ISMEC 2019

International Symposium on Metal Complexes
Hajdúszoboszló/Debrecen, June 11-14, 2019

Debrecen University Symposium, 2019

BOOK OF ABSTRACTS

UNIVERSITY of DEBRECEN

International Symposium on Metal Complexes (ISMEC 2019) June 11-14, Hajdúszoboszló/Debrecen, Hungary

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ISMEC 2019 and the International Year of the Periodic Table of Chemical Elements (IYPT 2019)

Imre TÓTH

Department of Physical Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary
e-mail: imre.toth@science.unideb.hu

2019 has been proclaimed as the International Year of the Periodic Table of Chemical Elements (IYPT 2019) by the United Nations General Assembly. The celebrations are organized by the UNESCO. (The IYPT 2019 official website: https://www.iypt2019.org)

The genius theory/presumption of Mendeleev published 150 years ago in 1869 attracts many people in the 21th century all over the word including both chemists and layman. This positive public relation may help us, chemists, restoring confidence of the (chemistry-socked) society.

The short talk will highlight the key points of Mendeleev's original chart constructed without important fundamental peaces of physical knowledge (being trivial (?) nowadays for secondary school students, e.g. the existence of electron, electronic shell and nucleus of atoms, atomic number, isotopes etc.) A comparison of the 150 years old ~60 element Table of Mendeleev to the newest, complete 7 row, 118 element Table of IUPAC will also be presented. (https://iupac.org/what-we-do/periodic-table-of-elements/)

2/3 of the elements are metals in the Periodic Table. International Symposium on Metal Complexes (ISMEC 2019) is focused on these metallic elements, the word „**metal**" is written in most of the titles of main topics: ***Metal*** complexes of biological and environmental interests, ***Metal***-complex interactions with biomolecules, ***Metal****s* in diseases: transport, ***Metal***-complexes in therapy and diagnosis, ***Metal***loenzymes, Analytical methods and sensors, based on ***metal*** complexes. What are the most fashionable metals in our program? What are the hottest fields of the research being reported at ISMEC 2019? The speaker is willing the make this analysis at the level of popular science.

Acknowledgements: This research was funded by the GINOP-2.3.2-15-2016-00008 project supported by the EU and co-supported by the European Regional Development Fund.

International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Set aside when building the periodic table 150 years ago, are rare earths any better considered by chemists in the 21st century?

Claude PIGUET

Department of Inorganic and Analytical Chemistry, University of Geneva, 30 quai E. Ansermet, CH-1211 Geneva 4, (Switzerland).
e-mail: Claude.Piguet@unige.ch

A hundred and fifty years ago, the Rare Earths posed a serious problem to Mendeleyev because of their very similar chemical properties, although their atomic mass dispersions pointed to different elements (Figure 1).

IA	IIA	IIIB	IVB	VB	VIB	VIIB	VIIIB			IB	IIB	IIIA	IVA	VA	VIA	VIIA	VIIIA
H 1766																	He 1868
Li 1817	Be 1798											B 1808	C -3700	N 1772	O 1771	F 1810	
Na 1807	Mg 1755											Al 1825	Si 1824	P 1669	S -2000	Cl 1774	
K 1807	Ca 1808		Ti 1791	V 1801	Cr -1	Mn 1774	Fe -5000	Co 1732	Ni 1751	Cu -9000	Zn -1000			As -2500	Se -2000	Br 1825	
Rb 1861	Sr 1784	Y 1794	Zr 1789	Nb 1801	Mo 1778		Ru 1844	Rh 1804	Pd 1803	Ag -4000	Cd 1817	In 1863	Sn -3500	Sb -3000	Te 1782	I 1811	
Cs 1860	Ba 1772	La 1838	Ce 1803	Ta 1802	W 1781		Os 1803	Ir 1803	Pt 1735	Au -8000	Hg -2000	Tl 1861	Pb -7000	Bi 1753	Te 1782	I 1811	
		U 1789	Th 1829														

Not included: Di 1838, Tb 1842, Er 1842

Figure 1. The periodic table proposed by Mendeleyev in 1869 and the non-included 'yellow vests' Rare Earths.

This difficulty persisted for several decades and only the emergence of the atomic theory provided some legitimacy for their consideration as a full series of 15 elements resulting from the filling of the 4f orbitals (La-$4f^0$ to Lu-$4f^{14}$), to which scandium and yttrium were added for the sake of chemical similarities (Figure 2).[1] However, it is difficult to give up bad habits and major advances in transition metal chemistry started systematically with d-block cations prior to extension to f-block analogues, and this despite the broader perspectives often brought by the latter. The technology-oriented society put in place for economic reasons during the last five decades has reactivated scientific interest in the Rare Earths, which have now become essential for many applications in telecommunications, lasers, magnetic materials and optical devices.[2],[3]

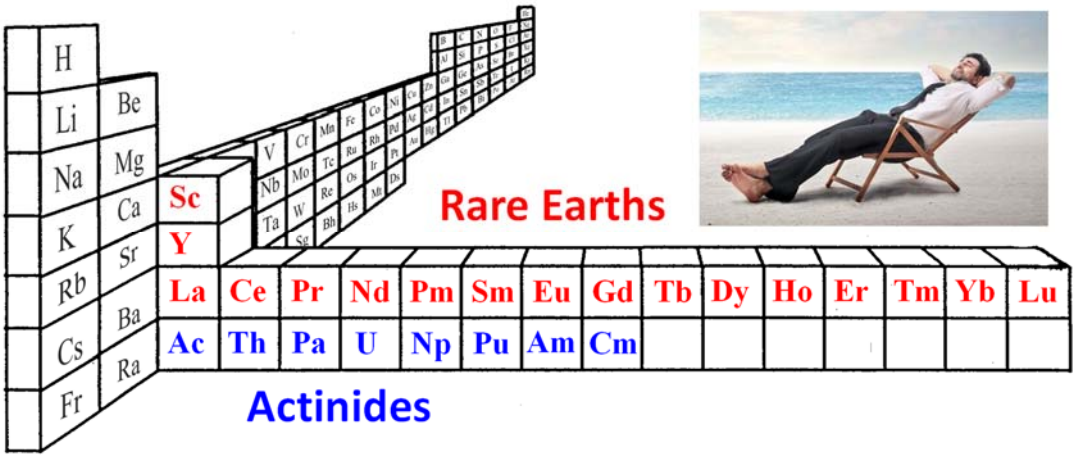

Figure 2. The periodic table in 1945 after the discovery of the last natural elements: Pm.

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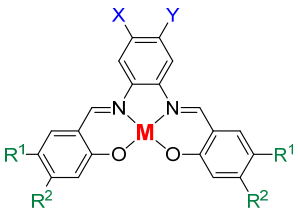
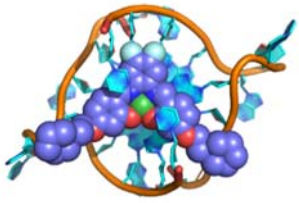
Targeting DNA with metal complexes - exploring their therapeutic and imaging properties

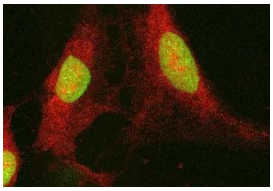
Ramon VILAR

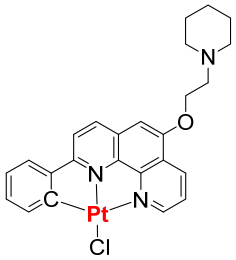
Department of Chemistry, Imperial College London, White City Campus, Wood Lane, W12 OBZ London, United Kingdom
e-mail: r.vilar@imperial.ac.uk

Besides the canonical double helix, DNA can fold into a range of different topologies some of which have been proposed to play key biological roles. One of these topologies are the G-quadruplexes (G4) where guanine rich sequences are able to fold into stable tetra-helical assemblies. G4s have been proposed to play regulatory roles in transcription, replication and telomere maintenance and therefore have been identified as attractive drug targets.[1] Consequently, there is increasing interest in developing small molecules that can interact selectively with this topology over others. Metal complexes are one class of such compounds which have been intensively studied as G4 binders over the past two decades.[2,3] Our group has developed several families of metal complexes with high affinity and selectivity for quadruplexes.[4,5] One of the key features that makes metal complexes attractive as DNA binders is the possibility of easily fine-tuning their properties by changing the metal centre. This lecture will present an overview of recent findings in our laboratory where metal complexes have been designed to bind selectively to G4s and in doing so provide molecular tools to study these non-canonical DNA structures in cells.[6,7]









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Metal-based antibiotic drug candidates: how new structures lead towards new modes of action

Nils METZLER-NOLTE

Ruhr University Bochum, Universitätsstraße 150, 44797 Bochum, Germany
e-mail: nils.metzler-nolte@rub.de

Since the discovery of modern antibiotics such as the penicillins in the first half of the last century, bacterial infections that would have been fatal only 100 years ago can be successfully treated for a relatively small cost. On the other hand, resistance against many common antibiotics develops rapidly and in fact often quicker than novel antibiotics reach the market. Therefore, there is an urgent need for new classes of antibiotics, preferably with novel modes of action.

To match this need, metal-containing compounds hold particular promise.[1] In our group, we have successfully modified the activity of anti-microbial peptides (AMPs)[2] by metallocene substitution and we discovered bis(picolylamine)$Re(CO)_3$ derivatives as a novel lead structure for antibiotics.[3] Depending on the nature of the metallocene and its place within the peptide sequence, we could extend the activity of the AMPs to otherwise resistant strains.[4] In collaboration with microbiologists, the mechanism of action of our new metal-containing AMPs was elucidated.[5, 6]

In a related project, the antibacterial activity of a unique tri-metallic peptide derivative was discovered, and a new lead structure for anti-microbial activity was established.[7] These results will be related to earlier work in our group on medicinal organometallic chemistry in general.[8, 9]

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Supramolecular coordination complexes for biomedical applications: a new generation of drug delivery systems and beyond

Angela CASINI

School of Chemistry, Cardiff University, Park Place, CF10 3AT, Cardiff, United Kingdom
e-mail: casinia@cardiff.ac.uk

The biomedical application of discrete supramolecular coordination complexes (SCCs) is still an emergent field of study. However, pioneering studies over the last 10 years demonstrated the potential of SCCs as novel anticancer drugs, endowed with different mechanisms of action compared to classical small-molecules, often related to their peculiar molecular recognition properties.[1] In addition, the robustness and modular composition of supramolecular metal-based structures allows for an incorporation of different functionalities in the same system to enable imaging in cells via different modalities, but also active tumor targeting and stimuli-responsiveness. Thus, SCCs may constitute ideal scaffolds to develop multimodal *theranostic* agents. Of note, the host-guest chemistry of 3D self-assembled supramolecular structures – within the metallacages family - can also be exploited to design novel drug delivery systems for anticancer chemotherapeutics.[2] Here, we aim at summarizing the pivotal concepts in this fascinating research area, starting with the main synthetic and design principles and illustrating representative examples from our group while providing a critical discussion of the state-of-the-art. Certainly, the myriad of possible SCCs and their almost limitless modularity and tunability suggests that the biomedical applications of such complex chemical entities will continue along this already promising path.

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Exploiting a multi-targeted prodrug strategy to combat drawbacks associated with existing therapeutic regimes

Ziga UDE, [a] Reece KENNY, [b] Tadhg McGIVERN, [a] Andrew KELLETT, [b] Celine J. MARMION [a]

[a] Department of Chemistry, Royal College of Surgeons in Ireland, Dublin 2, Ireland
[b] School of Chemical Sciences and the National Institute for Cellular Biotechnology, Dublin City University, Dublin 9, Ireland
e-mail: cmarmion@rcsi.ie

Cancer remains a major global health burden despite significant advances in treatment regimens. Current drug treatments have major drawbacks including dose limiting toxic side effects which can lead to poor drug compliance as well as both intrinsic and acquired drug resistance. The development of safer and more effective drug treatments remains a key research goal. This presentation will endeavor to highlight how a multi-targeted approach may be exploited to bring forward a new class of therapeutic which may address both toxicity and/or drug resistance issues.

Inspired by the clinical success of (i) platinum-based drugs [1] and (ii) small molecule inhibitors of enzymes such as histone deacetylases (HDAC), we have developed innovative dual-targeting Pt-HDAC inhibitor conjugates for therapeutic exploitation.[2] Building on this research, we have more recently turned our attention to other redox active metal ions including Cu.[3] Changing the metal offers a number of advantages, not least the ability to change the chemistry and thus change the mode of action. Paul Ehrlich, the founding father of chemotherapy, pioneered the concept of the "magic bullet". Our endeavors to date to move a step closer to Ehrlich's vision will be presented – the presentation will include results related to our early Pt-HDAC inhibitor conjugates to provide context, and more recent results on other Pt-based and Cu-based complexes targeting not only DNA and HDAC enzymes but also other enzymes that are known to play key roles in cancer cell progression.

Acknowledgments: This material is supported by Science Foundation Ireland under Grant Nos. [11/RFP.1/CHS/3095], [12/TIDA/B2384] and [17/TIDA/5009], the RCSI Apjohn scholarship program and the European Regional Development fund (BioAT program). We also gratefully acknowledge Onxeo for funding.

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Host-guest interactions between biomolecules and metal compounds: a contribution from Computational Chemistry

Giampaolo BARONE

University of Palermo, Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Viale delle Scienze, Edificio 17, 90128, Palermo, Italy
e-mail: giampaolo.barone@unipa.it

Recent studies from our group have been focused on the binding of first row transition metal compounds, in particular of nickel(II), copper(II) and zinc(II), with DNA as biomolecular target, by the combination of experimental and computational approaches. [1-4] Atomic level details of the host-guest supramolecular complexes have been obtained through molecular dynamics (MD) simulations and/or by density functional theory/molecular mechanics (DFT/MM) calculations. The results obtained provided support for the interpretation of the binding mechanism and for design of new compounds with improved biomolecular selectivity, often related to their *in vitro* anticancer activity.

In collaboration with outstanding European research groups, such computational approach has been recently extended to the study of the role of metal compounds on the machinery of selected protein targets.

In this presentation, the advantages and limits of the proposed approaches will be discussed.

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Sequence-structure-stability relations in zinc hook, zinc clasp and altered zinc finger protein domains

Katarzyna KLUSKA, Olga KERBER, Anna KOCYŁA, Józef TRAN, Michał PADJASEK, Artur KRĘŻEL

Department of Chemical Biology, Faculty of Biotechnology, University of Wroclaw, Joliot-Curie 14a, 50-383 Wroclaw, Poland
e-mail: artur.krezel@uwr.edu.pl

Zinc proteins are an integral component of proteome of all domains of life. Zinc is the most widespread d-block metal element that serves multiple functions as catalytic co-factor, structural site and regulatory component. The questions how Zn(II)-dependent protein folds, how its dissociation occurs, and which factors modulate zinc protein affinity as well as stability remains not fully understood. In classical structural zinc sites of proteins Zn(II) ion is bound by various number of Cys and His residues in structurally diverse tetrahedral cores. They commonly demonstrate high Zn(II) affinity and compact architecture required for their structural functions such as macromolecules recognition or elevation of protein stability. Our recent studies demonstrate that multiple natural amino acid sequence variation of classical zinc fingers are responsible for affinity modulation and structural changes.[1] We found that zinc fingers with altered binding sites or substitution of Cys and His with Asp and Glu residues are not rare and are commonly encoded in mammalian genomes.[1] Our spectroscopic studies revealed that altered ZFs may adopt an open coordination geometry with one or two water molecules bound to a central metal ion.[1] Besides typical intraprotein zinc cores, proteins utilize Zn(II)-mediated intermolecular interactions to form different class of zinc cores responsible for the formation of large protein complexes, functioning of signal transduction or protein modulation. The mechanism how such interactions are form and what structural factors drive their thermodynamic and kinetic properties remains still not fully understood. The cytosolic C-terminal tail of the CD4 receptor forms a unique zinc-mediated interaction (zinc clasp) with an N-terminal fragment of non-receptor protein tyrosine kinase (Lck) critical for the initial stage of T cell activation. Recently, we rationally optimized the CD4 cytoplasmic tail to gain heterodimer selectivity with high femtomolar affinity towards Zn(II). Our study on the zinc clasp-based motif highlights the utilization of metal-driven interactions to develop reversible protein heterodimerization systems.[2] Efficient formation of the compactly folded zinc clasp scaffold providing stability, specificity, and reversibility has been used to show its potential in protein modification and purification. Another remarkable example of binding metal ions at the interface of protein complexes to form larger assembly is the Rad50 zinc hook domain, which is highly conserved and facilitates the Zn(II)-mediated homodimerization of Rad50 molecules.[3] The zinc hook is conserved in Rad50 homologs in all forms of life, from archaea to humans and even viruses. The destabilization of the zinc hook complex has a long-range allosteric effect on the several hundred angstroms distant globular domain of Rad50, affecting the DNA damage response, DNA recombination, telomere integrity and meiosis. The precise role of the zinc hook complex in these processes and how the stability of this complex

relates to its function are unknown. Our group's recent findings indicate that metal binding by the hook motif initiates a nucleation process resulting in rigid quaternary structure corresponding to superhelix.[3] These results point to conclusion that coiled-coil formation is dependent on the presence of Zn(II) coordination sphere and longer the helices the more stable protein-metal complex is being formed. Crystals obtained for globular domains showing two structurally and functionally distinct states, as well as zinc-hook model structure from *Pyrococcus furiosus* Rad50, alongside AFM images, paints a picture of two major conformational assemblies – open and closed form.[4] Our newest research data performed on zinc hook domain show that Zn(II) can be replace with Cd(II) causing overall conformational swap. These data is important in terms of exploring the significance of cadmium genotoxicity effects on zinc hook domains. Our group using a set of chemical strategies, spectroscopic and structural approaches aim to shed more light on the stability and function of divergent Zn(II) protein complexes and principles of their action [1-4].

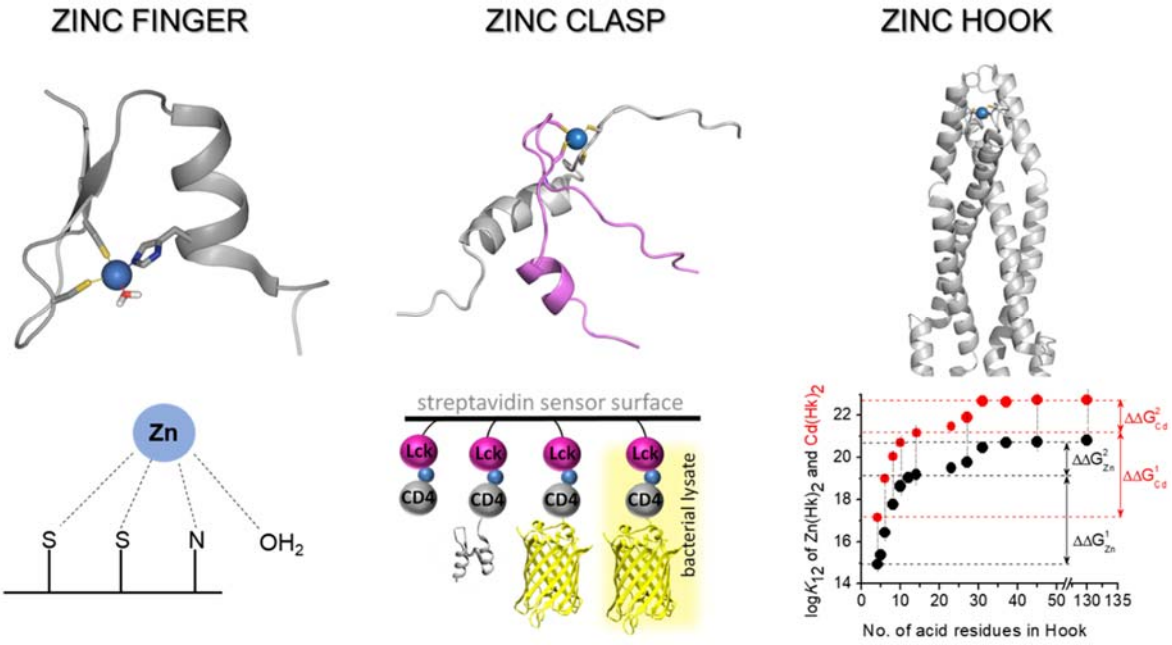

Figure 1. Graphical representation of various nonclassical zinc binding sites in proteins and their properties.

Acknowledgements: The study was sponsored by the National Science Centre of Poland, grant no. 2016/21/B/NZ1/02847 (to A. Krężel).

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Debrecen Hungary 11-14 June

The formation and reactivity of intermediates in iron-catalyzed oxidations: some insights from kinetic studies

Manuel G. BASALLOTE

Departamento de Ciencia de los Materiales e Ingeniería Metalúrgica, Facultad de Ciencias, Universidad de Cádiz, Campus Universitario Río San Pedro s/n, 11510 Puerto Real, Cádiz, Spain
e-mail: manuel.basallote@uca.es

In nature the selective oxidation of organic molecules is efficiently carried out under mild conditions by oxygenase metalloenzymes, which frequently contain one or more iron centers either of the heme or nonheme types. In contrast, current industrial oxidations are usually energy-demanding and lack of the desired selectivity. For those reasons, the development of useful bioinspired catalysts that mimic the behavior of oxygenases is highly desirable. To achieve this purpose a detailed knowledge of the reaction mechanisms involved in those oxidation processes is required. For the case of the oxygenases, the process goes through several high-valent oxygenated reaction intermediates, which finally perform oxidations through complex mechanisms involving hydrogen and oxygen atom transfers. In the last decades an increasing number of model complexes, both heme and nonheme, have been developed that carry out selective oxidations using intermediates that resemble those found in natural enzymes. One of the most interesting complexes reported in the last years is $[Fe^{II}(CF_3SO_3)_2(PyNMe_3)]$, which reacts with peracetic acid to generate a reaction intermediate that is kinetically competent for breaking strong C-H bonds of alkanes (up to c.a. 100 kcal mol^{-1}).[1] The present communication will focus on sequential cryo-stopped-flow kinetic studies carried out with this compound, especially on the processes leading to the formation of the active reaction intermediates and their reactivity against substrates.

The reaction of $[Fe^{II}(CF_3SO_3)_2(PyNMe_3)]$ with peracetic acid in acetonitrile solution at -35ºC occurs with complex spectral changes typical of processes with polyphasic kinetics (Figure 1). Those changes can be satisfactorily fitted to a model with three consecutive reaction steps using global fitting procedures.

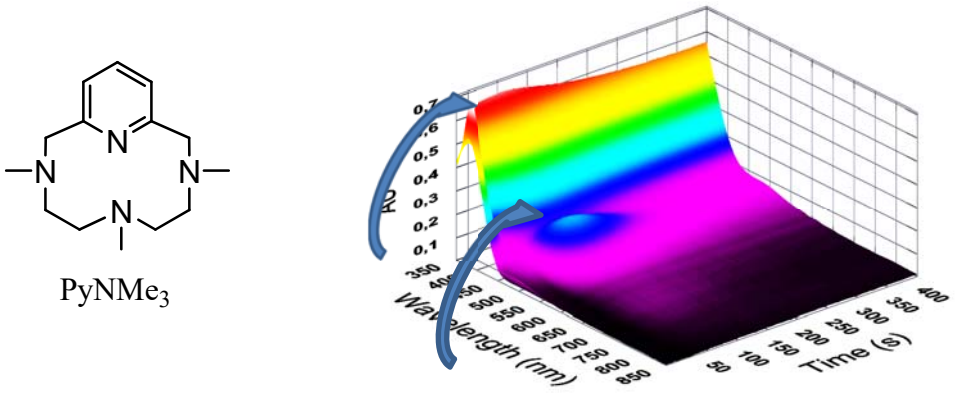

Figure 1. Molecular drawing of the $PyNMe_3$ ligand (left) and typical spectral changes for the reaction of $[Fe^{II}(CF_3SO_3)_2(PyNMe_3)]$ with peracetic acid in acetonitrile solution.

The first step is first order both on the Fe^{II} complex and the oxidant, and it leads to the formation of a Fe^{III} complex. More interestingly, the second resolved step leads to an intermediate I with an absorption band at 490 nm which, on the basis of additional characterization data, has been proposed to consist of an equilibrium mixture of two species: $[Fe^{III}(OOAc)(PyNMe_3)]^{2+}$ and $[Fe^{V}(O)(OAc)(PyNMe_3)]^{2+}$.[1] The kinetics of reaction of intermediate I with substrates was measured using sequential stopped-flow experiments in which the intermediate is generated by reaction of the Fe^{II} complex with the oxidant, and when I reaches its maximum concentration the solution containing the intermediate is mixed with the substrate. In this way, it could be established that those reactions are first order both in the intermediate and the substrate, the second order rate constants showing an inverse kinetic isotope effect and an inverse dependence with the strength of the activated C-H bond, features typical of hydrogen atom processes.

Intermediate I is also very efficient in oxygen atom transfers to olefins, forming epoxides with stereoretention.[2] Sequential stopped-flow experiments revealed that I is the fastest OAT agent described to date, and also allowed determining the impact of the electronic and steric properties of the substrate on the reaction rate. Importantly, the relative reactivity with different olefins determined for the catalytic oxidations could be reproduced by kinetic studies, thus showing that I is the actual active species responsible for epoxidations.

