hydrolysis. At pH values close to the precipitation onset, olation ($M–OH + M–OH_2 \rightarrow M–OH–M + H_2O$) and oxolation ($2\ M–OH \rightarrow M–O–M + H_2O$) account for the formation of polynuclear oxo/hydroxo aggregates. Condensation products ultimately evolve upon aging into colloids possessing an ordered M–O–M backbone. As a matter of facts, the solution chemistry of the hydrolysis products of these metal cations is quite rich and often hampers the precise measurement by classical methods of metal-ligand equilibrium constants. It explains, among other factors, why thermodynamic data for tetravalent elements are rarer and less reliable, even for those possessing stable isotopes, in spite of their technological relevance for the nuclear industry and spent-fuel processing.

Over the last decade, the coordination chemistry of zirconium(IV) has experienced a great upsurge that was spurred by the development of new ^{89}Zr-based radiotracers for positron emission tomography (PET).[6,7] State-of-the art applications of this β^+ emitting isotope in nuclear medicine rely on antibody bioconjugates incorporating a suitable zirconium chelator that specifically accumulate at tumor cells. To date, the only chelator used in clinics is the hexadentate siderophore desferrioxamine B (DFB), although several preclinical studies on mice have revealed the impaired in vivo stability of the ^{89}Zr-DFB complex, resulting in partial dissociation and subsequent accumulation in mineral bone tissue of the released radionuclide.

While the scientific community is currently devoting considerable efforts towards the design of more efficient octadentate chelators by increasing the stability and inertia of the zirconium complexes,[8] it is extremely puzzling to figure out that the solution equilibrium chemistry of the Zr^{4+}/DFB system remained fully ignored until June 2019! Despite the publication of two independent reports by reputed groups, the speciation is unfortunately still not well understood and further scientific endeavor is mandatory to reach a consensus.[9,10] Participants of NECTAR Working Groups will be invited to join their forces and contribute to the fundamental understanding of the solution coordination chemistry of tetravalent metal complexes with various relevant ligands by setting up reliable working guidelines.

References:

[1] P. L. Brown, E. Curti, B. Grambow, C. Ekberg, *Chemical Thermodynamics of Zirconium*, Chemical Thermodynamics Series, Vol. 8. Elsevier: Amsterdam, **2005**.

[2] I. Grenthe, J. Fuger, R. J. M. Konings, R. J. Lemire, A. B. Muller, C. Nguyen-Trung, H. Wanner, *Chemical Thermodynamics of Uranium*, 2nd édition, Chemical Thermodynamics Series, Vol. 1. OECD Nuclear Energy Agency: Paris, **2004**.

[3] R. J. Lemire, J. Fuger, H. Nitsche, P. Potter, M. H. Rand, J. Rydberg, K. Spahiu, J. C. Sullivan, W. J. Ullman, P. Vitorge, H. Wanner, *Chemical Thermodynamics of Neptunium and Plutonium*, Chemical Thermodynamics Series, Vol. 4. Elsevier: Amsterdam, **2001**.

[4] M. H. Rand, J. Fuger, I. Grenthe, V. Neck, D. Rai, *Chemical Thermodynamics of Thorium*, Chemical Thermodynamics Series, Vol. 11, Vol. 11, OECD Publishing, Issy-les-Moulineaux, **2008**.

[5] P. L. Brown, C. Ekberg, *Hydrolysis of Metal Ions*. Wiley-VCH: Weinheim, **2016**.

[6] G. Fischer, U. Seibold, R. Schirrmacher, B. Wängler, C. Wängler, *Molecules* **2013**, *18*, 6469-6490.

[7] S. Heskamp, R. Raavé, O. Boerman, M. Rijpkema, V. Goncalves, F. Denat, *Bioconjugate Chem.* **2017**, *28*, 2211-2223.

[8] R. Raavé, G. Sandker, P. Adumeau, C. B. Jacobsen, F. Mangin, M. Meyer, M. Moreau, C. Bernhard, L. Da Costa, A. Dubois, V. Goncalves, M. Gustafsson, M. Rijpkema, O. Boerman, J.-C. Chambron, S. Heskamp, F. Denat, *Eur. J. Nucl. Med. Mol. Imaging* **2019**, *46*, 1966-1977.

[9] M. Savastano, C. Bazzicalupi, G. Ferraro, E. Fratini, P. Gratteri, A. Bianchi, *Molecules* **2019**, *24*, 2098.

[10] Y. Toporivska, E. Gumienna-Kontecka, *J. Inorg. Biochem.* **2019**, *198*, 110753.

OC2
Accumulation mechanisms of radionuclides in marine macroalgae

Romualdo BIANCO,[a),b)] Catherine LEBLANC,[c)] Pier Lorenzo SOLARI,[d)] Christophe DEN AUWER,[a)] Tarita BIVER,[b)] Maria Rosa BECCIA [a)]

[a)] Université Côte d'Azur, Institut de Chimie de Nice, Nice, France.
[b)] Università di Pisa, Pisa, Italy.
[c)] Station Biologique de Roscoff, France
[d)] SOLEIL Synchrotron, MARS beamline, Gif sur Yvette, France.
maria-rosa.beccia@univ-cotedazur.fr

The fate of radionuclides in marine environment and their interactions with marine organisms are a crucial scientific issue, but also a concern of societal impact [1,2]. Among marine organisms, algae play a paramount role in marine ecosystem and the environment in general: they are at the basis of several trophic chains and economical resources, provide habitats for a wide range of marine organisms, produce more than 50% of the world's oxygen via their photosynthesis. Therefore, assessing the environmental impact of radionuclides necessarily involves assessing their impact on marine algae, because of the crucial function of these organisms. Such impact, together with radionuclide bioavailability and mobility in the environment, strongly depends on radionuclide chemical speciation and their accumulation mechanisms at the molecular scale [3,4].

We present here a multi-spectroscopic investigation of the interaction of two radionuclides, Uranium (^{nat}U) and Europium (^{152}Eu), with the model brown alga *Laminaria digitata*. Uranium is the most widely used natural radioelement for nuclear energy production. Europium is used in this work as a chemical surrogate of Americium, because of similar ionic radii, same oxidation state and because of the too high specific activity of Am.

The uptake of both metal ions has been quantified by ICP-OES and by γ spectrometry; Uranium and Europium distribution within the algae compartments were also described. First results on the accumulation mechanisms and the *in vivo* speciation of both metal ions were obtained through the use of XAS spectroscopy and imaging techniques (TEM).

As a complementary study, the role of glutathione (GSH) in Eu(III) ion complexation for possible intracellular detoxification was examined. We performed thermodynamic analysis to determine the value of the equilibrium constant for the GSH/Eu(III) complex formation through UV-vis absorption spectrophotometry, which gives deeper insights to the possible mechanisms of detoxification processes.

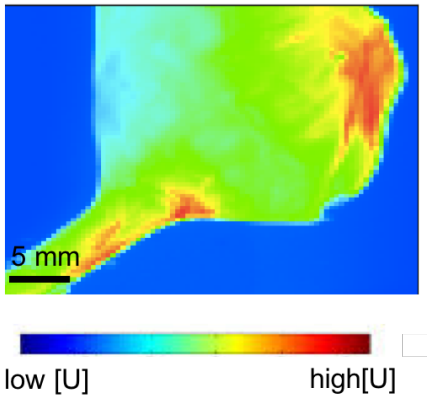


Figure 1. Uranium(VI) distribution in the meristem of a contaminated specimen of *Laminaria digitata.* Image obtained by micro-XAS measurements at Uranium L3 edge.

References:

[1] K. Maher, J.R. Bargar, G.E. Brown, *Inorg. Chem.* **2013**, 52(7), 3510-3532.

[2] J. Vives i Batlle, M. Aoyama, C. Bradshaw, J. Brown, K. O. Buesseler, N. Casacuberta, M. Christl, C. Duffa, N. R. E. N. Impens, M. Iosjpe, P. Masqué, J. Nishikawa, *Sci. Total Environ.* **2018**, 618, 80-92.

[3] M. R. Beccia, P. L. Solari, M. Monfort, C. Moulin, C. Den Auwer, *New J. Chem.* **2018**, 42, 7582-7591.

[4] B. Reeves, M. R. Beccia, P. L . Solari, D. E. Smiles, D. K. Shuh, C. Berthomieu, L. Mangialajo, S. Pagnotta, M. Monfort, C. Moulin, C. Den Auwer, *Environ. Sci. Technol.* **2019**, 53(14), 7974-7983.

OC3
Speciation in polynuclear assemblies with lanthanides: from structural and physico-chemical data to thermodynamic modeling

Josef HAMACEK

Center for Molecular Biophysics (CBM, UPR 4301), CNRS Orléans, rue Charles Sadron, 45071 ORLEANS, France.
josef.hamacek@cnrs.fr

Lanthanide-containing compounds have found numerous applications as catalysts, in material sciences and in bioanalysis due to their exciting photophysical and magnetic properties. The design of such molecular and supramolecular devices can include several cations organized in a specific way to provide desired microscopic/macroscopic functionalities. Suitable coordinating polytopic ligands must be thus designed to satisfy high coordination numbers of lanthanides and to achieve good thermodynamic and kinetic stability in solution. Globally, the organization of multicomponent mixtures into stable discrete compounds becomes a complicated process with a number of relatively slow self-repairing reaction steps before reaching a thermodynamic equilibrium. However, if the complexation occurs rapidly under kinetic control, the self-organisation of components is strongly hindered and the process may results in badly defined products. The nature of formed complexes may also vary along the Ln(III) series due to small differences in their ionic radius.

Since several years, our research interest is focused on designing discrete polynuclear lanthanide helicates [1,2] as artificial models mimicking natural systems, and on understanding key parameters governing their assembly. We will present here few polytopic ligands for Ln(III) complexation, the targeted helicates [3-5] and the evolution of different complex species with respect to Ln(III) ionic radii, ligand structures and their relative stoichiometries (Figure 1.). In addition to several qualitative aspects, we will present the principles of the site-binding thermodynamic model developed few years ago by us [6]. Its adaptation to polynuclear helicates allows quantifying elemental binding affinities as well as intermetallic interactions from known stability constants. These values can be consequently used for thermodynamic predictions of analogous, generally more complex supramolecular systems. This approach is potentially applicable for the analysis of other assemblies and multicomponent systems.

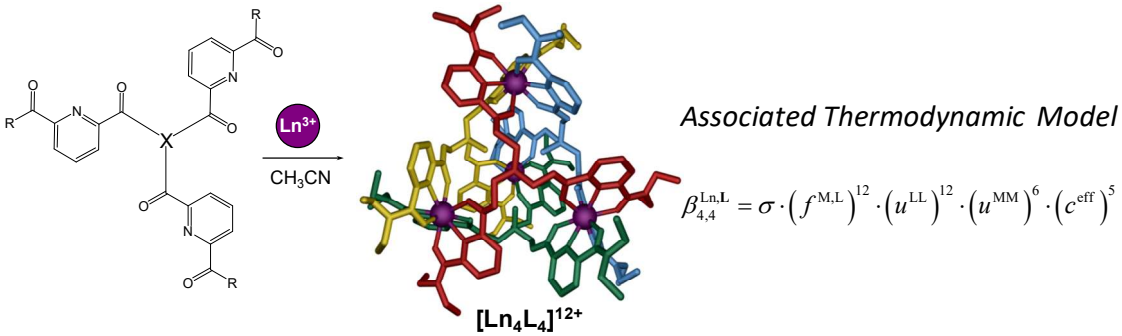


Figure 1. Self-assembly of 3D tetranuclear lanthanide helicates and the related thermodynamic model.

References:

[1] S. Zebret, E. Vögele, T. Klumpler, and J. Hamacek, *Chem. Eur. J.*, **2015**, 21, 6695-6699.
[2] B. El Aroussi, S. Zebret, C. Besnard, P. Perrottet, and J. Hamacek, *J. Am. Chem. Soc.*, **2011**, 133, 10764-10767.
[3] J. Hamacek, C. Besnard, T. Penhouet, P.-Y. Morgantini, *Chem. Eur. J.,* **2011**, 17 (24), 6753-6764.
[4] S. Zebret, E.Vögele, T. Klumpler, J. Hamacek, *Chem.Eur. J.* **2015**, *21*, 6695-6699.
[5] A. Vuillamy, S. Zebret, C. Besnard, V. Placide, S. Petoud, J. Hamacek, *Inorg. Chem.* **2017**, 56 (5), 2742–2749.
[6] J. Hamacek, M. Borkovec and C. Piguet, *Chem. Eur. J.*, **2005**, 11, 5227-5237.

OC4
Speciation determinations with the technique AGNES: from In to Sb; from humic acids to ZnO nanoparticles

Josep GALCERAN, Encarna COMPANYS, Calin A. DAVID, Carlos REY-CASTRO and Jaume PUY

Departament de Química. Universitat de Lleida, and AGROTECNIO, Av. Rovira Roure 191, 25198 Lleida, Catalonia, Spain.
galceran@quimica.UdL.cat

A key idea in the electroanalytical technique AGNES (Absence of Gradients and Nernstian Equilibrium Stripping) is the attainment of equilibrium between the target analyte in solution and a reduced form of an element of this analyte that amalgamates in a mercury electrode [1-2]. The fulfilment of this electrochemical equilibrium together with equilibrated (flat) concentration profiles, allows AGNES to retrieve thermodynamic information such as the concentration of some metal free ions or some hydroxocomplexes.

Free metal ion concentration in a medium has been highlighted as a key factor in its (bio)availability to organisms, for instance, in the Free Ion Activity Model (FIAM) or the Biotic Ligand Model (BLM). So, the information provided by AGNES (e.g. free metal concentrations of Zn^{2+}, Cd^{2+}, Pb^{2+} or Sn^{2+}), can be very useful, *e.g*, in the study of toxicants in the environment. Moreover, the mobility of many species heavily depends on their speciation, *e.g.* a given ion bound to a large molecule such as a humic acid will diffuse more slowly than its free form.

In this presentation, we will review the principles, limitations, developments and outstanding applications of AGNES including matrices such as river, estuarine and sea waters, soil extracts, humic acids dispersions, growth media, wine, etc. As recent advances, we will explain: 1) how AGNES has provided thermodynamic and kinetic information on the dissolution of ZnO nanoparticles in artificial saliva; 2) how In(III) speciation has been tackled and 3) how $[Sb(OH)_3]$ has been determined.

The free Zn concentration in saliva (either with its full compositon or without the inorganic components) for increasing amounts of total Zn (added as a nitrate salt or as nZnO) was measured by AGNES [3]. Relatively small additions of ZnO NPs to saliva with or without organic components (below total Zn concentrations of 4 to 6×10^{-6} M) led to a fast and complete dissolution of the NPs. The obtained linear curve (see Figure 1) indicates ligand-excess conditions and from its slope the corresponding collective stability constants can be derived. Larger additions of Zn led to an initial plateau in the $[Zn^{2+}]$ vs. time plot, which is attributed to the (transient) formation of $ZnHPO_4$ whose slow evolution towards hopeite ($Zn_3(PO_4)_2{\bullet}4H_2O$) is the rate limiting step. The solubility product of $ZnHPO_4$ (at 37 ºC) will be presented. AGNES results compared favourably with data obtained by ultrafiltration and inductively coupled plasma mass spectrometry (UF-ICP-MS) in terms of speed, reproducibility and access to the free metal ion concentration.

Indium has been tackled by developing a new calibration procedure needed because of In^{3+}/In^{0} quasi-reversibility [4-5]. Conflicting reported nitrilotriacetic acid-In stability constants have been elucidated. The NIST solubility product for $In(OH)_3$ has been confirmed, with measurements of $[In^{3+}]$ down to picomol per litre. A titration of humic acid with In^{3+} was performed.

Due to the extensive hydrolysis of antimony, calibrations and AGNES measurements have been done in terms of the $Sb(OH)_3$ concentration, rather than that of the "free" ion [6]. The determined $[Sb(OH)_3]$ in the titration of Sb with oxalate agrees very well with the values predicted with complexation constants recently reported.

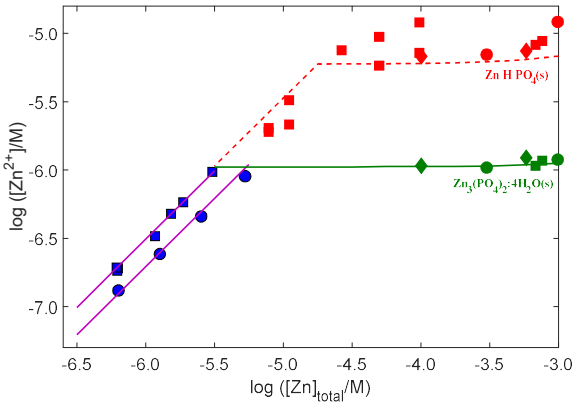


Figure 1. Free Zn^{2+} concentration in saliva without the organic component (square markers) or full synthetic saliva (circle markers). Green and red colours represent the equilibrium and metastable values, respectively, reached after the addition of nZnO. The diamond markers indicate the experiment where Zn has been added as standard (not nanoparticle). The blue colours (markers) represent the under-saturation experiment with their fittings (purple lines).

References:

[1] J. Galceran, E. Companys, J. Puy, J. Cecília, J.L. Garcés, *Journal of Electroanalytical Chemistry* **2004**, 566, 95-109.

[2] E. Companys, J. Galceran, J.P. Pinheiro, J. Puy, P. Salaün, *Current Opinion in Electrochemistry* **2017**, 3, 144-162.

[3] C.A. David, J. Galceran, F. Quattrini, J. Puy, C. Rey-Castro, *Environmental Science & Technology* **2019**, 53, 3823-3831.

[4] M.H. Tehrani, E. Companys, A. Dago, J. Puy, J. Galceran, *Science of the Total Environment* **2018**, 612, 269-275.

[5] E. Rotureau, P. Pla-Vilanova, J. Galceran, E. Companys, J.P. Pinheiro, *Analytica Chimica Acta* **2019**, 1052, 57-64.

[6] P. Pla-Vilanova, J. Galceran, J. Puy, E. Companys, M. Filella, *Journal of Electroanalytical Chemistry* **2019**, 849 (issue), 113334.

OC5
Solution equilibria know-how: challenges depending on the nature of metal-ligand pair

Malgorzata OSTROWSKA, Yuliya TOPORIVSKA, Elzbieta GUMIENNA-KONTECKA

Faculty of Chemistry, University of Wroclaw, 50-383 WROCLAW, Poland.
malgorzata.ostrowska@chem.uni.wroc.pl

In almost all of the fields on which bioinorganic chemistry has been focused on, it is absolutely essential to understand what happens to the coordination complex and its components, the metal and the ligand(s), when they are placed in the solution. When someone is thinking about some biomedical application of coordination compounds, they need to start from the beginning – complete physicochemical and thermodynamic characterization of ligands and their metal complexes.

In our research group we are focused on two main goals in which we can take advantage of our experience in the field of coordination chemistry, (i) the development of novel chelators that provide a strong association with metal ions and a high thermodynamic stability of their complexes required by their potential applications [1-4]; (ii) study on the interactions of metal ions with peptides, being the key to understand the mechanisms of some important activities in biological systems and giving a new insight of them [5-7].

On examples ofour recent results, we will present the experimental approach allowing us to get a full picture, with the thermodynamic and spectroscopic parameters, of studied systems (Figure 1.). Depending on the type of metal ion and ligand structure, by the apropriate combination of the phisicochemical methods we are able to characterize thermodynamic stability and perform structural analysis of complexes, being the first step to understand their biological implications.

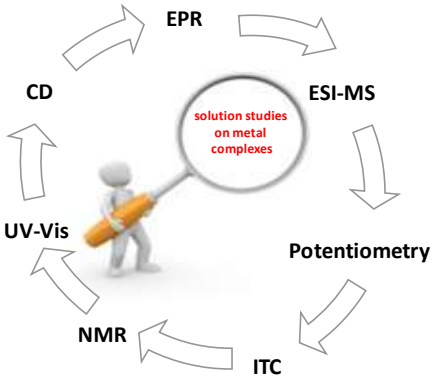


Figure 1. The most useful techniques for studying metal-ligand interactions in solution.

Our experience are in line with the tasks envisaged in WG1 and WG2.

References:

[1] M. Ostrowska, I. A. Golenya, M. Haukka, I. O. Fritsky, E. Gumienna-Kontecka, *New Journal of Chemistry*, **2019**, 43, 10237-10249.

[2] M. Ostrowska, Y. Toporivska, I. A. Golenya, S. Shova, I. O. Fritsky, V. L. Pecoraro, E. Gumienna-Kontecka, *Inorganic Chemistry*, **2019**, 58, 16642-16659.

[3] E. Gumienna-Kontecka, I.A. Golenya, A. Szebesczyk, M. Haukka, R. Krämer, I.O. Fritsky, *Inorganic Chemistry*, **2013**, 52, 7633-7644.

[4] Y. Toporivska, E. Gumienna-Kontecka, *Journal of Inorganic Biochemistry,* **2019,** 198, 110753/1-110753/7.

[5] M. Peana, E. Gumienna-Kontecka, F. Piras, M. Ostrowska, K. Piasta, K. Krzywoszynska, S. Medici, M. A. Zoroddu, *Inorganic Chemistry,* submitted.

[6] M. Peana, S. Medici, H. A. Pangburg, J. T. Lamkin, M. Ostrowska, E. Gumienna-Kontecka, M. A. Zoroddu, *Journal of Inorganic Biochemistry,* **2016**, 164, 49-59.

[7] R. Maurizio, M. Peana, S. Medici, M. Ostrowska, E. Gumienna-Kontecka, M. A. Zoroddu, *Dalton Transaction,* **2016**, 45, 5151-5161.

OC6
Insight into problems accompanying of research on anticancer agents based on organometallic complexes

Joanna MASTERNAK, [a] Barbara BARSZCZ, [a] Agnieszka GILEWSKA, [a] Katarzyna KAZIMIERCZUK [b]

[a] Jan Kochanowski University in Kielce, Institute of Chemistry, Uniwersytecka 7, 25-406 KIELCE, Poland.
[b] Gdańsk University of Technology, Faculty of Chemistry, G. Narutowicza 11/12,80-233 GDAŃSK, Poland.
joanna.masternak@ujk.edu.pl

In the light of successfully application of platinum-based complexes in anticancer therapy we and other scientists concern research on looking for new generations of transition-metal anticancer complexes which will be more efficient and safer. Notwithstanding many active Ru^{n+}, Ir^{n+}, Rh^{n+}, Os^{n+}-based compounds have been discovered, their mechanism of activity (MoA) frequently remains unclear and their targets still unidentified [1]. As a consequence it is important to understand the thermodynamic and kinetics of binding in buffer/aqueus media through investigation of potential interactions with biomolecules such as DNA, HSA, GSH which is very challenging and is still the main goal of many studies. In this context, I would like to summarize our recent study on the new organo-ruthenium, rhodium and iridium complexes with potential antitumor activity. Until recently much of the research on design of metalorganic complexes focused on correlation between anticancer activity and modulation of arene ring (Cp or p-cym) and/or type of donor atoms of chelating ligand. While the main goal of our efforts was to determine the influence on cytotoxic activity of different central ion [Ru(II), Rh(III) and Ir(III)] of isostructural complexes. Additionally, we try to obtain a potential chemotherapeutics that does not affect normal cell lines but possesses better cytotoxic activity against cancer cell lines.

Thus, three new complexes, $\{[RuCl(H_2biim)(\eta^6\text{-}p\text{-cymene})]PF_6\}_2 \cdot H_2O$ (**1**), $[(\eta^5\text{-}Cp)RhCl(H_2biim)]PF_6$ (**2**), and $[(\eta^5\text{-}Cp)IrCl(H_2biim)]PF_6$ (**3**), were fully characterized by elemental and X-ray diffraction analysis, UV-Vis, FTIR, ^1H, ^{13}C and ^{15}N NMR spectroscopies. The complexes exhibited a typical pseudooctahedral piano-stool geometry, in which the aromatic arene ring (*p*-cymene or Cp) forms the seat, while the bidentate κ^2N,N'-2,2′-biimidazole and chloride ion form the three legs of the piano stool. It should be underline that ruthenium complex exists in the dimeric form which consists of two symmetrically independent $[RuCl(H_2biim)(\eta^6\text{-p-cymene})]^+$ cations held together via $\pi\cdots\pi$ interactions between the parallel-displaced imidazole rings and an N-H···Cl interaction (see Figure 1.).