On the other hand, the reaction of $[Fe^{II}(CF_3SO_3)_2(PyNMe_3)]$ with H_2O_2 at low temperatures leads to formation of an $[Fe^{III}(OOH)(MeCN)(PyNMe_3)]^{2+}$ intermediate.[3] Kinetic studies showed that addition of different substrates after maximum formation of the $Fe^{III}(OOH)$ intermediate does not lead to changes in the rate of disappearance of the intermediate, which indicates that this species is not kinetically competent to perform their oxidation. However, addition of acid causes its transformation into a much more reactive compound towards organic substrates that is capable of oxidizing unactivated C-H bonds with high stereospecificity. Combined stopped-flow and theoretical studies support the occurrence of an acid-assisted heterolytic cleavage of the O-O bond to form a putative strongly oxidizing oxoiron(V) species.

Acknowledgements: Financial support by the Spanish Ministry of Science and FEDER funds from the E.U. (grant CTQ2015-65707-C2-2-P) is gratefully acknowledged.

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International Symposium on Metal Complexes 2019
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Recognition of the proper metal ion: how does the metalloregulatory protein CueR discriminate metal ions with similar coordination properties?

Ria K. BALOGH, [a] Béla GYURCSIK, [a] Dániel SZUNYOGH, [a] Éva HUNYADI-GULYÁS, [b] Peter W. THULSTRUP, [c] Niels Johan CHRISTENSEN, [c] Monika STACHURA, [d] Lars HEMMINGSEN, [c] Attila JANCSÓ [a]

[a] Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720 Szeged, Hungary
[b] Laboratory of Proteomics, Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Temesvári krt. 62, H-6726 Szeged, Hungary
[c] Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark
[d] TRIUMF, 4004 Wesbrook Mall, V6T 2A3 Vancouver, BC, Canada
e-mail: jancso@chem.u-szeged.hu

Metalloregulatory proteins are transcription factors that control metal ion homeostasis and resistance in bacteria by regulating the production of proteins participating in metal ion transport/uptake/removal processes.[1] These proteins sensitively respond to the change in the level of the regulated metal ions via metal ion coordination to a specific region of the protein. A fascinating feature of metalloregulators is their ability to select a specific, or a limited number of metal ions (the so-called "cognate" ions). The amino acid sequence of the metal binding domain clearly plays a role in this metal ion selectivity, nevertheless, it is also widely accepted that metal ion induced changes in the conformation of metalloregulators allosterically influence the protein-DNA interaction and thus initiate or inhibit the transcription process.[1,2]

The copper efflux regulator CueR, a member of the broad MerR protein family, represents a nice example of such systems. This protein selectively activates transcription in the presence of the monovalent transition metal ions Cu^+, Ag^+ and Au^+ wile remains inactive for Hg^{2+} and Zn^{2+}.[3] The former ions were demonstrated to be bound by two cysteine residues located in a loop near the *C*-terminus, restricting the metal ions to a linear coordination environment.[3] While the binding of these monovalent ions to CueR and the structural impacts of metal ion coordination both for the protein alone and for the protein-DNA complex has been thoroughly discussed,[2,3] it is still unclear why Hg^{2+}, a metal ion with similar coordination preferences to Cu^+, is not recognized by the protein.

Besides providing a brief summary of what was unraveled so far about the structure and function of this protein, we are going to present our efforts for exploring the molecular details of the metal ion recognition process and the possible reasons for the discrimination of Hg^{2+} ions. Metal ion binding studies with peptide models, comprising the metal ion binding loop of the protein, and Ag^+, Zn^{2+}, Cd^{2+} and Hg^{2+} ions, demonstrating fundamental differences in the coordination behavior of Ag^+ and the divalent ions, will be discussed.[4,5,6] Experiments performed with *E.coli* CueR and its carefully planned mutants, allowing to elaborate on the effects of pH, metal ion to protein ratio, but most importantly on the possible role of metal ion binding amino acids outside the loop region in the protein function, will also be presented.

Acknowledgements: This work was supported by the Hungarian National Research, Development and Innovation Office-NKFIH through project GINOP-2.3.2-15-2016-00038 and grant No. K_16/120130.

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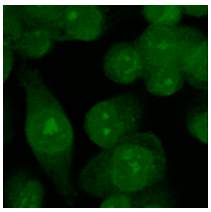
Highly thermodynamic and kinetically stable Ln^{3+} and Cu^{2+} azamacrocyclic chelates tailored for diagnosis and therapy: full control of the ligand design makes the difference!

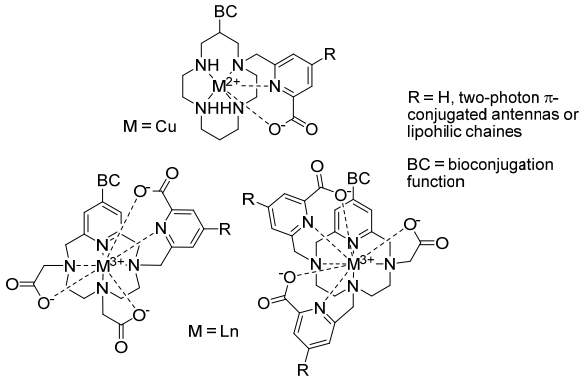
Raphaël TRIPIER

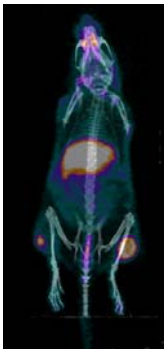
Université de Bretagne Occidentale, UMR-CNRS 6521, IBSAM, 6 Avenue Victor le Gorgeu, C.S. 93837, 29238 Brest Cedex 3, France.
e-mail: raphael.tripier@univ-brest.fr

Lanthanide(III) and transition metal ions belong to the large panel of cations strongly complexed by tetraazacycloalkanes, presenting sufficient coordination sites. The obtained chelates are then widely used for several applications ranging from diagnostic (MR, PET or Optical Imaging) or therapy (Radiotherapy, PDT…) depending on the nature of the central metal ion. However, even if current chelates are already well-performing for such uses, the room for improvement is still great, both to design specific agents for a specific use and to develop agents that allow the combination of different modalities.

We recently reported picolinate *N*-functionalized tetraazamacrocycles presenting astonishing coordination properties with Ln(III) and Cu(II) cations, leading to new potential chelates for both imaging and therapeutic applications. Especially highlighted is that the full control of the regiospecific *N*-functionalization of the macrocycles governs not only the final kinetic and thermodynamic properties of the chelates but also their magnetic or photophysical characteristics in case of Ln(III). These physicochemical properties will be discussed and first examples of PET imaging or two-photon absorption microscopy explored [1-3].


2γ imaging




PET imaging

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New approaches to optical imaging with luminescent lanthanides

Alexia COSBY, Kirsten MARTIN, Eszter BOROS

Department of Chemistry, Stony Brook University, 100 Nicolls Road, Stony Brook, NY 11790 (USA)
e-mail: eszter.boros@stonybrook.edu

Lanthanide-based luminescence represents an attractive alternative to conventional organic chromophores used for in vitro and in vivo imaging applications. The unique electronic configuration of trivalent lanthanides gives rise to sharp emission bands independent of the coordinative environment of the metal with maxima between 490-1500 nm. Due to the Laporte-forbidden nature of *f-f* transitions, aromatic chromophores ('antennas') are required for efficient excitation of metal-based luminescence after intersystem crossing and energy transfer. The antenna must possess triplet state energy comparable to lanthanide acceptor states and allow efficient energy transfer with excitation wavelengths, which is typically achieved with short-wavelength excitation between 250-400 nm. Because of the large difference in antenna excitation and lanthanide emission wavelength, the effective stokes-shift is conveniently large; however, external high-energy excitation is not feasible *in vivo* due to absorption of short wavelength excitation by surrounding biological media. This renders luminescent lanthanides not suitable for *in vivo* applications.

We have developed a system that addresses this shortcoming by efficient *in situ* excitation of terbium and europium complexes with Cherenkov radiation. Cherenkov radiation (CR) is emission of short wavelength light with a maximum intensity below 400 nm, generated by $\beta^{+/-}$ emitting isotopes in dielectric media. We have identified CL as an ideal, inter- and intramolecular excitation source for lanthanide antennas. [1] In this talk, we will present our recent progress on developing lanthanide based CRET probes for high-throughput quantum yield determination of lanthanide complexes, lanthanide-emission based multiplexing and targeted in vitro imaging.

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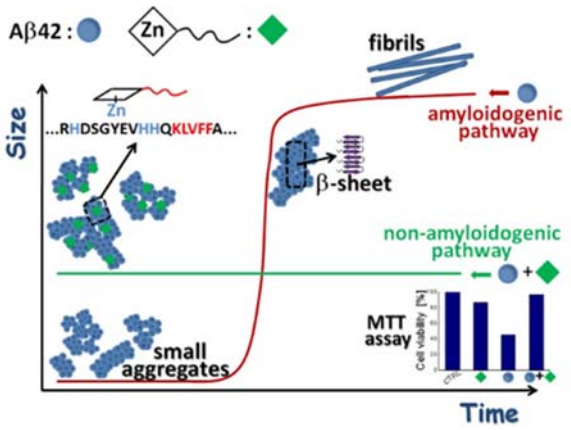
The use of peptides for the management of Amyloid β: metal complexes, fibril formation and neuroprotection

Giuseppe PAPPALARDO

CNR-Institute of Crystallography,Via P. Gaifami 18, 95126, Catania Italy
e-mail: giuseppe.pappalardo@cnr.it

Due to aging populations, the incidence of Alzheimer's disease (AD) is rapidly increasing worldwide. It is estimated that more than 100 million people will suffer from AD by 2050. Global society costs will inexorably raise and especially developed countries are going to face serious AD related problems within a few decades time [1]. Such a scenario outlines an urgent need to better understand, diagnose and treat AD. There is a number of emerging strategies aimed at developing tools to early diagnose and treat AD. Specifically, peptide conjugates as theranostic agents have attracted much attention due to their synthetic accessibility and high degree of specific binding. Chemical strategies for the design and synthesis of multifunctional peptides are now available and suitable biologically active moieties can be easily introduced into an existing peptide backbone. One very demanding goal, when designing these compounds, is the development of highly specific molecules. For this purpose, scientists have been studying the physiological role and molecular features of monomeric amyloid β (Aβ) in order to generate peptide systems for therapeutic applications. Currently, the tendency of Aβ peptide to self-assemble into soluble oligomers is known as a key pathogenic event leading to the interruption of synapses and brain degeneration [2]. Thus the stabilization of the monomeric form of Aβ, whose functional role in the brain is now established, may represent an appealing therapeutic target [3]. Furthermore, targeting neurotoxic Aβ oligomers can help recognize the disease at an early stage or denoting a further potential therapeutic approach. Current research efforts in this area focus on the construction of di-functional systems capable of synergic and/or additive actions to counteract the adverse effects of Aβ aggregated forms. Such molecules generally consist of a known Aβ recognition group combined to other moieties able to explicate additional or complementary functions, including antioxidant, metal chelation or aggregates disassembly [4-6]. In this talk, recent applications of peptide-based inhibitors of Aβ aggregation will be discussed. After a brief introduction of the "state of the art" in this field, the discussion will focus on the interaction of selected peptide-conjugate systems with Aβ, their hypothetical mechanism of action and their neuroprotective action.



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Aquation of equatorial ligands of Pt(IV) complexes under physiological conditions

Christian R. KOWOL, [a), c)] **Alexander KASTNER,** [a)] **Isabella POETSCH,** [b)] **Petra HEFFETER,** [b), c)] **Bernhard K. KEPPLER** [a), c)]

[a)] *Institute of Inorganic Chemistry, Faculty of Chemistry, University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria*
[b)] *Institute of Cancer Research, Medical University of Vienna, Borschkegasse 8a, A-1090 Vienna, Austria*
[c)] *Research Cluster "Translational Cancer Therapy Research", Vienna, Austria.*
e-mail: christian.kowol@univie.ac.at

Platinum-based anticancer drugs are still of very high importance in the daily clinical routine and their impressive synergistic activity with some checkpoint inhibitor immuno-therapeutics[1] will guarantee their significance also in the future. However, due to the severe side effects of platinum(II) drugs, the current research strongly focuses on platinum(IV) prodrugs which have to be activated by reduction to the active platinum(II) complexes[2].

We investigated the aqueous stability of a series of biscarboxylato platinum(IV) compounds under physiologically relevant conditions. Although platinum(IV) complexes are considered as kinetically inert, especially the oxaliplatin-core and satraplatin derivatives revealed fast hydrolysis in equatorial position (even in cell culture medium and serum). For [Pt(IV)(DACH)oxalate(OAc)$_2$] (DACH = (1*R*,2*R*)-(−)-1,2-diaminocyclohexane) the formed hydrolysis products could also be synthesized and in detail characterized. Notably, they showed strong differences in their reduction kinetics, the crucial parameter for activation of platinum(IV) drugs. Furthermore, also the anticancer potential of the compounds in cell culture was investigated.

This discovery that intact platinum(IV) complexes can hydrolyze at equatorial position, contradicts the dogma on the general kinetic inertness of platinum(IV) compounds and needs to be considered in the future screening and design of novel platinum(IV) anticancer drugs.

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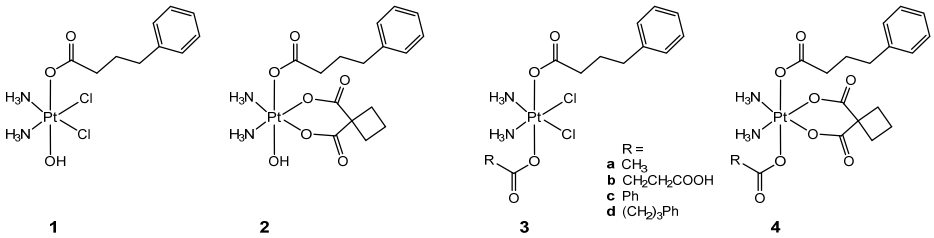
Platinum(IV) pro-drugs with an axial HDAC inhibitor

Andrea ERXLEBEN, [a] **Awatif ALMOTAIRY,** [a] **Orla HOWE,**[b] **Michael DEVEREUX,** [b] **Diego MONTAGNER** [c]

[a] *School of Chemistry, NUI Galway, University Road, H91 TK33, Ireland*
[b] *School of Biological & Health Sciences, Technological University Dublin, City Campus, Kevin Street, D08 X622, Dublin, Ireland*
[c] *Department of Chemistry, Maynooth University, Maynooth, Ireland*
e-mail: andrea.erxleben@nuigalway.ie

Cisplatin is routinely used in the treatment of testicular, head and neck, bladder and ovarian cancer. However, the tremendous clinical success of cisplatin is somewhat limited due to the problem of inherent and acquired resistance towards platinum chemotherapy. Cisplatin resistance is a consequence of genetic and epigenetic changes that affect cellular accumulation or result in enhanced DNA repair, enhanced DNA damage tolerance and late apoptotic response. DNA methylation and histone methylation or acetylation are the most important types of epigenetic alterations. Histone acetylation and deacetylation regulate gene expression by opening and closing the chromatin and are catalyzed by histone acetyltransferase and histone deacetylase (HDAC). Histone acetylation plays a fundamental role in DNA repair and has also been linked to the development of drug resistance.

In this lecture our recent work on platinum(IV) pro-drugs with the HDAC inhibitor phenylbutyrate in axial position will be presented [1,2]. Out of the series of complexes shown in Scheme 1 complex **3c** was found to be highly cytotoxic towards cisplatin-sensitive and cisplatin-resistant ovarian cancer cells with IC_{50} values approximately 40-fold and 16-fold lower than cisplatin in A2780 and A2780cis cells. The results of detailed mechanistic studies including (i) activation of the pro-drugs, (ii) reaction with cellular DNA, (iii) HDAC inhibition, (iv) DNA damage by immuno-detection of γ-H2AX foci, (v) cellular ROS induction and (vi) induction of apoptosis will be discussed.



Scheme 1. Pt(IV) pro-drugs for cisplatin and carboplatin with an axial HDAC inhibitor ligand.

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International Symposium on Metal Complexes 2019
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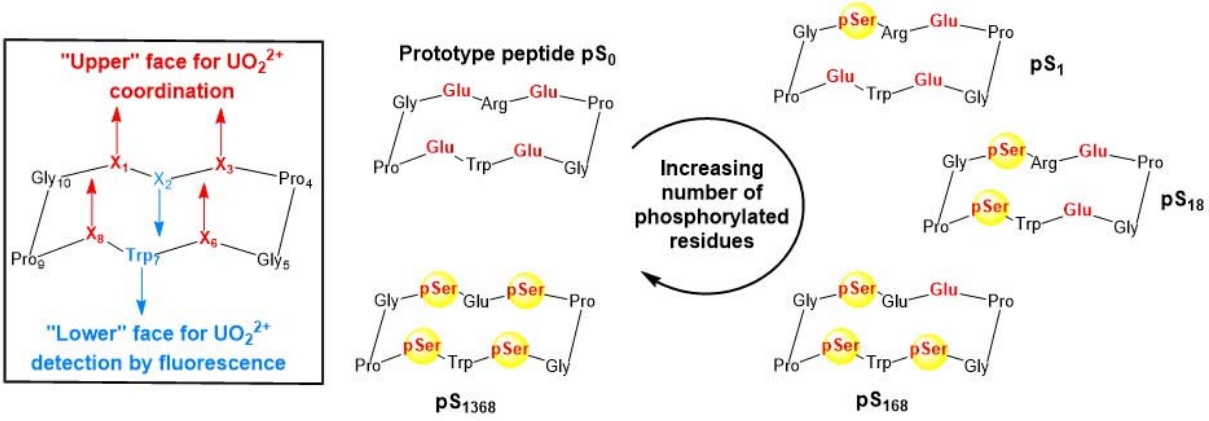
Uranyl speciation with phosphate-rich biomimetic peptides predicts high affinity uranyl binding sites in phosphoproteins

Fanny A. LAPORTE, [a] Colette LEBRUN, [a] Claude VIDAUD, [b]
Pascale DELANGLE [a]

[a] INAC SyMMES, Université Grenoble Alpes, CEA, CNRS, F-38000 Grenoble, France
[b] CEA, Fundamental Research Division, Biosciences and Biotechnologies Institute of Aix-Marseille, 30207 Bagnols sur Céze, France
e-mail: pascale.delangle@cea.fr

Uranium is a natural element widely found in the environment, due to both natural occurrence in mineral ores or in sea water and industrial applications. The production of nuclear energy uses enriched uranium in ^{235}U for nuclear fission. Despite its ubiquitous distribution, uranium has no essential role in living organisms and presents radiological and chemical toxicities. Despite significant recent advances in the field, there is still a serious lack of knowledge about the molecular interactions responsible for uranium toxicity. The underlying mechanisms need to be unravelled to predict the effect of uranium on living organisms and also to help in designing efficient detoxification agents, to be used in case of dirty bombs or accidental release of uranium in the environment.

Peptides are simple models of proteins that help understanding the interactions of metals with biological molecules, relevant to their regulation and toxicity.[1] Indeed, short peptide sequences are simple models of metal-binding sites in proteins that provide structural and thermodynamic data, which are always not accessible directly with large biological molecules. Such a biomimetic strategy was applied for uranium with constrained peptides, in our laboratory. This metal most stable form *in vivo* is the uranyl cation, UO_2^{2+}, which prefers four to six oxygen donors in its equatorial plane, perpendicular to O-U-O bonds. The cyclic constrained peptide scaffolds shown in scheme 1 orient four metal-coordinating groups found in proteins toward the equatorial plane of the uranyl cation and revealed to be highly effective uranyl-binding peptides.[2]



Scheme 1. Uranyl-binding pre-organized cyclic peptides.

A combination of peptide synthesis, analytical chemistry and spectroscopies allowed us to correlate the amino acid sequence to the stability of the uranyl complexes. Uranium-coordinating amino acids with side-chains containing oxygen donors, such as aspartic acids, glutamic acids and phosphoserines were inserted in the cyclic peptide sequences. The largest uranyl complexes stabilities were obtained when four coordinating amino acids were converging to the uranyl equatorial plane.[2] Importantly, phosphate groups significantly enhance the affinity of the biomimetic peptides for uranyl, which strongly supports the importance of phosphoamino acids in uranyl binding in proteins.[3-4]

The two hyperphosphorylated cyclic peptides **pS$_{168}$** and **pS$_{1368}$** containing up to 4 phosphoserine residues over the ten amino acids present in the sequences were synthesized with an original all on-support synthetic pathway, involving post-phosphorylation of serines. Importantly, increasing the number of pSer residues up to 4 in the cyclodecapeptide scaffolds allows to reach an affinity constant for UO_2^{2+} as large as that reported for the hyperphosphorylated uranyl target protein osteopontin at physiological pH.[6-7]

The phosphate-rich peptide **pS$_{1368}$** can thus be considered as a relevant model of UO_2^{2+} coordination in this intrinsically disordered protein, which can wrap around the metal ion to gather 4 phosphate groups in the UO_2^{2+} coordination sphere. These model hyperphosphorylated peptides are also good starting structures for UO_2^{2+} selective complexation since they are highly selective for UO_2^{2+} with respect to the endogenous Ca^{2+} cation.

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Tailoring of catalysts to the needs of aqueous organometallic catalysis: coordination chemistry, solution speciation and catalytic properties of water soluble transition metal *salan* complexes

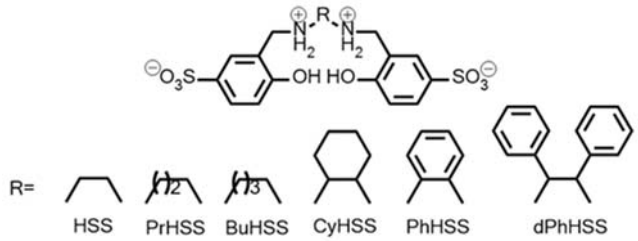
Szilvia BUNDA, [a] Norbert LIHI, [b] Antal UDVARDY, [a] Ferenc JOÓ [a,b]

[a] *University of Debrecen, Department of Physical Chemistry, 1 Egyetem tér, 4032, Debrecen, Hungary*

[b] *MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group, 1 Egyetem tér, 4032, Debrecen, Hungary*
e-mail: joo.ferenc@science.unideb.hu

The increasing pressure on chemistry to diminish its negative environmental impact and to introduce less polluting (green) technologies requires steady design and implementation of new procedures, of which selective catalytic reactions stand out due to their efficiency and low amounts of byproducts. Soluble catalysts often show outstanding activities and selectivities, however, their recovery and repeated use requires special operations. Homogeneous catalysis by transition metal complexes in aqueous solutions, as well as aqueous-organic biphasic organometallic catalysis have become important methods enabling the use of such catalysts in important synthetic procedures (hydrogenation, hydroformylation, C-C couplings, redox isomerization, alkene metathesis, etc.).[1, 2] Investigations into the mechanism of a given synthetic transformation rely heavily on identification and on establishing the fate of reaction intermediates along the catalytic cycle. Nevertheless, identification of the various possible complex species and determination of their concentration distributions in aqueous solutions of the catalysts as a function of important parameters (such as e.g. the pH) with the use of well-established methods of coordination chemistry, are practically missing from the armoury of catalysis research.

For some time now, we have been interested in the use of water-soluble transition metal complexes with hydrogenated salan-type ligands (salans) sulfonated in their aromatic rings. A series of such ligands were synthetized in the reactions of salicylaldehyde and various diamines having different bridging units between the amine groups, followed by hydrogenation of the obtained imines with $NaBH_4$. Finally, sulfonation of the resulting salans yielded the water-soluble sulfosalans used for complexation studies (Scheme 1). [3]



Scheme 1. Sulfosalan ligands used in this study.

Complex formation between Ni^{2+} and Cu^{2+} and the various sulfosalans took place sufficiently fast to allow the direct use of pH-potentiometry. The ligand protonation constants and the stability constants of their respective Ni^{2+} and Cu^{2+} complexes were determined in the $3 < pH < 10$ range. The same solutions were also characterized by uv-vis spectroscopy. EPR spectra of the CuL complexes were recorded and showed characteristic changes in the coordination geometry with the increase of the bridging alkyl chain length between the two nitrogens in the ligand. A similar study was undertaken with Pd^{2+} and sulfosalans, too.

Pd^{2+}-complexes of the above sulfosalans were successfully applied for C-C bond formation reactions such as the Sonogashira [4] and Suzuki-Miyaura [5] cross-couplings; Na_2[Pd(HSS)] and Na_2[Pd(BuHSS)] were primarily studied. In addition, Na_2[Pd(HSS)] catalyzed efficiently the hydrogenation of aldehydes,[6] and the hydrogenation and redox isomerization of allylic alcohols.[3] Na_2[Ni(HSS)] showed low activity in Suzuki-Miyaura couplings and Na_2[Cu(HSS)] did not catalyze the same reaction. These findings will be discussed in the light of the coordination chemistry of the metal complexes containing such sulfosalan ligands.

Acknowledgements: The research was supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004.

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International Symposium on Metal Complexes 2019
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The new era of theranostics radiopharmaceuticals: A challenge to metal-chelate complex chemistry

Frank ROESCH

Institute of Nuclear Chemistry, Fritz-Strassmann-Weg 2, Johannes Gutenberg University, 55128 Mainz, Germany
e-mail: froesch@uni-mainz.de

The recent development of radiometal-based radiopharmaceuticals for diagnosis and treatment of tumors is attributed by the wording THERANOSTICS. Radiometal-based theranostics are increasingly used in precision oncology and personalized medicine. The diagnostic version of the radio-theranostic is applied mainly in PET/CT to identify the disease and to quantify its expression for a single patient. Here, positron-emitting radionuclides such as ^{68}Ga, ^{44}Sc and ^{64}Cu are utilized. The theranostics version substitutes these radiometals by others, which emit β^- electrons or alpha particles. Prominent examples are ^{177}Lu and ^{90}Y for β^- emitters and ^{225}Ac and ^{213}Bi for alpha emitters.

The design of a theranostics compound is a covalently attached molecular targeting vector to a bifunctional chelate, which in turn allows to complex the radiometal. The ideal theranostics compound should allow radiolabeling the same bifunctional chelate with all of those radiometals. Because the radiometals differ in their coordination chemistry, the development of the "ideal chelator" is of great importance. Until now, only the macrocyclic DOTA derivatives serve as a general platform – yet DOTA-conjugated theranostics must be radiolabeled at elevated temperatures close to 100°C.

The presentation will introduce recent developments towards the development of alternative chelators, which allow radiolabeling at room temperature for selected radionuclides. The strategy is to allow for instant kit-type labelling technologies and to open access to labelling temperature-sensitive theranostics.

International Symposium on Metal Complexes 2019
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Photoinduced electron transfer in luminescent lanthanide complexes

Daniel KOVACS, [a] Emilie MATHIEU, [a] Salauat KIRAEV, [a] K. Eszter BORBAS [a]

[a] Uppsala University, Department of Chemistry, Ångström Laboratory, Box 523, 75120, Uppsala, Sweden
e-mail: eszter.borbas@kemi.uu.se

Trivalent lanthanide (Ln(III))-based emitters and now established in numerous areas ranging from lasers to luminescent cellular markers.[1] Ln(III) luminescence arises from Laporte-forbidden f-f transitions, which makes direct excitation inefficient. Therefore, sensitization is often performed through a light-harvesting antenna, usually an organic chromophore, that after excitation can transfer energy to the Ln(III).[1] Energy transfer is a complicated process, furthermore, the antenna and Ln(III) excited states are susceptible to quenching via multiple processes.[2] For this reason, the development of bright emitters requires extensive optimization.

Molecular emitters, i.e. well-defined, small-molecular, typically monometallic complexes are attractive for a number of reasons, such as complete synthetic control over well-defined structures, and minimal batch-to-batch variations in the physico-chemical properties. Such entities enable the in-depth investigation of photophysical processes using a wide range of techniques, including the probing of structure-activity relationships through systematic structural variations.

We have recently reported the synthesis and photophysical characterization of a focused library of luminescent Ln(III) complexes carrying coumarin or carbostyril sensitizing antennae.[3] In the course of this work we have identified photoinduced electron transfer (PeT) as a prominent quenching mechanism. PeT was active in most of the Eu(III) complexes, and was found feasible for Sm(III), and potentially even Dy(III) and Nd(III) complexes. In these species, PeT is most likely detrimental to luminescence. In Yb(III) complexes bearing light-harvesting antennae, however, a sensitization mechanism based on stepwise energy transfer is well known.[4] This sensitization mechanism was likely active in our emitters, too.

To evaluate the contribution of PeT to the quenching of Ln(III) luminescence, we have synthesized complexes shown in Figure 1. The complexes were characterized using a combination of chemical (NMR spectroscopy, X-ray crystallography), electrochemical (CV) and photophysical methods. We found that the stabilization of the Eu(III) oxidation state, i.e. the shifting of the Eu(II)/Eu(III) redox potential to more negative values by encapsulation into a suitable ligand framework decreased PeT quenching, and a recovery of the Ln(III) emission.

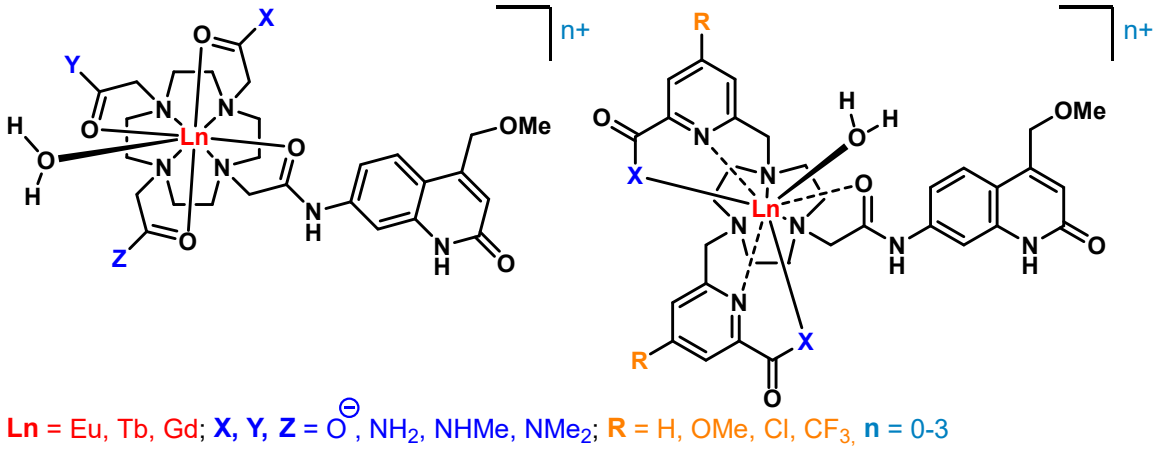

Figure 1. Ln(III) complexes prepared in this work. Gd(III) analogues serve as non-emissive reference compounds, and Tb(III) as emissive, non-redox active analogues.

Acknowledgements: This work was supported the Swedish Research Council (project grant to K.E.B.) and the Carl Tryggers foundation (post-doctoral fellowship to E.M.).

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International Symposium on Metal Complexes 2019
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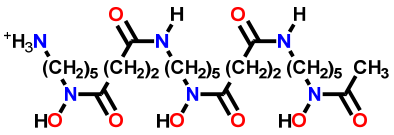
Solution studies of hydroxamic siderophores: from the chelation of actinides to the development of promising nuclear imaging agents

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
e-mail: michel.meyer@u-bourgogne.fr

Siderophores are ubiquitous, high-affinity iron(III) chelators excreted by virtually all micro-organisms under iron-stress conditions. Their primary biological role is to supply them with iron, an essential nutrient and growth factor. As a mean to circumvent the extremely low bioavailability of this element at physiological pH, siderophores react with ferric (oxo)hydroxides and form thereby water-soluble complexes, which are transported across the cell membranes according to an energy-driven mechanism involving specific outer-membrane uptake receptors. Hydroxamates are common bidentate chelating groups found in many siderophores, such as the emblematic desferrioxamine B (DFB).



Desferrioxamine B

As their concentration in soils is typically in the µg/kg range, these compounds might significantly increase the solubility, migration rate, and bioavailability of highly toxic actinides in case of environmental contamination. In relation to the management and remediation of contaminated fields or the disposal of nuclear wastes in geological repositories, it is of outmost importance to gain a deeper understanding of the coordination chemistry of f-elements by siderophores and related chelators [1].

After addressing the conformational and UO_2^{2+} binding properties of linear and cyclic monohydroxamic acids [2,3], the speciation of the uranyl/DFB system as inferred from potentiometric, visible spectrophotometric, and affinity capillary electrophoretic measurements will be discussed. We will also show how X-ray absorption, Raman, and ^{17}O NMR spectroscopies can provide structural information about the chemical environment around the uranyl cation in the different species prevailing in solution. Uranium and plutonium dissolution tests performed on naturally (pitchblende) or artificially contaminated soils will be presented too.

Finally, the development of a new β^+ radiotracer for position emission tomography (PET) will be reported. Currently, the most common chelator to label antibodies with ^{89}Zr for immunoPET is DFB. However, several preclinical studies revealed that the impaired in vivo stability of the ^{89}Zr-DFB complex results in the release of ^{89}Zr and subsequent accumulation in mineral bone tissue. In vitro and in vivo data of our novel biomimetic DFB analog, which allows octacoordination of the radionuclide, show markedly improved stability over the "gold standard" DFB, suggesting that the corresponding bioconjugates are highly promising candidates to become the new clinically used standard for ^{89}Zr immunoPET.

Acknowledgments: The Centre National de la Recherche Scientifique (CNRS), the Université de Bourgogne (BQR program), the Conseil Régional de Bourgogne (CRB, program PARI II CDEA), the European Regional Development Fund (FEDER), the program "Défi NEEDS Environnement" (projects ACTISOL and PiRATE), and the Horizon 2020 funded project TRISTAN are gratefully acknowledged for their financial support.

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International Symposium on Metal Complexes 2019
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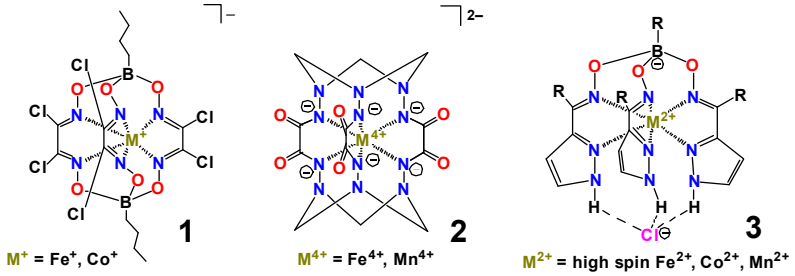
Encapsulation phenomenon: unusual behavior of an encapsulated metal ion in confined space of the designed caging ligands

Yan VOLOSHIN

Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky prosp. 31, Moscow, 119991, Russia
Gubkin Russian State University of Oil and Gas (National Research University) Leninsky prosp. 65, Moscow, 119991, Russia
e-mail: voloshin@ineos.ac.ru, voloshin@igic.ac.ru

The molecular design of transition metal (pseudo-)clathrochelates [1] for accession of unusually high and low oxidation numbers and rare spin states of their (pseudo-) encapsulated metal ions is based on the use of electron-withdrawing or electron-donating substituents in the ribbed chelate fragments of a quasiaromatic caging (Scheme, **1** and **2**) or that of the pseudoencapsulating hydrogen-bonded tripodal (Scheme, **3**) ligands. Hexahalogenoclathrochelate [2,3] and tris-oxalodihydrazide macrobicyclic [4] ligands have been used for the stabilization of metal(I) (Scheme, **1**) and metal(IV) (Scheme, **2**) complexes, respectively. The former are recognized as the efficient electro(pre)catalysts for hydrogen production from acidic media [1,3], while efficient visible light-driven water oxidation catalysed by an iron(IV) clathrochelate is recently reported [5].



Scheme

The designed tris-pyrazoleoximate cobalt(II) pseudoclathrochelates (Scheme, **3**) possess the largest Co-based axial anisotropy of magnetic susceptibility, which results from their unusual TP geometry and translates into large negative values of the zero-field splitting energy, D. These large D values are high enough to promote paramagnetic pseudocontact shifts at a distance beyond 2 nm; thus, paving the way towards the development of prospective paramagnetic probes and single-ion molecular magnets [6].

Acknowledgments: This work was supported by RSF (grant 17-13-01468) and RFBR (grant 18-03-00675).

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International Symposium on Metal Complexes 2019
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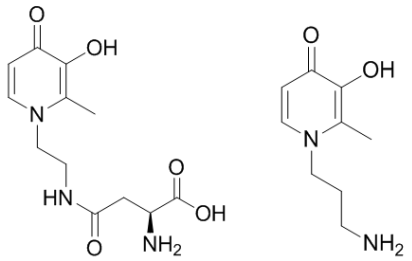
Thermodynamic parameters for the M^{2+}/bifunctional 3-hydroxy-4-pyridinones complex formation at different experimental conditions

Anna IRTO, [a] Paola CARDIANO, [a] Karam CHAND, [b] Rosalia Maria CIGALA, [a] Francesco CREA, [a] Concetta DE STEFANO, [a] Giuseppe GATTUSO, [a] Silvio SAMMARTANO, [a] Maria Amélia SANTOS [b]

[a] Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche e Ambientali, Università di Messina, Viale F. Stagno d'Alcontres, 31 – 98166 Messina, Italy
[b] Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovísco Pais 1, 1049-001 Lisboa, Portugal,
e-mail: airto@unime.it

This contribution is the result of a speciation study of two bifunctional 3-hydroxy-4-pyridinones (*see* **Figure 1**) in aqueous solution and in the presence of biological relevant divalent metal cations, at different temperatures and ionic strengths.



L1 *L2*

Figure 1. Structures of the 3-hydroxy-4-pyridinones under study.

The 3-hydroxy-4-pyridinones are a family of compounds developed in view of applications in metal chelation therapy and for the detoxification of human body from *hard* metal cations (*e.g.* Al^{3+}, Fe^{3+}). They represent a good alternative to the use of Deferoxamine (DFB),[1] due to their effectiveness at physiological pH range as well as in all the biological conditions, low costs, oral activity and the absence of side effects. These bidentate ligands are derivatives of 1,2-dimethyl-3-hydroxy-4-pyridinone (commercially known as deferiprone, DFP) featuring an aromatoid *N*-heterocyclic ring and a hydroxyl and a ketone group in *ortho* position, which confer them a high binding ability toward metal cations such as M^{2+} and M^{3+}. [3-6] Although this family of metal chelators proved an inherently high affinity towards *hard*-metal cations, such as Fe^{3+} and Al^{3+}, it appeared also important to study its interaction with other biological relevant M^{2+}, in order to assure that along with their sequestering role of those *hard* M^{3+} there is no significant depletion of important M^{2+} bio-metal cations.

The acid-base properties of the ligands, previously studied at $I = 0.15$ mol L^{-1} in $NaCl_{(aq)}$ and $T = 298.15$ K and 310.15 K,[5] were further investigated by potentiometric and UV-Vis spectrophotometric measurements, carried out at the same I and $T = 288.15$ K and at $0.50 \leq I$ / mol $L^{-1} \leq 1.00$ and $T = 298.15$ K. Furthermore, their binding ability towards Ca^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+} was studied at $0.15 \leq I$ / mol $L^{-1} \leq 1.00$ in $NaCl_{(aq)}$ and $288.15 \leq T$ / K ≤ 310.15 using the

same analytical techniques employed for the acid-base properties investigation. The dependence of the determined protonation and stability constants on ionic strength and temperature was modeled by means of an extended-type Debye-Hückel and the Van't Hoff equations, respectively. ^{1}H NMR spectroscopic titrations and computational studies were also performed to gain information on the Zn^{2+}-ligands coordination-mode. Finally, the sequestering ability of the 3-hydroxy-4-pyridinones towards M^{2+} was investigated by the calculation of the empirical parameter $pL_{0.5}$, already proposed by the research group,[7] at different pH, ionic strength and temperature conditions. It represents the total concentration of ligand required to sequester the 50% of the metal cation present in trace in solution.

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International Symposium on Metal Complexes 2019
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Synthesis and study of SOD mimetics: from aza-macrocyclic complexes to nano-structured systems

Álvaro MARTÍNEZ-CAMARENA,[a] Estefanía DELGADO-PINAR,[a] Concepción SORIANO,[b] José M. Llinares,[b] Roberto TEJERO,[c] Enrique GARCÍA-ESPAÑA [a]

[a] ICMol, University of València, C/Catedrático José Beltrán 2, 46980, Paterna, Spain
[b] Organic Chemistry dept., University of València, C/Dr Moliner s/n, 46100, Burjassot, Spain
[c] Physical Chemistry dept., University of València, C/Dr Moliner s/n, 46100, Burjassot, Spain
e-mail: alvaro.martinez@uv.es

The imbalance between the generation and clearance of reactive oxygen species (ROS) causes oxidative stress, which is related to a variety of health issues that include neurodegenerative disorders such as Parkinson's and Alzheimer's disease (AD).[1] In order to remove ROS, living organisms have developed a battery of protective enzymes, such as superoxide dismutases (SODs), which are not useful for a therapeutic treatment due to the drawbacks that they present -such as the absence of oral activity-. In this respect, it has been reported that several copper complexes of aza-macrocyclic ligands have SOD activities in vitro which rank among the highest ones so far reported for synthetic systems.[2,3] A step forward to improve the activity, the likely-cell uptake and bio-distribution of these low molecular weight mimetics might be their incorporation in non-toxic nanoparticles (NPs). The grafting of the molecules to the surface of the nanoparticles may yield pre-concentration and amplification of the signal.

As a proof of concept, here we report the synthesis of a new Cu^{2+} binucleating aza-macrocyclic ligand (**L1**) functionalized with a hydroxo group rightly disposed to permit its covalent anchorage to oxidic nanoparticles (**L1**-BNP) without loss of SOD activity.[4]

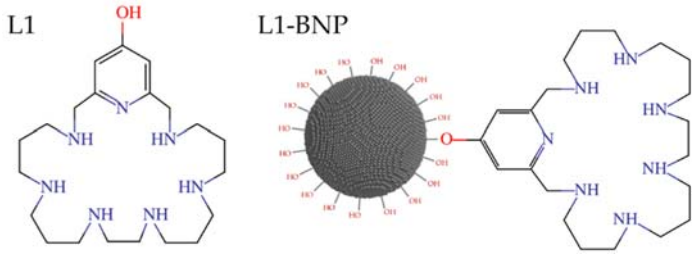

Figure 1. Ligands drawing.

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International Symposium on Metal Complexes 2019
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Rational design and development of a new class of prophylactic metallo-antibiotic possessing potent anti-cancer and anti-microbial properties

Ziga UDE, [a] Isolda ROMERO-CANÉLON, [b] Kevin KAVANAGH, [c] Deidre FITZGERALD HUGHES, [d] Peter J. SADLER, [b] Andrew KELLETT, [e] Celine J. MARMION [a]

[a] Department of Chemistry, Royal College of Surgeons, Dublin 2, Ireland
[b] Department of Chemistry, University of Warwick, Coventry CV4 7AL, United Kingdom
[c] Department of Biology, Maynooth University, Maynooth, Co. Kildare, Ireland
[d] Department of Clinical Microbiology, Royal College of Surgeons in Ireland, Dublin, Ireland
[e] School of Chemical Sciences and the National Institute for Cellular Biotechnology, Dublin City University, Dublin 9, Ireland
e-mail: zigaude@rcsi.ie

Cancer patients, particularly those who develop neutropenia (where the white blood cell counts is lower than normal) during the course of their disease, are at high risk of developing infections. Furthermore, therapy-related myelosuppression and immune defects inherent in cancer disease process add to their risk.[1] With this in mind, we rationally designed and developed an innovative ruthenium(II)-antibiotic complex, [Ru(η^6-p-cym)(CipA$_{-H}$)Cl], with a view to generating not only a highly effective anti-cancer agent but also one that might be able to act as a prophylactic antibiotic.[2] While the complex was highly cytotoxic in terms of its ability to kill tumour cells, both cisplatin-sensitive and cisplatin-resistant, it only exhibited moderate anti-microbial activity. Given that copper(II) complexes have demonstrated great potential as anti-microbial agents, we decided to substitute the ruthenium(II) ion in our lead complex with that of copper(II). We subsequently developed a family of copper(II)-antibiotic complexes, that combine into one drug entity not only a copper(II)-phenazine framework capable of destroying cancer cell DNA *via* oxidative DNA cleavage but also an antibiotic derivative capable of destroying bacteria, Fig. 1. A summary of our results will be presented.

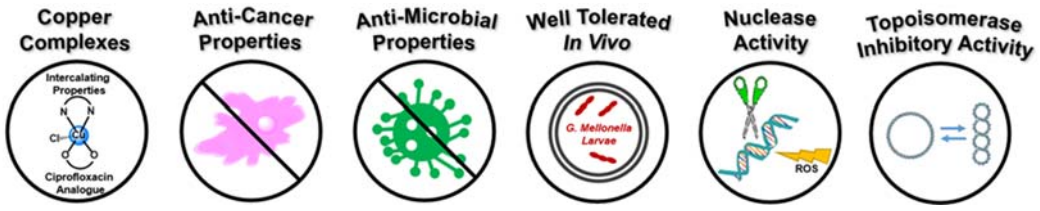

Figure 1: Properties of our novel prophylactic copper-antibiotics.

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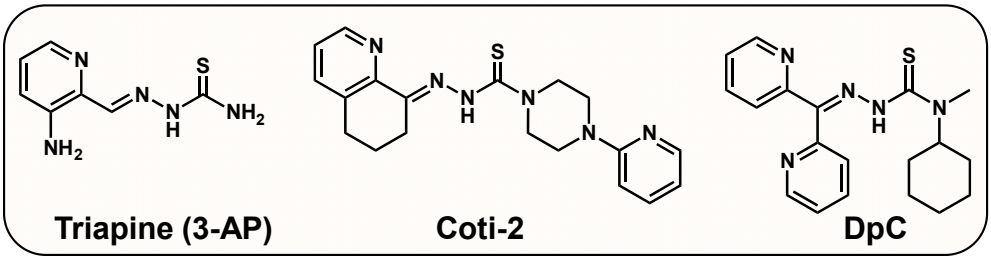
Impact of structural modifications of the α-*N*-pyridyl thiosemicarbazone scaffold on solution properties, copper binding and cytotoxicity

Éva A. ENYEDY, [a)] Vivien PÓSA, [a)] Orsolya DÖMÖTÖR, [a)] Nóra V. MAY, [b)] Sonja HAGER, [c),d)] Petra HEFFETER, [c),d)] Veronika F.S. PAPE, [e),f)] Gergely SZAKÁCS, [c),e)] Bernhard K. KEPPLER, [d),g)] Christian R. KOWOL, [d),g)]

[a)] Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary
[b)] Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2., H-1117 Budapest, Hungary
[c)] Institute of Cancer Research, Medical University of Vienna, Borschkeg. 8a, A-1090 Vienna, Austria
[d)] Research Cluster 'Translational Cancer Therapy Research', University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria
[e)] Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar Tudósok körútja 2, H-1117 Budapest, Hungary
[f)] Department of Physiology, Faculty of Medicine, Semmelweis University, , H-1094 Budapest, Tűzoltó utca 37-47, Hungary
g) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria
e-mail: enyedy@chem.u-szeged.hu

Thiosemicarbazones (TSCs) are versatile compounds regarding their chemical structures, metal binding abilities and pharmacological properties including antituberculosis, antiviral, antimalaria and anticancer effects [1]. Especially α-*N*-pyridyl derivatives are extensively investigated as they exhibit significant anticancer activity. Among them, the most prominent and studied representative is Triapine (3-AP), which has already been evaluated in multiple clinical phase I/II trials [2]. 3-AP showed promising results against hematological diseases, although it was not efficient in case of solid tumors due to a rather short biological half-life, and its administration was accompanied by severe side effects [2]. Very recently, two novel TSCs (Coti-2 and DpC) have entered clinical trials [3]. These compounds belong to the family of α-*N*-pyridyl TSCs and share a common chelating moiety with a tridentate ($N_{pyridyl}$,N,S) donor set.



It was previously shown that *N*-terminal substitution frequently results in an enhanced cytotoxicity [4]. Additionally, a new derivative (Me_2NNMe_2) with nanomolar cytotoxicity with dimethylation at both primary amino groups of the 3-AP molecule induces paraptosis, a recently recognized programmed form of cell death, which is characterized by the formation of endoplasmic reticulum derived cytoplasmic vesicles [5].

TSCs possess strong metal binding ability and their interaction with essential cellular metal ions such as iron and copper is considered to play an important role in their biological activity. Ribonucleotide reductase, an iron-containing enzyme is considered as the main target of 3-AP, whereas *in vivo* formed redox-active iron complexes are supposed to be responsible for the enzyme inhibition. On the other hand, copper has also been associated with the mechanism of action of TSCs due to the redox activity of the formed complexes. In addition, copper complexes of numerous TSCs also exert enhanced antitumor effects. In this respect, knowledge on the stability and the most plausible chemical forms of the copper complexes in aqueous solution under physiological conditions is a mandatory prerequisite. We could build up a large library of solution speciation data completed by structural characterizations obtained for versatile TSCs possessing various donor sets, and substituents in the last years [6]. Herein, we show the differences in the proton dissociation processes, aqueous solution stability, isomer distribution in different solvents, fluorescence properties and lipophilic character of various TSCs. We also attempt to reveal correlations between the copper(II) binding ability, redox properties and biological activity (cytotoxicity, reactive oxygen species production, paraptosis induction) to understand the different behavior of TSCs better.

Acknowledgements: National Research, Development and Innovation Office-NKFIA projects GINOP-2.3.2-15-2016-00038, FK 124240; Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT; Austrian Science Fund (FWF) (grant number P31923).