The complexes activity were investigated *in vivo* against selected human tumour cell lines - LoVo, HL-60, MV-4-11, MCF-7 and healthy cells (BALB/3T3). The results have indicated that the most cytotoxic was Ru(II) dimer towards promyelocytic leukaemia (HL-60).

While anticancer activity of two isostructural half-sandwich rhodium and iridium complexes were different. The rhodium complex was approximately two fold more active against MV-4-11 but the iridium complex was only slightly more active against the HL-60 cell line. Looking for an explanation such differences we postulated that that the reason for this is absorption and distribution into different cell components (log $P < 0$ - nuclei and lysosomes, log $P > 0$ - mitochondria and endoplasmic reticulum [2]), depending on their lipophilicity (log P(**1**) +0.22±0.0, log P(**2**) −0.54±0.02, log P(**3**) +1.55±0.04). The next question that we addressed was: where the activity comes from? It must be remarked that, most attention in relation to transition metal complexes, anticancer activity MoA has focused on DNA as the target. This hypothesis originates from functional compounds as cisplatin which activity derives from direct biding to biological target (DNA) [3]. But results of our research (UV-Vis, NMR) point on significant solution stability of the obtained compounds which suggests different mechanism of action. Namely, the complexes interact with CT-DNA (in non-covalent way) due to electrostatic interactions between the positively charged complex units and the negatively charged phosphate backbone of CT-DNA (hyperchromic effect from UV-Vis and CD spectra).

Searching for more proofs which will explain different cytotoxic activity of Ru(II), Rh(III) and Ir(III) complexes we studied the interactions with GSH. The mass spectra confirmed that **1**, **2** and **3** complexes bound to GSH and formed adducts with GSH, with fragments of GSH or GSSG. Additionally, the UV-Vis results demonstrated that ruthenium complex **1** is considerably less active in the reaction with GSH than the rhodium (**2**) and iridium (**3**) complexes. Simultaneously, the ruthenium(II) dimer displays better cytotoxicity compared to complexes **2** and **3**.

Most significantly, the obtained organometallic complexes demonstrated no cytotoxic effects towards the normal BALB/3T3 cell line compared to cisplatin and suggested their cytotoxic selectivity.

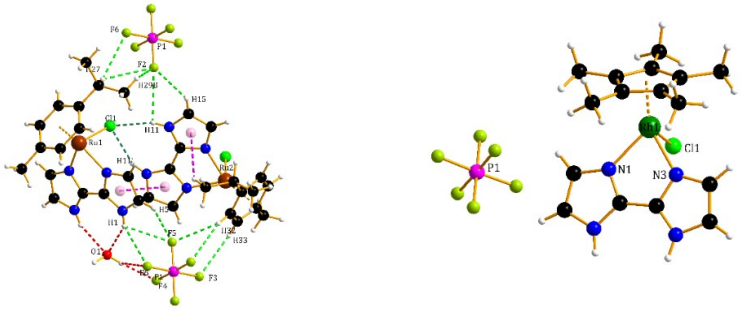


Figure 1. Molecular structure of Ru(II) and Rh(III), Ir(III) isostructural complexes.

References:

[1] T. Gianferrara, I. Bratsos, E. Alessio, *Dalton Transaction* **2009**, 7588-7598.
[2] R. W. Horobin, J. C. Stockert, F. Rashid-Doubell, *Histochemistry and Cell Biology* **2006**, 126, 165-175.
[3] A. M. Pizarro, P. J. Sadler, *Biochimie* **2009**, 91(10) 1198-1211.

OC7

A promising tripodal kojic acid derivative for metal chelation treatment: NMR and potentiometric studies

Rosita CAPPAI, [a] Massimiliano PEANA,[b] Maria de Guadalupe JARAQUEMADA-PELAEZ, [c] Valeria M. NURCHI, [a] M. Antonietta ZORODDU [b]

[a] Department of Life and Environmental Sciences, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy.
[b] Department of Chemistry and Pharmacy, University of Sassari, via Vienna 2, 07100 Sassari, Italy.
[c] Department of Chemistry, University of British Columbia, Vancouver Campus Main Mall, V6T 1Z1 Vancouver, Canada.
cappai@unica.it

Nuclear Magnetic Resonance spectroscopy, NMR, has been used to evaluate the coordination ability and affinity of a new promising tripodal chelator based on kojic acid (6,6',6''-(((nitrilotris(ethane-2,1-diyl))tris(azanediyl))tris(methylene))tris(3-hydroxy-4Hpyran-4-one)) (SC) (Figure 1.) toward several metal ions: Al^{3+}, Cu^{2+}, Mn^{2+}, Co^{2+}, Cd^{2+}, Zn^{2+}, Ni^{2+} together with Ga^{3+} as a diamagnetic probe for Fe^{3+}. The new ligand showed already remarkable chelation property in toward Fe^{3+} ions supporting its potential future use in clinical chelation treatment for iron overload diseases [1]. By the aid of NMR competition experiments, we evaluated the donor atoms and relative affinity of essential and non-essential metal ions in several ternary systems comprising the SC chelator and two different metal ions. The aim of this work was to monitor the potential interferences of SC in the homeostasis of essential metal ions. These studies showed a metal affinity order for the oxygen donor atoms of kojic unit as Ga^{3+} (Fe^{3+})>Al^{3+}> Mn^{2+}~Co^{2+}>Cu^{2+}>Ni^{2+}. Regarding the affinity for nitrogen donors of *tren* linker, Zn^{2+} and Cd^{2+} ions gave indication of a similar bonding ability. According with previous data, SC ligand is able to selectively bind Fe^{3+} ion [1].

However, our results showed that SC ligand is able to chelate at the same time Zn^{2+} together to Ga^{3+} ions. Since zinc is an essential element whose homeostasis must not be disturbed, in view of a potential application of the SC ligand in clinical practice, zinc supplements should be considered.

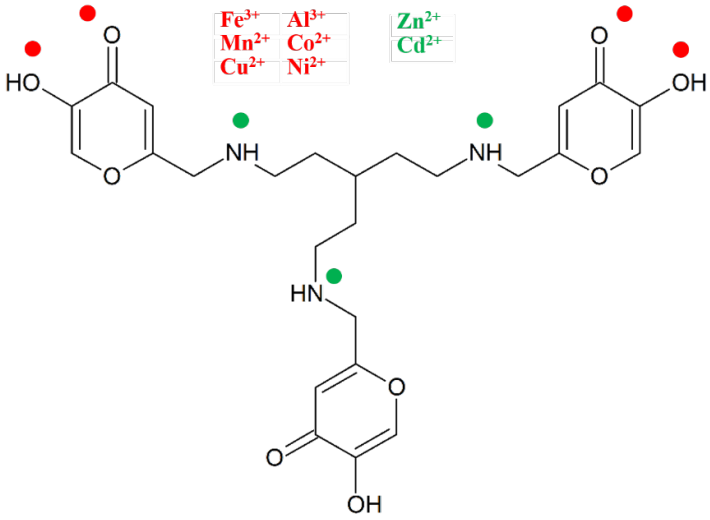


Figure 1. SC ligand and donor atoms and metal ions tested in the NMR experiments application of the SC ligand in clinical practice, a zinc supplements should be considered

References:

[1] V. M. Nurchi, M. G. Jaraquemada-Pelaez, G. Crisponi, J. I. Lachowicz, R. Cappai, L. Gano, M. A. Santos, A. Melchior, M. Tolazzi, M. Peana, S. Medici, M. A. Zoroddu, *J. Inorg. Biochem.* **2019**, Vol. 193, 152-165.

OC8
Coordination chemistry of Cu^{2+} complexes of small N-alkylated tetra-azacyclophanes with SOD activity

Álvaro MARTÍNEZ-CAMARENA,[a] Pedro A. SÁNCHEZ-MURCIA,[b] José M. LLINARES,[a] Leticia GONZÁLEZ,[b] Enrique GARCÍA-ESPAÑA[a]

[a] ICMol, University of València, C/ Catedrático José Beltrán 2, 4698 PATERNA, Spain
[b] Ins. Theoretical Chem., University of Vienna, Währinger Str. 17, A-1090 VIENNA, Austria
alvaro.martinez@uv.es

Tetra-azamacrocycles are among the ligands most widely studied in coordination and supramolecular chemistry. The interest in these ligands is related to their capacity for generating unsaturated coordination spheres, which is a requisite for many catalytic sites to work. Moreover, the introduction of aromatic rings in the ligand stiffens the macrocycle and changes the spatial arrangement of the donor atoms, thus generating open sites to which exogenous ligands or substrates may bind more efficiently [1].

Since as it has been extensively documented N-alkylation of polyamine ligands strongly affects the acid-base behavior, coordination ability toward metal ions and catalytic efficiency of such family of compounds [2], we have prepared a symmetrically N-alkylated derivative with two isopropyl groups and one methyl group (L1). In this work we discuss about the protonation and copper(II) coordination behavior in water of L1. Furthermore, we have made a preliminary analysis of antioxidant capability by means of the McCord−Fridovich method using nitroblue tetrazolium (NBT) as superoxide radical scavenger [3]. Finally, we have also modelled by means of theoretical tools (quantum mechanics and hybrid quantum mechanics/molecular mechanics methods) the reaction mechanism for catalytic transformation of superoxide into oxygen and hydro-peroxide by the complex Cu-L1, thus establishing the mechanistic pathway.

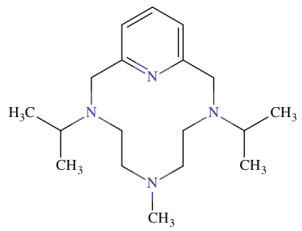


Figure 1. Structure of the studied aza-macrocycle.

References:

[1] Á. Martínez-Camarena, A. Liberato, E. García-España, *et al. Inorg. Chem.* **2018**, 57 (17), 10961-10973.
[2] T. J. Zerk, P. V. Bernhardt *Coord. Chem. Rev.* **2018**, 375, 173-190.
[3] J. Y. Zhou, P. Prognon *J. Pharm. Biomed. Anal.* **2006**, 40 (5), 1143-1148.

OC9
Isothermal titration microcalorimetry on divalent metal ions binding to N-terminal fragments of Hpn and Hpn-like proteins

Danuta WITKOWSKA, Jolanta KOZŁOWSKA

Public Higher Medical Professional School in Opole, Katowicka 68, 45-050 OPOLE, Poland.
witkowskad@wsm.opole.pl

The virulence of the *Helicobacter pylori* (human gastric pathogen) is highly dependent on nickel ions [1]. Two small proteins Hpn and Hpn-like are involved in Ni (II) trafficking and sequestration in this pathogen. Both Hpn and Hpn-like proteins have a Xaa-Xaa-His-His motif at the N-terminus. They are transcriptionally activated in the presence of nickel sensor NikR [2].

Our previous studies have shown that because of their albumin-like sequence the N-terminal parts of Hpn and Hpn-like proteins are very effective chelating agents for nickel and copper ions [3]. These peptides (MAHHEEQHG-NH_2 and MAHHEQQQQQQA-NH_2) proved to bind Ni(II) and Cu(II) ions with high affinity. The MAHHEQQQQQQA-NH_2 was better in binding these ions than MAHHEEQHG-NH_2 peptide and even than native albumin [3]. We suggested that poli-Q sequence stabilize very considerably the albumin-like coordination by the protein N-terminus.

However, to elucidate the entropic and enthalpic contributions to that binding more sophisticated technique is needed such as Isothermal Titration Calorimetry (ITC) [4]. Our studies proved that this technique is very useful in analysis of protein-ligand binding even in the presence of multiple, distinct binding sites [5].

Very recently we investigated the binding of Cu(II), Ni (II) and Zn(II) ions to (MAHHEEQHG-NH_2 and MAHHEQQQQQQA-NH_2) peptides using calorimetry (MicroCal PEAQ-ITC). The studies have been carried out at pH 6 and 7.4 in MES and CACO buffers for each pH respectively. At pH 6 both peptides showed strong affinity for Cu (II) ions with the best fit for the "Two sets of sites" model – showing that there are two different sites for binding of copper (II) ions. There was very weak binding of Zn (II) by one of these peptides and no binding of Ni (II) ions at this pH. There are distinct differences in signature plots showing Zn (II) binding by with favorable entropy. At pH=7.4 zinc ions bind both peptides with stronger affinity. We've seen very slow kinetic effect for Cu and Ni ions binding and the strange profile of titration curve. We changed the spacing to 500 sec but it didn't help. We are now due to optimizing the method and we need to repeat the measurements at the pH=7.4 probably doing it in another buffer, what will be done very soon.

References:

[1] R. G. Ge, D. X. Wang, M. C. Hao, X. S. Sun, *World J Gastroenterology* **2013**, 19(45), 8211-8.

[2] A. Contreras, J. M. Thiberge, M. A. Mandrand-Berthelot, A. Labigne, *Mol. Microbiology* **2003**, 49(4), 947-63.

[3] D. Witkowska, S. Bielińska, W. Kamysz, H. Kozłowski, *J Inorg Biochem* **2011**, 105, 208–214.
[4] D. Witkowska, M. Rowińska-Żyrek, *J Inorg Biochem* **2019**, 199, 110783.
[5] D. Witkowska, H. L. Cox, T. C. Hall, G. C. Wildsmith, D. C. Machin, M. E. Webb, *Biochim Biophys Acta Proteins Proteom* **2018**, 1866(2), 254-263

OC10
Thermodynamic study of the cation/anion structure influence on micellization process: The case of surface active ionic liquids

Isidora ČOBANOV,[a)] Bojan ŠARAC,[a)] Žiga MEDOŠ,[a)] Aleksandar TOT,[b)] Milan VRANEŠ,[b)] Slobodan GADŽURIĆ,[b)] Nebojša ZEC,[b,c)] Marija BEŠTER-ROGAČ[a)]

[a)] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia.*
[b)] *Department of Chemistry, Biochemistry and Environmental Protection, University of Novi Sad, Novi Sad, Serbia.*
[c)] *German Engineering Materials Science Centre (GEMS) at Heinz Maier-Leibnitz Zentrum (MLZ),Garching bei München, Germany.*
isidoracobanov@gmail.com

Lately, surface active ionic liquids (SAILs) have been investigated intensively. Since the smallest change in structure can considerably affect the micellization process, SAILs turned out to be excellent model systems for studies of ion-specific effect during micellization process [1,2]. Their behaviour is in many ways similar to those observed by classic ionic surfactants: for example, the micellization process is endothermic at low temperatures and exothermic at high temperatures, where counter-ions have an important role on magnitude and change of sign of the observed heat effects [3].

In this contribution, the influence of the cation structure change on micellization process in aqueous solutions will be presented first in systems where the chain length on N3 position of 1-dodecyl-3-(methyl-,ethyl- or butyl-) imidazolium cation is varied (Figure 1a), and second in systems where the position of methyl group on pyridinium ring of 1-dodecyl- (2-, 3- or 4-) methylpyridinium cation (Figure 1b) is different. Furthermore, the influence of the position of –OH group on hydroxybenzoate on the micellization process of 1-dodecyl-3-methylimidazolium cation will be discussed (Figure 1c).

All the studies were carried out by the isothermal titration calorimetry (ITC) in a broad temperature range. The results were analyzed by the corresponding model [4] and discussed in terms of ion-specific and isomer effect on micellization process in water.

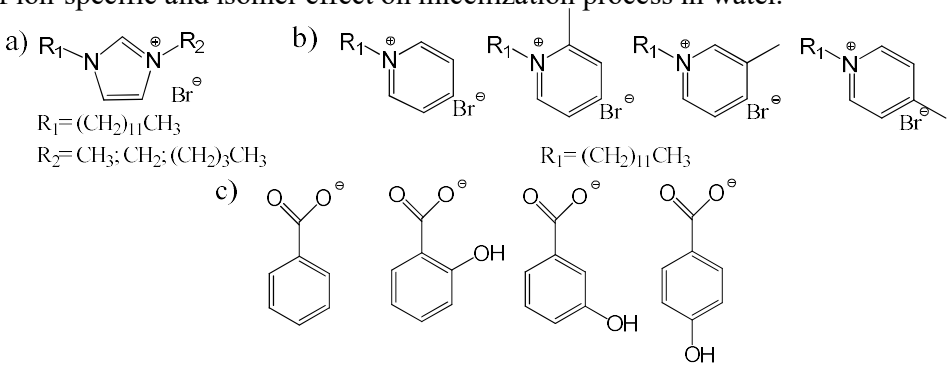


Figure 1. Structures of the investigated systems: a) 1-dodecyl-3-(methyl-, ethyl- or butyl-) imidazolium bromide b) the isomeric hydroxybenzoate anions; c) 1-dodecyl-(2, 3 or 4)-methylpyridinium bromides.

References:

[1] B. Šarac, Ž. Medoš, A. Cognigni, K. Bica, L.-J. Chen and M. Bešter-Rogač, *Colloids Surf., A*, **2017** 532, 609-617.

[2] I. Čobanov, B. Šarac, Ž. Medoš, M. Vraneš, S. Gadžurić, N. Zec, M. Bešter-Rogač, *J. Mol. Liquids*, **2018** 271, 437-442.

[3] I. Čobanov, B. Šarac, Ž. Medoš, A. Tot, M. Vraneš, S. Gadžurić, M. Bešter-Rogač *J. Mol. Liquids*, **2020** 301, 112419

[4] Ž. Medoš and M. Bešter-Rogač, *Langmuir*, **2017** 33, 7722

OC11
Molecular mechanisms ruling the formation of aqueous two-phase systems comprising ionic liquids

Mara G. FREIRE

CICECO-Aveiro Institute of Materials, Chemistry Department, University of Aveiro, 3810-193 Aveiro, Portugal.
maragfreire@ua.pt

Ionic liquids (ILs) have received relevant attention to be applied in a broad range of applications, with a significant fraction of the reported works focusing on their use in separation processes from aqueous media. In this field, a large interest has been placed in hydrophobic ILs due to their immiscibility with water and ability to create biphasic (liquid-liquid) systems. However, these tend to be more toxic and of higher cost, rendering the use of water-soluble (hydrophilic) ILs as a more appropriate choice. Although these ILs are water-soluble, aqueous two-phase systems can be created by combining them with inorganic or other organic salts with salting-out characteristics. These aqueous two-phase systems, if properly designed, are sustainable and biocompatible separation strategies due to their high water content [1-2]. Nevertheless, the design of these systems as effective separation processes requires a better understanding of the molecular-level mechanisms ruling the liquid-liquid phase behavior.
In this work, our contributions over the past years toward a comprehensive understanding of the molecular-level mechanisms ruling the formation of two-phase systems constituted by water, ILs and salts will be overviewed. These findings are based on a large set of experimental liquid-liquid and spectroscopic data and modeling results.

Acknowledgements:
This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement. M. G. Freire acknowledges the European Research Council for the ERC Grants 337753 and 899921.

References:
[1] Freire, M. G.; Cláudio, A. F. M.; Araújo, J. M. M.; Coutinho, J. A. P.; Marrucho, I. M.; Canongia Lopes, J. N.; Rebelo, L. P. N. *Chem. Soc. Rev.* **2012**, *41,* 4966.
[2] Ventura, S. P. M.; Silva, F. A.; Quental, M. V.; Mondal, D.; Freire, M G.; Coutinho, J. A. P., *Chem. Rev.* 2017, *17*, 6984.

OC12
Kinetic and equilibrium study for Hg(II) removal from aqueous solution by sorption onto functionalized halloysite

Salvatore CATALDO, [a] **Marina MASSARO,** [b] **Demetrio MILEA,** [c] **Alberto PETTIGNANO,** [a] **Serena RIELA** [b]

[a] *Dipartimento di Fisica e Chimica – Emilio Segrè, Università di Palermo, Viale delle Scienze,I-90128, Palermo, Italy.*
[b] *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università di Palermo, Viale delle Scienze, I-90128, Palermo, Italy.*
[c] *Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali (CHIBIOFARAM), Università degli Studi di Messina, Messina, Italy.*
salvatore.cataldo@unipa.it

Mercury is considered one of the most dangerous metal for humans and all living organisms as pointed out by numerous toxicological studies [1]. Environmental contamination comes from natural and anthropogenic sources and from the remobilization of previously settled mercury from soils and sediments [2]. It has been estimated that the amount of anthropogenic mercury released in natural waters is about 1000 tons per years [3]. Mercury in natural waters can be present in elemental (Hg^0), inorganic (Hg^+, Hg^{2+}) and organic [CH_3Hg^+, $(CH_3)_2Hg$] forms. Among the different forms, the Hg^{2+} species represents the most soluble and abundant in polluted waters [2]. A lot of scientists are nowadays involved in finding methods for the remediation of polluted water from mercury. One of the most promising techniques is the adsorption onto cheap, abundant and non-toxic materials [4]. The unique features of clay minerals have gathered great interest. Indeed, they have low price, are available in large quantities, have a low or non toxicity and are environmental friendly [5,6].

In this work are proposed new adsorbent materials derived from halloysite, a clay mineral with a mainly hollow tubular structure. Pristine halloysite (p-HNTs) have been functionalized with amino groups (HNTs-NH_2) and thiol groups (HNTs-SH) and tested as adsorbents for Hg^{2+} ion from aqueous solutions in different experimental conditions (pH, ionic medium, ionic strength, temperature). Batch kinetic and isotherm experiments have been carried out measuring the Hg^{2+} ion in water samples by means of Inductively Coupled Plasma Emission Spectroscopy (ICP-OES). Literature formation constants of the Hg^{2+} species and protonation constants of the binding groups of the adsorbents [7–9] have been used to delineate the speciation pictures of the metal ion and of the adsorbents in order to correlate the amount of mercury adsorbed and both the mercury species in solution and protonation degree of the functional groups of functionalized halloysites.

References:

[1] R. Ynalvez, J. Gutierrez, H. Gonzalez-Cantu, *Biometals* **2016,** 29, 781–788.
[2] Q. Wang, D. Kim, D.D. Dionysiou, G.A. Sorial, D. Timberlake, *Environmental Pollution* **2004**, 131, 323–336.

[3] U.N. Environment, *Global Mercury Assesment 2018*, Geneva, Switzerland, **2019**.
[4] S. De Gisi, G. Lofrano, M. Grassi, M. Notarnicola, *Sustainable Materials and Technologies* **2016**, 9, 10–40.
[5] Y. Dong, Z. Liu, L. Chen, *J Radioanal Nucl Chem* **2012,** 292, 435–443.
[6] S. Cataldo, N. Muratore, S. Orecchio, A. Pettignano, *Applied Clay Science* **2015,** 118, 162–170.
[7] A.E. Martell, R.M. Smith, Critical Stability Constants, Plenum Press, New York, **1977**.
[8] C. Bretti, S. Cataldo, A. Gianguzza, G. Lando, G. Lazzara, A. Pettignano, S. Sammartano, *J. Phys. Chem. C* **2016**, 120, 7849–7859.
[9] F. Crea, C. De Stefano, C. Foti, D. Milea, S. Sammartano, *Current Medicinal Chemistry* **2014,** 21 (33), 3819-3836.

OC13
Assignment of complex species by affinity capillary electrophoresis

Vladimir SLADKOV, [a] **Michel MEYER** [b]

[a] *UMR CNRS 8608 - Institut de Physique Nucléaire, 15 rue G. Clemenceau 91406 ORSAY, France.*
[b] *Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), UMR 6302, CNRS, Université Bourgogne–Franche-Comté, 9 avenue A. Savary, BP 47870, 21078 DIJON, France.*
sladkov@ipno.in2p3.fr

The thermodynamic parameters associated to the formation of metallic complexes involving either inorganic or organic ligands are generally derived from classical macroscopic approaches, such as spectrophotometric (UV-vis), potentiometric, or liquid-liquid extraction experiments. One of the major difficulties in modelling the equilibria is related to the correctness of the hypothesized stoichiometry of the various species prevailing in solution. Affinity capillary electrophoresis (ACE) has been successfully used for unravelling the speciation and measuring the equilibrium constants of labile (kinetically rapid) systems, for which the rate of ligand exchange between the various bound and unbound forms is substantially faster than the characteristic separation time in the capillary, typically a few minutes.

The aim of this work is to demonstrate the advantages of ACE over other classical methods applied in solution coordination studies. To that end, we will focus on the Th(IV)-desferrioxamine B (DFO) system. The latter ligand is a natural bacterial siderophore produced by *Streptomyces pilosus*. Siderophores are water-soluble, low molecular weight iron(III) carriers, which are common in soils, natural waters but also in the marine environment. Recently, they have also been recognized as effective actinide(IV) chelators and transporters. DFO, which incorporates three hydroxamate binding units and a terminal primary amine, can therefore be considered as a tetraprotic base susceptible to form at least four metal complexes depending upon the pH, having MLH_3, MLH_2, MLH, and ML stoichiometries.