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International Symposium on Metal Complexes 2019
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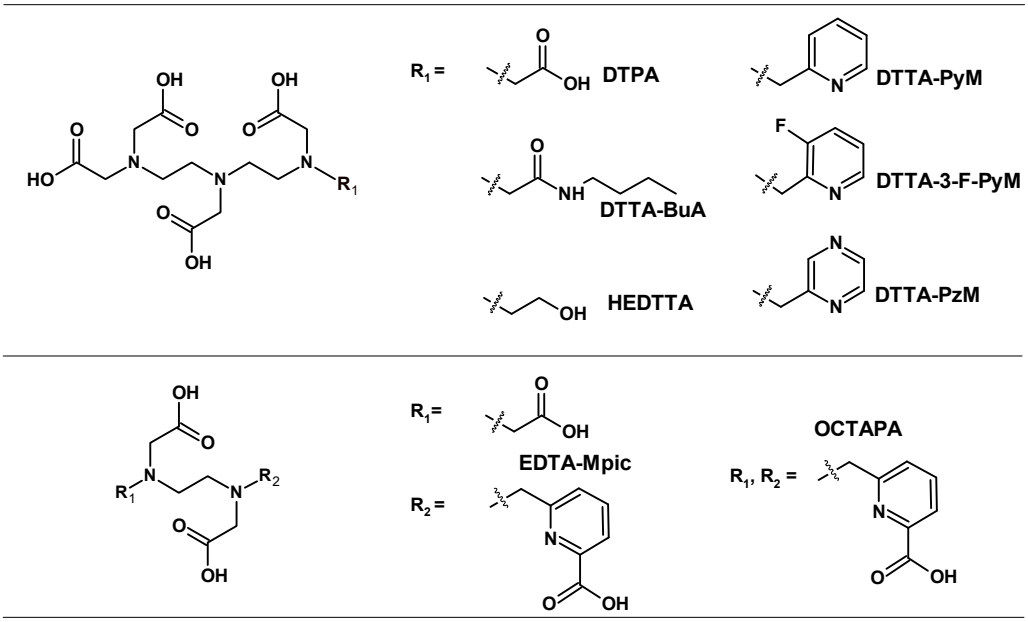
New aminopolycarboxylate chelators for trivalent actinide coordination

Peter ZALUPSKI, [a] Colt HEATHMAN, [a] Travis GRIMES, [a] Corey PILGRIM, [a] Santa JANSONE-POPOVA, [b] Santanu ROY, [b] Alexander IVANOV, [b] Vyacheslav BRYANTSEV, [b] Masahiko NAKASE [c]

[a] Idaho National Labolatory, Idaho Falls, Idaho, 83415, United States
[b] Oak Ridge National Labolatory, Oak Ridge, TN 37831, United States
[c] Tokyo Institute of Technology, Tokyo 152-8550, Japan
e-mail: peter.zalupski@inl.gov

The aminopolycarboxylate reagents, when composed of multiple aminoacetate structural building blocks, effectively sequester trivalent *f*-elements.[1-3] Such chelators form five-membered rings when coordinating metal ions, yielding strong, polydentate complexation. Due to weak covalent bonding interactions between the 5*f* elements and nitrogen donor atoms a stronger coordination of trivalent actinides (An^{3+}), relative to trivalent lanthanides (Ln^{3+}), is observed, especially with large polydentate ligands such as diethylenetriamine-*N,N,N′,N″,N″*-pentaacetic acid (DTPA).[4-8] The thermodynamic stabilization from the metal/ligand orbital overlap and π back-bonding interactions with the ligand is sufficient to differentiate 4*f* / 5*f* group of trivalent elements when using liquid-liquid or solid-liquid separation methods.[4,9]



Scheme 1. Generalized structures of the investigated aminopolycarboxylate reagents.

This contribution highlights recent structure-function relationship studies for a series of modified, DTPA-like complexants. Depending on a substituent a balance between the soft donor character and total ligand acidity may be modulated as reflected by changes in the An^{3+}/ Ln^{3+} differentiation. The structures of the investigated aminopolycarboxylate complexants are summarized in Scheme 1. Potentiometric, spectroscopic and computational studies were

supported with radioisotope distribution studies to describe the thermodynamic impact of the structural changes on the protonation, trivalent *f*-element complexation equilibria, the coordination environment, and An^{3+}/Ln^{3+} separation in aqueous acidic mixtures.

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International Symposium on Metal Complexes 2019
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Oxovanadium(IV) complexes with newly synthetized kojic acid derivatives

Silvia BERTO, [a] **Eugenio ALLADIO,** [a] **Pier Giuseppe DANIELE,** [a] **Andrea BONO,** [a] **Enzo LAURENTI,** [a] **Carmelo SGARLATA,** [b] **Gabriele VALORA,** [b] **Rosita CAPPAI** [c], **Joanna Izabela LACHOWICZ,** [d] **Valeria M. NURCHI** [c]

[a] *Università di Torino, Dipartimento di Chimica, Via Pietro Giuria 7, 10125 Torino, Italy*
[b] *Università degli Studi di Catania, Dipartimento di Scienze Chimiche, Viale Andrea Doria 6, 95125 Catania, Italy*
[c] *Università di Cagliari, Dipartimento di Scienze della Vita e dell'Ambiente, Cittadella Universitaria, 09042 Cagliari, Italy*
[d] *Università di Cagliari, Dipartimento di Scienze Chimiche e Geologiche, Cittadella Universitaria, 09042 Cagliari, Italy*
e-mail: silvia.berto@unito.it

The complexation capability of four kojic acid (5-hydroxy-2-(hydroxymethyl)-4-pyrone, KA) derivatives towards oxovanadium(IV) was tested.

Hydroxypyrones derivatives exhibit a good biocompatibility and have been used for drug development [1]. Moreover, they show interesting complexing capability towards vanadyl cation and are suitable for the development of compounds with insulin-mimetic properties. The complexes of vanadyl with hydroxypyrones derivatives show in fact the capability to control the blood glucose level and can be used as therapeutic agents for diabetes mellitus [2-5] .

The recently synthetized studied ligands show a structure in which two or three kojic acid units are linked through diamines or tris(2-aminoethyl)amine (Figure1). The synthesis and the characterization of the four ligands considered were previously presented, as well as their coordination capability towards Fe^{3+}, Al^{3+}, Cu^{2+} and Zn^{2+} cations [6-7].

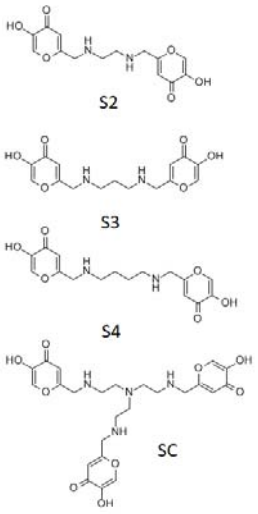

Figure 1 Molecular structure and acronym of the kojic acid derivatives studied. S2: [ethane-1,2-diylbis(iminomethanediyl)]bis(5-hydroxy-4H-pyran-4-one), S3: [propane-1,3-diylbis(iminomethanediyl)]bis(5-hydroxy-4H-pyran-4-one); S4: [butane-1,4-diylbis(iminomethanediyl)]bis(5-hydroxy-4H-pyran-4-one); SC: 6,6′,6″-(((nitrilotris(ethane-2,1-diyl))tris(azanediyl))tris(methylene))tris(3-hydroxy-4H-pyran-4-one).

In the present study, the chemical systems were studied by potentiometry, UV-visible and EPR spectroscopy at 25°C and ionic strength 0.1 mol L^{-1}. For all the systems a chemical model was hypothesized elaborating experimental data by a thermodynamic approach and by chemometric methods. The spectroscopic data, in particular, were elaborated by HypSpec® software [8] and by Multivariate Curve Resolution - Alternating Least Squares - MCR-ALS method [9]. The formation constants of the complexes and the pure UV-vis and EPR spectra were estimated.

For the ligands S2, S3 and S4 a chemical model with two complex species was hypothesized in which the two kojate groups were inserted successively, $[VOLH_3]^{3+}$ and

$[VOLH_2]^{2+}$. The formation constants are comprised between logβ = 33.0 and 35.8 for the species $[VOLH_3]^{3+}$ and between logβ = 29.4 and 32.5, for the specie $[VOLH_2]^{2+}$. The insertion of one kojate group leads to an energy gain similar to that due to the insertion of a KA molecule in the cation coordination sphere, whereas the insertion of the second kojate moiety is less favored with respect the insertion of 2 KA unit [5,10]. For the SC ligand the species $[VOLH_5]^{4+}$, $[VOLH_4]^{3+}$ and $[VOLH_3]^{2+}$ were hypothesized. The first two species correspond to the insertion of one and two kojate groups, respectively, whereas the $[VOLH_3]^{2+}$ is probably due to the formation of an hydroxo complex [10]. For all the systems the coordination of the oxovanadium(IV) starts under acidic conditions and the cation is totally complexed at pH > 3-4.

The UV-vis and EPR spectra support the proposed chemical models and, by the elaboration of the experimental data, it was possible obtain the spectral features of the single species. The insertion of one or two kojate groups in the coordination sphere of the oxovanadium(IV) gave absorption maxima comprised between 819 - 834 nm and 854 - 870 nm, respectively, and A_0 values of ~$95.5 \cdot 10^{-4}$ cm^{-1}.

Acknowledgements: SB, VMN and EA acknowledge support by MIUR-PRIN 2015 - 2015MP34H3_002 that finances the research grant of EA.

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The anticancer activity and biological properties of novel mixed ligand platinum(II) complex with 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine

Mateusz JAKUBOWSKI, [a] **Iwona ŁAKOMSKA,** [a] **Janusz DĄBROWSKI,**[b] **Jacek SZYMAŃSKI** [c]

[a] *Bioinorganic Chemistry Research Group, Faculty of Chemistry, Nicolaus Copernicus University in Torun, Gagarina 7, 87100, Toruń, Poland*
[b] *Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30387, Cracow, Poland*
[c] *Central Laboratory, Medical University of Lodz, Mazowiecka 6/8, 92215, Lodz, Poland*
e-mail: mjakub@doktorant.umk.pl

The anticancer activity of cisplatin (CDDP), which is currently used to treat various type of cancers was discovered in the 1960s. However, poor water solubility, drug resistance and several side effects of CDDP motivate the development of novel platinum-based drugs. The information that dicarboxylato ligands can reduce the toxic drawback of CDDP led to the worldwide approval of carboplatin and oxaliplatin.[1] The next step in modifying of platinum(II) drugs has concentrated on replacing stable amine ligands with other non-living N-donors capable of bumping up the cytotoxicity of novel compounds. The attractive idea is an application of triazolopyrimidine derivatives resembling the nucleobases adenine and guanine in DNA as N-donor ligands.

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.[2] 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 epithelial (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. On the other hand, it was proven that [Pt(mal)(dmso)(dptp)] displays lower reactivity towards glutathione than currently used platinum(II) drugs – cisplatin and carboplatin. These hot results have decided to undertake flow cytometry and *in vivo* studies, which will be talked-about in an oral presentation.

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International Symposium on Metal Complexes 2019
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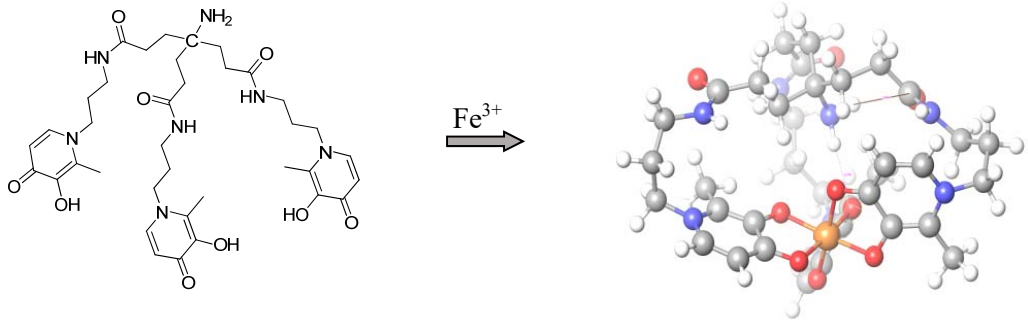
A new tripodal-3-hydroxy-4-pyridinone: synthesis, protonation, complex formation studies with Fe^{3+}, Al^{3+}, and Zn^{2+}, and *in vivo* bioassays.

Valeria M. NURCHI,[a] Rosita CAPPAI,[a] Karam CHAND,[b] Sílvia CHAVES,[b] Lurdes GANO,[c] Massimiliano PEANA,[d] M. Antonietta ZORODDU,[d] M. Amélia SANTOS [b]

[a] Dipartimento di Scienze della Vita e dell'Ambiente, Università di Cagliari, Cittadella Universitaria, 09042, Monserrato-Cagliari, Italy
[b] Centro de Quimica Estrutural, Instituto Superior Tecnico, Universidade de Lisboa, Av, Rovisco Pais 1, 1049-001, Lisboa, Portugal
[c] Centro de Ciencias e Tecnologias Nucleares(C2TN), Instituto Superior Tecnico, Universidade de Lisboa, Estrada Nacional 10, 2695-006, Lisboa, Portugal
[a] Dipartimento di Chimica e Farmacia, Università di Sassari, Via Vienna 2, 07100, Sassari, Italy
e-mail: cappai@unica.it

Elevated levels of iron and aluminium in the body can lead to tissue damage, organ failure and eventually death. To reduce complications of iron overload, specific chelating agents have been used. Following our recent developments in a series of hexadentate 3-hydroxy-4-pyridinones (3,4-HP) with high M^{3+} sequestering capacity [1,2], we herein present a novel tripodal tris-(3,4-HP) (LH_3, see below) and the study of its metal complexation capacity. This compound differs from the previous analogues mainly in the corresponding anchoring backbone, which includes one terminal amino group. This amino group is not involved in iron complexation, but it is suitable for extra-functionalization for the sake of either improving the lipo-hydrophilic balance, therefore facilitating the crossing of specific bio-membranes, or for providing sensing or bio-targeting capacity.



LH_3 FeL

Besides the synthesis of the new ligand, solution studies have been performed to evaluate the acid-base properties and complexation capacity towards Fe^{3+}, Al^{3+} and Zn^{2+} using potentiometry and a panoply of spectrometric techniques. The pFe and pAl values present a reliable increase with respect to the analogue ligands so far studied. This can be rationalized on the basis not only of the high affinity of the 3,4-HP chelating moieties for these hard metal ions, but also due to the high flexibility of the anchoring moiety and the adequate length size of the

arms connecting both moieties, as otherwise indicated by the DFT model of FeL complex. The complexation capacity of this ligand with Zn^{2+} was also assessed and it was verified that its strong sequestration capacity towards Fe^{3+} and Al^{3+} does not lead to the depletion of this bio-relevant divalent metal ion. The ability of this new ligand to facilitate metal-mobilization from the body has been investigated using a mice model injected with ^{67}Ga. The new chelating agent, with its high pM^{3+} values, shows extremely interesting ability to remove Fe and Al under *in vivo* conditions.

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International Symposium on Metal Complexes 2019
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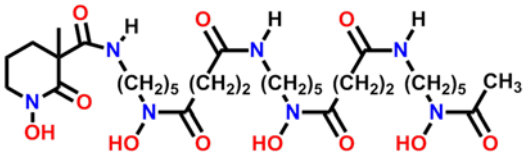
DFO-PIPO:
An optimized ligand for tetravalent cations

Sofia GAMA,[a] Osian FONQUERNIE,[a] Floriane MANGIN,[a] Stéphane BRANDES,[a] Jean-Claude CHAMBRON,[b] Vladimir SLADKOV,[c] Michel MEYER [a]

[a] 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
[b] Institut de Chimie de Strasbourg (IC-UNISTRA), UMR 7177 CNRS, Université de Strasbourg, 1 rue B. Pascal, 67008 Strasbourg, France
[c] Institut de Physique Nucléaire d'Orsay (IPNO), UMR 8608 CNRS, Université Paris-Sud, 15 rue G. Clemenceau, 91400 Orsay, France
e-mail: sofia.gama@u-bourgogne.fr

The presence of actinides (An^{4+}) in soils and waters is one of the contemporary environmental issues resulting from the increasing nuclear activities worldwide. These radionuclides are mostly used in energy production and defense operations (nuclear weapons), being found in considerable amounts in nuclear waste and in areas accidentally contaminated (as Chernobyl and Fukushima). Also Zr^{4+}, an important component in used nuclear fuel, due to its chemical similarities with tetravalent actinides, is found to co-extract with them, making it one of the major contaminants of the fission products.[1]

One of the most common decontamination techniques of waters and soils is the use of chelating agents that could selectively sequester the contaminating cations. In this line, the development of high-affinity chelators for specific binding of An^{4+} and its surrogate cation Zr^{4+} is topical. Actinides are hard Lewis acids, as well as Fe^{3+}. For this reason, several ligands inspired by the structure of siderophores have been tested for An^{4+} sequestering.



DFO-PIPO

Based on desferrioxamine B (DFO), a trihydroxamic acid, we developed a new ligand (DFO-PIPO) bearing four hydroxamate moieties, aiming a higher selectivity for tetravalent cations. Its complexation properties towards the metals of interest will be discussed. Model compounds will be also considered. [2,3]

Acknowledgements: This work has been supported by the Centre National de la Recherche Scientifique (CNRS), the Université de Bourgogne, the Conseil Régional de Bourgogne (CRB, program PARI II CDEA), the European Regional Development Fund (FEDER), the program "Défi NEEDS Environnement" (projects ACTISOL), and the Agence Nationale de la Recherche (ANR project PLUTON, grant N° ANR-17-CE08-0053).

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International Symposium on Metal Complexes 2019
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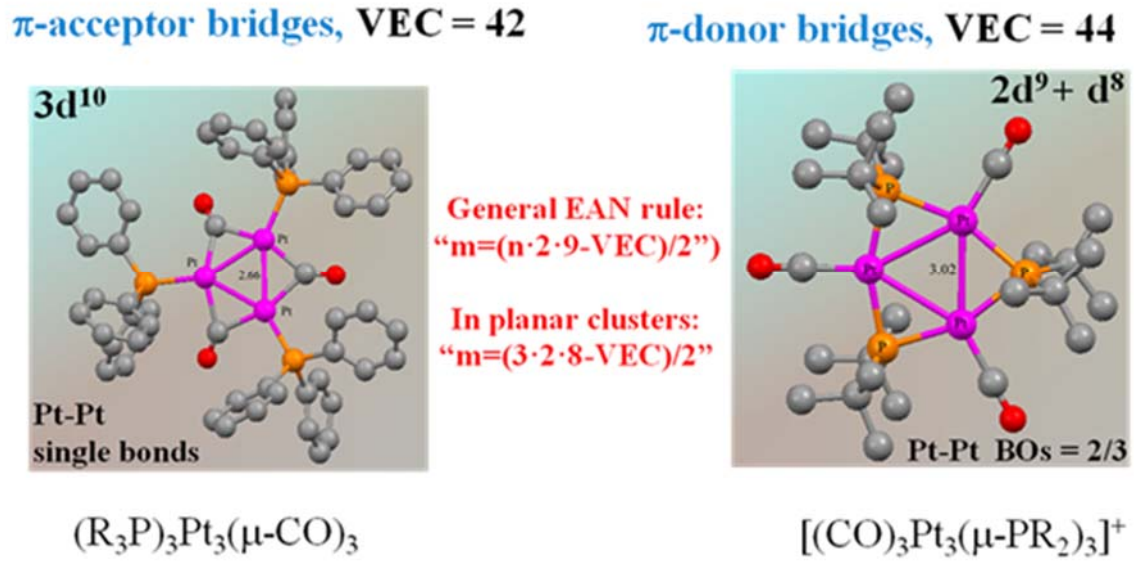
Phosphido-bridged trinuclear platinum clusters: density functional study

Abdelatif MESSAOUDI, [a] **Gabriele MANCA**, [b] **Andrea IENCO**, [b] **Carlo MEALLI** [b]

[a] *Laboratoire de Chimie des Matériaux et des Vivants : Activité & Réactivité, Département chimie, Faculté des S M, Université Batna1, Algeria*
[b] *ICCOM-CNR, Via Madonna del Piano 10, 50019 Sesto Fiorentino Firenze, Italy*
e-mail: amessaoudi@univ-batna.dz

The stereochemistry and electronic features of dinuclear and trinuclear Ptn or Pdn species have been deeply investigated in the past. Since a long time, we are also active in the field with the aim of interpreting electronic properties and potential reactivity. For the Pt3 clusters with three equivalent terminal ligands, the acceptor/donor nature of the bridges favors either the 42 or 44 Valence Electron Count (VEC), respectively. In the former case, the Pt-Pt distances correspond to single bonds (~ 2.7 Å) involving d^{10} metals. The VEC=44 instead implies mixed metal oxidation state (d^8 + $2d^9$) with expansion or deformation of the Pt3 framework. In the former case, the Pt-Pt distances stretch up by about 0.3 Å, whereas a different terminal ligand may force the triangle to become isosceles with the weakening or cleavage of one Pt-Pt linkage. In a single case, both limiting structures are accessible by the same compound Ph(PPh3)2Pt3(μ-PPh2)3, which is at the basis of the cluster core isomerism (CCI), separately highlighted by Carty and Braunstein to depend on the crystallization solvent. In this work, we report a computational study of trinuclear platinum clusters performed using Gaussian program package.



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Electronic spectroscopic study of and quantum chemistry calculations on Ca^{2+}-morin complexes

Diksha JANI THAVILIGADU, Aurélien MONCOMBLE, Jean-Paul CORNARD

Univ. Lille, CNRS, UMR 8516 - LASIR - Laboratoire de Spectrochimie Infrarouge et Raman, F-59000 Lille, France
e:mail: diksha.jani-thaviligadu@univ-lille.fr

Calcium is an alkaline-earth metal widely present in the environment and the human body, but is not very common in complexation reactions. Nevertheless, Ca^{2+} has an important role to play not only in the growth of plants but also in the good functioning of the nerves, muscles and regeneration of bones.

To evaluate the complexation ability of calcium ions with respect to several binding sites, the interaction of these ions with multisite ligands were performed, enabling the Ca^{2+} cation to freely choose its preferential fixation site on the molecule. Morin (2',3,4',5,7-pentahydroxyflavone), a compound belonging to the family of flavonoids and largely present in the natural environment possesses four different fixation sites.

The methodology applied to our system is the use of electronic spectroscopy and quantum calculations. The association of spectroscopic techniques together with quantum chemistry has proven to be a strong method in the determination and analysis of complexation reactions [1].

Experimentally, the titration of morin was carried out with a solution of $CaCl_2$ at fixed pH and temperature so as not to alter the protonation state of the ligand. The set-up was coupled to both a UV-vis spectrometer and a fluorescence spectrometer. The data of the experiments were retrieved in the form of a set of spectra. Regarding the theoretical part of the work, DFT and TD-DFT calculations were processed. B3LYP/6-311+G** describes well the free ligand and hence was used on all the conceivable hypotheses for the complex. The environment of the complex (especially its solvation sphere) was carefully represented during the calculations [2]. The data processing consists of the overlap of the experimental spectrum and the electronic transitions obtained with TD-DFT to investigate which computed complex reproduces fairly the experimental results. Further experiments and calculations were also performed to see the evolution of the complex while the pH varies. Subsequent computational studies were also performed to enlighten the nature of chemical bonds in this system.

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International Symposium on Metal Complexes 2019
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Theoretical study of the reactivity of the monofunctional anticancer Pt(II) compound phenanthriplatin

Daniele VECLANI,[a] José-Pedro CERON-CARRASCO,[b] Marilena TOLAZZI,[a] Andrea MELCHIOR [a]

[a]DPIA, Chemistry Laboratories, Università di Udine, Via del Cotonificio 108 33100 Udine, Italy
[b]Bioinformatics and High Performance Computing Research Group (BIO-HPC) Universidad Católica San Antonio de Murcia (UCAM), 30107, Murcia, Spain
e-mail: andrea.melchior@uniud.it

Since the discovery of the first complex which exhibited anti-tumor properties, cisplatin, numerous Pt(II) complexes have been used as anti-cancer drugs, but only few have been approved for clinical use [1]. The accepted mechanism of action of cisplatin consists in two stages: intracellular activation by the hydrolysis of a ligand and formation of intra-strand cross-links in DNA which produces a bending that causes the generation of defective proteins and ultimately the cell death. Unfortunately, the therapeutic efficacy of many current Pt(II) complexes is compromised by occurrence of serious side effects. To overcome these limitations, several strategies have been employed to find new platinum drugs with an equivalent or improved range of activity and less toxic side effects.

A recently discovered mono-functional Pt(II) compound, phenanthriplatin [2] has been demonstrated to be much more active than cisplatin in vitro towards a panel of 60 cancer cell lines [2]. The proposed mechanism of action of this compound is rather different than that of cisplatin as no bifunctional adducts are possible. Phenanthriplatin forms an adduct with DNA and interacts through the phenanthridine moiety via π -π stacking with DNA bases interfering with the action of RNA polymerase II enzyme and consequently the replication of malignant cells [3].

In the last decades, many theoretical studies have been carried out to obtain structure-reactivity relationships in order to predict the properties of anticancer Pt(II) complexes and their interaction with DNA [4]. In this contribution we update our recent results [5] on the computational modelling of the interaction of phenanthriplatin with DNA by means of DFT (Density Functional Theory) and hybrid QM/MM calculations.

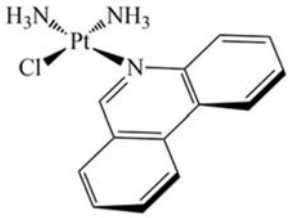

Figure 1: Phenanthriplatin.

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Different complexation modes of silolide ions and dianions

Csaba FEKETE, [a] **Ilona KOVÁCS,** [a] **Tamás HOLCZBAUER,**[b] **László NYULÁSZI** [a]

[a] *Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, and MTA-BME Computation Driven Chemistry Research Group Szt. Gellért tér 4. Budapest, H-1111, Hungary*
[b] *Institute of Organic Chemistry, and Instrumentation Centre, of the Research Centre for Natural Sciences, Hungarian Academy of Sciences, POB. 206, H-1519 Budapest, Hungary*
e-mail: malkavie@gmail.com

Cyclopentadienide ion, is a textbook example for planar aromatic compounds. Replacement of a carbon atom by silicon results in the silacylopentadienyl (silolide) anion, which is isoelectronic with phosphole, and by removal of substituent on the silicon silolide dianions – isoelectronic with thiophene, - can be synthesized. These five membered rings can be complexed by the counterion alkaline metal cation in different ways (see Figure 1). In the presentation we give X-ray structural evidences, together with NMR spectroscopic data and DFT calculations for the different complexation modes for the different alkali metal complexes, depending on the solvent and the substituents of the five membered ring.

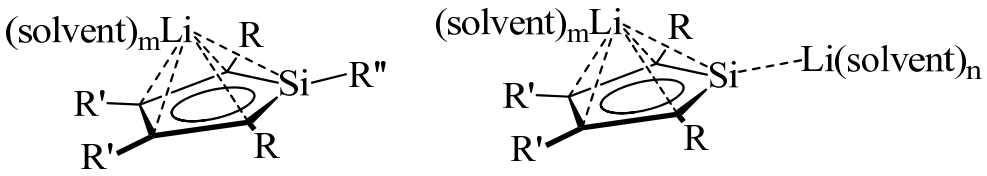

Figure 1. Silodile anion and dianion complexes.

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Ru/Rh half-sandwich organometallic cations are able to induce amide-nitrogen deprotonation well below the physiological pH: interaction with His-containing peptides

Attila SZORCSIK, [a] LÍVIA FÜLÖP, [b] Tamás GAJDA [a]

[a] Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, 6721, Szeged, Hungary
[b] Department of Medical Chemistry, University of Szeged, Dóm tér 8, 6721, Szeged, Hungary
e-mail: gajda@chem.u-szeged.hu

Ru(II) and Rh(III) half-sandwich (arenyl bound) organometallic cations have gained increasing interest (among others) in the development of potential therapeutic agents, as such complexes show promising in vitro anticancer activity. The mechanism of this activity and the biological fate of these complexes are largely unknown. Moreover, our knowledge on the solution chemistry of these organometallic cations and their complexes, which is the prerequisite for the correct answers of above questions, is rather limited. The available information suggest the His-imidazole and Cys-thiol groups are the main binding sites in for these cations in proteins. The monodentate coordination of (Ru/Rh)(arene)(L-L) complexes to these groups is less affected by the environment of His/Cys units. However, when chelate coordination is possible, the nearby donor atoms have fundamental impact, and the (L-L) ligand may even be displaced from the coordination sphere of the metal ion.

In order to better understand the binding of (Ru/Rh) half-sandwich cations to proteins, we studied their interaction with a number of His derivatives (histamine, histidine, histidine-amide, GGH, GHG, HGG, and HHH) in aqueous solutions by potentiometry, UV-Vis and ^{1}H NMR. Due to the slow kinetics, complete solution equilibrium study was not possible in case of Ru complexes, but the two half-sandwich cations behave rather similarly. With Rh^{III}(Cp*) cation the above ligands form highly stable $\{NH_2,N_{im}\}$ coordinated complexes, of which relative stability - obviously - depends on the size of the chelate ring, and the presence of additional donors. The $\{NH_2,N_{im}\}$ type binding is an efficient anchoring site for metal promoted amide deprotonation. The pK of the latter process is < 6 for histidine-amid, GHG and HGG. Somewhat higher value (pH ~ 7) was observed for GGH, due to the presence of macro-chelate ring even in the amide coordinated species. In Rh^{III}(Cp*)(HHH) the histamine-like coordination is supplemented by an additional imidazole binding, which significantly stabilizes this parent complex, therefore the pK of amide deprotonation is considerably increased (pK = 9.58). Generally speaking, below the neutral pH HHH, above it HGG has the highest sequestering ability. Among the listed compounds, interestingly the peptide GGH, mimicking the ATCUN-motif of human serum albumin, provides the weakest binding site for Rh^{III}(Cp*). Nevertheless, the calculated conditional dissociation constant (K_D = 0.3 nanoM) indicates strong interaction even is this case. Further details will be discussed in site.

Acknowledgements: This research was supported by National Research, Development and Innovation Office-NKFI through project GINOP-2.3.2-15-2016-00038

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Copper binding to R1 and R3 fragments of Tau protein

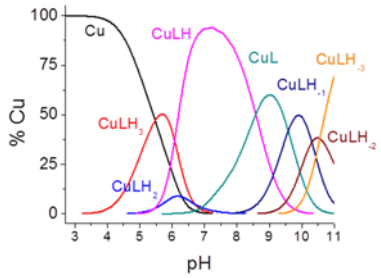
Silvia GENTILI, [a] **Matteo TEGONI,** [a] **Denise BELLOTTI,** [b] **Chiara BACCHELLA,** [c] **Alice MAZZA,** [a] **Eleonora QUARTIERI,** [a] **Maurizio REMELLI,** [b] **Simone DELL'ACQUA,** [c] **Luigi CASELLA,** [c] **Daniela VALENSIN** [d]

[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] *Department of Biotechnology, Chemistry and Pharmacy, University of Siena, via Aldo Moro 2, 53100, Siena, Italy*
e-mail: 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] In this contribution we examine the stability and the structural models of Cu(II) adducts with two peptide fragments which are encompassed in the R1 and R3 repeats of tau (Fig. 1).

R1 (HL):
Ac-^{257}VKSKIGSTENLKHQGGG^{273}-NH_2

R3 (L):
Ac-^{323}GSLGNIHHKPGGG^{335}-NH_2



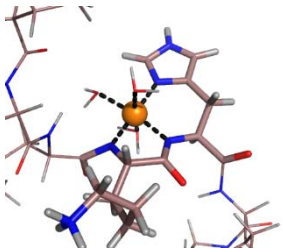


Figure 1. **Left.** Sequences of the R1 and R3 peptides. **Center.** Distribution diagram of the Cu(II)/R1 system (C_{Cu} = 470 μM, L:Cu = 1.5, charges omitted). **Right.** Proposed structure of the species $[CuLH]^{2+}$ (HL = R1).

Copper(II) binding to R1 (HL) starts at pH 4. The relevant species at pH 7.4 is $[CuLH]^{2+}$, where R1 is tridentate: the copper(II) equatorial coordination positions are occupied by the imidazole ring, two amidic nitrogen atoms, and a water molecule. As for the R3 peptide, at pH 7.4 the two most abundant species are $[CuL]^{2+}$ and $[CuLH_{-1}]^{+}$ (in a ratio of ca. 1:2). In the case of $[CuL]^{2+}$, the two imidazole groups of R3 and one deprotonated amidic nitrogen atom are bound to the equatorial plane. In $[CuLH_{-1}]^{+}$, a further amidic nitrogen bounds the metal ion in

the equatorial plane, most likely pushing one imidazole group to the axial position. The redox and NMR behavior of these complexes will be discussed in terms of their speciation.

Having the Cu(II)-tau peptides binding constants in our hands, we decided to investigate the copper(I) adducts with the R1 and R3 tau fragments via spectrophotometric competition titrations with the metallochromic ligand ferrozine (Fz).[4] The titration of a Cu(I) solution with ferrozine causes the formation of the chromophoric complex $[Cu^{I}(Fz)_2]^{3-}$ which presents two characteristic absorption bands at 470 nm and 600 nm. By back titrating this solution with the R1 and R3 fragments, we observed a decrease in the absorbance values (Fig. 2).

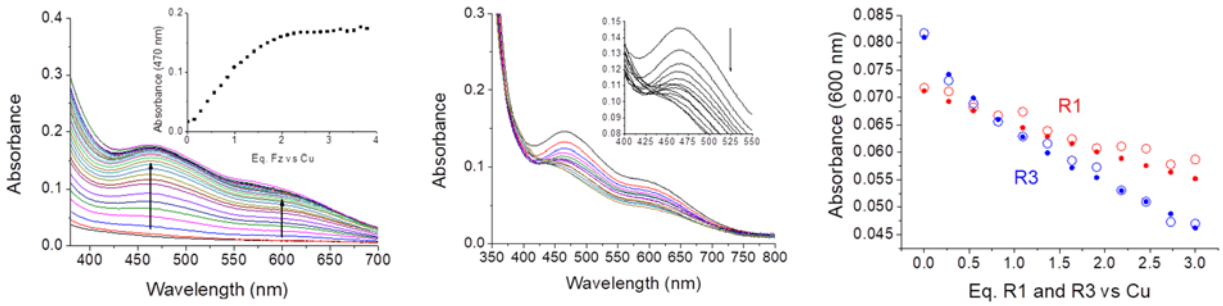


Figure 2. **Left.** Absorption spectra for the titration of Cu(I) with Fz (C_{Cu} = 55 µM, Fz:Cu = 2:1, C_{ASC} = 10 mM). **Center.** Absorption spectra for the titration of $[Cu^{I}(Fz)_2]^{3-}$ with R3 (C_{Cu} = 55 µM, R3:Cu = 0-4.77:1, C_{ASC} = 10 mM). **Right.** Plot of absorbance values at 600 nm as a function of the equivalents of R1 and R3 added to $[Cu^{I}(Fz)_2]^{3-}$ (open circles: observed; filled circles: calculated).

The addition of R3 to $[Cu^{I}(Fz)_2]^{3-}$ causes a significative change in the absorbance, which decreases of almost 0.40 units. As for the R1 peptide, a decrease of only 0.20 units is observed and can be fully accounted by dilution effects. Data treatment using HypSpect program yields a log β value of 5.9(1) for the Cu(I)-R3 complex. Data treatment for the back titration of $[Cu^{I}(Fz)_2]^{3-}$ with R1 confirms the absence of significant interactions of Cu(I) with R1. NMR data suggest that the binding of Cu(I) to R3 occurs at the tandem HH site, as it occurs for Cu(II).

The authors acknowledge MIUR for financial support through the project "Metal ions, dopamine, and oxidative stress in Parkinson's disease" (PRIN 2015T778JW).

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Metal ions as regulatory elements of artificial nucleases

Heba A. ABD ELHAMEED, [a] Bálint HAJDU, [a] Enikő HERMANN, [a] Mohana Krishna GOPPISETTY, [b] Mónika KIRICSI, [b] Ditta UNGOR, [c] Edit CSAPÓ, [c] Wojciech BAL, [d] Béla GYURCSIK [a]

[a] Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary
[b] Department of Biochemistry and Molecular Biology, University of Szeged, Középfasor 52, H-6726, Szeged, Hungary
[c] MTA-SZTE Supramolecular and Nanostructured Materials Research Group and Department of Medical Chemistry, Faculty of Medicine, University of Szeged, Dóm square 8, H-6720, Szeged, Hungary and Department of Physical Chemistry and Materials Sciences, University of Szeged, Aradi v.t.1, H-6720, Szeged, Hungary
[d] Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Pawinskiego 5a, 02-06, Warsaw, Poland
e-mail: heba.alaa@chem.u-szeged.hu

Nuclease-mediated genome editing offers a powerful tool for gene therapy, since it allows the targeted correction/alteration of genomic sequences in cells. Artificial DNA nucleases have provided scientists with the unprecedented ability to probe, regulate, and manipulate the genome. [1] Noteworthy, metal ions play key role both in the recognition of the specific DNA sequences in zinc-finger type domains, as well as in the catalytic action of the DNA hydrolysis in the active center of the HNH nucleases, such as the Cas9 enzyme. Our research focuses on new type of Zinc Finger Nucleases (ZFNs), which can be regulated in multiple manners by the help of metal ions. Based on our previous studies the C-terminal nuclease domain of the Colicin E7 protein (NColE7), another member of the HNH family, can be a good candidate for this purpose. This protein contains the HNH metal binding motif at its C-terminus, which can only become functional in the spatial vicinity of the N-terminal positively charged amino acids. The metal ion binding, which is essential for catalysis, depends on the 3D structure of the protein. The proper folding on NColE7 is also facilitated by the amino acids in the N-terminal sequences.

To obtain a regulated artificial metallonuclease, we need to learn more about the effects of the intramolecular allostery on metal ion and DNA binding, specificity, structure and catalytic activity. We have designed and synthesized various protein chimera by combining zinc fingers and NColE7 so that the N- and C-termini, *i.e.,* the regulatory and catalytic segments of the nuclease are separated by the zinc finger, but expected to approach each other upon specific DNA binding (Figure 1). [2] The zinc finger sequences are designed to target various oncogenes in cancer cell lines. To decide about the best target sequences, we have also applied the well-established CRISPR/Cas9 tool for genome editing, probing various oncogenic sequences. This will allow us to compare the genome editing efficiency of the new ZFNs, as well. To increase the efficiency within the cancer cell lines we have also encapsulated the DNA encoding for the artificial nuclease using cationic polymeric delivery systems.

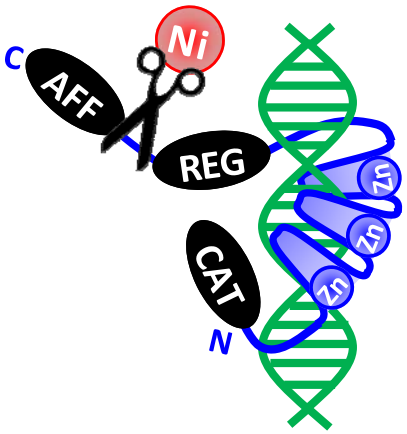

Figure 1. Schematic representation of the chimeric nuclease in which the allosteric activation can be triggered by nickel(II)-induced affinity tag cleavage.

The *in vitro* experiments require large amounts of purified proteins with precisely determined amino acid sequence. Simple affinity-based purification cannot be applied because the affinity tags - or the remaining amino acids after the cleavage of the affinity tags - may interfere with the function of the nucleases. Therefore, we elaborated a new purification method is which the affinity tag is cleaved off by protease mimicking nickel(II) ions targeting an SXHY amino acid sequence specifically, while observing the additional regulatory effect of the affinity tags. This gives opportunity to use the metal ion-induced protein cleavage to trigger the nuclease action (Figure 1).

Acknowledgements: This work has been supported by COST Action CA15126; GINOP-2.3.2-15-2016-00038; NKFIH K_16/120130.

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International Symposium on Metal Complexes 2019
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Enhancing the selectivity towards G4 DNA of triphenylamine derivatives: sensing and biochemical applications

Isabel PONT, [a),b)] Àlvar MARTÍNEZ-CAMARENA, [a)] Jorge GONZALEZ-GARCÍA, [a)] M. Teresa ALBELDA, [a)] Ramon VILAR, [b)] Enrique GARCÍA-ESPAÑA [a)]

[a)] ICMol, University of Valencia, C/ José Beltran, 2, 46980, Paterna, Spain.
[b)] Dep. of Chemistry, Imperial College London, South Kensington, London SW72AZ, UK.
e-mail: isabel.pont@uv.es

Several non-canonical DNA structures are well-known, such as hairpins, triplexes or G-quadruplexes.[1] This latter sort of DNA can be found at the end of chromosomes, the telomeres. Each time a normal cell divides, the telomeres are not completely copied.[2] However, the enzyme telomerase can deal with the shortening. Since high telomerase activity has been detected in approximately 90% of tumour cells, its inhibition is considered an appealing target for antitumor drugs.[3]

Recently, we have reported the G4 selectivity of triphenylamine derivatives containing an aza-macrocyclic polyamine as pending arm.[4] Herein, we present three novel TPA derivatives functionalised with a commercially available acyclic polyamine. Their interaction with a panel of different DNA topologies has been studied by means of FRET-Melting assays, fluorescence spectroscopy and circular dichroism. The G4 selectivity of the novel tribranched compound (TPA3P) and its sensing properties have been remarkably improved in comparison with the aza-macrocyclic derivative already reported.

In order to get insight into the application of these compounds as antitumoral therapeutic agents, MTT assays were carried out using tumoral cell lines. Furthermore, aiming to enhance the cell uptake, TPA3P was encapsulated inside liposome nanoparticles, which are supposed to act as a drug delivery vehicle.

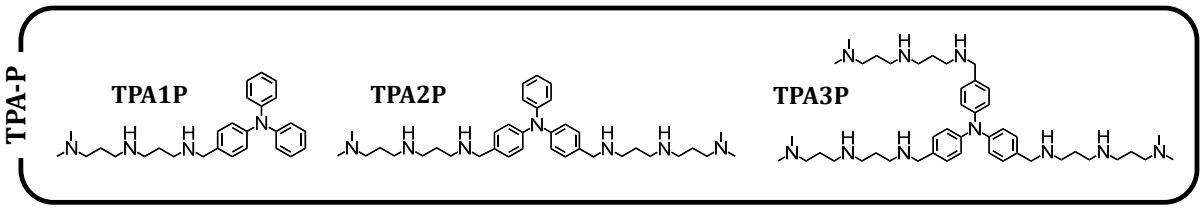

Figure 1: Depiction of the molecular structure of the studied novel triphenylamine derivatives.

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Stand-alone and networked multicomponent catalytic machinery: how the machine speed impacts catalytic activity

Michael SCHMITTEL, Pronay BISWAS, Indrajit PAUL, Abir GOSWAMI, Suchismita SAHA

Department of Chemistry and Biology, University of Siegen, D57072 Siegen, Germany
e-mail: schmittel@chemie.uni-siegen.de

While nature has built and optimized rotating catalysts (e.g. ATP synthase) over millions of years with the purpose to improve catalytic conversion for instance by eliminating product inhibition, abiotic examples using analogous nanomechanical action in catalysis have been lacking. Based on metal-ligand coordination tools, we have recently developed different types of multicomponent machinery that operate by distinct novel mechanisms. The first machinery uses dynamic allosteric effects to increasingly liberate the catalyst into solution the higher the rate of the machine motion.[1] In the second example, product inhibition is increasingly reduced at augmented machine speed (Figure 1).[2] In both cases the machine speed controls the turn-over rate of the catalytic system, as shown by a variety of data, including VT-NMR to determine the machine speed, evaluation of the catalytic rate at zero conversion (v_0), binding constants, speciation analysis and product liberation studies.

In order to further mimic the operational mode of natural machines, we have imbedded stand-alone multicomponent machinery [3] in signaling and in off-equilibrium networks.

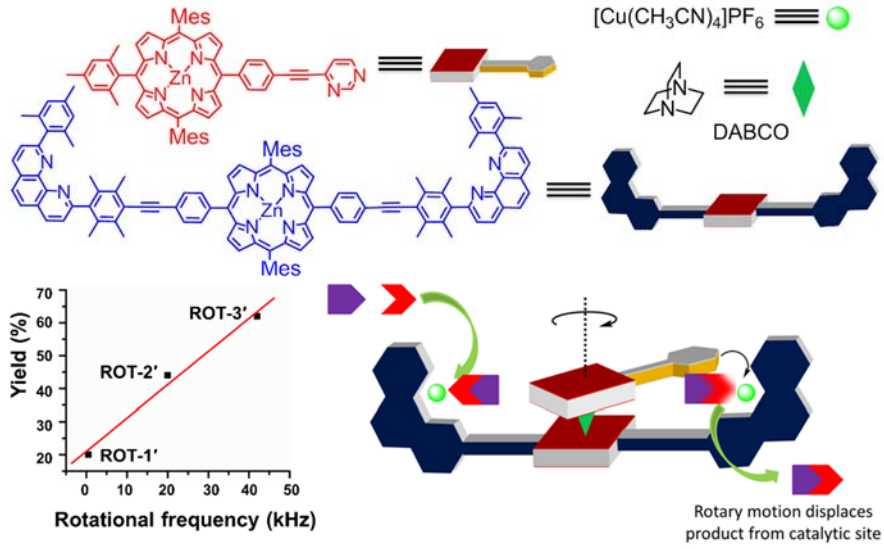

Figure 1. Cartoon representation of the four-component catalytic machinery that increases conversion due to reduction of product inhibition at higher machine speed (only one rotor is displayed).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

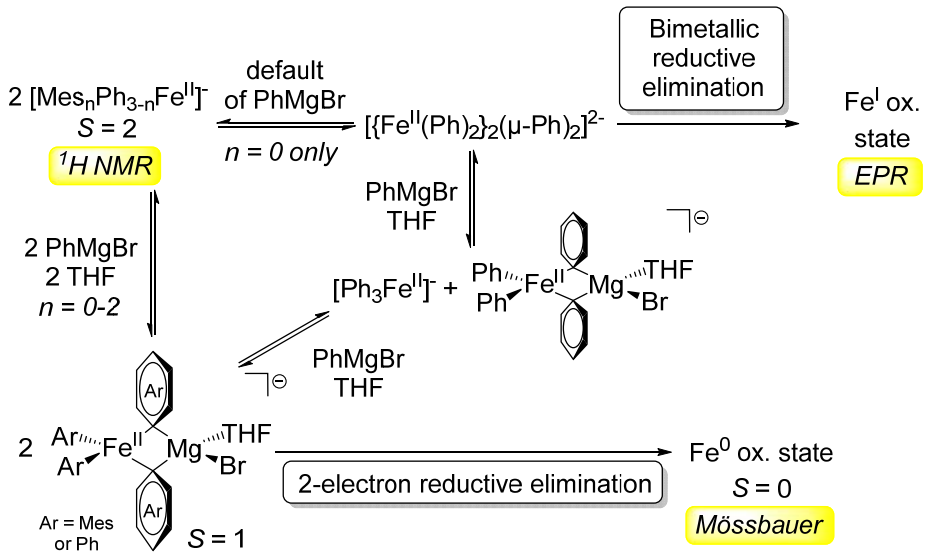
Formation of low-valent Fe^0 and Fe^I species in Fe-catalyzed cross-coupling chemistry: key role of *ate*-Fe^{II} intermediates

Guillaume LEFEVRE, [a,b] **Lidie ROUSSEAU,** [a,b] **Christian HERRERO,**[c] **Martin CLEMANCEY,** [d] **Geneviève BLONDIN,** [d] **Jean-Marc LATOUR** [d]

[a] *Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, CSB2D, 75005 Paris, France*
[b] *NIMBE, CEA, CNRS, Univ. Paris-Saclay, 91191 Gif, France*
[c] *Institut de Chimie Moléculaire et des matériaux d'Orsay (UMR 8182) Univ Paris Sud, Université Paris Saclay. 91405 Orsay cedex, France*
[d] *Univ. Grenoble Alpes, CEA, CNRS, LCBM (UMR 5249), pmb, 38000 Grenoble, France*
e-mail: guillaume.lefevre@chimieparistech.psl.eu

ate-iron(II) species such as $[Ar_3Fe^{II}]^-$ (Ar = aryl) are key intermediates in Fe-catalyzed cross-coupling reactions between aryl Grignard reagents (ArMgX) and organic electrophiles. They can be active species in the catalytic cycle, or lead to Fe^0 and Fe^I oxidation states.[1] In some cases, these low oxidation states can be themselves active in the coupling process.[2] However, their presence in the reaction medium most often leads to unwished organic byproducts. The development of new and efficient Fe-mediated cross-coupling processes therefore requires new frameworks enabling a fine control of the iron species distribution in the reaction medium, giving the possibility to inhibit the formation of unwanted oxidation states. So far, the formation of Fe^0 and Fe^I species in cross-coupling mediums can be hardly controlled. A deep understanding of the formation mechanism of these oxidation states is thus fundamental if one wants to finely monitor their presence in the reaction medium.

We report in this work our efforts related to the understanding of the elementary steps connecting *ate* $[Ar_3Fe^{II}]^-$ species (Ar = Mes, Ph), formed by transmetallation of aryl Grignard reagents with $FeCl_2$, to the formation of Fe^0 and Fe^I low oxidation states. A particular focus is put on the role of the steric and electronic effects of the aryl group in the reduction process. We demonstrate that a steric decompression induced by progressive substitution of the mesityl groups in $[Mes_3Fe^{II}]^-$ by phenyl anions leads to the formation of $[Mes_nPh_{3-n}Fe^{II}]^-$ species (n = 0-2; observation by ^1H NMR). Thanks to this steric decompression, formation of Fe^0 and Fe^I oxidation states is concomitantly observed by EPR and Mössbauer spectroscopies (Scheme 1).



Scheme 1. Summary of the different pathways connecting *ate*-Fe^{II} species with Fe^0 and Fe^I oxidation states; *S* denotes the spin multiplicity.

Analysis of the reactivity pattern by DFT computation shows that at early stages of the transmetallation process, for low PhMgBr:Fe ratios, dimerization of $[Ph_3Fe^{II}]^-$ into $[\{Fe^{II}(Ph)_2\}_2(\mu\text{-}Ph)_2]^{2-}$ [3] leads to the formation of Fe^I oxidation state by a bimetallic reductive elimination, enabled by an antiferromagnetic coupling between the two Fe^{II} subunits. This dimerization is hampered for $[Mes_nPh_{3-n}Fe^{II}]^-$ intermediates involving one or more bulky aryl groups (Ar = Mes), which explains why Fe^I oxidation state is not detected when sterically hindered Grignard reagents are used as nucleophiles in these systems. In the presence of an excess of PhMgBr, quaternarization of the Fe^{II} ions in $[Mes_nPh_{3-n}Fe^{II}]^-$ species affords $[Mes_nPh_{4-n}Fe^{II}\bullet MgBr(THF)]^-$ (n = 0-2), which leads to the formation of Fe^0 oxidation state by 2-electron reductive elimination. This two-step mechanism involves two successive intersystem crossings, and connects high-spin $[Ar_3Fe^{II}]^-$ species with a diamagnetic Fe^0 complex, demonstrating the importance of spin acceleration in this process.