The electrophoretic mobility change of DFO, monitored by UV absorption spectrophotometry upon increasing the thorium(IV) concentration in the background electrolyte, was used to assess the speciation model and estimate the equilibrium constants. ACE turned out to be helpful in distinguishing the complexed species and ascertaining their protonation state. The apparent equilibrium constants obtained by ACE will be compared to those available in the literature for other metal ions. After that, the different ways of studies of Zr(IV), as more hydrolysable cation than Th(IV) by ACE will be discussed. Two approaches will be considered: (i) using a protecting ligand to avoid hydrolysis or (ii) taking hydrolysis constants into account for equilibrium calculations at fixed pH.

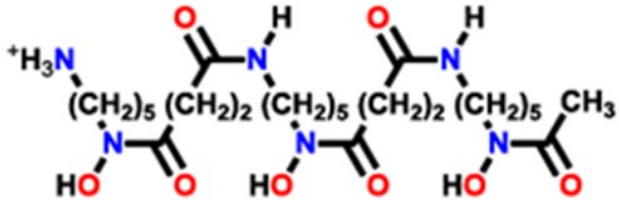


Figure 1. Structures of the desferrioxamine B.

Acknowledgment
The Agence Nationale de la Recherche is gratefully acknowledged for financial support (ANR project PLUTON, grant N° ANR-17-CE08-0053).

OC14
Rare earth metal ions sensing by using metal receptors and multivariate analysis

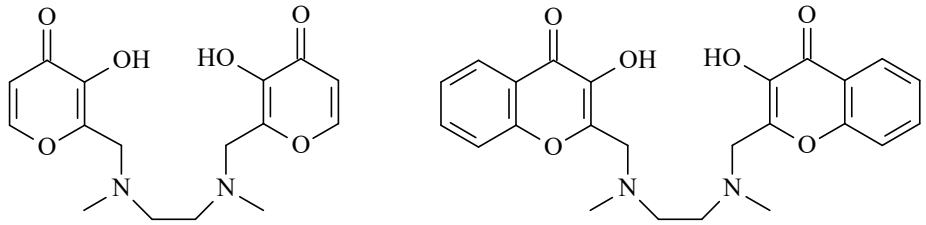
Daniele PADERNI, Luca GIORGI, Eleonora MACEDI, Vieri FUSI, Mauro FORMICA

Department of Pure and Applied Sciences University of Urbino "Carlo Bo", Via della Stazione N.4, 61029 URBINO, Italy.
Luca.giorgi@uniurb.it

Rare earth elements (REEs) are a group of fifteen elements ranging from lanthanum (Z=57) to lutetium (Z=71), also called lanthanides. Two further elements, namely scandium (Z=21) and yttrium (Z=39), are often referred to as REEs because they have chemical properties similar to lanthanides and are commonly found in the same mineral assemblages.

The modern applications of REEs are countless; these elements constitute critical components of many of our modern-day technological devices, everyday electronics and new functional materials, as well as they are extensively used in medical diagnostic applications [1], thus REEs are raising new interests of scientists worldwide. The search for chemical sensors suitable for selective sensing of trivalent REE ions represents an important and hard challenge because the coordination properties of these ions are complicated by not well-defined stereo-chemical requirements and uncertain coordination number, especially in aqueous solution. All REEs have very similar chemical behaviour with smooth variation attributed to their atomic number and ionic radii, which are inversely correlated; these attributes make REEs well suited to the study of coordination by organic molecules [2].

Our research group reported the synthesis of a preorganized metal-receptor suitable to bind RE ions in water based on ligand **L1** (Figure 1.) containing two maltol units linked as side arms to a N,N'dimethylethylenediamine scaffold.[3] This system can be preorganized by a transition metal ion like Cu(II) or Pd(II) forming a neutral [M(II)(H_{-2}**L1**)] complex, two units of which stabilize one RE metal ion giving rise to a trinuclear $[RE(III)[M(II)(H_{-2}\mathbf{L1})]_2]^{3+}$ species. In order to improve their photochemical properties to allow the use of these systems as fluorescent sensors we designed a parent ligand in which the maltol unit has been replaced by a 2-hydroxychromone fragment (**L2**) (Figure 1). Pd(II) complex of (H_{-2}**L2**) can bind RE(III) metal ions and these metal-receptors may be applied to sense RE ions.



L1 **L2**

Figure 1. Structure of Ligands **L1** and **L2**

The presence of a fluorescent fragment could allow the use of fluorescence excitation–emission matrix (EEM) spectroscopy, which is a technique that allows for the complete, quantitative determination of the fluorescence profile of a given sample. Unlike simple emission spectroscopy that is commonly used to visualize the fluorescence of metal clusters, EEM spectroscopy can afford information on the emission profile concurrently with excitation wavelength data, creating a three dimensional map of fluorescence characteristics. The observed electronic transitions are telling of the structure and properties of a sample, and most importantly herein, provide greater insight into sample purity, composition and sensing behavior.

The high amount of data collected will be subjected to statistical analysis with different approaches, including multivariate analysis by projection pursuit. Projection pursuit is a multivariate statistical technique aimed at finding interesting low-dimensional data projections. Projection pursuit deals with three major challenges of multivariate analysis: the curse of dimensionality, the presence of irrelevant features and the limitations of visual perception. Projection pursuit looks for the data projection which maximizes the projection pursuit index, that is a measure of its interestingness [4]. In Chemometrics, the projection pursuit index is often the kurtosis, that is the fourth standardized moment [5], whose properties have been recently investigated [6].

References:

[1] Engineering Technical Support Center Land Remediation and Pollution Control Division National Risk Management Research Laboratory Office of Research and Development Cincinnati, Rare Earth Elements: A Review of Production, Processing, Recycling, and Associated Environmental Issues, OH, EPA 600/R-12/572 | December 2012.

[2] J.-C. G. Bünzli, *Acc. Chem. Res.* **2006**, 39, 53−61.

[3] C. Benelli, E. Borgogelli, M. Formica, V. Fusi, L. Giorgi, E. Macedi, M. Micheloni. P. Paoli, P. Rossi, *Dalton Trans.* **2013**, 42, 5848-5859.

[4] Sun, J. Projection Pursuit. *Encyclopedia of Statistical Sciences* **2006**, Vol. 10.

[5] Hou S., Wentzell, P.D., *J. Chemom.* **2014**, 28, 370-384.

[6] N. Loperfido, *Eur. J. Finance* **2020**, 26, 142-164.

OC15

Complexes of organic anions with tetrazine-based ligands in water or how multifaceted equilibria can arise from apparently simple systems

Matteo SAVASTANO,[a] Carla BAZZICALUPI,[a] Celeste GARCÍA,[b] Maria Dolores LÓPEZ DE LA TORRE,[b] Manuel MELGUIZO,[b] Antonio BIANCHI [a]

[a] Department of Chemistry "Ugo Schiff", University of Florence, Via della Lastruccia 3, 50019 SESTO FIORENTINO, Italy.
[b] Department of Inorganic and Organic Chemistry, University of Jaén, 23071 JAÉN, Spain.
matteo.savastano@unifi.it

Features and nature of any complex species are the result of the interplay of the interactions keeping it together. Yet, at least for classic (cation) coordination chemistry, such interplay is bound to be dominated by the strength of coordination bonds, which generally far exceeds the sum of the contributions from non-covalent forces [1].

When designed to do so, anion complexes offer the opportunity to "level the playfield", offering the chance to observe what happens when different types of supramolecular forces (H-bonds, π-π stacking, anion-π, solvent effect, etc.), all falling within a similar energy range, dialogue among themselves to determine the stability and structure of a complex [1,2].

Disentangling the contribution of each type of interactions to the resulting complex and understanding their fine game is hardly practicable for single complexes. However, a rational experimental design featuring homologous molecules as ligands and analogous organic anions as substrates, allowed in our case the achievement of a superior understanding of the forces in play.

Homologous tetrazine-based L1 and L2 ligands [3], both amenable to anion-π, π-π stacking and H-bonding interactions, but differing in size, were studied with a series of selected and structurally related organic anions in water, as illustrated in Figure 1. "Basic" carboxylate anions were compared to "non-basic" sulfonate analogues, deeply influencing the intrinsic strength of H-bond interactions, while benzenic vs. methylenic derivatives were used as prototypes for aliphatic and aromatic substrates, fostering the possibility of π-π interactions and increasing the magnitude of hydrophobic effect. Dicarboxylate anions were also considered to account for the presence of a second charged groups, and phthalate regioisomers were investigated to show the effect of substituent position on the interaction modes [4].

Initially, for monovalent anions, expectable stability trends were found for complex stability (carboxylate > sulfonates, aromatic > aliphatic), which could potentially (and mistakenly) be rationalized in terms of strength of H-bonds, possibility of π-π stacking and increased contribution from solvent effect to complex stability. However, complete speciation data, which required the potentiometric determination of over 40 equilibrium constants, NMR evidences, DFT simulation and solution of 3 crystal structures, revealed a much more complicated picture, where the geometry of the anion and the size of the receptors are crucial factors in play [4].

Addition of a second charged group to the substrates brings forth additional effects to be taken into account, adding further depth to the study. It is worth mentioning that the pH dependent selective recognition of phthalate or isophthalate regioisomer is possible in aqueous solution for both ligands [4]. This feature is not generally easily obtained and adds to the fact that detailed understanding of the interplay of different supramolecular forces and its impact on complexes stability, beyond academic interest, has the potential to meet pragmatic scopes, as it foreshadows applications in separation processes.

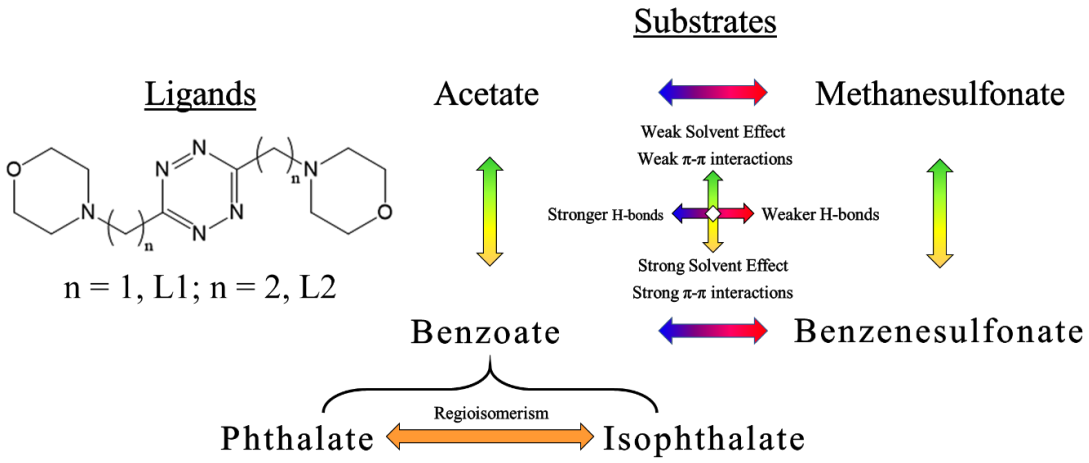


Figure 1. General outlook of the ligand/substrate systems considered within present study.

References:

[1] J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, 2nd Edition, John Wiley & Sons, Ltd, Chichester, **2009**.

[2] A. Bianchi, E. García-España, Thermodynamic Aspects of Anion Coordination in *Anion Coordination Chemistry*, K. Bowman-James, A. Bianchi, E. Garcia-España, Eds., Wiley-VCH, New York, **2012**.

[3] M. Savastano, C. Bazzicalupi, C. García, M.D. López de la Torre, F. Pichierri, A. Bianchi, M. Melguizo, *Inorg. Chem.* **2016**, 55, 8013–8024.

[4] M. Savastano, C. Bazzicalupi, C. García, M.D. López de la Torre, A. Bianchi, M. Melguizo, *Org. Chem. Front.* **2019**, 6, 75-86.

OC16
Untangling the driving forces of molecular recognition processes in solution

Carmelo SGARLATA

Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale Andrea Doria 6, 95125 Catania, Italy.
sgarlata@unict.it

Non-covalent, weak interactions are major tools used in supramolecular and coordination chemistry to manage molecular recognition and self-assembly processes for the design and synthesis of intriguing structures such as molecular capsules, cages, flasks and nano-containers [1]. By mimicking the active sites and pockets of enzymes, synthetic assemblies are able to isolate proper guest molecules from the surrounding media and promote chemical reactions in a controlled fashion. The dramatic differences between the bulk solvent and the inner space within a molecular container provide the "thermodynamic boost" to guest complexation which cannot be driven only by structural complementarity or fitting between host and guest [2]. Consequently, the determination of complex species and thermodynamic parameters at the base of molecular recognition, guest-templated assembling, host-guest encapsulation, micellar aggregation and related phenomena is a key point for the rational design and efficient application of supramolecular containers in solution.

The entropic and enthalpic driving forces for guest binding to supramolecular receptors in solution are very different, which significantly complicates the determination of these thermodynamic parameters. The advantageous use of complementary techniques, such as for examples NMR, UV−vis/fluorescence and isothermal titration calorimetry (ITC), enables the disentanglement of such multiple host-guest interactions. Data collected by each technique measure different components of the host−guest equilibria and together provide a complete picture of the solution thermodynamics. The analysis of the data is often puzzled by the variety of responses given by each of the different techniques and by a stepwise series of mutually linked equilibria usually occurring is solution.

We developed a procedure for the simultaneous refinement of multiple parameters (ΔG, ΔH and ΔS) by handling different observables through a weighted non-linear least-squares analysis of a constrained model [3,4]. By applying this procedure to different sets of observables, each looking at different components of multiple and often competing host–guest equilibria, the binding constants and the enthalpy and entropy change for the interior and multiple exterior guest binding to a supramolecular receptor were determined.

Furthermore, a new general-purpose computer program for the simultaneous determination of both standard enthalpy of reaction and binding constant values from data obtained by ITC was also established [5]. The program does not impose limits on the complexity of the chemical systems that can be treated, including competing ligand systems, or on the quantity of experimental data to be analyzed. The chemical system is defined in terms of species of given stoichiometry rather than in terms of binding models (e.g. independent, cooperative,

etc.). Many titration curves may be treated simultaneously. The program can also be used as a simulation program for the experiment design. Typical applications are for the study of ligand protonation, host-guest reactions, metal-ligand complexation and competition reactions.

All the above data refinement tools have been successfully applied on our recent studies on the molecular recognition of charged guests by metal-ligand clusters [6], calixarene receptors bearing sulphonato [7] or ammonium functionalities [8] as well as on the formation of anion-templated capsules and compartments [9] or supra-amphiphiles and aggregates in aqueous solution. A combination of different datasets from NMR, UV-vis and/or ITC titrations allowed for the deconvolution of the host-guest equilibria and the determination of the species forming in solution. In particular, ITC data allowed for splitting the Gibbs free energy term into the ΔH and ΔS components thus unveiling the different and often opposing forces, not expressed in the logK value, driving guest recognition and self-assembly processes [10]. The significance of the chemical calibration of an isothermal calorimeter is also highlighted as a crucial point for yielding accurate values of the thermodynamic parameters [11].

References:

[1] F. J. Rizzuto, L. K. S. von Krbek, J. R. Nitschke, *Nature Rev. Chem.* **2019**, 3, 204–222.
[2] J. H. Jordan, B. C. Gibb, *Chem. Soc. Rev.* **2015**, 44, 547-585.
[3] C. Sgarlata, K. N. Raymond, *Anal. Chem.* **2016**, 88, 6923–6929.
[4] C. Sgarlata, J. S. Mugridge, M. D. Pluth, V. Zito, G. Arena, K. N. Raymond, *Chem. Eur. J.* **2017**, 23, 16813-16818.
[5] G. Arena, P. Gans, C. Sgarlata, *Anal. Bioanal. Chem.* **2016**, 408, 6413−6422.
[6] C. Sgarlata, J. S. Mugridge, M. D. Pluth, B. E. F. Tiedemann, V. Zito, G. Arena, K. N. Raymond, *J. Am. Chem. Soc.* **2010**, 132, 1005–1009.
[7] C. Bonaccorso, R. Migliore, M. A. Volkova, G. Arena, C. Sgarlata, *Thermochim. Acta* **2017**, 656, 47–52
[8] C. Bonaccorso, G. Brancatelli, G. Forte, G. Arena, S. Geremia, D. Sciotto, C. Sgarlata, *RSC Adv.* **2014**, 4, 53575–53587; C. Bonaccorso, C. Sgarlata, G. Grasso, V. Zito, D. Sciotto, G. Arena, *Chem. Commun.* **2011**, 47, 6117−6119.
[9] C. Sgarlata, A. Giuffrida, E. R. Trivedi, V. L. Pecoraro, G. Arena, *Inorg. Chem.* **2017**, 56, 4771−4774.
[10] G. Arena, C. Sgarlata, Modern Calorimetry: An Invaluable Tool in Supramolecular Chemistry. In *Comprehensive Supramolecular Chemistry II*, J. L. Atwood, Ed. Elsevier: Oxford, **2017**, Vol. 2, pp. 213–237.
[11] C. Sgarlata, V. Zito, G. Arena, *Anal. Bioanal. Chem.* **2013**, 405, 1085−1094.

P1
Neclu_MT1: a combined approach

Monica PERINELLI, [a] **Matteo TEGONI,** [b] **Eva FREISINGER** [b]

[a] Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 ZUERICH, Switzerland.
[b] Dipartimento di Scienze Chimiche, University of Parma, Parco Area delle Scienze 17/A, 43121 PARMA, Italy.
monica.perinelli@chem.uzh.ch

Metallothioneins (MTs) are a large super-family of small, cysteine-rich metallo-proteins. Due to the high content of cysteine residues, and sometimes assisted by histidine, these tiny proteins are able to efficiently coordinate most of the transition metal ions, from the essential Zn(II) and Cu(I) to the most toxic such as Cd(II) and Hg(I) [1].

Owing to their large metal ion binding capacity, many biological roles were proposed for MTs: involvement in metal ion transport, resistance against oxidative stress and detoxification processes. Neclu_MT1, for example, is one of the smallest MTs (only 24 amino acids of which eight are cysteines), and it is produced by *Heliscus lugdunensis*, an aquatic fungus that is able to survive in a polluted spring in a former mining area in German with metal ion concentrations as high as 25 µM of Cd(II) and 30 mM of Zn(II) [2,3].

Neclu_MT1 was proven to be the first cadmium specific MT, since only this metal ion is able to trigger and regulate protein expression and translation. In addition, quite peculiar is the presence of one histidine at precisely the protein C-terminus. In order to investigate the role of this 'special guest' in the sequence, the histidine was mutated to a non-coordinating arginine (*H24R*) and potentiometric studies were performed on both the mutant and the wild-type protein. Results were corroborated by 2D-heteronuclear NMR experiments. On one side, potentiometry allows us to calculate the consecutive, individual pK_a values for many residues and to observe, how these values are affected by the mutation. It also allows to observe the stepwise coordination of metal ions. On the other side, when we follow the pH titration of the proteins by NMR, we are able to explicitly observe the protonation event of the histidine residue, and in this way could identify a distinct difference in the coordination pathway of Zn(II) compared to Cd(II).

References:

[1] G. Isani, E. Carpenè, *Biomolecules* **1957**, 4, 435–457.
[2] J. Miersch, K. Grancharov, *Amino Acids* **2008**, 34, 271–277.
[3] J. Loebus, B. Leitenmaier, D. Meissner, B. Braha, G. Krauss, D. Dobritzsch, E. Freisinger, *J. Inorg. Biochem.* **2013**, 127, 253-260.

P2

Complexes of NOTA-monoamides: model compounds for copper and gallium radiopharmaceuticals

Jan KUBINEC, Vojtěch KUBÍČEK, Jan KOTEK, Petr HERMANN

Charles University (Universita Karlova), Faculty of Science, Department of Inorganic Chemistry, Hlavova 2030, Prague 2, Czech Republic.
petrh@natur.cuni.cz

Copper and gallium radioisotopes are utilized as tracers in nuclear medicine. To avoid non-specific deposition of the isotopes in tissues, the metal ions must be administered in the form of thermodynamically stable and kinetically inert complexes. Macrocyclic polyamines substituted with coordinating pendant arms are the most common complexing agents for copper and gallium radioisotopes. An important group of the chelators are derivatives of NOTA (Figure 1.) which are good complexing agent for both, Cu^{II} and Ga^{III} ions [1,2].

Significant attention has been recently devoted to development of "targeted" radiotracers where the radioisotope complex is conjugated to a biologically active compound – vector. The vector has a high affinity to specific receptors and, thus, its presence in the tracer molecule assures preferential accumulation of activity in the tissue in question. The most common attachment of the vector to the radioisotope complex is attachment through amidic bond on the core carboxylate. Despite that, only limited attention has been devoted to chemical characterization of NOTA-monoamides. Here, we present coordination study of two NOTA-monoamides (Figure 1.) as model compounds for the coordination part of the conjugates. Thermodynamic stability of the complexes was studied by combination of potentiometry and spectroscopic methods. As expected, stability constants of the complexes are lower than those of NOTA. Kinetic properties of the complexes were studied by UV-VIS and NMR spectroscopy. Kinetic inertness of the Cu^{II} complexes is even slightly higher than that of the Cu^{II}-NOTA complex. Mainly, the results show that the NOTA-monoamides are suitable for complexation of copper radioisotopes due to a good selectivity for Cu^{II} over Zn^{II} ions. On the other hand, the ligands are not fully suitable for Ga^{III} ions due to a limited hydrolytic stability of the amidic bond induced by coordination of the very hard trivalent metal ion.

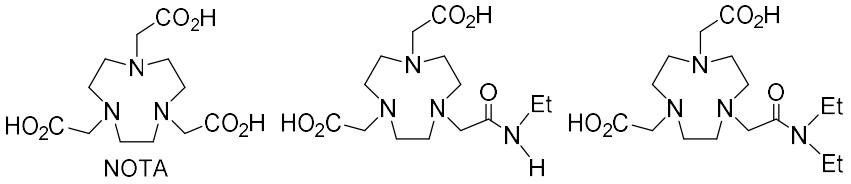


Figure 1. Structures of NOTA and the studied monoamides.

Acknowledgement:
Financial support from the Grant Agency of the Czech Republic (19-17380S) is acknowledged.

References:

[1] J. Šimeček, M. Schulz, J. Notni, J. Plutnar, V. Kubíček, J. Havlíčková, P. Hermann, *Inorg. Chem.* **2012**, *51*, 577–590.

[2] V. Kubíček, Z. Böhmová, R. Ševčíková, J. Vaněk, P. Lubal, Z. Poláková, R. Michalicová, J. Kotek, P. Hermann, *Inorg. Chem.*, **2018**, *57*, 3061−3072.

P3
Kinetic study of Cu(II) complexes of mono- and bis-tetraazamacrocyclic ligands

Ellen STEHLÍKOVÁ, [a] Přemysl LUBAL, [a] Jana HODAČOVÁ, [b]

[a] *Department of Chemistry, Masaryk University, Kamenice 5, 625 00 BRNO, Czech Republic.*
[b] *Department of Organic Chemistry, University of Chemistry and Technology, Technická 5, 166 28 PRAGUE, Czech Republic.*
lubal@chemi.muni.cz

Polyaza-macrocyclic ligands have been recently used to bind some radioisotopes for application in medicinal chemistry ($^{60–64,67}$Cu, $^{66–68}$Ga, ^{86,90}Y, ^{111}In) [1,2]. These metal complexes have to exhibit high thermodynamic stability and kinetic inertness for possible *in vivo* use for medical purposes [1,2]. Several copper(II) and zinc(II) complexes of bis-polyaza-macrocyclic ligands catalyse some hydrolysis-like chemical reactions and therefore they can be used as model systems mimicking enzymes activity [3].

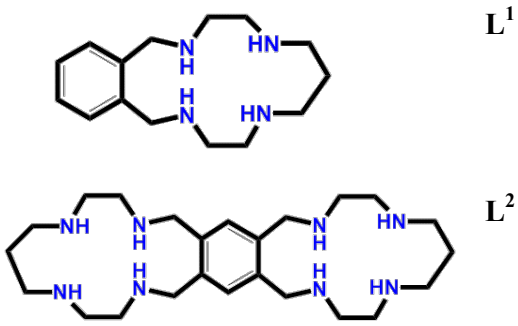


Figure 1. The structural formulas of studied macrocyclic ligands.

The thermodynamic studies of Cu(II) complexation by both ligands show that these complexes are stable [4-6] due to fact that copper(II) ion is fully coordinated by all four nitrogen donor atoms [4-6]. In this work, the formation of the copper(II) complexes of both ligands was studied as function of pH and possible reaction mechanism is proposed. The study of acid-assisted dissociation of both copper(II) complexes does not differ within experimental error. The results for both formation and dissociation of Cu(II) complexes indicate that there is no cooperative effect for binucleating ligand.

Acknowledgement:
Financial support from the Masaryk University (MUNI/A/1424/2019) is acknowledged.

References:

[1] G. Anderegg, F. Arnaud-Neu, R. Delgado, J. Felcman, K. Popov, *Pure App. Chem.* **2005**, 77(8), 1445-1495.

[2] T. J. Wadas, E.H. Wong, G.R. Weisman, C.J. Anderson, *Chem. Rev.* **2010**, 110(5), 2858–2902.

[3] D. Bím, E. Svobodová, V. Eigner, L. Rulíšek, J. Hodačová, *Chem. Eur. J.* **2016**, 22(30), 10426-10437.

[4] M. Chadim, P. Diaz, E. Garcia-España, J. Hodačová, P. C. Junk, J. Latorre, J.M. Llinares, C. Soriano, J. Závada, *New J. Chem.* **2003**, 27(7), 1132–1139.

[5] M. Chadim, P. Diaz, E. Garcia-Espana, J. Hodačová, J. Latorre, M. Liu-Gonzalez, S.V. Luis, J.M. Llinares, J. Závada, *Inorg. Chem.* **2005**, 44(21), 7503-7510.

[6] B. Verdejo, M.G. Basalotte, A. Ferrer, M. A. Máñez, J.C. Hernandéz, M. Chadim, J. Hodačová, J.M. Llinares, C. Serriano, E. Garcia-España, *Eur. J. Inorg. Chem.* **2008**, (9), 1497-1507.

P4
Thermodynamic and kinetic study of Ln(III) complexes of NOTA

Filip SMRČKA, [a] **Jakub VANĚK,** [a] **Přemysl LUBAL,** [a] **Vojtěch KUBÍČEK,** [b] **Petr HERMANN** [b]

[a] *Department of Chemistry, Masaryk University, Kamenice 5, 625 00 BRNO, Czech Republic.*
[b] *Department of Inorganic Chemistry, Charles University, Hlavova 2030, 128 40 PRAGUE, Czech Republic.*
filip.smrčka@gmail.com

Lanthanide(III) complexes of polyaza-macrocyclic ligands (primarily DOTA-like ligands) are utilized in many areas of medicine (*e.g.* complexes of metal radioisotopes as ^{90}Y, ^{153}Sm, ^{166}Ho, ^{177}Lu in nuclear medicine, Gd(III) complexes as MRI contrast agents, Eu(III) or Tb(III) complexes as luminescent probes). For any biomedical applications, such metal complexes should exhibit a high thermodynamic stability as well as kinetic inertness under physiological conditions and, therefore, knowledge of these properties is important.

One of frequently used triazamacrocycle-based ligands is NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid; Figure 1.). Since basic data regarding thermodynamic properties of its metal complexes are, surprisingly, very scarce [1,2], we report here on NOTA protonation constants as well as on stability constants of its complexes with selected Ln(III) ions. Their values show that NOTA cavity is too small for large Ln(III) ions in comparison with that of DOTA-like ligands. In addition, stability constants of Ln(III) complexes are significantly increasing for smaller Ln(III) ions. Kinetic properties of several Ln(III) complexes of NOTA were studied by molecular absorption and luminescence spectroscopies in UV/VIS region. Reaction mechanisms of formation (pH = 4.0–6.0, t = 25 °C, I = 0.1 M KCl) and acid-assisted dissociation (t = 10–37 °C, I = 3.0 M (Na,H)ClO_4) of Eu(III) complex were proposed from time-resolved luminescence spectroscopy. The results were compared with data obtained for Ln(III) complexes of similar tetraaza-macrocyclic ligands [1,3,4]. Complexation of Eu(III) with NOTA is significantly slower than that for Cu(II) [2] and the complexation rate is moderate in comparison for DOTA-like ligands (DO2A vs. DOTA [4]). The Eu(III)/Tb(III) complexes are kinetically inert ($t_{1/2}$ ~1 h at pH 2 and t = 25 °C).

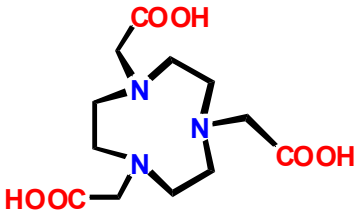


Figure 1. 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA).

Acknowledgement:

Financial support from the Masaryk University (MUNI/A/1424/2019), and the Grant Agency of the Czech Republic (19-17380S) is acknowledged.

References:

[1] G. Anderegg, F. Arnaud-Neu, R. Delgado, J. Felcman, K. Popov, *Pure App. Chem.* **2005**, 77(8), 1445–1495.

[2] V. Kubíček, Z. Bőhmová, R.Ševčíková, J. Vaněk, P. Lubal, Z. Poláková, R. Michalicová, J. Kotek, P. Hermann, *Inorg. Chem.* **2018**, 57(6), 3061–3072.

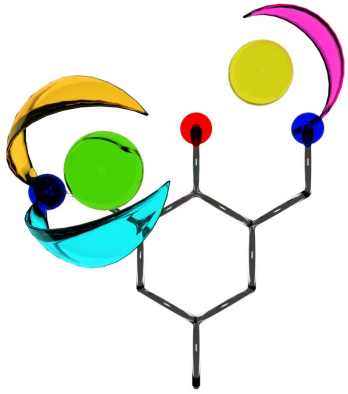
[3] P. Táborský, I. Svobodová , P. Lubal, Z. Hnatejko, S. Lis, P. Hermann, *Polyhedron* **2007**, 26(15), 4119–4130.

[4] F. Smrčka, P. Lubal, *New. J. Chem.* **2018**, 42(10) 7993–8000.

P5
Unsymmetric and dinuclear
- simple design of biorelevant complex models -

Maximilian HAAS, Andreas KIEßLING, Axel BUCHHOLZ, Winfried PLASS

Friedrich Schiller University Jena, Humboldtstr. 8, 07743 JENA, Germany.
sekr.plass@uni-jena.de



Many biological processes are catalyzed by enzymes containing a binuclear complex in the active site. The properties of individual metal centers are tuned by their coordination environment, while the use of bridged binuclear complexes often leads to cooperative effects. The deliberate tuning of the compartments in a binuclear system can lead to specific reactivity. Model complexes are a commonly used approach to address the underlying effects that specify the reactivity in such systems.

In our group, different ditopic ligand systems are utilized to generate dinuclear coordination compounds of transition metal ions. The unsymmetric design of the ligands allows explicit tuning of individual binding pockets. This has proven to be a potent tool not only to tune catalytic properties, but also to investigate cooperativity, unsymmetric reactivity, and metal-ligand affinity.

References:

[1] A. Roth, E. T. Spielberg, W. Plass, *Inorg. Chem.* **2007**, 46, 4362-4364.
[2] A. Roth, A. Buchholz, M. Rudolph, E. Schütze, E. Kothe, W. Plass, *Chem. Eur. J.* **2008**, 14, 1571-1583.
[3] M. Schmidt, H. Görls, W. Plass, *RSC Adv.* **2016**, 6, 75844-75854.

P6
Active metallodrugs: speciation or activation?

Jorge M. HERRERO,[a] Daniel CAMINO,[a] Amparo ALVAREZ-VALDES,[a] Ana MATESANZ,[a] Leticia CUBO,[a] Isabel SANCHEZ-PEREZ,[b] Adoracion G. QUIROGA [a]

[a] Inorganic Chemistry Dept, Cantoblanco, Universidad Autónoma de Madrid (UAM) 28045.
[b] BioChemistry dept, Medical Campus, (UAM) 28045.
adoracion.gomez@uam.es

Cancer is still in between the 10th top causes of deaths in upper-middle income countries [1]. These numbers advice about the needs of society and research motivation. The European Commission has maintained cancer disease as one of the most important topics of research since Horizon 2020. Their new program work on major research has continued creating innovation research missions in cancer, climate, oceans and soil. This mission-oriented policy underlines one more time the importance of improving cancer treatments [2]. Chemotherapy (with or without surgery) commonly uses the clinical metallodrug cisplatin, a small coordinating molecule whose therapy drawbacks (resistance and some important side effects) have driven anticancer research to study platinum drugs [3].

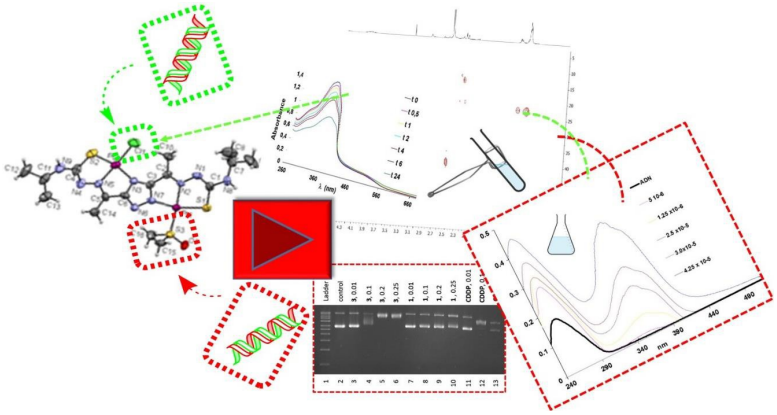
In our research group, we believe that the preparation of innovative compounds is the most promising approach to drug design for cancer treatment. In particular, we use the conjugation of well design ligands to metallodrugs for improving selectivity and reducing the side effects of drugs. Our chemical approaches have been mentioned in the most important revision in Chemical biology regarding metallodrugs [4]. In spite of the challenging chemistry of some of these examples, we have achieved an efficient methodology and the resulting compounds improved the cytotoxicity of the ligands becoming always more active or more specific using our proposed chemical modifications.

The unexpected difference of the antitumoral action of some of our examples in solution manifest the importance of studying the role of buffer anions [4] and solvents used in biological systems [5]. Solvents as DMSO (standard solvent used in biological assays) have an important impact in the stability and mechanism of cisplatin's solution, while other metallic compounds solutions do not get affected [6]. Unfortunately this task is very difficult to study and both aspects, role and reactivity, are very difficult to establish with precision. This is because the metal drug speciation increases in complexity with the use of such coordinating solvents; therefore, the identification of the active species of the drugs should be standard experimental protocol. Our group of research have developed adequate protocols to investigate the solution behavior of these matallodrug candidates. We vary our procedures according to the metallodrugs' properties such as solubility and stability. The bases of a successful methodology is the combination of techniques, above all we found NMR, mass spectrometry and HPLC most useful tools. However, the use of computational protocols for the accurate prediction of the ^{31}P

NMR chemical shifts has recently helped us to overcome the sensitivity problems for the assignment of species in solution (paper highlighted as cover) [7].

From these studies, it is clear that the implication of several techniques in revealing the solution behavior is in many cases essential to validate the metallodrug speciation.

The analysis of the metallodrugs chemical properties and their biological action demand not only the knowledge of the species but the role and their impact in the biological action. In this contribution, we will present some of these examples highlighting the importance of the chemical speciation impact produced by the solvent or the buffer ions in the biological action of the complexes. We use DMSO solutions due to the limited aqueous solubility of some metallodrug candidates, and we present a detailed study of the stability and cytotoxicity further proved with X-ray structural determinations [8].



References:

[1] https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.

[2] https://ec.europa.eu/info/news/commission-launches-work-major-research-and-innovation-missions-cancer-climate-oceans-and-soil-2019-jul-04_en.

[3] T. C. Johnstone, K. Suntharalingam, S. J. Lippard, *Chem. Rev*. **2016**, 116, 3436.

[4] R. C. Todd, K. S. Lovejoy, S. J. Lippard, *JACS* **2007**, 129, 6370.

[5] M. D. Hall, K. A. Telma, K.-E. Chang, T. D. Lee, J. P. Madigan, J. R. Lloyd, I. S. Goldlust, J. D. Hoeschele, M. M. Gottesman, *Cancer Res.* **2014**, 74, 3913.

[6] M. Patra, T. Joshi, V. Pierroz, K. Ingram, M. Kaiser, S. Ferrari, B. Spingler, J. Keiser, G. Gasser, *Chemistry Eur. J.* **2013**, 19, 14768.

[7] A. C. Castro, H. Fliegl, M. Cascella, T. Helgaker, M. Repisky, S. Komorovsky, M. A. Medrano, A. G. Quiroga, M. Swart, *Dalton Trans.* **2019**, 48, 8076.

[8] A. I. Matesanz, J. Herrero, E. J. Faraco, L. Cubo, A. Gomez Quiroga, *ChemBioChem* **2019**, https://doi.org/10.1002/cbic.201900545.

P7
Transformation of oxalocalcic kidney stones: influence of common urine inhibitors

Iris H.VALIDO, Victor FUENTES-CEBRIAN, Manuel VALIENTE, Montserrat LÓPEZ-MESAS

Grup de Tècniques de Separació en Química (GTS), Departament de Química, Facultat de Ciències, Edifici Cn. Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès (Barcelona), Spain

iris.henriquez@uab.cat

Renal nephrolithiasis is a clinical condition that implies the formation of microcrystals aggregates on the kidney. This painful disease presents an incidence around 6-12% worldwide, with an increasing recurrence of 50% on the following five years from the first episode. Kidney stones are classified into seven major groups by morpho-constitutional analysis guidelines [1], being calcium oxalate, both, the mono (COM) and the dihydrate (COD) species, the 66% of the incidence [2]. COD is the kinetic species that is converted into COM, the thermodynamic one [3,4]. The stone resulting after a total transformation (named TRA) is chemically monohydrated, since its crystalline structure has one water molecule, what makes difficult the differentiation with COM, but its nucleation corresponds to a dihydrated species, COD [5]. The differentiation between COM and TRA is of great importance since they are caused by different pathologies [5,6]. Therefore, the studies of this transformation process, as well as the stabilization of the dihydrated species, are important to understand the physiopathology, to propose an adequate treatment and, to prevent the patients' recurrence [7].

The present study is focused on the *in vitro* monitoring of the transformation process and how it is affected by the most common calcium oxalate inhibitors. Among the selected inhibitors, all of them studied at the average and the highest concentration presented in the human urine, phosphate promotes the COD transformation; on the other hand, phytate seems to have a great potential to stabilize the metastable species of calcium.

In previous studies in our research group, where calcium oxalate kidney stones with different transformation degrees where analyzed by synchrotron radiation based μXRD, it was observed the presence of hydroxyapatite (a type of calcium phosphate) between COD crystals that where not transformed or with a lower transformation. With the idea of identifying which species of calcium phosphate influences the transformation inhibition, since phosphate by itself promotes it, a comparison of different concentration ratios of Ca:Phosphate has been performed at pH 6 and 7. With these results, it has been possible to identify which calcium phosphate species participates in the transformation inhibition, as well as the conditions that favor it.

In brief, the *in vitro* study of the calcium oxalate inhibitors as potential stabilizers of the COD transformation process has allowed us to identify their roles over this process. On

the other hand, the Ca:Phospate ratio study gives us further information to determine the calcium phosphate species responsible of the COD stabilization.

References:

[1] M. Daudon, A. Dessombz, V. Frochot,E. Letavernier, J. P. Haymann, P. Jungers, D. Bazin. *Comptes Rendus Chim.* **2016**, 19 (11-12), 1470-1491.

[2] F. Grases, A. Costa-Bauzá, M. Ramis, V. Montesinos, A. Conte. *Clin. Chim. Acta* **2002**, 322 (1-2), 29-36.

[3] C. conti, M. Casati, C. Colombo, M. Realini, L. Brambilla, G. Zerbi. *Spectrochim. Acta – Part A Mol. Biomol. Spectrosc.* **2014**, 128, 413-419.

[4] J. T. Kloprogge, T. E. Boström, M. L. Weier. *Am. Mineral.* **2004**, 89 (1), 245-248.

[5] D. Bazin, C. Leroy, F. Tielens, C. Bonhomme, L. Bonhomme-Coury, F. Damay, D. Le Denmat, J. Sadoine, J. Rode, V. Frochot, E. Letavernier, J. P. Haymann, M. Daudon. *Comptes Rendus Chim.* **2016**, 19 (11-12), 1492-1503.

[6] F. Grases, A. Costa-Bauza, R. M. Prieto. *Nutr. J.* **2006**, 5 (1), 1-7.

[7] M. Daudon, P. Jungers, D. Bazin. *AIP Conference Proceedings.* **2008**, 1048 (1), 199.

P8
Pharmaceutical co-crystals: an interesting strategy to modify the physicochemical properties of bioactive molecules

Alicia DOMINGUEZ-MARTIN, [a] **Noelia RUIZ-GONZALEZ**, [a), b)]
Duane CHOQUESILLO-LAZARTE [b)]

[a)] *Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, Campus Cartuja s/n, E-18071 Granada, Spain.*
[b)] *Laboratorio de Estudios Cristalográficos, IACT (CSIC-UGR), Avda. de las Palmeras 4, 18100, Armilla, Granada, Spain.*
adominguez@ugr.es

The knowledge of the 3D structure of molecules is essential for the understanding of almost any molecular process in life sciences, including their behaviour in solution. In this context, crystal engineering is increasingly being used to modify specific physicochemical properties of molecules by the rational design of an intricate network of non-covalent interactions in solid state. Such interactions involve not only the classical H-bonds but also other weak interactions such as π-π interactions, van der Waals forces or halogen bonds.

In the past decade, cocrystals have called the attention of the pharmaceutical industry, which has included crystal engineering as a novel strategy in their drug development process. But what is a cocrystal? And why is it interesting?

Cocrystals are neutral crystalline single-phased solid materials composed of two or more different compounds, with molecular and/or ionic nature, in a definite stoichiometric ratio, which are neither solvates nor simple salts [1]. Each of the components that form a cocrystal is called coformer. Thus, a pharmaceutical cocrystal could be defined as a multicomponent compound in which, at least, one coformer is an API (Active Pharmaceutical Ingredient), Figure 1. Of course, biocompatibility is desirable for the other coformers, but at least non-toxicity is required [2].

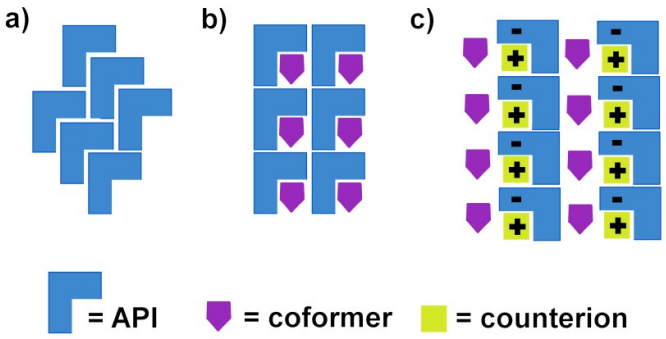


Figure 1. Scheme of possible cocrystals involving an API: (a) as one single component, b) molecular cocrystal, (c) ionic cocrystal. Additional solvate and hydrate forms of co-crystals are avoided for clarity reasons.

Oral drug delivery is the most preferred route of drug administration of pharmaceuticals due to its low sterility constraints, high patient compliance and high cost-effectiveness, among other advantages. In this delivery system APIs are formulated in solid state. Thus, if we are able to modify the supramolecular structure of such solids, we will also be able to manipulate their macroscopic properties such as solubility and rate of dissolving (and therefore its bioavailability), stability, flowability or compressibility. Therefore, the development of solid-state approaches that effectively improve the physicochemical properties of APIs is certainly of great interest for the pharmaceutical industry [3,4]. This is especially true if we consider that: (1) the formation of cocrystals is significantly less expensive that traditional drug development process and (2) besides working on new drugs, this strategy can be applied to improve the properties of drugs already in the market or can even bring to life 'old' discarded drugs while still offering the opportunity for intellectual property protection [3,4].

Nevertheless, if the solid-sate approach is important, the solution approach is even more important, because we must prove that the cocrystal still remains intact while oral administration! In this context, special attention is paid to the integrity of the reported non-covalent interactions by different solution methods such as ITC or DSC. In addition, further techniques to evaluate these interactions will be discussed.

Acknowledgements:
Financial support from MICINN of Spain (project PGC2018-102047-B-I00 funds) is gratefully acknowledged.

References:

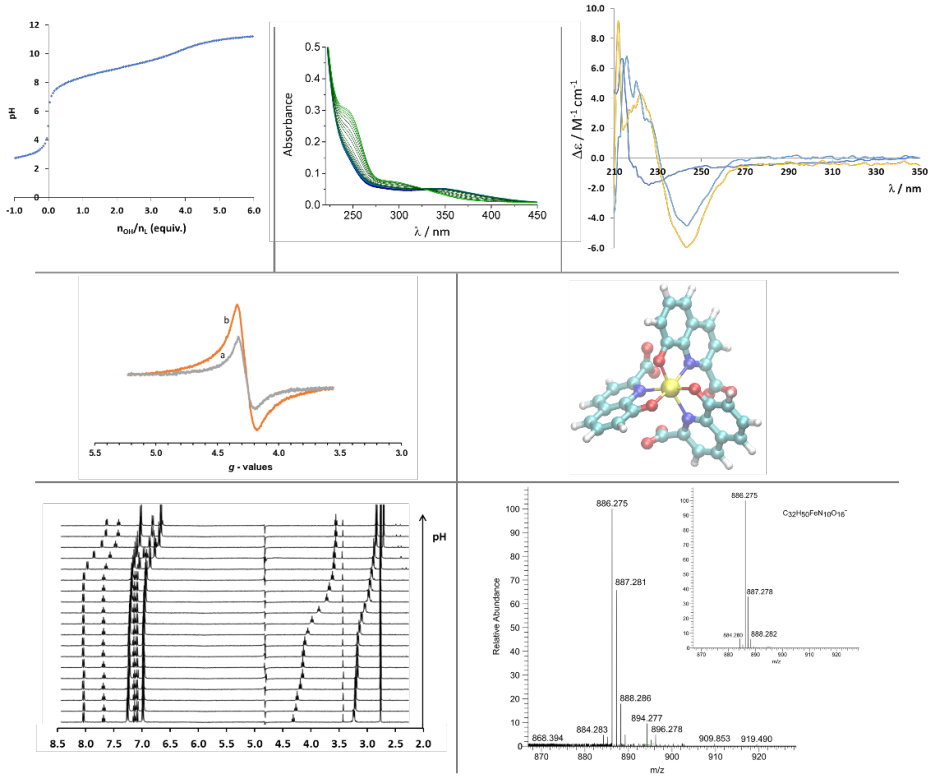
[1] S. Aitipamula et al. *Cryst. Growth Des.* **2012**, 12 (5), 2147−2152.
[2] M. Karimi-Jafari, L. Padrela, G.M. Walker, D.M. Croker, *Cryst. Growth Des.* **2018**, 18 (10), 6370−6387.
[3] N.K. Duggirala, M.L. Perry, Ö. Almarsson, M.J. Zaworotko, *Chem. Commun*. **2016** 52, 640-655
[4] R. Shaikh, R. Singh, G.M. Walker, D.M. Croker, *Trends Pharmacol. Sci.* **2018,** 39 (12) 1033-1048.

P9
Accurate assessment of the chemical speciation of complex systems: the use of multi-technique approaches

Sofia GAMA, [a,b,c] Beata GODLEWSKA-ŻYŁKIEWICZ, [a] Michel MEYER, [b] Demetrio MILEA, [d] Winfried PLASS [c]

[a] Faculty of Chemistry, University of Białystok, Białystok, Poland.
[b] Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), UMR 6302 CNRS, Université de Bourgogne Franche-Comté, Dijon, France.
[c] Institute for Inorganic and Analytical Chemistry (IAAC), Friedrich-Schiller-Universität Jena, Jena, Germany.
[d] Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali (CHIBIOFARAM), Università degli Studi di Messina, Messina, Italy.
sofia.gama@u-bourgogne.fr

Potentiometry and UV/Vis spectrophotometry, followed by computer data analysis, are the most widely used techniques in chemical speciation studies, and they still remain among the most adequate and accurate for the determination of the stability constants in solution. Nevertheless, the investigation of more and more complex systems (e.g., ligands with several and different binding sites, very strong chelants, unconventional conditions, multicomponent solutions, etc.) opened up new challenges and questions for solution chemists.