Overall, this work enlightens the role played by steric and electronic factors in the evolution of *ate*-Fe^{II} species towards the low-valent Fe^0 and Fe^I oxidation states. Such mechanistic findings can give new guidelines for the design of finely tailored ligands in iron-mediated C─C bond formation strategies, opening up the possibility to selectively obtain a sole iron oxidation state upon the reduction process.[4]

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International Symposium on Metal Complexes 2019
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Decorating graphitic surfaces with Pd(II) complexes: towards discrete metal ion catalytic sites

Matteo SAVASTANO, [a] Paloma ARRANZ-MASCARÓS, [b] María Paz CLARES, [c] María Luz GODINO-SALIDO, [b] Lluís GUIJARRO, [c] María Dolores GUTÍERREZ-VALERO, [b] Mario INCLÁN, [c] Antonio BIANCHI, [a] Enrique GARCÍA-ESPAÑA, [c] Rafael LOPEZ-GARZÓN [b]

[a] Dept. of Chemistry "Ugo Schiff", University of Florence, 50019 Sesto Fiorentino, Italy
[b] Department of Inorganic and Organic Chemistry, University of Jaén, 23071 Jaén, Spain
[c] Institute of Molecular Science, University of Valencia, 46071 Valencia, Spain
e-mail: matteo.savastano@unifi.it

Pd-based catalysts have long been in the spotlight for a plethora of catalytic purposes. In recent times we reported about the construction of nanostructured heterogeneous catalysts spontaneously assembled in a supramolecular manner from aqueous solution.[1-3] A pictorial depiction of the preparation of such catalysts is given in Figure 1. These systems are assembled by conjugating a polyamine containing a small tetraaza-macrocycle with a highly electron-deficient aromatic moiety (Figure 1a). The resulting ligand spontaneously adsorbs on graphitic surfaces by simply dispersing carbonaceous supports in its aqueous solution (Figure 1b). These functionalized materials can be further decorated with Pd(II) (as tetrachloropalladate in Figure 1c) (other metals are also feasible)[2], resulting in supported Pd(II) complexes (Figure 1d). This is a delicate point, requiring precise understanding of the coordination environment of the transition metal cation: our systems were designed and demonstrated to present an ancillary chloride anion in the first coordination sphere of Pd(II), the possibility of efficient ligand exchange mechanism being a prerequisite for catalytic activity. The resulting heterogeneous catalysts were originally assayed as catalyst for C-C bond formation in water (Cu-free Sonogashira cross-coupling).[1]

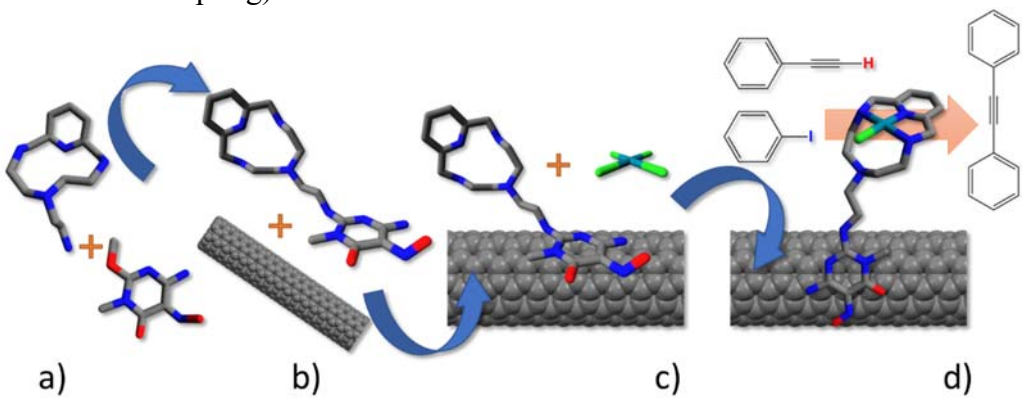

Figure 1. Pictorial preparation scheme of our supramolecular Pd(II)-based heterogeneous catalysts: a) ligand synthesis by conjugation of the different functional moieties; b) spontaneous chemisorption of the ligand from its aqueous solution onto suspended CNTs; c) feeding of $PdCl_4^{2-}$ to the hybrid material suspended in water to afford discrete Pd(II) complexes at the surface; d) usage of the prepared catalysts in the Sonogashira cross-coupling reaction.

Despite the initial success,[1] which prompted us to extend this strategy for other purposes, such as Cu(II) coordination and reduction to give CNTs-supported Cu(0) nanoparticles[2] and electrode materials for oxygen reduction reactions in fuel cells,[3] even our most promising ligand (HL2, Figure 2) displayed limited reusability for Sonogashira cross-coupling.[1] This was found to be mainly due to the competition of the hydrophobic reactants and products of the reaction for the surface sites of the graphitic walls, causing a gradual detachment of the Pd(II) complexes from the surface.

Accordingly, we propose a novel molecular candidate which should maintain the catalytic efficiency while giving rise to stronger chemisorption. To that end we have prepared and studied the bipedal ligand **1** (Figure 2), which maintains unmodified the macrocyclic moiety, eventually granting the same activated coordination environment, while hopefully providing a more stable chemisorption owing to its 2 hydrophobic pendants.

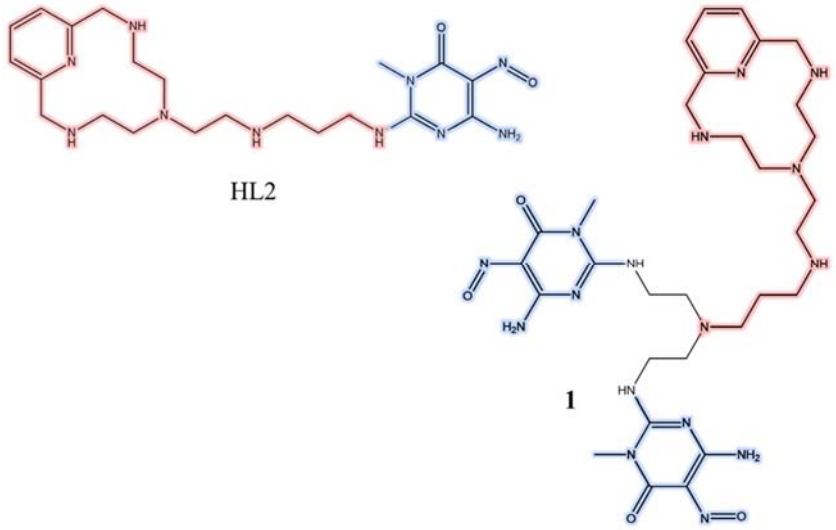

Figure 2. Chemical formulas of our best performing ligand reported so far (HL2) and of the novel derivative (**1**). Hydrophilic (red) and hydrophobic (blue) functional moieties that we decided to maintain unmodified since proved working for HL2 are highlighted.

Moreover, in view of the higher steric hindrance due to the second pyrimidine and in search of sorbents that could bear a high loading of our molecular catalysts, we replaced CNTs with graphene as carbonaceous substrate. Here we disclose the principal results obtained so far with our rational approach for the construction of supramolecular heterogeneous catalysts based on macrocyclic complexes of Pd(II).

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International Symposium on Metal Complexes 2019
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Kinetics and mechanism of catalytic oxidation of phenol by hydrogen peroxide using Cu(II)cyclen functionalized silica aerogel catalyst

Attila FORGÁCS, [a,b] **Zoltán BALOGH**, [a] **József KALMÁR**, [a] **István FÁBIÁN** [a,b]

[a] *Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1., H-4032 Debrecen, Hungary*
[b] *MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group*
e-mail: forgacs.attila@science.unideb.hu

Mesoporous silica aerogels covalently functionalized with Cu(II)cyclen were synthesized earlier.[1] The aerogels were characterized by SEM, N_2 adsorption-desorption porosimetry, ICP-OES and SANS measurements. The wetting mechanism of the parent silica aerogel was also investigated by NMR (cryoporometry, relaxometry, diffusiometry) techniques. The functionalized aerogel effectively catalyzes the oxidation of phenol by H_2O_2. First, we used HPLC to follow the conversion of phenol into primary oxidation products. Interestingly, the immobilized Cu(II)-complex has a higher specific catalytic activity than the dissolved complex. Detailed kinetic experiments were conducted by using UV-VIS spectrophotometry. The partial kinetic orders of the reagents were determined. From the kinetic and spectroscopic data, we postulated a possible reaction mechanism and suggested a mathematical model for the reaction.[2] Clear evidence has been obtained that the catalytic system behaves kinetically differently due to the immobilization of the metal-complex on a porous carrier.

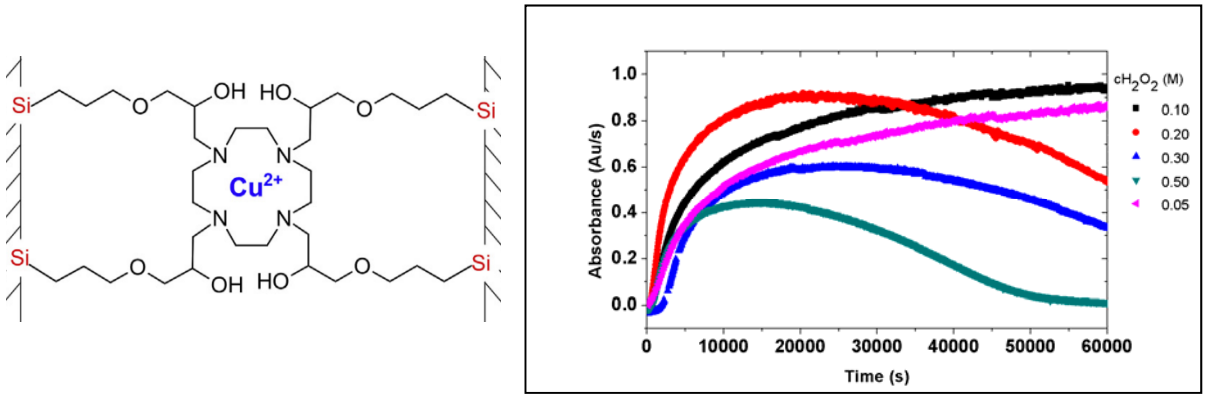

Figure 1. Left: Schematic structure of the aerogel catalyst. Right: Catalytic oxidation of phenol. Measured absorbance as a function of time at different H_2O_2 concentrations (λ = 400 nm; c_{phenol} = 4.3 mM; 0.11 mg/ml Cu(II)cyclen; 70°C; pH = 3.5).

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International Symposium on Metal Complexes 2019
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Tris-hydroxypyridinone based ligand (KC18) as receptors in new polymeric optical sensors for Fe(III)

Lisa Rita MAGNAGHI,[a)] Karam CHAND,[b] Maria Amélia SANTOS,[b)] Giancarla ALBERTI,[a)] Camilla ZANONI,[a)] Raffaela BIESUZ[a)]

[a)] Dipartimento di Chimica, Università di Pavia, via Taramelli 12, 27100 Pavia, Italy
[b)] Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal
e-mail: lisarita.magnaghi01@universitadipavia.it

Iron is an important biological metal ion that plays an essential role in many metabolic pathways, such as the uptake and transport of oxygen to tissues, in the electron transport chain (respiration) and for reduction of carbon dioxide (photosynthesis). [2] Since both iron deficiency and overloading can induce various biological disorders, the presence of Fe (III) in biological systems has to be efficiently moderated. [1] Under physiological conditions, the level of iron in the organism is controlled by homeostatic regulation that is mostly due to intestinal absorption or erythropoiesis in the bone marrow. [2]

Our body is not able to protect cells against iron overload, as a consequence of hereditary disorders or caused by multiple frequent blood transfusions of patients affected by different kinds of anemia, like b-thalassemia major, or sickle cell anemia. [1] For this reason various human iron intoxications and overloaded metal-induced pathologies need to be treated by administration of a chelating agent, which sequester the excess of iron, without catalyzing the Fenton reaction. [2] The iron chelators, currently employed in chelation therapy, are bidentate, tridentate or hexadentate and, in order to fill the first coordination sphere, create complexes with stoichiometry 3:1, 2:1 and 1:1.

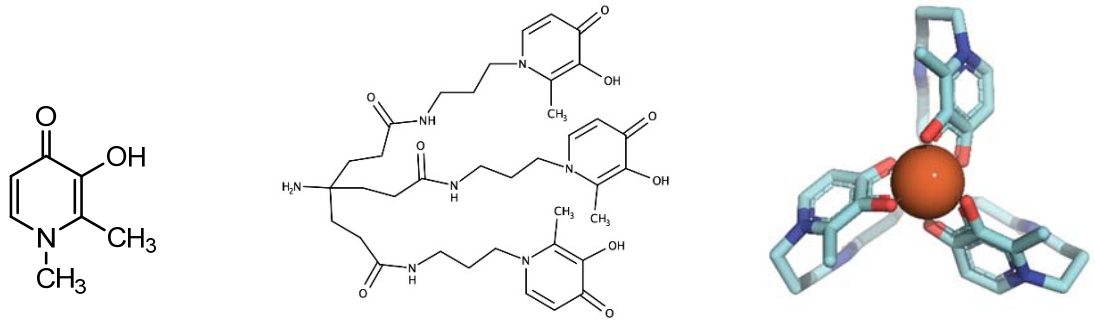
Among suitable iron chelators, hydroxypyridinones (HPO) have been intensively developed towards potential therapeutic applications in chelating therapy, after the disclosure of deferiprone (DFP), a member of 3-hydroxy-4-pyridinone class (3,4-HP), as an effective iron-sequestering agent [3], (see Fig 1 A).

These compounds are able to chelate iron with the two oxygen atoms of the structure, in order to form an iron complex with stoichiometry Fe:HPO 1:3. Their great interest in medicinal chemistry derives from the association of high/specific metal-chelating capacity with low toxicity and easy derivatization. In addition, chelating efficacy can be further improved increasing the denticity of the chelator, by conjugating two or more chelating units in the same skeleton. [3]

Thanks to their strong affinity for iron (III), these molecules can be exploited for analytical applications, for instance as selective receptors in sensing devices for iron (III) in biological fluids, which is an important challenge in analytical clinical chemistry. [1,2,5] In fact, these devices can be employed in studies on chelation therapy, to evaluate the ability of a sequestering agent and the efficacy of chelation therapy. [1,2]

On the sequence of our previous research involving the grafting of a monohydroxypyridinone enclosing an alkylamine substituent group, *N*-(3'-aminopropyl)-3-

hydroxy-2-methyl-4-pyridinone (AHP), on a mesoporous silica,[5] in this work we used a tris-hydroxypyridinone based ligand (KC18), also with a terminal amino group, not involved in iron complexation, and suitable to be functionalized, for example to be grafted into a solid phase. In this case, the complex with iron can be fully coordinated with only one molecular unity, thus endowed with higher thermodynamic and kinetic stability. Furthermore the complex of KC18 with Fe (III) in water is coloured, a feature which is promising for sensing.



A **B** **C**

Figure 1. Structure formulae of DFP (A) and KC18 (B); molecular model of [FeKC18] (C).

As solid support we chose ethylene–vinyl alcohol copolymers, EVOH, since this polymer is insoluble in water, is biocompatible and it is commercially available. Therefore, these copolymers are excellent candidates to obtain materials with potential applications in biology or biomedicine. However, EVOH copolymers often exhibit as disadvantage their low chemical reactivity with the active compounds at low temperature. To solve this problem, we created new highly reactive functional groups in the polymer structure, able to bind the active agent. [4] The structure of intermediates and final polymer were investigated by IR and ^{1}H-NMR spectroscopy.

The final devices are characterized studying their sorption properties towards Fe(III). For their analytical application, the entire UV-vis spectra of the sensor and the RGB index of the pictures (taken by a common smartphone), before and after dipping it in Fe(III) solutions, are acquired and elaborated through univariate or multivariate analysis.

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International Symposium on Metal Complexes 2019
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An in-depth thermodynamic investigation on As(III) interaction with different classes of ligands and evaluation of the sequestering ability in different experimental conditions

Donatella CHILLÉ, [a] Giuseppe CASSONE, [b] Fausta GIACOBELLO, [c] Ottavia GIUFFRÉ, [a] Viviana MOLLICA NARDO, [c] Rosina C. PONTERIO, [c] Franz SAIJA,[c] Sebastiano TRUSSO [c] and Claudia FOTI [a]

[a] *University of Messina, Viale Ferdinando Stagno d'Alcontres 31, 98166, Messina, Italy*
[b] *Institute of Biophysics of the Czech Academy of Sciences, Královopolská 135, 61265, Brno, Czech Republic*
[c] *CNR-IPCF, Viale Ferdinando Stagno d'Alcontres 37, 98158, Messina, Italy*
e-mail: dchille@unime.it

The even more pronounced presence of arsenic in the environment is of particular relevance about human health as its poison effect is recognized since time immemorial. The primary source of arsenic is of natural type and derived, basically, from the interaction between groundwater and aquifer sediments as well as hard rocks of minerals. Also the anthropogenic activities, such as agricultural and industrial ones, play a marked role in the release of this metalloid in the environment, especially in groundwaters. It is supposed, in fact, that arsenic mainly reaches human organism as a consequence of the intake of drinking water derived from contaminated groundwater [1].

To evaluate the effect of arsenic on human health is crucial identify and quantify each chemical form since everyone shows different physiological and bioactive properties when interacts with biomolecules present in human body. In general, the inorganic forms are considered more toxic than the organic ones and, specifically, arsenic in its trivalent oxidation state is recognized more harmful than the pentavalent one [2]. Despite the chemical speciation represents a key point for investigating the mobility, bioavailability and toxicity of an element, very few studies are reported in literature as regards the thermodynamic behavior of arsenic, especially for As(III).

In light of this, this contribution intends to analyze the interactions of As(III) with various classes of ligands, in particular thiols, phosphonic acids and carboxylic acids. For each system, the combined use of different analytical techniques, such as potentiometry, spectrophotometry and calorimetry, allowed to obtain the best speciation model together with all the thermodynamic parameters (log β, ΔH, ΔG, TΔS). Since the stability constants are strictly dependent on the ionic strength, for systems affected by a more marked metal-ligand interaction, potentiometric measurements were carried out in a wide range of ionic strength. In order to verify the coordination mode of As(III) towards compounds containing both –COOH and –SH groups (for which As(III) exhibits a high affinity), Raman spectroscopy and *ab initio* molecular dynamics simulations were also performed.

Finally, the sequestering ability for every metal-ligand system was calculated, in different experimental conditions, by means of an empiric parameters known as $pL_{0.5}$. It represents the total ligand concentration required to "sequester" the 50% of metal present in traces and in can

be calculated by plotting the sum of the mole fraction (χ) of the complex species as a function of pL (pL = -log [L] and [L] = total ligand concentration) [3].

Table 1. Ligands under investigation

Ligands	Acronym
2-mercaptopropanoic acid or thiolactic acid	*tla*
2-mercaptosuccinic acid or thiomalic acid	*tma*
meso-2,3-Dimercaptosuccinic acid	*dmsa*
L-Cysteine	*Cys*
L-Glutathione reduced	*Gsh*
1,3-propanedicarboxylic acid or malonic acid	*mal*
Propane-1,2,3-tricarboxylic acid or tricarballylic acid	*tca*
Butane-1,2,3,4-tetracarboxylic acid	*btc*
Benzenehexacarboxylic acid	*mlt*
n-(Phosphonomethyl)iminodiacetic acid hydrate	*NTAP*
n,n-bis(phosphonometyl)glycine	*NTA2P*
Nitrilotri(methylphosphonic acid)	*NTA3P*

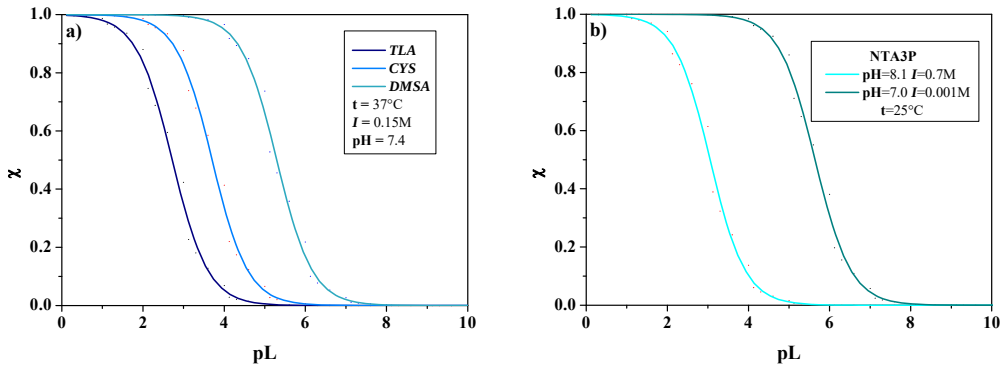

Figure 1. Examples of sequestration diagrams. [a)] As(III)-TLA, Cys and DMSA systems in physiological conditions; [b)] As(III)-NTA3P system in conditions simulating a fresh water and seawater.

Acknowledgements: The authors acknowledge FSE regional funds for PhD support to D.C

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International Symposium on Metal Complexes 2019
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Maltol-derived ligands as promising systems for poly-nuclear complexes

Luca GIORGI, [a] Mauro FORMICA, [a] Daniele PADERNI, [a] Vieri FUSI, [a] Paola PAOLI, [b] Patrizia ROSSI, [b] Gianluca AMBROSI [a]

[a] Department of Pure and Applied Sciences, University of Urbino "Carlo Bo", Via della Stazione 4, I-61029, Urbino (PU), Italy
[b] Department of Energy Engineering, University of Florence, Via S. Marta 3, I-50139 Florence, Italy
e-mail: mauro.formica@uniurb.it

Ligands able to form poly-nuclear metal complexes are of great interest because they are useful in many fields ranging from molecular recognition to transport, catalysis and many others.[1] At the same time, systems able to stabilize rare earth (RE) and alkaline earth series (AE) cations both in aqueous solution and in the solid state are attractive because they have recently found applications in fields ranging from new materials to medicinal chemistry.[2]

Recently, we developed a class of molecules based on two 3-hydroxy-2-methyl-4-pyrone units (maltol, Figure 1) linked to a polyamine scaffold that exhibited anti-neoplastic activity *in vitro*[3] and *in vivo*.[4]. These molecules were also investigated as potential ligands for metal ions thanks to their ability to coordinate M(II) transition-metal ions; the metals are stabilized by the polyamine functions and by the deprotonated hydroxyl oxygen atom of each maltol unit. This induces the formation of an electron-rich area allowing the transition-metal complexes to bind M(II) and M(III) hard metal ions. The results suggest that these systems can effectively behave as metal receptors suitable to bind rare earth and alkaline earth series ions. Following this aim we are widening the field, preserving the binding skeleton of the donor atoms, to confer different optical properties to the new synthesized ligands.

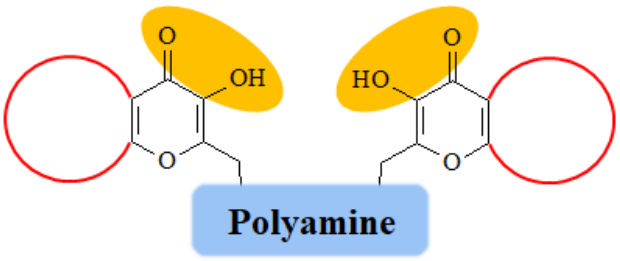

Figure 1: Schematic drawing of the 3-hydroxy-2-methyl-4-pyrone based ligands.

Acknowledgements: The authors would thank to the Italian Ministry of Education, University and Research for the financial support by MIUR-PRIN 2015 - 2015MP34H3_005.

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International Symposium on Metal Complexes 2019
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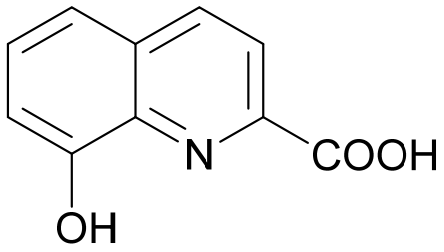
Interactions of 8-hydroxyquinoline-2-carboxylic acid with molybdate in aqueous solution

Giuseppe BRANCATO, [a] Francesco CREA, [b] Concetta DE STEFANO, [b] Sofia GAMA, [c, d] Gabriele LANDO, [b] Demetrio MILEA, [b] Winfried PLASS, [c] Silvio SAMMARTANO [b]

[a] Scuola Normale Superiore, Palazzo della Carovana, Classe di Scienze Matematiche e Naturali, Piazza dei Cavalieri, 7, 56126, Pisa, Italy.
[b] Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, Università degli Studi di Messina, Viale F. Stagno d'Alcontres 31, 98166 Messina, Italy.
[c] Institut für Anorganische und Analytische Chemie, Friedrich-Schiller-Universität Jena, Humboldtstr 8, 07743 Jena, Germany.
[d] Present address: Institut de Chimie Moléculaire, UMR 6302 CNRS, Université de Bourgogne - Franche Comté, 9, avenue A. Savary, 21078 Dijon Cedex, France.
e-mail: dmilea@unime.it

8-hydroxyquinoline-2-carboxylic acid (8-HQA, Scheme 1) has been found in high concentrations (0.5-5.0 mmol dm^{-3}) in the gut of Noctuid larvae (and in a few other lepidopterans), in which it seems it acts as a siderophore [1].