As such, other techniques and/or approaches are becoming even more necessary to get further information, for example, on the nature of species effectively formed, on their structure, and on their reactivity.

In this communication, some examples will be reported to evidence how these techniques and approaches have been exploited to complement potentiometric and/or spectrophotometric results to solve some issues related to the assessment of the chemical speciation of exceptionally complex systems. In particular, results relative to the binding ability of some multi-hetero-dentate ligands (namely natural and synthetic metallophores) towards iron, molybdate and thorium will be discussed.

Acknowledgments:
The Agence Nationale de la Recherche is gratefully acknowledged for financial support (ANR project PLUTON, grant N° ANR-17-CE08-0053) and the MIUR-DAAD Joint Mobility Program 2nd ed. (project nr. 34083).

References:

[5] S. Gama, M. Frontauria, N. Ueberschaar, G. Brancato, D. Milea, S. Sammartano, W. Plass, *New J. Chem.* **2018**, 42, 8062-8073.

[6] R. Hermenau, K. Ishida, S. Gama, B. Hoffmann, M. Pfeifer-Leeg, W. Plass, J. F. Mohr, T. Wichard, H.-P. Saluz, C. Hertweck, *Nat. Chem. Biol.* **2018**,14, 841-843.

P10
Attenuating copper-induced aggregation of amyloid beta with conformationally constrained peptides

Ana B. CABALLERO,[a] Olga IRANZO,[b] Guillem VÁZQUEZ,[a] Raimon SABATÉ,[c] Patrick GAMEZ [a),d)]

[a)] nanoBIC, Departament de Química Inorgànica I Orgànica, Facultat de Química, Universitat de Barcelona, Martí I Franquès 1-11, 08028 Barcelona, Spain.
[b)] CNRS, Centrale Marseille, Aix Marseille Université, iSm2, Avenue Escadrille Normandie-Niemen, F-13397 Marseille CEDEX 20, France.
[c)] Departament de Fisicoquímica, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Avda. Joan XXIII 27-31, 08028 Barcelona, Spain.
[d)] Institució Catalana de Recerca i Estudis Avançats (ICREA), Passeig Lluís Companys 23, 08010 Barcelona, Spain.
olga.iranzo@univ-amu.fr

Increasing evidence links copper misbalance with amyloid-related disorders; for instance, in Alzheimer's disease (AD), this redox-active metal ion appears to affect the aggregation of amyloid-beta (Aβ), and to facilitate the overproduction of reactive oxygen species (ROS) leading to oxidative stress [1]. However, the exact role of copper in amyloid aggregation and how copper-Aβ interaction is associated with oxidative stress still remain unclear [2,3].

We have shown that excessive, copper-mediated production of ROS can affect Aβ itself through several oxidative mechanisms. Among these oxidative modifications, cross-linking is probably the most important one regarding the production of highly toxic oligomers of the protein [4]. Soluble oligomers are considered to be the most toxic aggregates of Aβ, and they are directly related with the impairment of synaptic plasticity and behavior in AD.

A promising approach currently explored to lessen the deleterious effects of Cu−Aβ species is the use of copper-protein attenuating compounds (CuPACs). Particularly, the use of small peptides as CuPACs present key advantages, *e.g.* easy metal-binding tunability and favorable biocompatible properties.

In this communication, we present our latest results [5] on the use of conformationally constrained peptides, specifically designed to coordinate copper [6], to prevent the formation of harmful copper-Aβ species and hence favor the generation of less toxic aggregates of Aβ.

References:

[1] S.L. Sensi, A. Granzotto, M. Siotto, R. Squitti, *Trends Pharm Sci*, **2018**, 39(12), 1049.
[2] P. Gamez, A.B. Caballero, *AIP Adv.* **2015**, 5, 092503.
[3] X. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, *Redox Biol.* **2018**, 14, 450.
[4] G. Vázquez, A.B. Caballero, J. Kokinda, A. Hijano, R. Sabaté, P. Gamez, *J. Biol. Inorg. Chem.*, **2019**, 24, 1217.

[5] A.B. Caballero, O. Iranzo, A. Hautier, R. Sabaté, P. Gamez, *Inorg. Chem.*, **2020**, 59(1), 837.

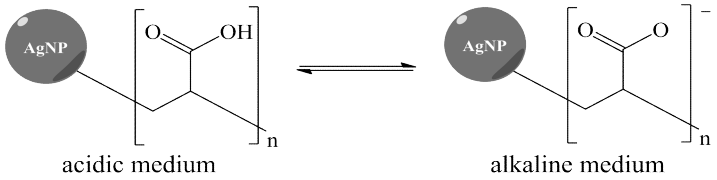
[6] a) A. Fragoso, P. Lamosa, R. Delgado, O. Iranzo, *Chem. Eur. J.*, **2013**, 19, 2076; b) A. Fragoso, T. Carvalho, P. Rousselot-Pailley, M. M. Correia dos Santos, R. Delgado, O. Iranzo, *Chem. Eur. J.*, **2015**, 21, 13100.

P11
Influence of inorganic acids during precipitation on stabilization of poly(acrylic acid) coated silver nanoparticles

Irena IVANIŠEVIĆ, Matej ZLATAR, Stjepan MILARDOVIĆ

Department of General and Inorganic Chemistry, Faculty of Chemical Engineering and Technology, Marulićev trg 19, 10000 ZAGREB, Croatia
ivanisevic@fkit.hr

In recent years, silver nanoparticles (AgNPs) have received great attention due to their unique optoelectronic and physicochemical properties resulting in various applications [1,2]. This study reports a wet chemical synthesis of AgNPs, using hydrazine monohydrate as a reducing agent and poly(acrylic acid) (PAA) as a capping agent [3]. PAA-coated silver nanopowders, precipitated with inorganic acids (perchloric, phosphorous and sulfuric), were used for nano-ink formulations. Characterization of the reaction mixture, as well as of the prepared conductive inks, was performed by cyclic voltammetry and UV-Vis spectroscopy, respectively.



Schematic presentation of PAA-encapsulated AgNPs in acidic and alkaline medium

PAA adsorbed on the nanoparticle surface behaves as a weak acid. In alkaline media, negative surface charge generated due to the dissociated PAA engenders repulsion forces between nanoparticles. Thus, efficiency of electrostatic stabilization of the prepared suspension depends on the acid dissociation rate. The stability of the formulated nano-inks was tested in a wide range of Britton-Robinson buffer solutions. The highest anodic current responses and maximum absorbance (λ = 419 nm) were plotted versus pH to determine the quantity of surface bound PAA.

References:

[1] S. Sundar, K.-J. Kim, S.-J. Kwon, *Nanomaterials* **2019**, 9 (12), 1-13.
[2] I. Fratoddi, *Nanomaterials* **2018**, 8 (1), 1-25.
[3] S. Milardović, I. Ivanišević, A. Rogina, P. Kassal, *Int. J. Electrochem. Sci*, **2018**, 13 (11), 11136-11149.

P12
Vanadium speciation in the samples of „Krka River“ estuary using ion chromatography inductively coupled plasma mass spectrometry

Lucija KNEŽEVIĆ, Niko BAČIĆ, Elvira BURA-NAKIĆ

„Ruđer Bošković“ Institute, Division for Marine and Environmental Research, Bijenička cesta 54, 10 000 ZAGREB, Croatia.
lknezev@irb.hr

Vanadium speciation in environmental samples of high salinity still present a challenging task in environmental and analytical chromatographic chemistry. Despite relatively high concentrations in seawater (around 35 nmol dm^{-3}), vanadium speciation analysis has been mainly neglected due to its complex chemistry and a vast number of oxidation states that vanadium takes form of. Redox states of vanadium are shown to be highly dependent upon pH and E_h values of the system, as well as biological activity and concentration [1]. In addition, seawater presents complex matrix for anion exchange chromatographic separation, where chloride anion is the source of most prominent interferences [2]. In oxic seawater (positive E_h and pH of 7-8), vanadium can be present as vanadium(V) in the form of hydrolysed HVO_4^{2-} and $H_2VO_4^-$ ions forming polynuclear species at higher concentration. In more reducing acidic environment it is expected that a part of vanadium is present as VO^{2+} which can be easily oxidized to pentavalent state at higher pH values. Under the E_h,as well as pH, values characteristic for modern anoxic environment (E_h of approximately -300 to -100 mV and pH of 7-8) the predominating V redox state is vanadium(IV), while the predominating form is $HV_2O_5^-$. Under these conditions vanadyl species can be reduced to vanadium(III) solid oxides $V(OH)_3$ or V_2O_3. Reduced vanadium species can be then easily accumulated into the sediment [1].

Estuaries play an important role in geochemical cycling of trace metals, where various physical and chemical gradients affect solubility and mobilization of species [2]. In the freshwater-seawater mixing zone of estuaries, metal-organic interaction can easily affect speciation and established equilibria between chemical species [3]. Vanadium in „Krka River“ estuary was studied before, but only in reference to its bulk concentrations. Due to the dependence of the toxicity and redox state that vanadium takes form of in given environment, speciation method allows better insight on vanadium chemistry and bioavailability of vanadium species.

A vanadium speciation method is conducted as on-line measurement via coupled IC with ICP MS as a detector with high detection limit. Presented analytical approach is suitable for quantification of vanadium species in „Krka River“ estuary water column samples. Separation of vanadium species on anion exchange column is based on the formation of negatively charged V-EDTA complexes, where present vanadium species within investigated samples are complexed on column with EDTA. Formed V(IV)-EDTA and V(V)-EDTA complexes have different charge enabling their separation using an eluent consisting of different anion (bicarbonate/sulphate/EDTA) and acetonitrile mixture as the mobile phase.

Due to the high affinity of chloride anion from the seawater samples towards anion exchange column, optimization of conditions from sample storage to choice of eluent is needed in order to reduce interferences and obtain accurate results. Samples were measured on anion exchange column Metrosepp A Supp 5-50/4.0 , on the flow rate of 0.3 mL min^{-1} with eluent containing 40 mmol dm^{-3} ammonium carbonate, 40 mmol dm^{-3} ammonium sulphate, 8 mmol dm^{-3} EDTA and 3% acetonitrile. Since vanadium speciation is highly pH and Eh dependant, samples before analysis were simply filtrated and stored on +4°C in order to avoid speciation changes during the time frame from sampling to analysis. Samples were collected on several differrent locations along „Krka River“ estuary on three different layers (surface fresh layer, freshwater-seawtaer interface and sewater layer) of vertical variable salinity gradient.

Based on developed chromatographic method for vanadium speciation on environmental samples of „Krka River“ estuary, it is found that vanadium is present mainly in the form of V(V) with concentrations varying with different salinity of collected layers. Determined concentrations of V(IV) could be attributed to stable complexes of V(IV) with organic matter from fluvial input of „Krka River“. Stated findings are in agreement with literature and suggest that various parameters such as pH, E_h and biology of the aquatic system are an important factor in establishing equilibrium between present vanadium species.

Acknowledgments:
This work was supported by the Croatian Science Foundation project IP-2018-01-7813: “Geochemistry and redox proxie’s signature under the diverse environmental conditions: towards better understanding of the past redox” – REDOX.

References:

[1] J.H. Huang, F. Huang, L. Evans, S. Glasauer, *Chemical Geology* **2015,** 417,68-89.
[2] M. Novič, B. Divjak, B. Pihlar, V. Hudnik, *Journal of Chromatography A* **1996,** 739, 35-42.
[3] E. Strady, G. Blanc, J. Schafer, A. Coynel, A. Dabrin, Estuarine, *Coastal and Shelf science* **2009,** 83, 550-560.
[4] T.-M. Florence, G.-E. Batley, P. Bene, *Critical reviews in Analytical Chemistry* **1980**, 9:3, 219-296.

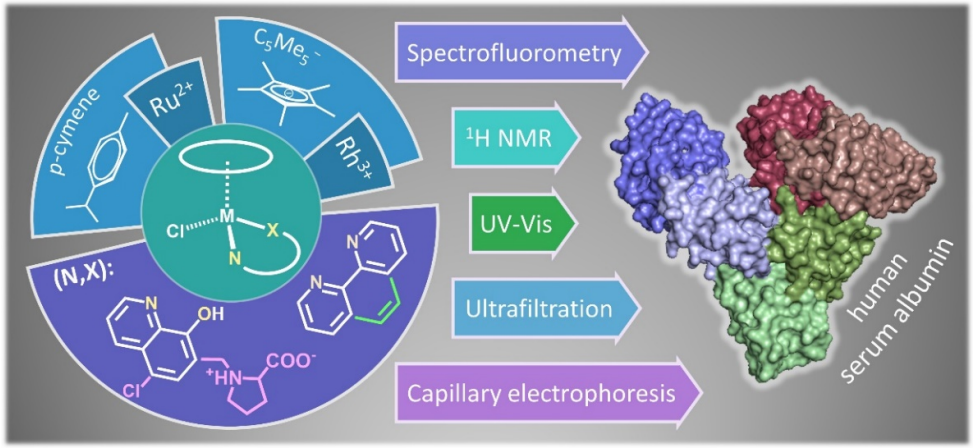
P13
Human serum albumin binding of high stability Rh(III)(η^5-C_5Me_5) and Ru(II)(η^6-p-cymene) complexes

Orsolya DÖMÖTÖR, [a,b] **Tamás PIVARCSIK**, [b] **János P. MÉSZÁROS**, [a,b] **Éva A. ENYEDY** [a,b]

[a] *Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720, SZEGED, Hungary.*
[b] *MTA-SZTE Momentum Functional Metal Complexes Research Group, University of Szeged, Dóm tér 7, H-6720, SZEGED, Hungary.*
domotor.o@chem.u-szeged.hu

Half-sandwich Ru(II)-η^6-arene complexes are extensively investigated, since there are clear evidences that the clinically relevant Ru(III) drug candidates NKP1339 and NAMI-A exert their anticancer effect in the reduced forms [1]. The organometallic fragments Ru(II)(η^6-*p*-cymene) and Rh(III)(η^5-C_5Me_5) themselves hydrolyze in aqueous solutions and have no anticancer activity [2]. This process can be hindered by complex formation with an appropriate ligand. Complexes bearing a bidentate ligand and a chlorido co-ligand (see figure) are widely studied, and recently numerous organoruthenium and organorhodium compounds with various bidentate ligands were synthesized and tested against human cancer cells. Although their actual mechanisms of action are not fully clarified yet, proteins, more likely than DNA, are presumed as their most probable targets [3,4].

Amino acid side chains of proteins provide different coordinating sites for metal ions. The question is how these Ru(II)-η^6-arene and Rh(III)-η^5-arenyl complexes can interact with protein donor groups. Sadler *et al.* reported the coordination of the rather accessible surface imidazole nitrogen donors (His) of lysozyme and HSA to the Ru(II) centre in the case of [Ru(η^6-biphenyl)(ethylenediamine)Cl]$^+$ complex [2,3]. Moreover, several single crystal X-ray structures confirm coordinative binding of various types of Ru(II)(η^6-*p*-cymene) and



Rh(III)(η^5-C_5Me_5) complexes towards various proteins [5]. In our former works we have investigated the human serum albumin (HSA) binding of [Rh(III)(η^5-C_5Me_5)$(H_2O)_3$]$^{2+}$ and

[(Ru(II)(η^6-*p*-cymene)(H_2O)$_3$]$^{2+}$ and their complexes formed with deferiprone, 2-picolinic acid derivatives, ethylenediamine and 2,2'-bipyridine [6].

HSA binding of anticancer agents can be advantageous due to the enhanced permeability and retention effect in solid tumor tissues resulting in the accumulation of protein bound drugs close to the cancer cells. However, an irreversible protein binding can decrease effective drug concentration and may be responsible for adverse effects as well. Our recent studies have shown that lower stability, labile complexes bind in dissociative manner to HSA (via the liberation of the bidentate ligand), while highly stable and/or kinetically inert complexes display preferably associative binding in the protein [6]. (Ru(II)(η^6-*p*-cymene) complexes bind in lower extent to HSA compared to their Rh(III)(η^5-C_5Me_5) congeners. Besides, low molecular mass constituents (e.g. histidine, cysteine, methionine, citric acid) of blood seem to interfere HSA binding of these complexes.

As a continuation of our work, herein we present the HSA binding of high stability complexes of Rh(III)(η^5-C_5Me_5) and (Ru(II)(η^6-*p*-cymene) formed with the (N,O) donor 8-hydroxyquinoline, its more soluble 5-chloro-7-methylproline hybrid and the (N,N) donor 2,2'-bipyridine and 1,10-phenantroline (see figure). Binding strength and location, kinetic aspects and the nature of these interactions will be discussed. Studies were implemented by spectroscopic and separation techniques (^{1}H NMR, UV-Vis and fluorescence spectroscopy; ultrafiltration-UV-Vis and capillary zone electrophoresis).

Acknowledgements:
National Research, Development and Innovation Office-NKFIA projects GINOP-2.3.2-15-2016-00038, PD 131472, FK 124240, FIKP program TUDFO/47138–1/2019-ITM.

References:

[1] C.G. Hartinger, S. Zorbas-Seifried, M.A. Jakupec, B. Kynast, H. Zorbas, B.K. Keppler, *J. Inorg. Biochem.* **2006**, 100, 891-904.

[2] Y. Geldmacher, M. Oleszak, W.S. Sheldrick, *Inorg. Chim. Acta* **2012**, 393, 84-102; A.M. Pizarro, A. Habtemariam, P.J. Sadler, *Top. Organomet. Chem.* **2010**, 32, 21-56.

[3] P.C.A. Bruijnincx, P.J. Sadler, *Adv. Inorg. Chem*. **2009**, 61, 1-62; Y.K. Yan, M. Melchart, A. Habtemariam, P.J. Sadler, *Chem. Commun.* **2005**, 4764-4776.

[4] R. Trondl, P. Heffeter, C.R. Kowol, M.A. Jakupec, W. Berger, B.K. Keppler, *Chem Sci.* **2014**, 5 2925-2932.

[5] Protein Data Bank (https://www.rcsb.org/) PDB codes: 1t3p, 3mnn, 3o7r, 3o7s, 4j8v, 4j8x, 4xuj, 5cp6, 5v4g, 5xf3, 6bo1, 4gjs, 4gjv.

[6] É.A. Enyedy, J.P. Mészáros, O. Dömötör, C.M. Hackl, A. Roller, B.K. Keppler, W. Kandioller, *J. Inorg. Biochem*. **2015**, 152, 93-103; O. Dömötör, É.A. Enyedy, *J. Biol. Inorg. Chem.* **2019**, 24, 703-719.

P14
Interaction of water-soluble deferasirox derivatives with Co(II) ions: a solution study

Linda BÍRÓ, Nikolett NYUJTÓ, Imre NAGY, Réka JÓZSA, Gergő FERENCZIK, Péter BUGLYÓ, Etelka FARKAS

University of Debrecen, Faculty of Science and Technology, Department of Inorganic and Analytical Chemistry, Egyetem tér 1, H-4032, DEBRECEN, Hungary.
linda.biro@science.unideb.hu

Huge efforts have been devoted to develop compounds with high selectivity for cancer treatment. In this field, hypoxia activated compounds are of utmost interest. Among them, kinetically inert Co(III) complexes are promising candidates as the decreased oxygen level in tumor tissues may lead to their selective reduction to quite labile Co(II) while releasing the bioactive ligand [1,2].

In this context it is important to know the thermodynamic stability of the various Co(III) complexes, however, it cannot be determined by conventional potentiometric and spectroscopic methods due to the inertness of these complexes.

To overcome this problem, stability of the complexes formed in the corresponding Co(II) – ligand system needs to be determined. It is known that the formal potential of complexes depends on the ratio of the formation constants of the reduced and the oxidized form. Therefore, based on the stability constant of a Co(II) complex being a major species at a given pH and the formal potential determined by cyclic voltammetry at the same pH, stability constant of the corresponding Co(III) complex can be calculated.

Deferasirox is an orally active iron chelator used in the treatment of iron overload diseases [3]. Since there is also an increased iron level in tumor cells combining deferasirox and Co(III) may result in complexes that are selectively be reduced to Co(II) while the released deferasirox may bind to iron inhibiting the proliferation of cancer cells. Furthermore, in the literature cytotoxicity of some Co(II) compounds (formed upon reduction and dissociation of the above complex) had also been described [4].

In our study two new disulfonic acid derivatives of deferasirox have been prepared and their complex formation with Co(II) ions has been studied in aqueous solution by the combined use of pH-potentiometry and UV/Vis spectrophotometry. Effect of oxygen on complex formation was studied and preliminary cyclic voltammetric measurements were also carried out. This contribution will summarize the most important results obtained.

Acknowledgements:
This research was funded by the EU and co-financed by the European Regional Development. Fund under the projects GINOP-2.3.2-15-2016-00008 and the Hungarian Scientific Research Fund (OTKA K112317).

References:

[1] B. J. Kim, T. W. Hambley and N. S. Bryce, *Chem. Sci.*, **2011**, 2, 2135-2142.
[2] T. W. Failes, T. W. Hambley, *Dalton Trans.*, **2006**, 1895-1901.
[3] S. Steinhauser, U. Heinz, M. Bartholoma, T. Weyhermüller, H. Nick, K. Hegetschweiler, *Eur. J. Inorg. Chem*., **2004**, 4177-4192.
[4] G. Wang, T. K. Hazra, S. Mitra, H-M. Lee and E. W. Englander, *Nucleic Acids Research*, **2000**, 28 (10), 2135-2140.

P15
Solution and solid phase study on Pd(II)- and Co(III)-complexes of a novel pyridinone based peptide conjugate

András OZSVÁTH, [a] Róbert DIÓSZEGI, [a] Attila Csaba BÉNYEI,[b] Péter BUGLYÓ [a]

[a] University of Debrecen Department of Inorganic & Analytical Chemistry, Egyetem tér 1., 4032 DEBRECEN, Hungary
[b] University of Debrecen Department of Physical Chemistry, Egyetem tér 1., 4032 DEBRECEN, Hungary
buglyo@science.unideb.hu

To overcome the lack of selectivity as well as the side effects of the clinically most commonly used anticancer metallodrug cisplatin, targeting the physiological differences between normal and cancer cells and tissues could be an advantageous strategy. It is known, that there is a more reductive environment inside the tumor tissues, compared to the normal ones, which allows the selective reduction of inert Co(III)-complexes, as (metallo)drug carrier units. [1,2] These cobalt(III) mixed ligand complexes may contain various (O,O) chelators such as hydroxamates or hydroxypyridinonates with proven anticancer properties, while the remaining coordination sites can be taken by a 4N donor ligand responsible for inertness and thermodynamic stability. Upon administration these complexes may undergo selective reduction in the cancer cells resulting in the formation of the appropriate Co(II) species with labile character and release of the bioligands. Incorporation of another metal containing unit with potential anticancer properties into the (O,O) donor leaving group allows the improvement of its biological activity. Derivatization of peptides could be useful for the synthesis of these ambidentate ligands, in which the peptide moiety is not only a good N-donor chelator for the square planar platinum metals, but it also can be used as a tumor targeting unit [3,4]. Some previously investigated peptidehydroxamic acids were found to be promising candidates to develop hetero bimetallic Co(III)/Pd(Pt) complexes [5].

We have synthesized and characterized a novel 3,4-hydroxypyiridinone based tripeptide conjugate as an ambidentate (O,O) and N-donor ligand. In order to study the complex formation equilibria between this ligand and Pd(II) as a Pt(II) model but with faster ligand exchange reactions, we have performed solution studies by the combined application of pH-potentiometric, ^{1}H NMR spectroscopic and mass spectrometric methods. Since the evaluation of the potentiometric data was limited by the rather slow complexation processes, detailed ^{1}H NMR studies were performed to get further equilibrium and structural information about the species formed in the solution. We have also investigated the interaction of Pd(II) with the Co(III)-complex of the ligand, in which the (O,O) donor unit was occupied by a $[Co(tren)]^{3+}$ cation, therefore only the peptide backbone was available for the Pd(II). This contribution will highlight our results on the ligand synthesis, and its interaction with Pd^{2+} as well as $[Co(tren)]^{3+}$ cations both in aqueous solution and in the solid state.

Acknowledgements:
The research was supported by the EU and co-financed by the European Regional Development Fund under the project GINOP-2.3.2-15-2016-00008 and the Hungarian Scientific Research Fund (OTKA K112317). The research was also supported by the ÚNKP-19-3 New National Excellence Program of the Ministry for Innovation and Technology.

References:

[1] T.W. Failes, T.W. Hambley, *Dalton Trans.* **2006**, 1895-1901.
[2] P.D. Bonnitcha, B.J. Kim, R. Hocking, J.K. Clegg, P. Turner, S.M. Neville, T.W. Hambley, *Dalton Trans.,* **2012**, 41, 11293–11304.
[3] Cs. G. Ágoston, T. K. Jankowska, I. Sóvágó, *J. Chem. Soc., Dalton Trans.*, **1999**, 3295-3302.
[4] S. Dissanayake, W. A. Denny, S. Gamage, V. Sarojini, *Journal of Controlled Release*, **2017**, 250, 62-76.
[5] A. Ozsváth, E. Farkas, R. Diószegi, P. Buglyó, *New Journal of Chemistry,* **2019**, 43, 8239-8249.

P16
Solution properties of metal complexes and ligands by DFT calculations

Giampaolo BARONE,[a)] Daniele PADERNI,[b)] Alessio TERENZI,[a)] Mauro FORMICA,[b)] Luca GIORGI [b)]

[a)]Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università degli Studi di Palermo, viale delle Scienze, Edificio 17, 90128 Palermo, Italy.
[b)]Dipartimento di Scienze Pure e Applicate (DiSPeA), Università di Urbino "Carlo Bo", via della Stazione 4, 61029 Urbino, Italy.
giampaolo.barone@unipa.it

In this presentation we propose a collaboration between two research units in Palermo and Urbino, with the aim to show the potentialities of a complementary experimental-theoretical approach to investigate interesting solution properties of metal complexes and ligands.

In the Palermo unit, density functional theory (DFT) and quantum mechanics/molecular mechanics (QM/MM) calculations, has been extensively used to investigate the duplex and G-quadruplex DNA binding mechanisms of transition metal complexes [1-3]. The DNA binding of such metal compounds, often related e.g. to their *in vitro* and *in vivo* biological properties [4], have been experimentally investigated by absorption, emission and circular dichroism spectroscopy. Moreover, in recent collaborations, the proposed computational approach has been extended to the study of host-guest binding of gold(III) compounds with selected protein targets [5,6]. The interpretation of the experimental results by atomistic models always shed light on the structure-activity, catalytic and spectroscopic properties of the considered metal complexes and ligands, experimentally detected.

The Urbino unit has a long experience on the synthesis, characterization and spectrophotometric properties of high emitting transition metal complexes and ligands, and in the investigation of the complexation mechanisms in mixed water/organic solvents [7-9]. Moreover, the two units have already collaborated in the past, in the investigation of the DNA-binding and biological properties of copper(II) and zinc(II) complexes [10].

A state-of-the-art subject of the Urbino unit concerns the investigation of the fluorescent behaviour of polyamine macrocyclic ligands, able to act as *ratiometric* sensors for metal ions though ESIPT (excited state intramolecular proton transfer) mechanism (Figure 1). Such ligands contain a fluorophore characterized by a double fluorescence emission imputed to a photo-induced tautomeric equilibrium strongly influenced by the presence of a suitable metal ion in the coordinative cavity. Taking advantage from the combination of UV-vis, fluorescence and NMR data, DFT calculation could provide a fundamental support to understand the coordination environment and the role of the metal ion in the regulation of photo-tautomerism.

In conclusion, our main contribution to the activity to the Nectar consortium could be to provide some proofs of the possible support, by DFT calculations, to the experimental investigation of the speciation in solution of polydentate ligands, including biological

macromolecules, and of their metal complexes, in particular to reliably provide the structures hypothesized at different pH solution conditions, addressing important aspects such as ligand/metal stoichiometry and ligand isomerism and tautomerism, on the basis of their calculated thermodynamic and/or kinetic stability. In fact, thermodynamic data, such as enthalpy and Gibbs free energy values, can be reliably obtained by DFT calculations, both in water and in other solvents.

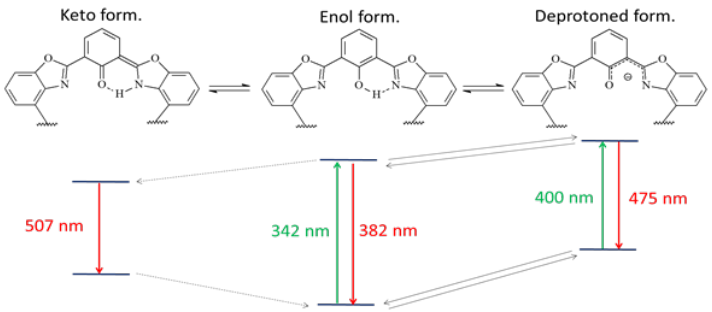


Figure 1. Hypothesized ESIPT mechanism of a bis-benzossaolylpnenol based fluorophore

References:

[1] G. Barone, A. Terenzi, A. Lauria, A.M. Almerico, J.M. Leal, N. Busto, B. García, *Coord. Chem. Rev.* **2013**, 257, 2848-2862

[2] A. Terenzi, D. Lötsch, S. van Schoonhoven, A. Roller, C.R. Kowol, W. Berger, B.K. Keppler, G. Barone, *Dalton Trans.* **2016**, 45, 7758-7767

[3] R. Bonsignore, F. Russo, A. Terenzi, A. Spinello, A. Lauria, G. Gennaro, A.M. Almerico, B.K. Keppler, G. Barone, *J. Inorg. Biochem.* **2018**, 178, 106-114

[4] G. Turturici, V. La Fiora, A. Terenzi, G. Barone, V. Cavalieri, *Biochemistry* **2018**, 57, 4391-4394

[5] M.N. Wenzel, R. Bonsignore, S.R.Thomas, D. Bourissou, G. Barone, A. Casini, *Chem. Eur. J.* **2019**, 25, 7628-7634

[6] R. Bonsignore, S.R. Thomas, W.T. Klooster, S.J. Coles, R.L. Jenkins, D. Bourissou, G. Barone, A. Casini, *Chem. Eur. J.* **2020**, 10.1002/chem.201905392

[7] M. Formica, G. Favi, V. Fusi, L. Giorgi, F. Mantellini, M. Micheloni, *J. Lumin.* **2018**, 195, 193-200.

[8] M. Formica, G. Ambrosi, V. Fusi, L. Giorgi, M. Arca, A. Garau, A. Pintus, V. Lippolis, *New J. Chem.* **2018**, 42, 7869-7883.

[9] P. Paoli, P. Rossi, G. Ambrosi, M. Formica, V. Fusi, L. Giorgi, M. Micheloni, E. Macedi, *Supramol. Chem.*, **2017**, 29, 896-911.

[10] A. Terenzi, M. Fanelli, G. Ambrosi, S. Amatori, V. Fusi, L. Giorgi, V. Turco Liveri, G. Barone, *Dalton Trans.* **2012**, 41, 4389-4395.

P17
Acid-base properties and adsorption ability towards Pb^{2+} ion of cyclodextrin-Calixarene nanosponges

Salvatore CATALDO,[a] Francesco CREA,[b] Paolo LO MEO,[c] Demetrio MILEA,[b] Alberto PETTIGNANO [a]

[a] Dipartimento di Fisica e Chimica – Emilio Segrè, Università di Palermo, Viale delle Scienze, I-90128, Palermo, Italy.
[b] Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali (CHIBIOFARAM), Università degli Studi di Messina, Messina, Italy.
[c] Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università di Palermo, Viale delle Scienze, I-90128, Palermo, Italy.
alberto.pettignano@unipa.it

In this work, the acid-base properties of fifteen pre and post modified cyclodextrin-calixarene nanosponges (CyCaNSs) have been studied by ISE-H^+ potentiometric titrations. Then, four CyCaNSs were selected to test their adsorption ability towards Pb^{2+} ion. CyCaNSs are interesting material considering that their adsorption and release properties can be varied depending on the molar ratio between the co-monomers, and on the substituent groups present on each co-monomer scaffold. Moreover, functional groups can be introduced by chemical post-modification in order to obtain materials with remarkable pH-responsive properties. Below is reported a scheme of the synthesis of the fifteen CyCaNSs (A1-A5, B1-B5, C1-C5) already fully characterized (FT-IR, $^{13}C\{^1H\}$ CP-MAS NMR, TGA, SEM) in previous papers [1,2]. The four CyCaNSs selected for the Pb^{2+} adsorption study were A1, A3, A4 and A5.

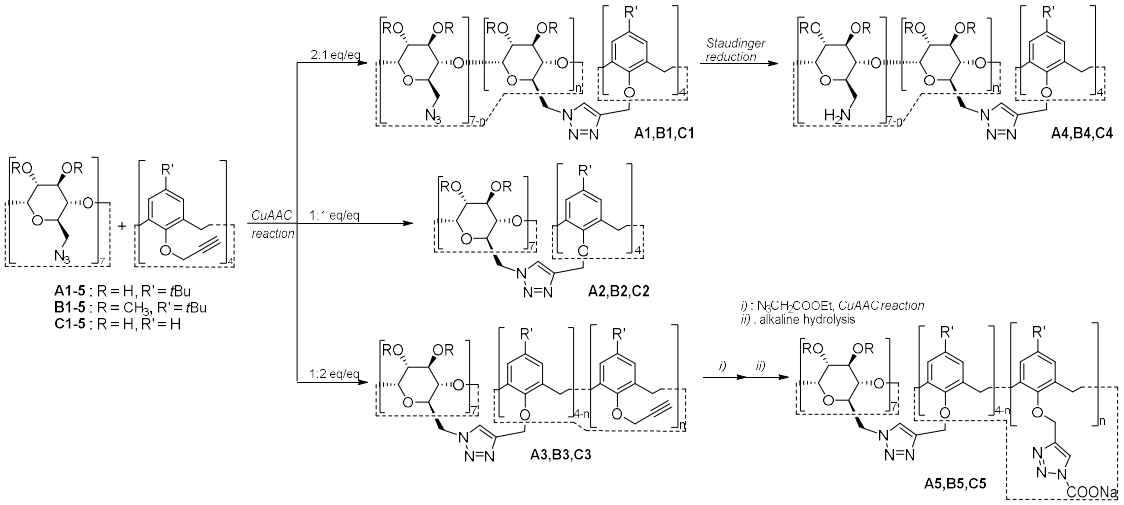


Figure 1. Synthesis of CyCaNSs [1]

Considering that the removal treatments may involve polluted waters with different characteristics, the adsorption experiments were carried out with and without the addition of background salts, at different pH, ionic strengths and temperatures. $NaNO_3$ and NaCl were

used, changing the ionic strength in the range 0.01 – 0.1 mol L^{-1}. The initial pH of metal ion solutions was fixed at 3 and 5, whilst, the effect of temperature was studied in the range 283.15 – 323.15 K. The adsorption ability and affinity of CyCaNSs towards Pb^{2+} were kinetically and thermodynamically investigated measuring the metal ion concentration in the water samples by means of Inductively Coupled Plasma Emission Spectroscopy (ICP-OES) and Differential Pulse Anodic Stripping Voltammetry (DP-ASV).

References:

[1] A. Di Vincenzo, M. Russo, S. Cataldo, D. Milea, A. Pettignano, P. Lo Meo, *Chemistry Select* **2019**, 4, 6155-6161;

[2] P. Lo Meo, G. Lazzara, L. Liotta, S. Riela, R. Noto, *Polym. Chem.* **2014**, 5, 4499-4510.

P18
Spectrophotometric and spectrofluorometric analysis of small molecules binding to biosubstrates

Tarita BIVER, [a),b)] **Francesca BINACCHI,** [b)] **Francesca MACII** [b)]

[a)] *Department of Pharmacy, University of Pisa, Via Bonanno 6, 56126 PISA, Italy.*
[b)] *Department of Chemistry and Industrial Chemistry, University of Pisa, Via G. Moruzzi 13, 56124 PISA, Italy.*
tarita.biver@unipi.it

Despite the gigantic efforts devoted by the scientific community to the analysis of solution equilibria for the binding of small molecules to biosubstrates, there is still room for new researches. The uncountable number of bio-reactions and their involvement in health make this area of extreme importance. In this frame, the small molecule is an exogenous species that can interfere with the process, either producing healthy effects (a drug) or damages (a cancerous/mutagen species).

These systems involve macromolecules (DNA, RNA, proteins) and are very complex. The mechanistic studies on the binding of the target to the biosubstrate will thus need many different approaches to be robustly elucidated [1]. The related solution equilibria can be tricky to be analysed and require careful use of different equations and approximations. Also, the number of researchers not strictly expert in the field, but which need to handle this data, is ever-growing. Therefore, the possible misuse of data collection and some equations can occur. This applies also in the frame of approaches that are usually considered "simple" as spectrophotometry and spectrofluorometry [2].

In the case of spectrophotometric titrations, targets that do absorb near to the UV bands of the biosubstrates produce data deconvolution problems. Melting studies of too diluted species can also be misleading. In the case of fluorescence, both the possible non-linear dependence of the signal on analyte concentration and the presence of auto-absorption phenomena need to be taken into account. Different systems will be presented to provide practical examples of these difficulties and discuss how to address them.

References:

[1] M. Lari, T. Biver, N. Busto, H.J. Lozano, J.M. Leal, F. Secco, B. García, *Dalton Trans.* **2017**, 46, 16671-16681.
[2] F. Macii, G. Salvadori, R. Bonini, S. Giannarelli, B. Mennucci, T. Biver, *Spectrochimica Acta A* **2019**, 223, 117313.

P19
Multivariate analysis applied in the study of ESIPT-mediated multichannel fluorescent metal ion sensors

Daniele PADERNI, Mauro FORMICA, Vieri FUSI, Eleonora MACEDI, Luca GIORGI

Department of Pure and Applied Sciences University of Urbino "Carlo Bo", Via della Stazione N.4, 61029 URBINO, Italy

Mauro.formica@uniurb.it

Recentely our research group synthesized a series of fluorescent ligands containing a phenol or naphthol group conjugated with one or two benzoxazole moieties [1]. These systems upon excitation undergo a phototautomerization called ESIPT (Excited State Intramolecular Proton Transfer) and shows a double fluorescent emission attributed to the keto and the enol form. The emission profile of these ligands depends on the solvent, pH, presence of metal ions and on the selected excitation wavelength. In fact tautomerism occur in both fundamental and excited state [2].

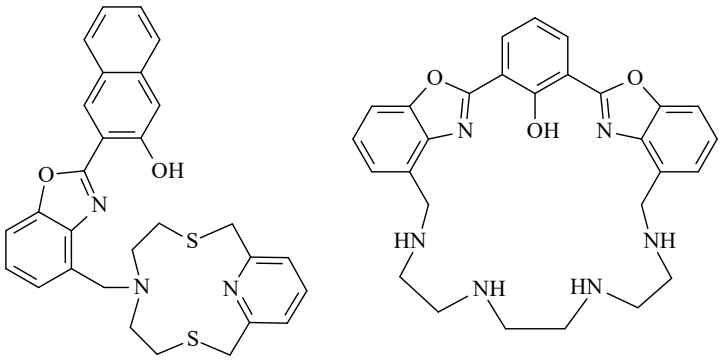


Figure 1. Two examples of ESIPT-responsive ligands

These kind of systems could be successfully studied by fluorescence excitation–emission matrix (EEM) spectroscopy, that allows a quantitative determination of the fluorescence profile of the system. This technique can afford information on the emission profile concurrently with excitation wavelength data, creating a three dimensional map of fluorescence characteristics. The observed electronic transitions are telling of the structure and properties of the system, and in particular can give informations about the phototautomerism of pnenol-benzoxazole-based ligands.

The high amount of data collected will be subjected to statistical analysis with different approaches, including multivariate analysis by principal component analysis and by projection pursuit. Projection pursuit is a multivariate statistical technique aimed at finding interesting low-dimensional data projections. Projection pursuit deals with three major challenges of multivariate analysis: the curse of dimensionality, the presence of irrelevant features and the limitations of visual perception. Projection pursuit looks for the data

projection which maximizes the projection pursuit index, that is a measure of its interestingness [3]. In Chemometrics, the projection pursuit index is often the kurtosis, that is the fourth standardized moment [4], whose properties have been recently investigated by Loperfido [5].

References:

[1] L. Lvova, F. Caroleo, A. Garau, V. Lippolis, L. Giorgi, V. Fusi, N. Zaccheroni, M. Lombardo, L. Prodi, C. Di Natale, R. Paolesse. *Front. Chem.* **2018**, Vol. 6, 258−267.
[2] A. C. Sedgwick, L. Wu, H-H. Han, S. D. Bull, X-P. He, T. D. James, J. L. Sessler, B. Z. Tang, H. Tian, J. Yoon. *Chem. Soc. Rev.* **2018**, 47, 8842−8880.
[3] Sun, J. Projection Pursuit. *Encyclopedia of Statistical Sciences* **2006**, Vol. 10.
[4] Hou S., Wentzell, P.D., *J. Chemom.* **2014**, 28, 370-384.
[5] N. Loperfido, *Eur. J. Finance* **2020**, 26, 142-164.

P20
Helicobacter pylori and metal ions: solution equilibria studies can help to find new therapies

Maurizio REMELLI, [a] **Denise BELLOTTI,** [a),b)] **Angelica SINIGAGLIA,** [a)] **Magdalena ROWIŃSKA-ŻYREK,** [b)] **Remo GUERRINI** [a)]

[a)] *Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via L. Borsari 46, 44121, Ferrara, Italy.*
[b)] *Faculty of Chemistry, University of Wrocław, F. Joliot-Curie 14, 50-383, Wrocław, Poland.*
rmm@unife.it

Nutritional immunity is the "process by which a host organism sequesters trace minerals in an effort to limit pathogenicity during infection" [1]. All living organisms need trace minerals to synthesize metalloproteins and metalloenzymes which are essential for biological processes, such as oxygen transport, protection from oxidative stress or, as in the case of *Helicobacter pylori*, the synthesis of ammonia for buffering the pH of its living environment. Pathogens must acquire these trace minerals from their host which, on the other hand, defends himself by putting in place effective competition actions. Studying the mechanisms of transport and supply of transition metals by bacteria can provide weapons to fight infections, helping the processes of nutritional immunity and overcoming the problems caused by the increasingly widespread resistance to classic antibiotic therapies.

H. pylori is a human gastrointestinal pathogen that can be responsible for disorders like gastritis, duodenal ulcers and even gastric cancer. For its survival in the human stomach, *H. pylori* needs two enzymes, urease and Ni-Fe hydrogenase, both containing Ni(II) ions as cofactors. On the other hand, an excess of nickel is potentially toxic. Hpn is a His-rich protein expressed by *H. pylori* that plays an important role in nickel homeostasis and protects the bacterium from too high concentrations of metal ions. This polypeptide of 59 amino acid residues is abundant in the cytoplasm of *H. pylori* and represents approximately the 2% of all the proteins synthesized by this bacterium. Recent studies [2] have shown that the N-terminal part of Hpn (MAHHEEQHG-) binds the Ni(II) and Cu(II) ions in the same way as human albumin, since it contains an ATCUN (Amino Terminal Cu and Ni binding)-type sequence, which allows the formation of complexes involving a set of four nitrogens as donor atoms: $\{NH_2, 2N^-, N_{im}\}$.

Starting from these results, the aim of the present work was to investigate the role of the individual histidines in the coordination of Cu(II) and Ni(II) by the N-terminal domain of the Hpn protein. Some model peptides were considered, corresponding to the N-terminal "wild-type" sequence and its analogues in which one or more histidines were replaced by alanine: MAHHEEQHG-NH_2 (WT, wild-type Hpn), MAAHEEQHG-NH_2 (H3A), MAHAEEQHG-NH_2 (H4A), MAHHEEQAG-NH_2 (H8A), MAHAEEQAG-NH_2 (H4A/H8A). The protonation and complex-formation equilibria were studied by means of potentiometric acid-base titrations and the analysis of the experimental data was obtained through the use of specific calculation programs [3-5]. From the mass spectra of the solutions under examination it was

possible to obtain confirmations of the stoichiometries of the formed complexes and through UV-Vis, CD and EPR spectroscopies information was acquired on the coordination geometries and on the set of donor atoms.

All the peptide sequences resulted strong ligands for Cu(II) and Ni(II), including the H3A peptide, although it lacks histidine in position 3, characteristic of the ATCUN-type site. For all ligands, the presence of two or more histidine residues in the sequence increases the stability of the metal complexes and also allows the formation of binuclear species. The latter have been studied by carrying out experiments in the presence of excess of metal. The results of this investigation suggest that, in the case of the wild-type peptide (MAHHEEQHG-NH_2), at a Cu(II)/ligand ratio of about 2:1 and in alkaline solution, a copper ion is bound to the N-terminal ATCUN site and the second one is instead anchored to the histidine residue in position 8 in the C-terminal domain (see Figure 1.). If Cu(II) and Ni(II) are simultaneously present in solution, the formation of ternary complexes is observed.

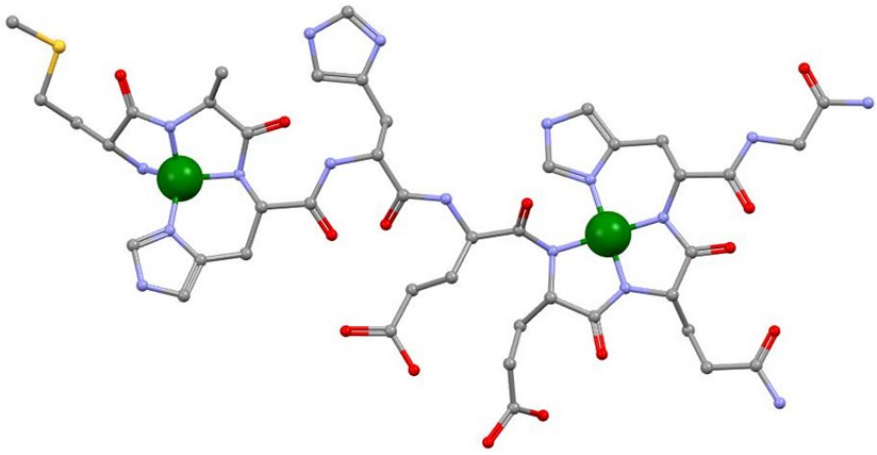


Figure 1. Molecular model proposed for the binuclear Cu(II) complex with MAHHEEQHG-NH_2, at pH 10. Water molecules and hydrogen atoms are omitted for simplicity.

References:

[1] S.R. Hennigar, J.P. McClung, *Am. J. Lifestyle Med.*, **2016**, 10(3), 170–173.
[2] D. Witkowska, S. Bielinska, W. Kamysz, H. Kozlowski, *J. Bioinorg. Chem.*, **2011**, 105(2), 208-214.
[3] L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini, A. Vacca, *Coord. Chem. Rev.*, **1999**, 184, 311-318.
[4] P. Gans, B. O'Sullivan, Talanta, 2000, 51, 33-37.
[5] P. Gans, A. Sabatini, A. Vacca, Talanta, 1996, 43, 1739-1753.