Scheme 1. 8-hydroxyquinoline-2-carboxylic acid (8-HQA).

Since it is known that many natural siderophores are also involved in the uptake and metabolism of other essential elements than Fe [2], this study reports some results on the investigation of 8-HQA interactions with molybdate (MoO_4^{2-}, i.e. the main Mo form in aqueous environments [3]), in order to understand the possible role of this ligand as molybdophore.

A multi-technique approach has been adopted, in order to derive a comprehensive set of information necessary to assess the chemical speciation of 8-HQA / MoO_4^{2-} systems, as well as the coordination behaviour and the sequestering ability of 8-HQA towards molybdate.

Chemical speciation studies have been performed in KCl aqueous solutions at I = 0.2 mol dm^{-3} and T = 298.15 K by ISE-H^+ (glass electrode) potentiometric and UV/Vis spectrophotometric titrations. Some results on NMR, quantomechanical and MS experiments are also reported, along with comparisons with 8-HQA / Fe^{3+} system.

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International Symposium on Metal Complexes 2019
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Ligands for chelation of bismuth and copper: complexation study and stability in biologically relevant media

Bayirta EGOROVA,[a)] Ekaterina MATAZOVA,[a)] Gleb ALESHIN,[a)] Anastasia ZUBENKO,[b)] Olga FEDOROVA,[b)] Yury FEDOROV,[b)] Alexey MEDVED'KO,[a)] Sergey VATSADZE,[a)] Anna PRISELKOVA,[a)] Stepan KALMYKOV[a)]

[a)] Lomonosov Moscow state university, Leninskie Gory, 119991, 1, Moscow, Russia
[b)] A.N.Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Vavilova St. 28, 119991, Moscow, Russia,
e-mail: bayirta.egorova@gmail.com

Nowadays radioisotopes of various cations are considered as perspective for diagnostic and therapeutic purposes. Compounds for targeted delivery labeled by ^{64}Cu, ^{213}Bi, ^{212}Pb, ^{90}Y, ^{177}Lu are undergoing preclinical and clinical trials for positron emission tomography and targeted alpha and beta therapy of oncological diseases. Among these compounds there are peptides and antibodies as well as their fragments with affinity to different types of malignancies. Basically labeling of these molecules by cations of radionuclides is carried out via bifunctional chelators – derivatives of such ligands as macrocyclic H_4DOTA or acyclic H_5DTPA. It is worth noting that H_4DOTA forms very stable complexes with plenty of cations even in extreme conditions that is not the case of H_5DTPA but the latter in contrast to former forms complexes much faster at room temperature that is very important for short-lived medical radionuclides and sensitive to heating biomolecules. In our study we systematically investigate ligands that to a certain degree combine acyclic and macrocyclic moieties to immediately form stable complexes at room temperature with cationic radionuclides promising for nuclear medicine.

We considered newly synthesized different azacrown-ethers with bigger cavity than H_4DOTA possesses and for Cu^{2+} bispidine type ligands were also evaluated (Fig. 1). All studied ligands were studied for their protonation ability (except a few bispidines that were not soluble in water) and complexation properties towards set of cations using potentiometric, spectrophotometric titration and radiochemical techniques.

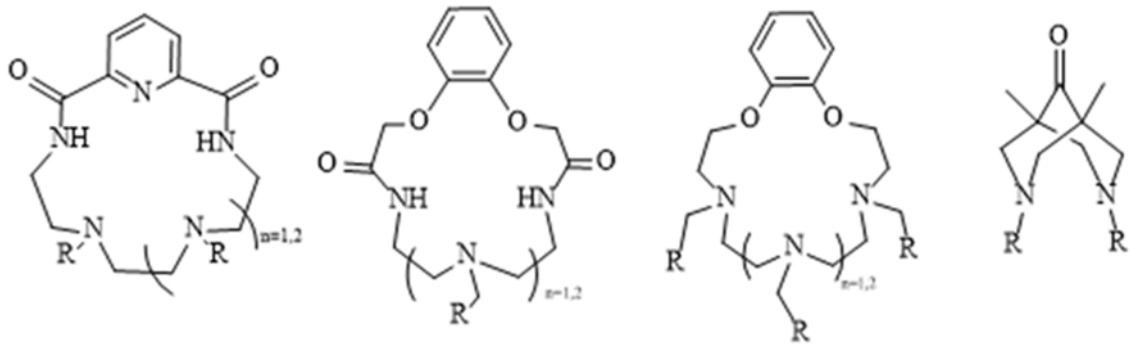

Figure 1. Ligands, considered in this work.

Among azacrown ethers not only number of heteroatoms in macrocycle was varied but also type of pendant arm: carboxylic, pyridine, picolinic or absence of any arm – to follow structure – property relationship. All azacrowns possessed benzo- or pyridine fragment in the cavity that could be further used for conjugation of ligand to biomolecule. Among them ligands with and without amide groups in the cavity were considered.

Starting from determination of complexation constants in model solutions with Cu^{2+}, Pb^{2+}, Bi^{3+} and rare earth elements by this time it was shown that Cu^{2+} and Bi^{3+} form the most stable complexes (logK(ML)>14) with ligands possessing carboxylic arms. Their radiolabeling conditions by ^{64}Cu and ^{207}Bi were optimized. It should be noted that all labeled compounds were obtained at room temperature in a few minutes that was confirmed by thin layer chromatography.

Indeed amide containing ligands demonstrated lower protonation as well as complexation ability but two of them: benzo-2 pic and pyridine-3 COOH – showed high enough complexation constants with Cu^{2+} (logK=15.6(1)) and Bi^{3+} (logK=21.3(2)). However they've been shown to dissociate in presence of competing cations and serum proteins.

Among bispidines such pendant arms as carboxylic, triazole-containing with different length were varied. Presence of triazole affected on solubility in water and only decrease of logK(CuL) was observed for such type of bispidines. However 2 ligands with carboxylic groups without triazoles have shown logK(CuL)=14,2 and >20 and were further tested for serum stability.

Radiolabeled ligands that have shown the lack of cation release in competing media (0-10%) in at least 2 hours (Cu^{2+}) and 1 day (Bi^{3+}) were further tested for their *in vivo* behavior and biodistribution in normal mice. The results of leading compound with Bi^{3+} were the same as obtained with DOTA-complex: fast clearance from the body and much lower accumulation of radioactivity in organs incl. liver and kidneys compared to blank experiment. Similar behavior was shown for copper-bispidine complex. These complexes are concluded to be perspective as components of copper and bismuth radiopharmaceuticals and bifunctional modifications of such ligands for their conjugation to peptides or antibodies are under development now.

Acknowledgements: We thank Russian Science Foundation, project №18-73-10035, for financial support.

International Symposium on Metal Complexes 2019
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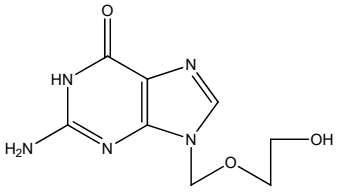
Metal-binding patterns of a synthetic adenine-nucleoside in copper(II) complexes with rigid-planar tridentate chelators of biological relevance

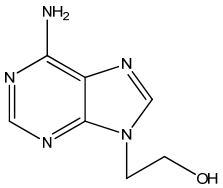
Noelia RUIZ GONZÁLEZ, [a] Fe María RAMOS-ROSA, [a] Alicia DOMÍNGUEZ-MARTÍN, [a] Duane CHOQUESILLO-LAZARTE, [b] Alfonso CASTIÑEIRAS, [c] Juan NICLÓS-GUTIÉRREZ [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain
[c] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
e-mail: noeliarg13@correo.ugr.es

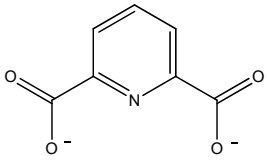
Active research regarding the metal binding patterns (MBP) of acyclovir (acv), a synthetic guanine nucleoside, has been carried out in our group, significantly enlarging the current panorama [1]. Recently, the μ-N1,N7 MBP was reported for the synthetic adenine-nucleoside N9-(2-hydroxyethyl)adenine (9heade) in a Cd(II) coordination polymer [2] but interligand (9heade)N6-H···O(carboxylate) interactions were overlooked. Here we report the synthesis and crystal structures of H9heade(pdc)·H_2O (**1**), trans-[Cu(pdc)(9heade)(H_2O)$_2$] ·3H_2O (**2**) and [Cu(glygly)(μ-N7,O(ol)-9heade)·Cu(glygly)(9heade)(H_2O)]·8H_2O (**3**). The two latter compounds are mixed-ligand Cu(II)-complexes with pyridine-2,6-dicarboxylate(2-) (pdc) or glycylglycinate(2-) (glygly) as rigid-planar tridentate chelators. Formulas of above referred ligands are:



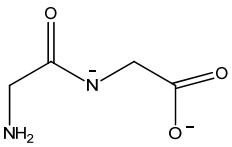
acv



9heade



pdc(2-)



glygly(2-)

In compound **1**, anion-cation molecular recognition consists of two unequal (9heade)N-H···O(carboxylate, Hpdc) interactions (figure 1), with the $N1^+$-H···O24 distance (2.528(2) Å, 168.1º) being shorter than N6-H···O25 (2.950(2) Å, 169.0º).

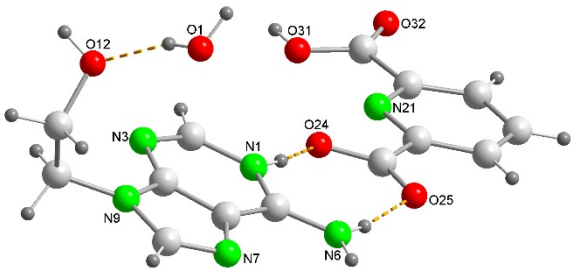


Figure 1. Detail of the anion-cation interaction in H9heade(pdc)·H_2O (**1**).

In figure 2-A, the complex molecule of **2** is shown. They exhibit elongated ~4+2 Cu(II) coordination and the MBP of 9heade consists of the cooperation between the Cu-N7 bond (1.962(3) Å) and the rather linear (9heade)N6-H···O24(carboxylate, pdc) interaction (2.886(4) Å, 174.2º).

The complex molecule of **3** contains an asymmetric dinuclear complex molecule. Both non-equivalent metallic centers (Cu1 and Cu2) essentially exhibit square-based pyramidal coordination, type 4+1, with an O-aqua and O-ol as apical-distal donor atoms (figure 2-B). Molecular recognition consist of the cooperation between the appropriate Cu-N7 bond and the intra-molecular interligand N6-H···O interaction: Cu1-N17 1.981(5) Å N16-H16B···O1 2.811(7) Å, 151.4º and Cu2-N37≠1 2.018(5) Å, N36-H36B···O21≠2 2.816(7) Å, 145.2º (#1 x,-y+1/2,z-1/2; #2 x,-y+1/2,z+1/2). Interestingly, 9heade acts as N7-unidentate for Cu1 and μ-N7,O(ol) between both metallic centers. The molecular topology is reinforced by the (aqua)O1-H···N21 H-bond and the water-mediated interactions N16-H···O15 and N29-H···O15 involving one among the eight non-coordinates water molecules.

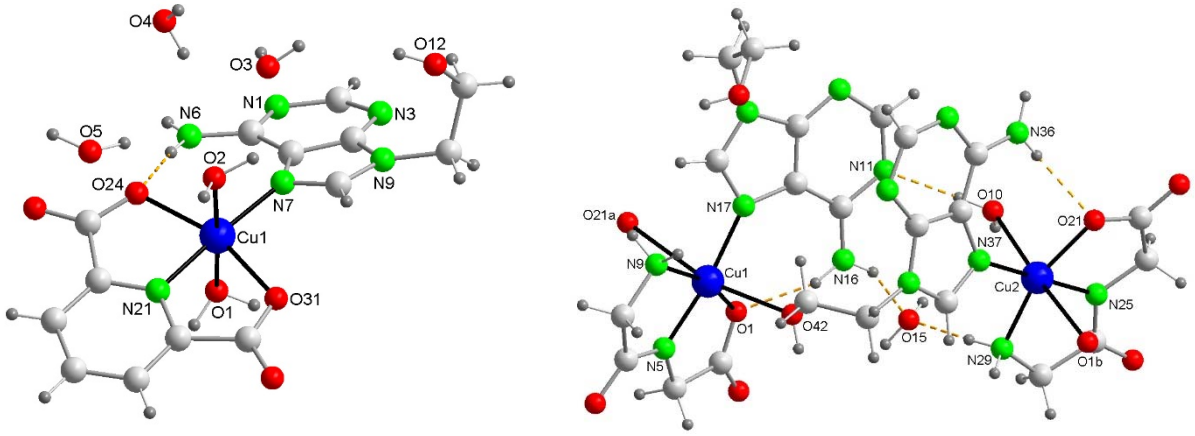


Figure 2. A) Asymmetric unit in the crystal of trans-[Cu(pdc)(9heade)(H_2O)$_2$]·3H_2O (**2**). B) Asymmetric dinuclear complex molecule in [Cu(glygly)(μ-N7,O(ol)-9heade)· Cu(glygly)(9heade)(H_2O)]·8H_2O (**3**), solvent water molecules except for O15 have been omitted for clarity.

In conclusion, the N1(9heade) atom exhibits the highest proton affinity. All N-atoms of 9heade are borderline Pearson bases, however the N7(9heade) atom is the preferred binding site for Cu^{II} (a borderline Pearson acid). That is mainly because N1 is more hindered by the exocyclic –NH_2 group than N7. Moreover, the O-ol atom of 9heade has also proven to bind a Cu^{II} center, thus leading to the unprecedented μ-N7,O(ol) MBP for this synthetic purine nucleoside. Why N1-9heade is not used for Cu^{II} coordination merits to be discussed in depth.

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International Symposium on Metal Complexes 2019
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Smart optical devices for ions sensing

Raffaela BIESUZ, Lisa Rita MAGNAGHI, Giancarla ALBERTI

Dipartimento di Chimica, Università di Pavia, via Taramelli 12, 27100 Pavia, Italy
e-mail: rbiesuz@unipv.it

Optical devices for ions sensing have been designed by immobilization of selective dyes on solid phases. In these last years we have tried different solid material, from chelating resins, to silica, or natural and synthetic polymers[1-5].

In the present work, the selected solid support is an extremely cheap cellulose based sheet, the "Colour Catcher®" (CC), a product of the detergents market, distributed, in Italy, by Grey a partner of the Henkel company, which exhibits strong anion exchange properties.

We selected, as receptors, different dyes that change their color when immersed in cations or anions solutions; so that the colour change has been used for qualitative and quantitative analysis (Figure 1)

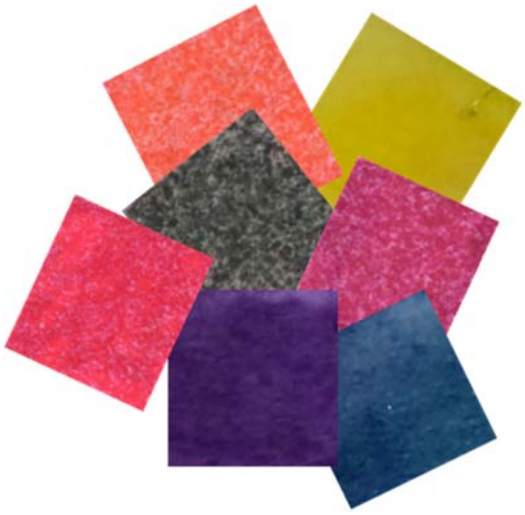

Figure 1. Optical devices based on Colour Catcher® solid material, functionalized with different dyes for cations and anions sensing.

The device is simply prepared dipping a clipping of CC in an enough concentrated solution of the day, in proper and well defined conditions. After washing and drying, the sensor is ready-to-use.

We have prepared different sensors, some most promising are those obtained by fixing the following dyes:

- Alizarin Red S. The Aliz-CC@ device is selective for Cu(II), Al(III) and Fe(III);
- PAN (1-[2-pyridylazo]-2-naphthol). The PAN-CC@ sensor can be used for Co(II), Ni(II), Zn(II) determination;
- NET (Black Eriochrome T). The NET-CC@ device is selective for Ca(II), Mg(II) and Zn(II);

- Ellman's reagent (5,5-dithio-bis-(2-nitrobenzoic acid)). The Ell-CC@ is useful for sulfur and thiols.

All devices were characterized studying their sorption properties towards the analytes. In particular, kinetic and sorption isotherms were investigated.

For their application as practical sensors, dose-responses curves were carried out for single or multi-analyte determinations. For this purpose, the entire UV-vis spectra and the RGB index of the sensor, before and after dipping it in the analyte solutions, were acquired and the chemometric tool of Partial Least Square analysis (PLS) was used for data treatment.

Since some success obtained, it can therefore be concluded that these optical devices could be promising for the determination of cations and anions in aqueous sample solutions.

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International Symposium on Metal Complexes 2019
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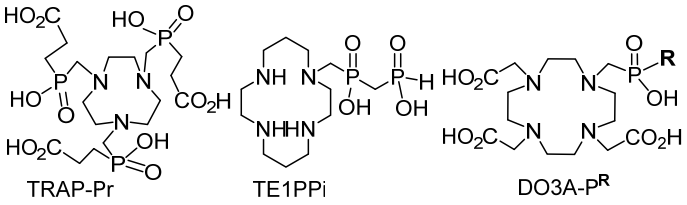
Influence of distant coordinating substituents in pendant arms on complexation of macrocyclic ligands

Vojtěch KUBÍČEK, Jan KOTEK, Petr HERMANN

Department of Inorganic Chemistry, Universita Karlova, Hlavova 2030, 12843 Prague 2, Czech Republic
e-mail: petrh@natur.cuni.cz

Complexes of macrocyclic ligands are used in medicine as contrast agents for MRI, carriers of metal radioisotopes for PET imaging or for therapy, chelators of fluorescence metal ion for optical imaging etc. Their properties to be tuned involve thermodynamic stability and complexation/decomplexation kinetics. The kinetic processes proceed with different mechanisms and complexation, important mainly for radiopharmacy, is the least understood. Thus, ligands facilitating complex formation but keeping kinetic inertness and high thermodynamic stability of the complexes are desired. There is accepted that formation of the complexes is a two-step process. The first step is a fast formation of weak *out-of-cage* complex where mostly pendant arm donor atoms are coordinated. It is followed by a slow re-arrangement to *in-cage* complex where macrocycle donor atoms are bound and the metal ion is fully encapsulated. Both steps can be influenced by proper ligand design.

In this contribution, influence of pendant arms on complex formation will be evaluated. The pendant arm substituents have different donor atoms, charge and hydrophobicity. Thus, the groups alter thermodynamic stability of the *out-of-cage* complexes as well as kinetics of their re-arrangement into the final *in-cage* complex where proton transfer from macrocyclic amines to bulk solvent plays important role. It will be exemplified on complexes several metal ions. For Ga(III), tacn-based ligands (e.g. TRAP-Pr [1]) exhibit wide range of complexation rates where *out-of-cage* complexation ability and/or charge of the pendants are important. For Cu(II), pendants in cyclam derivatives (e.g. TE1PPi [2]) will be compared showing that fast complexation even in cross-bridged cyclams can be reached. For Ln(III) and DOTA derivatives (e.g. DO3A-P^R [3]), proton transfer during *in-cage* complex formation seems to play the decisive role.



Acknowledgements: We thank GAČR and MŠMT for financial support.

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Novel phosphonic pyridyl cyclam macrocycles towards in vivo imaging and therapeutics

Richard C. KNIGHTON, [a] **Thibault TROADEC,** [a] **Loïc CHARBONNIERE,** [b] **Raphael TRIPIER** [a]

[a] *UMR 6521, Université de Bretagne Occidentale, 6 Avenue Victor Le Gorgeu, Brest, France*
[b] *IPHC, UMR 7178, ECPM, 25 Rue Becquerel, Strasbourg, France.*
e-mail: richard.knighton@univ-brest.fr

Azamacrocycles have a long and rich history in the fields of lanthanide and transition-metal coordination, due to their unique ability to strongly coordinate and encapsulate the metal ions of interest. [1] This is highly advantageous in biological applications, where decoordination and release of toxic metals into living organisms is clearly detrimental.
The 2-phosphonic pyridyl chelating moiety is a diverse ligand in coordination chemistry, [2] and has recently been employed in conjunction with aza-macrocycles for lanthanide coordination.[3] We describe a novel series of cyclam tetra-azamacrocycles functionalized with the 2-phosphonic pyridyl motif. The incorporation of both hard and soft oxygen and nitrogen donors facilitates coordination of a wide-range of metal guests (M = Ln^{3+}, Cu^{2+}, Mn^{2+}) and importantly, cyclam derivatives can easily be *C*-functionalized for bioconjugation.[4] Herein, we document the ligand complexation studies and coordination properties of these novel ligand systems.

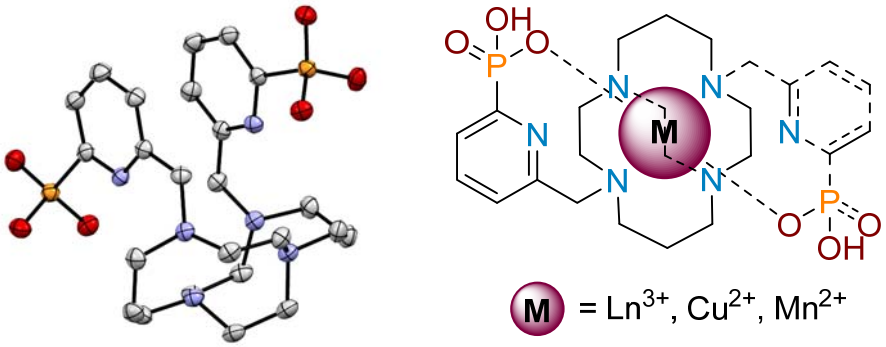

Figure 1. X-ray crystal structure of *cross-bridged* te2pp (left; ellipsoids plotted at the 50% probability level, H-atoms and counteranions omitted for clarity); General structure of reported complexes, M = Gd, Cu, Mn (right; counteranions omitted for clarity).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Zn(II) and Cu(II) binding sites of Calcitermin, an antimicrobial peptide found in human airways

Denise BELLOTTI, [a] Mattia TONIOLO, [a] Dorota DUDEK, [b] Magdalena ROWIŃSKA-ŻYREK, [b] Maurizio REMELLI [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
e-mail: blldns@unife.it

Antimicrobial peptides (AMPs) are evolutionarily conserved molecules with antimicrobial and/or immunomodulatory properties. Almost all antimicrobial peptides are cationic and amphipathic. AMPs are widely distributed in many tissues and cells and are potentially present in any species of invertebrate, plant and animal. They act as mediators of innate host defense, being able to target Gram-positive and Gram-negative bacteria as well as fungi and some enveloped viruses. Therefore, they represent a fertile ground for the design of novel therapeutics for the treatment of antibiotic-resistant infections and severe sepsis.[1] Mediators of innate host defense are also found in mucosal secretions of the respiratory tract and include substances, like antimicrobial proteins and (poly)peptides, that can sequester metal nutrients, such as Zn(II), Cu(II), Ni(II), Ca(II), etc.[2-3]

Among several uncharacterized molecules that contribute to the overall antimicrobial activity of human nasal fluid, a 15-residue antimicrobial peptide named Calcitermin has been identified.[4] Its sequence (VAIALKAAHYHTHKE) exactly corresponds to the C-terminal domain of Calgranulin C, a calcium-binding pro-inflammatory protein of the S100 family. Several studies have reported that cleavage fragments of parent proteins have potent antimicrobial activity (e.g. buforin I,[5] lactoferricin,[6] KDAMP,[7] vasostatin-1[8]).

While Calcitermin does not express, *in vitro*, any antimicrobial activity in phosphate buffer at pH 7.4, under more acidic conditions (pH 5.4) – which are quite common in inflammatory fluids – it was active against *E. coli*, *P. aeruginosa* and *C. albicans*. Furthermore, it was demonstrated that the presence of micromolar concentrations of Zn(II) enhances its antimicrobial activity against *E. coli* and *L. monocytogenes*.[4]

Calcitermin contains a putative metal-binding domain with three alternated histidine residues (His9, His11 and His13) and the free terminal amino group. In addition, it has the potential to adopt a helical conformation in membranes. The above results prompted us to deeply investigate the complex-formation equilibria of Calcitermin with Zn(II) and Cu(II), two endogenic and competing metal ions.

The unprotected peptide VAIALKAAHYHTHKE has been considered, along with its three mutants, in which each His residue is replaced with one alanine (VAIALKAAAYHTHKE, VAIALKAAHYATHKE, VAIALKAAHYHTAKE). The characterization of the complexes has been achieved by means of mass spectrometry, potentiometry, UV-Vis spectrophotometry, circular dichroism (CD) and nuclear magnetic resonance (NMR). Biological tests were also performed.