P21
Method for the determination of the equilibrium constants in the „slightly soluble complexonate - saturated aqueous solution" systems

Igor POVAR, Oxana SPINU

Institute of Chemistry, 3, Academiei str., MD2028, CHISINAU, Republic of Moldova.
ipovar@yahoo.ca

A new method for the determination of such equilibrium constants, as the solubility product K_S of the slightly soluble complexonates and their stability constants in aqueous solution, from the solubility data in combination with pH-metric measurements, has been developed. During the study of heterogeneous equilibria in the system „*slightly soluble complex (solid phase) - saturated solution (liquid phase)*" it is usually operated with the following experimental data set: solubility of precipitate (*S*) and pH of saturated solution. Further experimental information is obtained by the residual concentrations method [1], as a result of variation of the ratio of initial concentrations of the metal ion C_M^0 and the ligand C_L^0 in heterogeneous mixtures. Besides the pH equilibrium value, there are usually communicated the residual concentrations of both components of the precipitate C_M^r and C_L^r measured in solution after the removal of the solid phase and the excess concentrations of hydrogen ions C_H^0 or hydroxyl ions C_{OH}^0 known in the process of preparing the initial composition of the mixture ($C_H^0 = -C_{OH}^0$). The heterogeneous systems, which contain as a solid phase a slightly soluble protonated complexonate of the composition $M_1^{'}M_xH_yL_{z(S)}$ (type I) has been analyzed. In general, the complete set of above-mentioned equilibria is described in the form of the following equations (the species charges for simplicity are omitted):

$$M_1^{'}M_xH_yL_{z(S)} = 1M^{'} + xM + yH + zL, \qquad K_S = [M^{'}]^1[M]^x[H]^y[L]^z \tag{1}$$

$$M + (n-m)H + mH_2O + kL = MH_n(OH)_mL_k, \beta_{1n(m)k} = [MH_n(OH)_mL_k]/\left([M][H]^{(n-m)}[L]^k\right) \tag{2}$$

$$M + iH_2O = M(OH)_i^{m-i} + iH^+, \qquad K_i = [M(OH)_i][H]^i/[M] \tag{3}$$

$$L + jH = H_jL, \qquad K_j = [H_jL]/[H]^j[L] \tag{4}$$

The system of mass balance equations in this heterogeneous system can be formulated as follows:

$$\begin{aligned} C_M^0 &= C_M^r + x[M_1^{'}M_xH_yL_z]_{(S)} \\ C_L^0 &= C_L^r + z[M_1^{'}M_xH_yL_z]_{(S)} \\ C_H^0 &= C_H^r + y[M_1^{'}M_xH_yL_z]_{(S)} \end{aligned} \tag{5}$$

In the equations (5) C_i^r are denoted the residual concentrations of the ions; $M_1^{'}M_xH_yL_{z(S)}$ symbolizes the number of moles of precipitate in 1 L of solution. It should be mentioned that equations (5) are strictly fulfilled only in dilute solutions, when the volume of the heterogeneous mixture is practically equal to the volume of the liquid phase. The residual concentrations in the case of reactions (2) - (4) are expressed by the equations:

$$C_M^r = [M]\alpha_M + \sum_{n=1}\sum_{m=0}\sum_{k=0}\beta_{1n(m)k}[M][H]^{(n-m)}[L]^k \tag{6}$$

$$C_L^r = [L]\alpha_L + \sum_{n=1}\sum_{m=0}\sum_{k=0}k\beta_{1n(m)k}[M][H]^{(n-m)}[L]^k \tag{7}$$

$$C_H^r = [H] - K_W[H]^{-1} + [L]\varphi_L - [M]\varphi_M + \sum_{n=1}\sum_{m=0}\sum_{k=0}(n-m)\beta_{1n(m)k}[M][H]^{(n-m)}[L]^k \tag{8}$$

In these equations the notations are used:

$\alpha_M = \sum_{i=0} K_i[H]^{-i}$ $\alpha_L = \sum_{j=0} K_j[H]^{j}$ $\varphi_M = \sum_{i=1} iK_i[H]^{-i}$ $\varphi_L = \sum_{j=1} jK_j[H]^{j}$

If the solubility S of the complexonate $M_1^{'}M_xH_yL_{z(S)}$ is measured as a function of pH, therefore and C_H^0, then $zC_M^o = xC_L^0 = const$, $C_M^r = xS$ and $C_L^r = zS$. Based on the data S (pH) and known equilibrium constants of reactions (2) - (4), by solving the system of two equations (6) and (7) with two unknowns $[M]$ and $[L]$, the solubility product of the slightly soluble complexonate can be determined. When measuring the solubility in water, the equation (8) is required for calculation, because in this case $C_H^r = yS$. Then a system of equations (6) - (8) is obtained, by which it is possible to calculate the stability constant β of one of the complexonates in the solution. However, it is understood that the obtained value β based on a measurement S (pH) will only be indicative.

Table 1. The results of the analysis [2,3] and of the authors' calculations of the solubility product $pK_S = -logK_S$ in the systems $YH_2L_{(S)}$ (Y^{3+} - *yttrium ion,* L^{5-} - oxyethylidendiphosphonate, *system* ***A***) and $YH_2A_{(S)}$, where A^{5-} - glycine-bis-methylphosphonate, *system* ***B***), $C_Y = 0.01$ *mol* L^{-1}, $t = 25°C$, $n = C_L^0 / C_Y^0$.

System	***n***	**$[H^+] \cdot 10^2$, mol/L**	***I*, mol/L**	***pK*$_S$, *this work***
A[2]	0.90	2.51	0.034	34.21
	1.00	2.73	0.030	34.37
	1.10	2.82	0.032	34.23
	1.20	2.90	0.033	34.17
	1.40	3.08	0.036	34.31
	1.60	3.25	0.034	35.07
the average value	**34.40±0.34** 34.65±0.24 [2]			
B[3]	0.90	2.27	0.032	26.59
	1.00	2.96	0.032	27.84
	1.25	2.94	0.029	27.18
	1.50	2.95	0.031	26.64
	1.80	2.96	0.033	26.28
the average value	**26.91±0.61** 27.02±0.35 [3]			

References:

[1] Povar I., Ubaldini S., Spinu O., Lupascu T. *Can. J. Chem*. **2019**, vol. 97, issue 9, 651-658.

[2] Tereshin G.S., Kharitonova L.K., *Zh. Neorg. Khim*. **1974**, vol. 19, issue 5, 1264-1267.

[3] Tereshin G.S. et al. *Zh. Neorg. Khim*. **1974**, vol. 19, issue 4, 1131-1133.

P22
Solid state studies on model Pb(II) complexes with thiophene-carboxylate bioligands in terms of chelation therapy and fluorescent sensing

Mateusz KOWALIK, [a] Joanna MASTERNAK, [a] Katarzyna KAZIMIERCZUK, [b] Bogumiła KUPCEWICZ, [c] Oleksiy V. KHAVRYUCHENKO, [d] Barbara BARSZCZ [a]

[a] Institute of Chemistry, Jan Kochanowski University in Kielce, 7G Uniwersytecka Str., 25-406 Kielce, Poland
[b] Department of Inorganic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, 11/12 G. Narutowicza Str., 80-233 Gdańsk, Poland.
[c] Department of Inorganic and Analytical Chemistry, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 2 Jurasza Str., 85-089 Bydgoszcz, Poland.
[d] Shupyk National Medical Academy of Postgraduate Education (NMAPE), 9 Dorogozhytska Str., 04112 Kyiv, Ukraine.
mateuszkowalik.86@gmail.com

Among the p-block metals, lead draws a particular attention in coordination chemistry owing to various geometries of their coordination compound as well as in medicinal chemistry because of Pb^{2+} extreme toxicity. The structural diversity of Pb(II) complexes results from: (i) effect of a lone electron pair, (ii) broad range of coordination numbers (2 to 12), (iii) the kind of donating ligands and their flexibility, which can affect the biological properties. Biological studies on lead(II) compounds are motivated mainly by finding effective chelators for chelation therapy and remediation of polluted water and soil. However, it is also important to study Pb(II) complexes as fluorescent sensors [1,2].

To fully understand how lead behaves in biological and environmental systems, it is critical to understand not only the structure of lead complexes in the solid state (*this work*), but also the nature of lead-ligand interactions in solution (*future work*). Both the dynamics of lead-ligand binding and the stability of lead-ligand complexes affect the bioavailability of lead and thus its role as a toxin. By understanding the mechanisms of ligand exchange and the thermodynamic ligand preferences of Pb(II), we can also better design molecules for the immobilization of lead and treatment of lead poisoning [3].

The first stage of my research in looking for effective chelators of toxic metal ions involved solid state studies on model Pb(II) complexes with bioligands from group of heteroaromatic carboxylic acids with thiophene, pyrazole, imidazole, pyrrole and pyrimidine moiety. So, this paper is focused on the structural studies of four selected Pb(II) complexes with isomeric thiophene-carboxylate ligands, namely $[Pb(2tpCOO)_2]_n$ (**1**), $[Pb(3tpCOO)_2(H_2O)]_n$ (**2**), $[Pb(2tpacCOO)_2(H_2O)]_n$ (**3**), $[Pb(3tpacCOO)_2]_n$ (**4**) (where 2tpCOOH = thiophene-2-carboxylic acid, 3tpCOOH = thiophene-3-carboxylic acid, 2tpacCOOH = thiophene-2-acetic acid, and 3tpacCOOH = thiophene-3-acetic acid). The complexes were characterized by CHNS, FT-IR, TG, SC-XRD, PL methods. Moreover, DFT calculations and Hirshfeld surface analysis were provided to better understand the influence

of the lone electron pair on the molecular structure and non-covalent interactions on the crystal structure of Pb(II) complexes obtained. Additionally, the fluorescence in the solid state for ligands and complexes were determined.

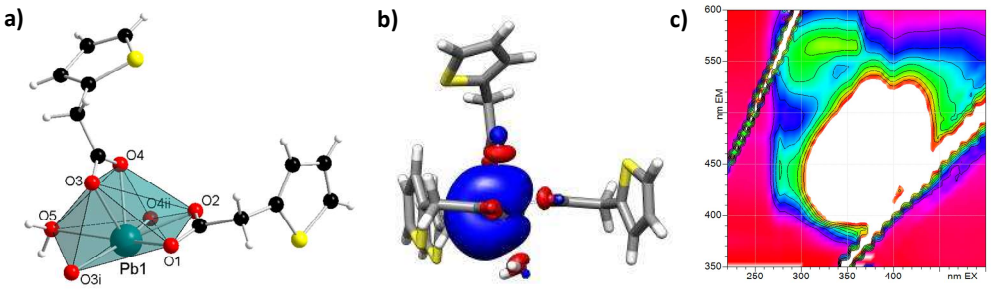


Figure 1. a) Molecular structure, **b)** molecular orbital of Pb(II), **c)** fluorescence spectrum of complex **3**

The SC-XRD and DFT results indicated that lone electron pair is strongly stereochemically active, which affect the significant distortion of the nearest coordination environment of Pb(II) centers. The crystal structures are stabilized mainly by conventional and non-conventional hydrogen bonds and π-π stacking interactions. Interestingly, the electron density of the lone electron pair in complexes **1**, **3** and **4** participate in the formation of rarely reported tetrel bonds, in which Pb(II) ion acts as Lewis acid and is a source of σ-hole, while the role of Lewis base plays thiophene aromatic moiety. Fluorescence studies revealed that ligands themselves with thiophene ring substituted in position 2 by carboxylic group (2tpCOOH and 2tpacCOOH) exhibits weak fluorescence, while ligands substituted in position 3 (3tpCOOH and 3tpacCOOH) don't exhibit fluorescence. Fluorescence of complexes **1–4** is much more pronounced, which may be attributed to the chelation of the ligand to the metal center, which improves the rigidity of the structure, as well as noncovalent interactions involving aromatic rings and metal centers that facilitate the charge and energy transfer between metal centers. Moreover there are observed emission bands related to metal-cantered transitions (MC) involving *s* and *p* orbitals of Pb(II). Their intensity is proportional to the contribution of *s* orbitals in the localization of the lone electron pair density. Additionally, compounds proved to be water soluble and non-toxic to selected microorganisms even in high concentrations, therefore thiophene-carboxylates are effective chelators of poisonous Pb(II) ions.

References:

[1] J. Aaseth, O.P. Ajsuvakova, A.V. Skalny, M.G. Skalnaya, A.A. Tinkov, *Coordination Chemistry Reviews* **2018**, 358, 1–12.

[2] M. Kowalik, J. Masternak, K. Kazimierczuk, B. Kupcewicz, O.V. Khavryuchenko, B. Barszcz, *Inorganica Chimica Acta* **2018**, 471, 446–458.

[3] K.D. Karlin, Progress in Inorganic Chemistry. John Wiley & Sons: New Jersey, **2003**, Vol. 51, pp. 1─144.

P23
The mixed ligand platinum(II) complex as potential anticancer drug with promising biological properties: *in vitro* and *in vivo* studies

Mateusz JAKUBOWSKI, [a] **Iwona ŁAKOMSKA,** [a] **Janusz DĄBROWSKI,** [b] **Barbara PUCELIK** [b]

[a] *Bioinorganic Chemistry Research Group, Faculty of Chemistry, Nicolaus Copernicus University in Toruń, Gagarina 7, 87100 TORUŃ, Poland.*
[b] *Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30387 CRACOW, Poland.*
mjakubowski@umk.pl

Cisplatin (CDDP) is currently used to treat various type of cancers [1]. However, poor water solubility, high affinity to glutathione and significant toxicity of CDDP towards normal cells became a motivation for a development of novel platinum-based anticancer agents. Long-term scientific studies in this field led to the worldwide approval of dicarboxylato platinum(II) complexes such as Carboplatin and Oxaliplatin, which exhibit lower than Cisplatin toxicity [2]. Unfortunately, these second-generation drugs are less cytotoxic towards some types of cancers too. Therefore, interdisciplinary research connected with consecutive modification of coordination sphere of platinum(II) are still valid. The attractive idea is replacing stable amine ligands with other non-living N-donors e.g. triazolopyrimidine derivatives, which are analogous of nitrogenous bases.

Following this direction, we synthesized novel, mixed ligand Pt(II) complex [Pt(mal)(dmso)(dptp)], where: mal – malonato, dmso – dimethyl sulfoxide, dptp – 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (Figure 1.) [3]. The preliminary biological studies demonstrated that our lipophilic compound (logP = +0.54) exhibits higher than Carboplatin (with the IC_{50} values of 10.1 μM and IC_{50} > 100 μM, respectively) and similar to Cisplatin (IC_{50} = 9.0 μM) *in vitro* anticancer activity against human lung adenocarcinoma cells (A549). Additionally, this complex shows more than 10-times less *in vitro* toxicity towards normal murine embryonic fibroblast cells (BALB/3T3) in comparison with Cisplatin.

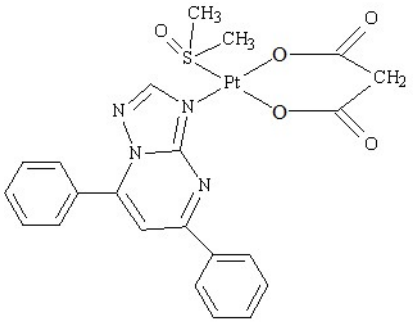


Figure 1. Structural formula of [Pt(mal)(dmso)(dptp)].

Moreover, it was proven that [Pt(mal)(dmso)(dptp)] displays lower reactivity towards glutathione than currently used platinum(II) drugs – Cisplatin and Carboplatin. On the other hand, the novel mixed ligand complex is able to modulate the cell cycle of A549 by induction of arrest in G_0/G_1 phase. These promising results have motivated us to undertake *in vivo* studies, which confirmed that our novel platinum(II) is less toxic than Carboplatin (Fig. 2). Additionally, it was observed that a treatment with use of the same dose dividing into three parts (x3) results in a decrease toxicity (Figure 2.).

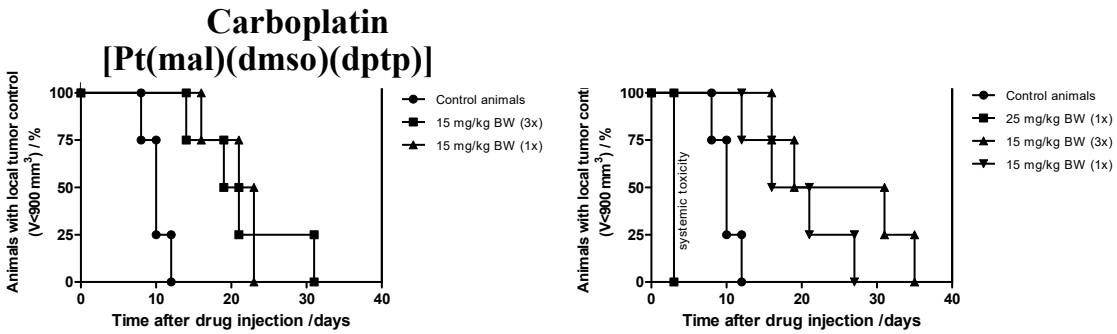


Figure 2. Kaplan-Meier plot showing the survival (days after tumor implementation) of BALB/c Nude mice bearing A549 treated with Carboplatin and [Pt(mal)(dmso)(dptp)].

References:

[1] L. Kelland, *Nature Reviews Cancer* **2007**, 7, 573-584.
[2] S. Dilruba, G.V. Kalayda, *Cancer Chemotherapy and Pharmacology* **2016**, 77, 1103-1124.
[3] M. Jakubowski, I. Łakomska, J. Sitkowski, J. Wiśniewska, *New Journal of Chemistry* **2018**, 42, 8113-8122.

P24
Does *Fusobacterium nucleatum* cell surface proteins increase the prooxidative activity of metal ions?

Kamila STOKOWA-SOŁTYS, [a] Valentyn DZYHOVSKYI, [a] Robert WIECZOREK, [a] Monika LESIOW, [a] Katarzyna KRUPA, [a] Agnieszka KYZIOŁ, [b] Anna KĘDZIORA, [c] Gabriela BUGLA-PŁOSKOŃSKA, [c] Małgorzata JEŻOWSKA-BOJCZUK [a]

[a] Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50-383 Wroclaw, Poland.
[b] Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Krakow, Poland.
[c] Department of Microbiology, Institute of Genetics and Microbiology, University of Wroclaw, S. Przybyszewskiego 63, 50-001, Wroclaw, Poland.
kamila.stokowa-soltys@chem.uni.wroc.pl

Cancer constitutes an enormous burden on all societies [1]. In recent years, the number of new cases have continued to increase [2]. Associations between human microbiota composition and colorectal carcinogenesis was found for the first time in the 1970s. Later, it was reported that the existence of over a dozen bacterial species as well as a kind of diet are associated with a higher risk of colon cancer [3]. In the next step of studies based on the mouse model of intestinal tumorigenesis, was concluded that *Fusobacterium nucleatum* increases neoplastic changes [4,5]. *Fusobacterium* is one of the most abundant Gram-negative anaerobic bacteria, part of the gut and oral commensal flora, generally found in the dental plaque of humans [6]. Its presence could be associated with various human diseases, including *e.g.* periodontal, angina, lung and gynecological abscesses [7, 8]. It has been proven that *F. nucleatum* migrates from its primary site of colonization in the oral cavity to other parts of the body [9]. For this reason it could cause numerous diseases, including cancers. In the cancerogenesis process outer membrane proteins are actively involved [4,5].

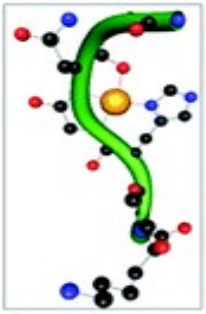
Therefore, it is very interesting to investigate the effect of metal ions coordination on the activity of outer-membrane proteins from *F. nucleatum* and to answer the question whether proteins increase the prooxidative activity of metal ions. Usage of a broad spectrum of experimental methods as well as theoretical calculations allowed to characterize: the protonation of designed peptides (fragments of outer-membrane proteins), the ability of the ligands to coordinate divalent metal ions, full description of the coordination process, competition in metal biding between different peptides as well as the specificity of different metals coordination by the same ligand. Moreover, it was also found that some forming complexes are able to generate reactive oxygen species (ROS) in the presence of hydrogen peroxide, ascorbic acid or their mixture. Therefore, complexes are able to cleave plasmid DNA. What is worth of note, complexes stimulate mouse colon carcinoma cells to generate high amount of ROS and lead to oxidative stress, what may be associated with cancerogenesis process [10]. Furthermore, both studied *F. nucleatum* strains (DSM 15643 and DSM 20482) are involved in ROS production in the presence of Cu(II) and H_2O_2 and free radicals generation takes place outside the cell. The level of ROS depends on the bacterial strain and is probably related to the molecular structure of the outer-membrane

proteins. All these findings suggest that enhanced ROS production in the presence of *F. nucleatum* may be crucial in colon cancer progression.

Table 1. The Cu(II)···X distances of Ac-KGHGNG-NH_2 complex. All values in [Å].

X	$CuH_{-1}L^+$ (3N)
H3 ($N_{(imidazole)}$)	1.975
G4 ($N_{(amide)}$)	1.991
N5 ($N_{(amide)}$)	1.931
G6 ($O_{(carbonyl)}$)	2.059

Figure 1. DFT calculated structure of the complex dominanting at pH 7.5



Acknowledgements:
The research was supported by the Polish National Science Centre (Grant NCN 2014/13/B/ST5/04359).

References:

[1] A. Jemal, F. Bray, M. M. Center, J. Ferlay, M.E. Ward, D. Forman, *CA Cancer J. Clin.* **2011**, 61 (2), 69-90.
[2] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet, Tieulent, A. Jemal, *CA Cancer J. Clin.* **2015**, 65 (2) 87-108.
[3] C.L. Sears, W.S. Garrett, *Host Microbe* **2014**, 15(3), 317-328.
[4] A.D. Kostic, E. Chun, L. Robertson, J.N. Glickman, C.A. Gallini, M. Michaud, T. E. Clancy, D.C. Chung, P. Lochhead, G.L. Hold, E.M. El-Omar, D. Brenner, C.S. Fuchs, M. Meyerson, W.S. Garrett, *Cell Host Microbe* **2013**, 14 (2), 207-215.
[5] M.R Rubinstein, X. Wang, W. Liu, Y. Hao, G. Cai, Y.W. Han, *Cell Host Microbe* **2013**, 14(2), 195-206.
[6] L. Flanagan, J. Schmid, M. Ebert, P. Soucek, T. Kunicka, V. Liska, J. Bruha, P. Neary, N. Dezeeuw, M. Tommasino, M. Jenab, J. H. M. Prehn, D. J. Hughes, *Eur. J. Clin. Microbio.l* Infect. Dis., **2014**, 33, 1381-1390.
[7] Y.W. Han, A. Ikegami, C. Rajanna, H.I. Kawsar, Y. Zhou, M.Li, H.T. Sojar, R.J. Genco, H.K. Kuramitsu, C.X. Deng, *J. Bacteriol.* **2005**, 187(15), 5330-5340.
[8] J. Strauss, G.G. Kaplan, P.L. Beck, K. Rioux, R. Panaccione, R. DeVinney, T. Lynch, E. Allen-Vercoe, *Inflamm. Bowel Dis.* **2011**, 17(9), 1971-1978.
[9] O.T. Keku, A.N. McCoy, A.M. Azcarate-Peril, *Trends Microbiol.* **2013**, 21(10), 506-508.
[10] M.K. Lesiów, U.K. Komarnicka, K. Stokowa-Sołtys, K. Rolka, A. Łęgowska, N. Ptaszyńska, R. Wieczorek, A. Kyzioł, M. Jeżowska-Bojczuk, *Dalton Trans.* **2018**, 47, 5445-5458.

P25
Hydroxamate chelators for efficient complexation of Zr (IV)

Yuliya TOPORIVSKA, [a] Remo GUERRINI, [b] Maurizio REMELLI, [b] Elżbieta GUMIENNA-KONTECKA [a]

[a] University of Wroclaw, Faculty of Chemistry, 14 F. Joliot-Curie, 50-383 WROCLAW, Poland.
[b] University of Ferrara, Dipartimento di Scienze Chimiche e Farmaceutiche, 46 Via Luigi Borsari, 44121 FERRARA, Italy.
elzbieta.gumienna-kontecka@chem.uni.wroc.pl

Radiometals are radioactive isotopes that can be used for applications in medical diagnosis, as well as for cancer therapy. When properly harnessed, these have valuable emission properties that can be used for positron emission tomography (PET). Zirconium-89 (89Zr), a positron-emitting radionuclide, possesses excellent physical properties for PET imaging when paired with antibodies, namely, an ideal 78.41 h half-life and low energy positron (βavg = 395.5 keV) [1,2]. A fundamental critical component is the chelator, the ligand system that binds the radiometal ion in a tight stable coordination complex and then attached to the antibodies so that it can be properly directed to a desirable molecular target in vivo. Currently, desferrioxamine (DFO) is the chelator most commonly used to radiolabel biomolecules with 89Zr, a large number of antibodies have been labeled with 89Zr-DFO and used in pre-clinical and clinical studies in recent years [3,4]. However, in a number of cases, the in vivo stability of the Zr-DFO complex has proven insufficient as seen by the accumulation of free, osteophilic 89Zr in bones 2 to 4 days after injection of the labeled antibody [4-6]. In order to improve stability of Zr(IV) complexes alternative ligands with oxygen-rich donor groups including hydroxamates, carboxylates, carbonyls, hydroxyquinolines have been tried [1,2]. However, there are certain difficulties in studies of coordination chemistry of such complexes, because of the strong hydrolysis of Zr(IV) (occurring in almost entire pH range) and lack of spectral information on solution Zr(IV) complexes formation.

Here we will present the detailed speciation studies of Zr(IV) – DFO system, as the knowledge of the speciation of Zr(IV) complexes, especially at physiological pH, can provide information concerning 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. Additionally, we will show the some novel hydroxamate chelators for Zr(IV), which should be able to form Zr(IV) complexes of significantly higher stability than DFO.

The financial support from the National Science Centre Poland, UMO-2015/19/B/ST5/00413, is gratefully acknowledged.

This work was supported by a STSM Grant from COST Action CA18202.

References:

[1] T. I. Kostelnik and C. Orvig, *Chem. Rev*. **2019**, ***119,*** 902−956.

[2] J. R. Dilworth and S. I. Pascu, *Chem. Soc. Rev.* **2018**, 47, 2554-2571.

[3] M. A. Deri, B. M. Zeglis, L. C. Francesconi and J. S. Lewis, *Nucl. Med. Biol.* **2013**, 40, 3-14.

[4] J. P. Holland and N. Vasdev, *Dalton Trans.* **2014**, 43, 9872-9884.

[5] Y. Toporivska and E. Gumienna-Kontecka, *J. Inorg. Biochem.* **2019**, 198, 110753/1-110753/7.

[6] B. M. Zeglis, J. L. Houghton, M. J. Evans, N. Viola-Villegas and J. S. Lewis, *Inorg. Chem.* 2014, 53, 1880-1899.

P26
Bio-based ionic liquid platforms for the extraction of IgG

Ana P. M. TAVARES, [a] Dibyendu MONDAL, [a] Mukesh SHARMA, [b] Maria V. QUENTAL, [a] Kamalesh PRASAD, [b] Mara G. FREIRE [a]

[a] *CICECO-Aveiro Institute of Materials, Chemistry Department, University of Aveiro, 3810193 AVEIRO, Portugal.*
[b] *Natural Product and Green Chemistry Division, CSIR-Central Salt & Marine Chemicals Research Institute, 364002 BHAVNAGAR - (Gujarat), India.*
aptavares@ua.pt

Due to the advances of therapeutic drugs in treating several ill-managed diseases, biopharmaceuticals based on antibody Immunoglobulin G (IgG) have been developed. However, requirement of IgG in bulk puts substantial economic pressure on the current processes of production of the antibody. Ionic liquid (IL)-based aqueous biphasic systems (ABS) are emerging as an alternative cost-effective methodology to improve the downstream processing of antibodies. In order to have more bio-compatible ILs, in this work, a series of new biocompatible ILs capable to form ABS for the extraction of IgG was evaluated [1]. The bio-based ILs are constituted by the cholinium cation and anions derived from plants natural acids. These ILs were designed, synthesized, characterized and used for the creation of ABS with polypropyleneglycol (PPG 400) as phase forming components. The ability of each bio-based IL to form two phases in the presence of PPG 400 was: cholinium-D-(–)-quinate ≃ cholinium-D-(+)-galactouronate > choline glycolate > cholinium pyruvate > cholinium-L-ascorbate > cholinium indole-3-acetate. This trend closely correlates with the octanol-water partition values of each acid and thus the IL hydration aptitude and/or their affinity for water seems to rule the phase separation ability [1]. Remarkably, as a proof of concept, the complete extraction of IgG in a single-step was accomplished in the IL-rich phase with 100% of recovery yield. The optimized systems were thereafter applied to the extraction and purification of IgG directly from rabbit serum samples and *ca* 85% recovery yield of IgG was recorded with 58.3% enhancement in the purity in comparison to the initial serum sample. For all bio-based ILs investigated, sharing the same cation, the ability to form ABS with PPG 400 depends on the anion counterpart. In most of the cases, IgG was found to be retained its native structure without degradation or denaturation which further suggested that these bio-IL-based ABS can be considered for the purification of high-cost biopharmaceuticals.

Acknowledgments:
This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement. A. P. M. Tavares acknowledges FCT for the research contract and exploratory project under the FCT Investigator Programme (IF/01634/2015).

References:

[1] D. Mondal, M. Sharma, M.V. Maria V. Quental, A.P.M. Tavares, K. Prasad, M.G. Freire, *Green Chemistry* **2016**, 18, 6071–6081.

P27
Exploring the metal coordination of 8-hydroxyquinoline derivatives

Isabel CORREIA, Nádia RIBEIRO, João COSTA PESSOA, Adelino GALVÃO

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Complexo Interdisciplinar, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal
icorreia@tecnico.ulisboa.pt

Cancer remains a leading cause of death, estimated to rise with the increase of life expectancy. The quest for new metal-based chemotherapeutics targeting cancer represents both a challenge and an opportunity. Among current strategies, the use of alternative metals to platinum offers different mechanisms of action. The interest in 8-hydroxyquinolines (8HQ), a subclass of quinolones, has grown exponentially in the last decades. The literature abounds with examples of the exceptional anticancer, antifungal and bactericidal activity of these compounds.[1-3] With the current project we aim to: (1) prepare and characterize new 8-hydroxyquinoline Schiff base metal complexes; (2) evaluate its aqueous and biochemical speciation; (3) screen its ability to treat cancer diseases and (4) evaluate its mode of cell death.

Taking advantage of the exceptional biological activity of 8-hydroxyquinolines we have developed new metal complexes of a Schiff base derived from 8HQ and benzothiazole (HL, Fig. 1). Hence, nine different metal complexes were prepared with L:M stoichiometry 1:1 and 2:1 and characterized in solution and solid state.

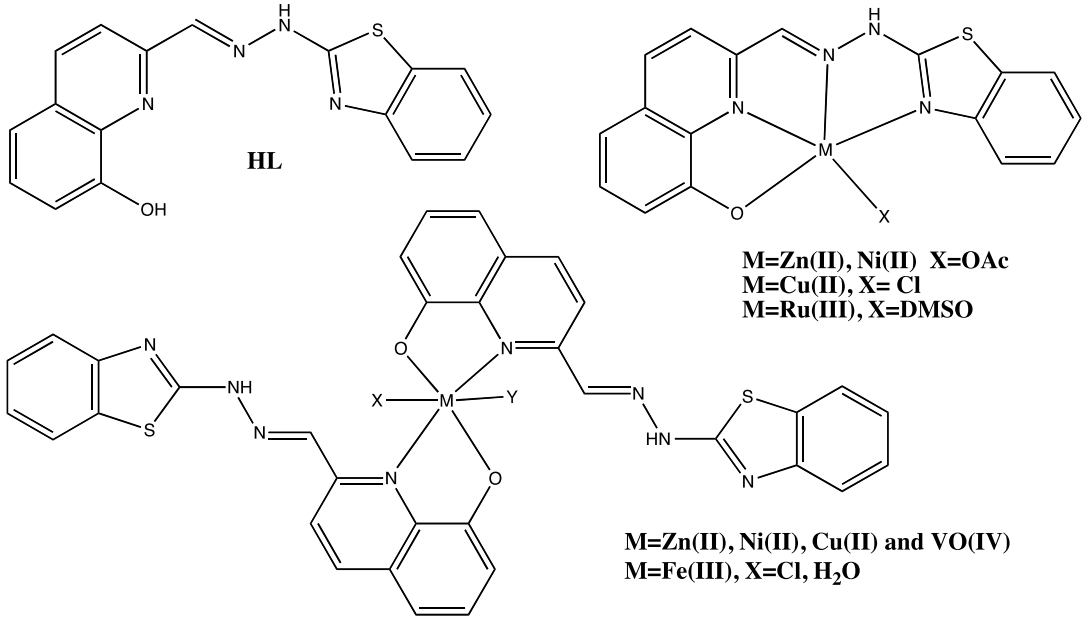


Figure 1. – Molecular formulation of HL and its metal complexes.

An estimate of the ligand acid base properties, using spectrophotometry, shows the existence of three species in the pH range 7-12, with pKa values of 7.81±0.04 and 10.98±0.11

(10% v/v DMSO, KCl 0.2 M). The photophysical properties of HL were evaluated and fluorescence emission was only observed at pH values higher than 11, resulting from the dianionic $[L\text{-}H]^{2-}$ species.

Metal complexes were prepared by reaction of different metal salts with the deprotonated ligand. The following complexes were obtained and characterized (Figure 1.): $[Zn^{II}(L)(OAc)]$, $[Zn^{II}(L)_2]$, $[Ni^{II}(L)(OAc)]$, $[Ni^{II}(L)_2]$, $[Cu^{II}(L)Cl]$, $[Cu^{II}(L)_2]$, $[Ru^{III}(L\text{-}H)(DMSO)Cl]$, $[Fe^{III}(L)_2Cl(H_2O)]$ and $[V^{IV}O(L)_2]$. Penta- or hexa-coordinated structures are proposed for the metal complexes, based on spectroscopic signatures, elemental analysis and mass spectrometry data. Their stability in aqueous solutions at physiological pH was evaluated.

All compounds are currently being screened for their cytotoxic activity against melanoma (MNT-1), colorectal (HCT-116) and breast (MCF-7) cancer cells as well as a non-tumoral skin (HaCat) cell line. Theoretical calculations are ongoing to understand the photophysical and spectroscopic properties of the ligand and its metal complexes and will be presented.

Due to the limited aqueous solubility of HL and its complexes, new ligands have been synthesized derived from condensation of 8HQ with several hydrazides (Figure 2.). Its metal complexes are being prepared and will also be presented.

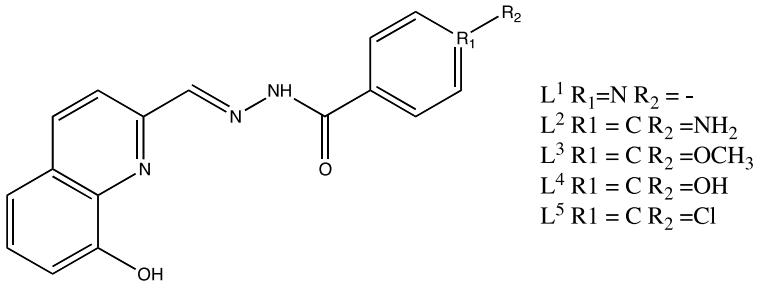


Figure 2. Molecular formulation of new 8HQ ligands.

References:

[1] W.-Q. Ding, B. Liu, J. L. Vaught, H. Yamauchi and S. E. Lind, *Cancer Res.* **2005**, 65 (8), 3389-3395.

[2] H. Gershon, D.D. Clarke, M. Gershon, *Monatsh Chem.*, **1994**, 125(1), 51-595.

[3] S. Tardito, A. Barilli, I. Bassanetti, M. Tegoni, O. Bussolati, R. Franchi-Gazzola, C. Mucchino, L. Marchio, *J. Med. Chem.*, **2012**, 55(23), 10448−10459.

P28
Designing of biocompatible ionic liquids – thermodynamic and computational approach

Aleksandar TOT, Milan VRANEŠ, Jovana PANIĆ, Snežana PAPOVIĆ, Sanja BELIĆ, Nikolett BÁGÁNY, Slobodan GADŽURIĆ

Faculty of Sciences, Department of Chemistry, Biochemistry and Environmental Protection, University of Novi Sad, Trg Dositeja Obradovića 3, 21000, Novi Sad, Serbia.
aleksandar.tot@dh.uns.ac.rs

Over the past decades a raising awareness of environmental protection prompted the rapid development of green and sustainable technologies. Due to low volatility and stability, ionic liquids (ILs), so called "green" solvents, emerged as a potential replacement for traditional volatile and harmful organic solvents. Despite the argued advantage of having low vapor pressure, even the most hydrophobic ILs show some degree of solubility in water, allowing their dispersion into aquatic systems and raising concerns on its pollutant potential. Nevertheless, although the toxicity and biodegradability of ILs have been widely assessed in recent years, the adequate understanding of thermodynamic and theoretical parameters on this properties is still absent

The aim of this research was to find reliable physico-chemical properties that correlated with ILs toxicity and biodegradability. Moreover, the DFT calculations were applied to obtain molecular descriptors that explain why particular structures express toxic behaviour. The obtained toxicity results of various commercial, functionalized and biocompatible ionic liquids suggest deciding effect of lipohilic/lipohobic parameter, viscosity B coefficient and degree of ionization on overall ILs toxicity. Furthermore, the investigation of ionic liquids transport through lipid bilayer using molecular dynamic simulations, suggest importance of similarity between membrane consituents with ionic liquid structure.

P29
The use of isothermal titration calorimetry in studying thermodynamics of high-heat micellization processes

Žiga MEDOŠ, Isidora ČOBANOV, Marija BEŠTER-ROGAČ, Nevena ĐEKIĆ, Bojan ŠARAC

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia.
bojan.sarac@fkkt.uni-lj.si

Calorimetry research of self-aggregation (micellization) of surfactants spans for more than 70 years. From the 1980s, with the advent of commercial dynamic power compensation isothermal titration calorimeters (ITC), a majority of papers have been published using ITC as a central method for studying energetics of micellization, which, furthermore, strengthened the connection between speciation modelling and thermodynamic parameters of micellization.

This talk will be devoted to the problems associated with power compensation ITC. It will be presented how the choice of setup parameters in modern calorimeters – in the case of high-heat processes mainly – affects the magnitude of the measured heat effects, which consequently determine the shape of enthalpograms and (final) results. For this purpose, a series of titrations of potassium decanoate (KC10) in water at different temperatures with different modes of operation and intervals between injections using three instruments (TAM, Nano ITC and VP-ITC) were performed (Figure 1.). Since the enthalpy is a function of state and therefore must not be dependent on the path how it is measured, some "traps", to which user has to pay attention when using ITC for investigation of high-heat processes will be shown [1,2].

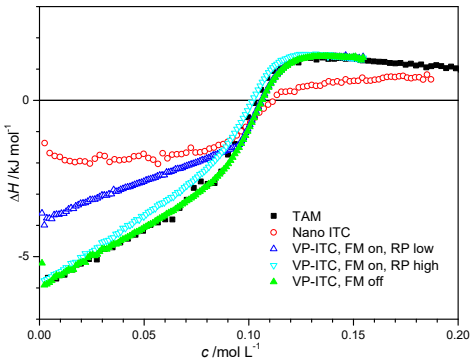


Figure 1. Enthalpograms for KC10 obtained by integration of raw signals at 35 °C for TAM [2], Nano ITC and VP-ITC.

References:

[1] Ž. Medoš, M. Bešter-Rogač, Isidora Čobanov, B. Šarac, *J. Therm. Anal. Calorim.*, **2020**, *under revision*.

[2] Ž. Medoš, M. Bešter-Rogač, *Langmuir*, **2017**, *33*, 7722-7731.

STSM1
Synthesis of bioinspired de novo designed peptides for copper complexation and redox catalysis

Silvia GENTILI, [a] **Denise BELLOTTI**, [b] **Chiara BACCHELLA**, [c] **Alice MAZZA**, [a] **Maurizio REMELLI**, [b] **Simone DELL'ACQUA**, [c] **Luigi CASELLA**, [c] **Olga IRANZO**, [d] **Matteo TEGONI** [a]

[a] *Department of Chemistry, Life Sciences, and Environmental Sustainability, University of Parma, Parco Area delle Scienze 11/a, 43124 Parma, Italy.*
[b] *Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via Luigi Borsari 46, 44121 Ferrara, Italy.*
[c] *Department of Chemistry, University of Pavia, Via Taramelli 12, 27100 Pavia, Italy.*
[d] *CNRS, Centrale Marseille, Aix Marseille Université, iSm2, Marseille, France.*
silvia.gentili@unipr.it

Tau is a 441-mer peptide present in significant amounts in neurons, where it contributes to the stabilization of microtubules. Insoluble amyloid aggregates of tau are associated with over 20 neurological disorders known as tauopathies, among which is Parkinson [1]. In neurons, tau binds tubulin through its microtubule binding domain which comprises four repeats (R1-R4) characterized by the presence of histidine residues. These regions are potential binding sites for metal ions [2]. The elucidation of the binding capacities toward metal ions, especially those redox active such as copper(II), may shed light on the biomolecular processes that underlie the progression of tauopathies [3]. Recently, our research group examined the stability of Cu(II) and Cu(I) adducts with two peptide fragments which are encompassed in the R1 and R3 repeats of tau (Figure 1.) [4].

R1:
Ac-^{257}VKSKIGSTENLKHQGGG^{273}-NH_2

R3:
Ac-^{323}GSLGNIHHKPGGG^{335}-NH_2

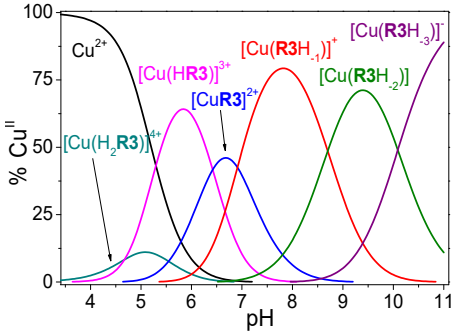


Figure 1. Left. Sequences of the R1 and R3 peptides. **Right.** Distribution diagram of the Cu(II)/R3 system (C_{Cu} = 100 μM, R3:Cu = 1.5).

The presence of a tandem of two His residues in the R3 peptide sequence significantly increases the Cu(II)/Cu(I) reduction potential of the copper center by modulating the ligand donor set. By reflection, the catalytic propensity of the adduct in promoting catechol oxidation increases dramatically.

Several neuropeptides, actually, contain other His residues beyond those of the His-His dyad (e.g. β-amyloid). Although much is known about copper/peptides that promote oxidative reactions, the relationship between the catalytic properties and the position of the His residues within the peptide sequence is still far from being fully elucidated [5,6].

In the framework of COST 18202 Action, and during my STSM, I have synthesized four peptides, derived from the tau R3 fragment, that bear a His-His dyad and a third additional His residue located a different positions along the amino acid sequence.

In this communication I will present the design, synthesis and characterization of the different peptides as well as our initial Cu(II) coordination studies.

References:

[1] M. Goedert, D. S. Eisenberg, R. A. Crowther, *Annu. Rev. Neurosci.* **2017**, 40, 189-210.
[2] M. G. Savelieff, S. Lee, Y. Liu, M. H. Lim, *ACS Chem. Biol.* **2013**, 8, 856-865.
[3] A. Soragni, B. Zambelli, M. D. Mukrasch, J. Biernat, S. Jeganathan, C. Griesinger, S. Ciurli, E. Mandelkow, M. Zweckstetter, *Biochemistry* **2008**, 47, 10841-10851.
[4] C. Bacchella, S. Gentili, D. Bellotti, E. Quartieri, S. Draghi, M. C. Baratto, M. Remelli, D. Valensin, E. Monzani, S. Nicolis, L. Casella, M. Tegoni, S. Dell'Acqua, *Inorg. Chem.* **2020** 59 (1), 274-286.
[5] V. Pirota, S. Dell'Acqua, E. Monzani, S. Nicolis, L. Casella, *Chem.–Eur. J.* **2016**, 22 (47), 16964-16973.
[6] Pham, A. N.; Waite, T. D., *J. Inorg. Biochem.* **2014**, 137, 74-84.

Acknowledgements:

The authors acknowledge MIUR for financial support through the project "Metal ions, dopamine, and oxidative stress in Parkinson's disease" (PRIN 2015T778JW). This work was supported by a STSM Grant from COST Action CA18202.

STSM2
Studies on adsorption of environmental pharmaceutical persistent pollutants on nanostructured molecularly imprinted polymers

Dong HAN, Manuel VALIENTE

Universitat Autonoma de Barcelona. Department of Chemistry. Centre GTS. 08193. Bellaterra Barcelona, Spain.
Dong.Han@uab.cat

Increasing consumption of cytostatic drugs (CDs) have made them one of the greatest environmental threats, because CDs not fully metabolized in human organisms could be excreted with urine by patients undergoing chemotherapy, and then were detected worldwide at ng/L to μg/L in surface water bodies in different countries [1,2]. Because of their toxicity to both humans and aquatic organisms, coupled with the low treatment capacities of conventional wastewater treatment plants, it is important to find an efficient and cost-effective method for wastewater depuration [3].

The planned work considers development of Molecularly imprinted polymers (MIPs) for adsorption of targeted CDs. Well-organized MIPs provide the high selective molecular recognition ability, which show great potential in application of separation of pharmaceutical compounds in environmental samples. Briefly, ideal MIPs will be prepared with highly crosslinked organic polymers or silica-based materials by simple polymerization. The adsorption capacity of expected MIPs on targeted CDs will be carefully tested, and several critical influence parameters including initial concentration of adsorbates, temperature, pH value, and contact time will be studied during the adsorption process. The trace concentration of targeted CDs will be detected with Solid phase extraction (SPE) and Inductively coupled plasma mass spectrometry (ICP-MS). Additionally, adsorption isotherm experiments will be performed and several classic isotherm models will be fitted, including Langmuir and Freundlich models. Meanwhile, studies on adsorption kinetics will also be performed, models including Pseudo-first-order and Pseudo-second-order will be selected to fit experimental data. Isothermal titration calorimeter (ITC) will be utilized to investigate thermodynamics of the adsorption process. The successful synthesis of efficient, highly selective, and cost-effective MIPs adsorbents will provide ideas for removal and recovery of CDs or other hazardous environmental pharmaceutical persistent pollutants from wastewater, showing great potential and good environmental benefits.

Keywords: cytostatic drugs; adsorption; molecularly imprinted polymers; isothermal titration calorimetry.

Acknowledgements:
This work was supported by a STSM Grant from COST Action CA18202.

References:

[1] Y. Valcárcel, S. González Alonso, J.L. Rodríguez-Gil, A. Gil, M. Catalá, *Chemosphere* **2011**, 84 (10), 1336–1348.

[2] J.-P. Besse, J.-F. Latour, J. Garric, *Environment International* **2012**, 39 (1), 73–86.

[3] P. Mazierski, A.F. Borzyszkowska, P. Wilczewska, A. Białk-Bielińska, A. Zaleska-Medynska, E.M. Siedlecka, A. Pieczyńska, *Water Research* **2019**, 157 610–620.

STSM3
An organometallic approach to alzheimer's disease treatment

Emel YILDIZ, Elem SABAHSAN

Cukurova University, Arts & Science Faculty Dept.of Chemistry 01330 Adana, Turkey.
eeyildiz@cu.edu.tr

β-amyloid (Aβ) plaques or metal deposition in the brain thought to be among the causes of Alzheimer's Disease. As the Yildiz group, we carry out experiments based on organometallic studies for both cases together with the pharmacology department [1,2]. We care about the synergy created by the joint work of the Chemistry and Medical Sciences to reduce heavy metal accumulation or to prevent beta amyloid deposition in some tissues.

Sulfa drugs have a special interest in bacterial diseases as well as their therapeutic effects. Sulfa drug ligands are among the important stereochemical models due to their ease of preparation and structural diversity in coordination complexes [3].

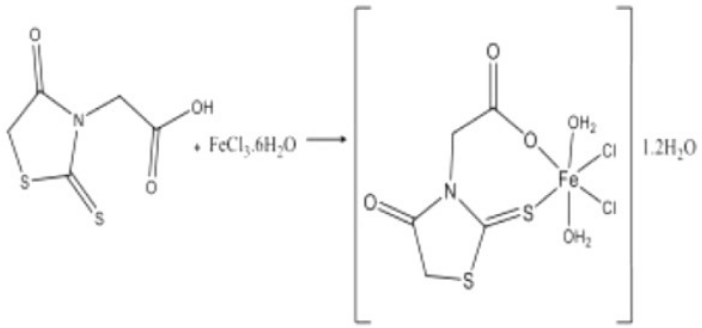


Figure 1. Formation of Fe-Rodanin-N-Acetic Acid chelate complex.

The metal complexes of chelate-forming Rodanin-N-Acetic Acid ligand with Fe(III), Mn (III) and Cu(II) were synthesized in vitro conditions (Figure 1.). It was found that the metal accumulations observed in the liver, spleen and blood of laboratory rats decreased using the ligand in vivo studies. When the iron accumulation overloaded in the tissues, the iron binding capacity of the ligand also increased, and the results were presented biostatistical.

Our study will be able to contribute to the research of biochemical and pharmacological activities of new azo-sulfa drug derivatives to be synthesized. Moreover, it is in line with the tasks envisaged in WG2, NECTAR.

References:

[1] N.Biçer, E.Yildiz, A.A.Yegani, F.Aksu, New Journal of Chemistry **2018**, (42), 8098-8104.

[2] E.S.Sabahsan, **2019**, Supervisor: E.Yildiz, Cukurova University Natural Sci.Ins.,MSc. Thesis, "Synthesis of Complexes of Rhodanine-N-Acetic Acid with Iron(III), Aluminium(III), Chromium(III), Copper(II), Manganese(III) and Investigation of Bioactive Characteristics".

[3] A.Z., El-Sonbatı et.al., *Inorganica Chimica Acta* **2013**, (404), 175-187.