The comparison among the behaviors of the different analogues helps to shed light on the role played by each His residue in metal coordination geometry and complex stability also in the view of its antimicrobial activity. The preliminary results show that all the investigated peptides are efficient ligands for the considered metal ions and are able to form mono-nuclear complexes where the histidine residues are by far the first metal anchor (Fig.1).

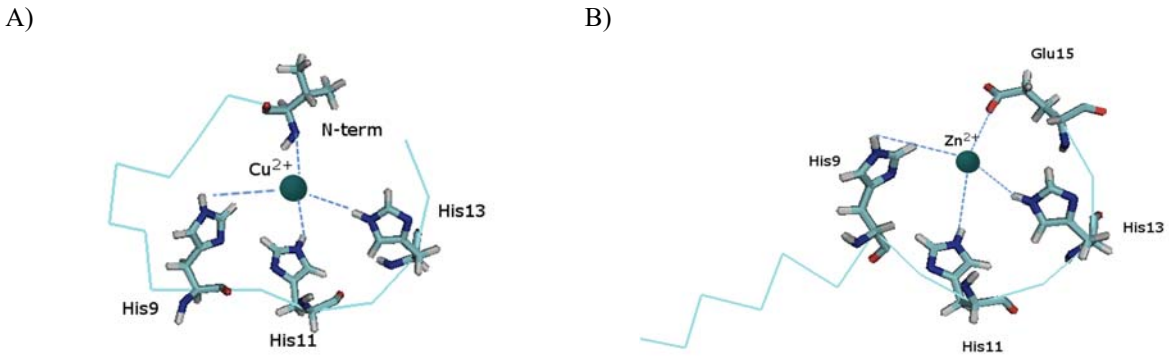

Figure 1. Proposed coordination sphere of A) Cu(II) and B) Zn(II) complexes with wild-type Calcitermin.

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International Symposium on Metal Complexes 2019
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Versatility in the interaction between Pd(II) and peptide hydroxamic acids

<u>András OZSVÁTH</u>, Etelka FARKAS, Róbert DIÓSZEGI, Péter BUGLYÓ

University of Debrecen, Department of Inorganic and Analytical Chemistry, Egyetem tér 1, 4032, Debrecen, Hungary
e-mail: ozsvath.andras@science.unideb.hu

In recent years cisplatin is the most widely used metallodrug in cancer treatment, however it is able to cause several side-effects due to its low selectivity. Selectivity can be increased by targeting the physiological differences between normal and cancer tissues. One of these differences is that the cancer tissues have lower oxygen level, therefore they have more reductive environment compared to the normal ones. This property of cancer cells and tissues can be targeted by coupling the platinum(II) containing moiety to another metal complex, which is able to act as a carrier unit. This type of dinuclear complexes could be kinetically inert $[Co^{III}(4N)L]^{n+}$ (4N = a tripodal amine, L = Pt(II)-containing bidentate ligand) type complexes. Reduction of these to labile Co^{II} species in the hypoxic tissues and release L with antitumor potential may provide with a high selectivity. [1, 2]

For the design of these hypoxia-activated heterodinuclear complexes, it is also necessary to find an ambidentate ligand, which is able to bind both of the Pt(II)- and Co(III)-ions. It is well-known from the literature, that simple oligopeptides without any side chain donor are able to form high stability, square planar complexes with Pt(II) and Pd(II) ions. It is also known, that hydroxamic acids have strong metal ion binding ability, furthermore some hydroxamic acids (e.g. SAHA) are well-known antitumor agents. Based on these previous results, peptide hydroxamic acids (in which the C-termini contains C(O)N(R)OH moiety) can be promising candidates for ambidentate ligands of these potentially hypoxia-activated dinuclear complexes.

In this study we have synthesized primary and secondary di- and tripeptide hydroxamic acids (AlaAlaNHOH, AlaAlaN(Me)OH, AlaGlyGlyNHOH and AlaGlyGlyN(Me)OH) [3, 4], and we have investigated the interaction of these ligands with Pd(II) ions (as a model of the kinetically more inert Pt(II)) in aqueous solution to explore the formation conditions of likely heterodinuclear Co(III)/Pt(II) complexes. This contribution obtained by the combined use of pH-potentiometry and ^{1}H NMR spectroscopy will summarize the results of these systems, which show that not only complexation, but Pd(II)-assisted hydrolysis of the ligands occurs in these systems. [5]

Acknowledgements: The research was also 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).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Zinc complex with azacrown-derivative and its *in vitro* stability

Gleb ALESHIN,[a)] Bayirta EGOROVA,[a)] Sofia KHABIROVA,[a)] Anastasia ZUBENKO,[b)] Olga FEDOROVA,[b)] Anna PRISELKOVA,[a)] Stepan KALMYKOV[a)]

[a)] Lomonosov Moscow State University, Leninskie gory 1 b.3, 119991, Moscow, Russia
[b)] A. N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Vavilova 28, 119991, Moscow, Russia
e-mail: gleb.aleshin@gmail.com

One of the ways to design radiopharmaceutical is to use biological vector (e.g. peptide), connected with a suitable radionuclide via a stable chelate complex. In this case the key factor of complexes' applicability is *in vivo* stability. Radionuclides Zn-62, Zn-63 and Zn-69m has a potential to be used in nuclear medicine. According 3R principles [1] to reduce laboratory animals use we need first to study its stability *in vitro*, i.e. define complex stability constants, study complex dissociation kinetics in biological media etc.

In this work we used long-lived Zn-65 to study its complexes with azacrown-derivative L (fig. 1) as a potential radiopharmaceutical. In particular, labeling conditions and *in vitro* stability were investigated.

Zn-65 was produced by deuteron-induced reaction from copper metal on cyclotrone (beam energy is 14.8 MeV). Zn-65 separation from copper was carried out using Dowex 1x8 anion-exchange resin with two different eluents: 2M HCl (zinc is sorbed on resin and copper passes through the column) and distilled H_2O (Zn^{2+} is desorbed).

Thin layer chromatography conditions were defined for Zn-65 complexes with L using cellulose on aluminium plates (Sigma). Labeling efficiency experiments were carried out in 0.15 M sodium acetate buffer solution with final pH 7.0–7.5. Labeling yields for ligands concentrations in a range from $1 \cdot 10^{-6}$ to $1 \cdot 10^{-3}$ M were defined using TLC technique and gamma-spectrometry. It was established that appropriate labeling yield is achieved at L concentrations of $1 \cdot 10^{-4}$ M or higher.

In order to analyze it before *in vivo* experiments, the set of *in vitro* experiments with fetal bovine serum was performed. Complex for *in vitro* experiment was prepared in 0.15 M sodium acetate buffer solution with pH 7.0–7.5 and L concentration $1 \cdot 10^{-4}$ M. 100 µl of Zn-65 blank or ZnL was added to 900 µl of fetal bovine serum, mixed and incubated at 37°C. Aliquotes of 100 µl were taken at 1, 5, 15, 30, 60, 120, 180, 240, 360 minutes and 1 day and treated with 300 µl of ethanol for protein precipitation. After centrifugation the supernatant was separated and measured by gamma-spectrometry. As a result, it was shown that ZnL, despite the relatively low stability constant (logK = 12.6 [2] comparing with ZnDOTA complex logK = 18.7 [3]), is highly stable in serum at least for 1 day: no rechelation by serum proteins is observed while Zn-65 in a blank sample quickly binds with serum proteins.

Thus, it was shown that ZnL is suitable as a part of radiopharmaceutical and should be further investigated *in vivo*.

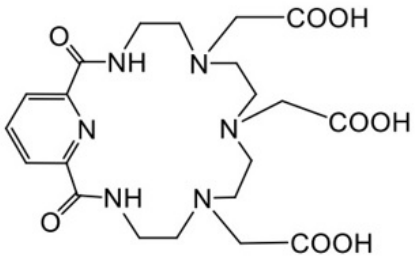

Figure 1. azacrown-derivative L.

Acknowledgements: The reported study was funded by Russian Foundation for Basic Research according to the research project № 18-33-00824.

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International Symposium on Metal Complexes 2019
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Novel ternary metal-organic framework materials for carbon dioxide storage

Miroslav ALMÁŠI, [a] **Vladimír ZELEŇÁK,** [a] **Zuzana VARGOVÁ,** [a] **Ivana CÍSAŘOVÁ** [b]

[a] *Department of Inorganic Chemistry, Faculty of Science, P. J. Šafárik University, Moyzesova 11, SK-041 54 Košice, Slovak Republic*
[b] *Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, CZ-128 43 Prague 2, Czech Republic*
e-mail: miroslav.almasi@upjs.sk

Metal−organic frameworks (MOFs) have attracted tremendous interest in the recent years because of their unique structural features and perspective applications in gas storage and separation, catalysis, sensing, drug delivery, and nanoparticle preparation [1]. This is because of their diversity and modularity, which offers the opportunity to systematically finetune and control their properties and performance. The metal complexes containing polycarboxylate anions as ligands represent the most interesting group of MOFs. Carboxylate anion, 1,4-benzenedicarboxylate (BDC), is known to form microporous polymeric complexes with high surface areas and pore volumes. The structures of such compounds contain clusters of the MOx coordination polyhedra, serving as secondary building units (SBUs) in the structure [2]. Up to date many metal-organic frameworks of different topologies and compositions were prepared and characterized.

In our work we have focused on the preparation of MOFs from ternary systems. We have used neutral organic ligand (4,4′-azobispyridine (AZPY)), metal ion (Zn(II)) and polycarboxylate ligand (BDC) for the synthesis. AZPY contains two uncoordinated azo-nitrogen atoms which can act as active centres important for gas adsorption. In this work we describe the synthesis, structure, properties and carbon dioxide sorption over the prepared materials.

The synthesis of MOFs can be considered as “construction game”, because the final architecture depends on the building blocks their compatibilities. Depending on the synthetic conditions (room temperature, solvothermal conditions, pH) we have prepared the compounds of different composition and topology. The complex prepared under ambient condition have 1D structure and can be formulated as $\{[Zn(AZPY)(H_2O)_4]\cdot(BDC)\cdot H_2O\}_n$ (I). The MOFs prepared under solvothermal conditions comprise 2D complex formulated as $\{[Zn(AZPY)(BDC)]\}_n$ (II), $\{[Zn_2(OH)(AZPY)(BDC)_{1.5}]\cdot H_2O\}_n$ (III) (two-fold interpenetrated frameworks with (4,4)-network topology) [3] and 3D compound $\{[Zn_2(AZPY)(BDC)_2]\cdot 2H_2O\cdot 2DMF\}_n$ (two-fold interpenetrated frameworks). The complexes were characterized by single crystal X-ray diffraction (see Fig. 1), spectral and thermal techniques and nitrogen/carbon dioxide adsorption measurements.

The compounds (II), (III) and (IV) contain voids in the structure, therefore we have investigated the carbon dioxide and nitrogen adsorption on these materials. Compounds adsorb only limited amounts of nitrogen because of the small pore volume and weak interactions

between adsorbate molecules and polymeric frameworks. It should be noted, that compounds surprisingly adsorb carbon dioxide and the CO_2 sorption capacity as determined for the compounds (II), (III) and (IV) at the temperature 273 K and relative pressure p/p^0 = 0.9 was 0.8, 1.04 and 2.87 mmol.g^{-1}, respectively.

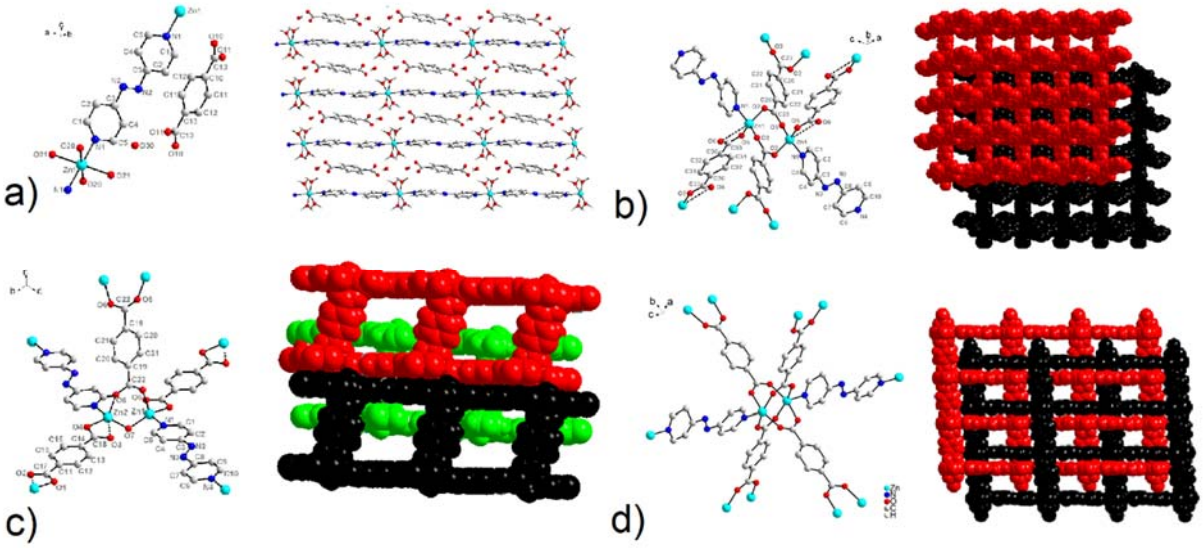

Figure 1. The view of the structure of a) {[Zn(AZPY)(H_2O)$_4$]·(BDC)·H_2O}$_n$ (I), b) {[Zn(AZPY)(BDC)]}$_n$ (II), c) {[Zn_2(OH)(AZPY)(BDC)$_{1.5}$]·H_2O}$_n$ (III) and d) {[Zn_2(AZPY)(BDC)$_2$]·2H_2O·2DMF}$_n$ (IV).

Acknowledgement: This work was supported by KEGA 008UPJŠ-4/2018, VEGA 1/0745/17 and VVGS 2019-1033. Authors M.A., V.Z. and Z.V. thank to the Ministry of Education, Science, Research and Sport of the Slovak Republic and the Accreditation commission for the financial support of the TRIANGEL team in the frame of the scheme "Top Research Teams in Slovakia". The presented research has been developed by students who have been directly involved in a research topic that is directly related to real-world practices used by commercial companies and industry.

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International Symposium on Metal Complexes 2019
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PIDAZTA: structurally constrained chelators for efficient formation of stable gallium-68 complexes at physiological pH

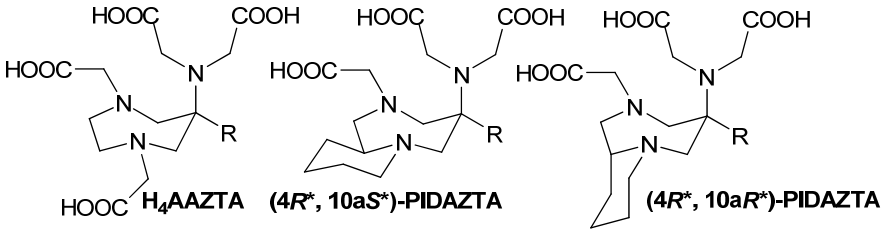
Edit FARKAS, [a] Adrienn VÁGNER, [a] Roberto NEGRI, [b] Luciano LATTUADA, [c] Imre TÓTH, [a] Valentina COLOMBO, [d] David ESTEBAN-GÓMEZ, [e] Carlos PLATAS-IGLESIAS, [e] Johannes NOTNI, [f] Giovanni B. GIOVENZANA, [b] Zsolt BARANYAI [a,c]

[a] Dep. of Inorganic and Analytical Chemistry, University of Debrecen, H-4032, Debrecen, Egyetem tér 1., Hungary
[b] Dip, di Scienze del Farmaco, Università del Piemonte Orientale, Largo Donegani 2/3, 28100 Novara, Italy.
[c] Bracco Research Center, Via Ribes 5, 10010 Colleretto Giacosa (TO), Italy.
[d] Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy
[e] Dep. de Química, Facultade de Ciencias, Universidade da Coruña, 15071 A Coruña, Galicia, Spain
[f] Lehrstuhl für Pharmazeutische Radiochemie, Technische Universität München, Walther-Meißner-Strasse 3, D-85748 Garching, Germany
e-mail: zsolt.baranyai@bracco.com

There are two radioisotopes of gallium, which are practically available for clinical application. While the γ-emitter ^{67}Ga ($t_{1/2}$ = 78.3 h) only plays a subordinate role for scintigraphy, the clinical use of the positron emitter ^{68}Ga ($t_{1/2}$ = 67.7 min) has seen a particularly strong increase within the last decade.[1] Like other radiometal ions, the introduction of $^{67/68}Ga^{III}$ in a diagnostic vector (peptides, antibodies) does not rely on complex reaction sequences used for lighter isotopes such as ^{18}F or ^{11}C, but rather requires a suitably designed chelating agent,[2] which is covalently linked to the (bio)vector[2] and binds the radiometal by complex formation. However, many novel Ga^{III} radiopharmaceuticals are still prepared using the well-known chelating agent DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), despite its slow Ga^{III} complexation kinetics which are surpassed by many other chelators, for example, the hexadentate analogue NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid) and its bifunctional derivatives. In this context, the chelator AAZTA[4] (Scheme 1) was recently shown to be a highly interesting scaffold, since it quickly forms thermodynamically stable and kinetically inert complexes with Ga^{III} and other ions of diagnostic interest.[5] The strong affinity of AAZTA and its derivatives for Ga^{III} combined with the fast kinetics of the complex formation prompted us to explore the possibility to improve these promising properties by designing new related chelating agents. For this purpose, we have chosen to pursuit the conformational locking of the 6-amino-1,4-diazepane substructure of this family of chelating agents by ring-fusion with an additional six-membered ring. The ring-fusion was planned to include one of the coordinating nitrogen atoms, to maximise its influence on the restricted conformational freedom of the complex arising from the hexadentate chelating agent.

In the present work, we report on the preparation of two novel isomeric chelating agents, *i.e.*: 4-amino-4-methylperhydro-pyrido[1,2-a][1,4]diazepin-*N,N′,N′*-triacetic acids, ("PIDAZTA*s*", isomers hereinafter referred to as L1 and L2 in Scheme 1), thermodynamics, transmetallation kinetics and structural properties of the Ga^{III}-, Ca^{II}-, Mn^{II}-, Zn^{II}-, Cu^{II}- and Ln^{III}- complexes formed

with the two PIDAZTA isomers. Furthermore, in order to elucidate their practical value for application in ^{68}Ga radiopharmaceuticals, both isomers were characterized in terms of ^{68}Ga labelling properties and kinetic inertness of the resulting radiometal complexes.



Scheme 1. The chelating agents **AAZTA**, (**4*R**, 10a*S**)-PIDAZTA (L1)** and (**4*R**, 10a*R**)-PIDAZTA (L2)**.

A detailed equilibrium studies reveal that unexpected [Ga(L1)OH] and [Ga(L2)OH] species predominates at physiological condition. A comparison of the log$\beta_{Ga(L)OH}$ values of the [Ga(L)OH] species ([Ga(AAZTA)OH]$^{2-}$: log$\beta_{Ga(L)OH}$=16.56, [Ga(L1)OH]$^{-}$: log$\beta_{Ga(L)OH}$=14.74, [Ga(L2)OH]$^{-}$: log$\beta_{Ga(L)OH}$=17.94, 0.15 M NaCl, 25°C) indicate that [Ga(**L2**)OH]$^{-}$ is characterized by the highest cumulative stability constant among the Ga^{III}-complexes formed with AAZTA derivatives. Kinetic studies of the transmetallation and transchelation reactions with Cu^{II} and transferrin indicates that the reactions occur through the spontaneous (k_0) and the OH^{-}-ion assisted (k_{OH}) dissociation of the dominant [Ga(L1/L2)OH]$^{-}$ species, followed by a fast reaction between the released L1/L2 ligand and the free Cu^{II} ion or between the transferrin and the free Ga^{III} ion. The comparison of the half-life ($t_{½}$) calculated for the Ga^{III}-complexes indicates that the kinetic inertness of [Ga(L2)OH]$^{-}$ is about 1000 and 13 times higher than those of the [Ga(L1)OH]$^{-}$, and [Ga(AAZTA)OH]$^{2-}$ complexes, respectively. The radiochemical investigations proved that the optimal pH for labelling of PIDAZTA isomers with $^{67/68}$Ga isotopes lies between 7 and 8 while at pH 7.5, nearly quantitative labelling at room temperature is achieved already at chelator concentrations below 10 μM. These peculiar behaviours of L2 ligand were rationalized on the basis of molecular modelling and appears to be related to a better fit in size of Ga^{III} into the cavity of L2.

In summary, the equilibrium, kinetic, radiochemical and theoretical investigations proved the suitability of L2 for the elaboration of radiopharmaceuticals based on $^{67/68}$Ga isotopes, combining highly efficient labelling and strong resistance against demetallation in physiological conditions.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Thermodynamic analysis of POPs interaction with biosubstrates

Tarita BIVER, [a),b)] **Rebecca DETTI,**[b)] **Stefania GIANNARELLI,**[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*
email: tarita.biver@unipi.it

Persistent organic pollutants (POPs) as polycyclic aromatic hydrocarbons (PAH), pesticides and herbicides are nowadays ubiquitous [1]. These species are highly lipophilic and all at least suspected of carcinogenic effects [2,3]. However, information on their toxic activity is often related to *in vitro/in vivo* studies, whereas a detailed analysis of the mechanistic/chemical aspects of the binding to biosubstrates is sometimes missing.

To contribute to this field and in the frame of our participation to PNRA (National Antarctic Research Program) we have done some tests on the binding of model targets (two PAHs, two pesticides and two herbicides, **Fig. 1**) to biosubstrates (natural DNA and bovine serum albumin - BSA). The interaction with micelles and liposomes was also tested, both as to scale the lipophilicity and to get information on the possible accumulation on membranes.

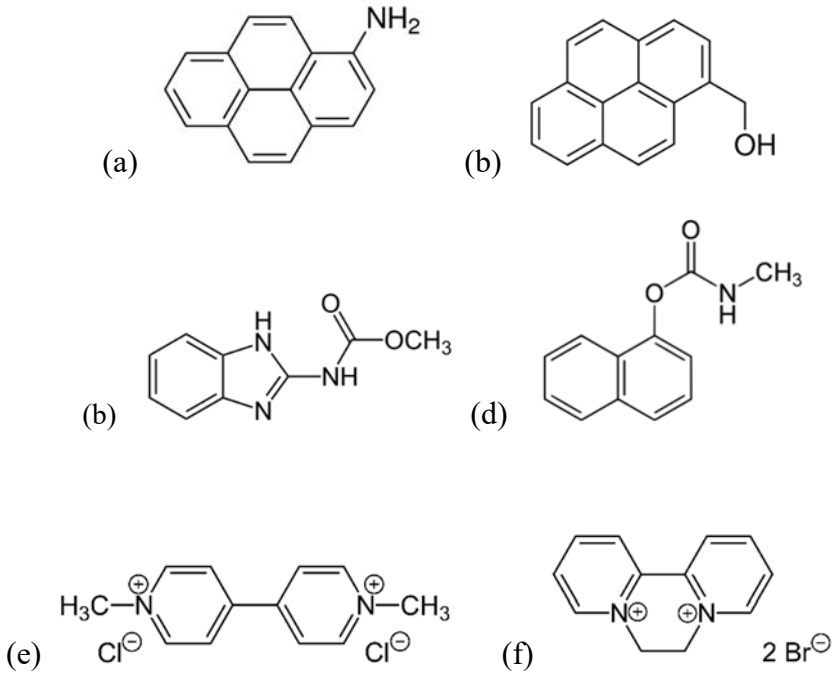

Figure 1. The target molecules used in this study. PAHs: 1-aminopyrene (a) and 1-hydroxymetilpyrene (b). Pesticides: carbendazim (c) and carbaryl (d). Herbicides: paraquat (e) and diquat (f).

The results collected show that the high hydrophobicity of these species turns into very high affinity for DNA. Absorbance and fluorescence titrations suggest complex binding modes that are discussed in relation with the different pollutant/DNA ratio. BSA binding is also found to occur.

Ultrafiltration coupled with absorbance spectroscopy enables the percentage of retention (R%) on the micelle/liposome be measured. R% dependence on the molecule and on the type of system (sodium dodecyl sulphate anionic micelles, TritonX-100 neutral micelles, dodecyl trimethyl ammonium chloride positive micelles and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine liposomes) is discussed.

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Debrecen Hungary 11-14 June

Speciation studies of Fe^{3+} in fairly concentrated solutions and enhancement of hydrolysis through the formation of mixed hetero-metal species: Fe^{3+}/Al^{3+}

Rosalia Maria CIGALA, Francesco CREA, Concetta DE STEFANO, Anna IRTO, Silvio SAMMARTANO

Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Viale F. Stagno d'Alcontres, 31, I-98166 Messina (Vill. S. Agata), Italy.
e-mail: rmcigala@unime.it

The investigation on the acid-base properties of a metal cation in solution, referred either to an aqueous solution or fresh water or biological fluid, it is of fundamental interest to understand in which form the metal is available and how it can interact toward other components present into the system considered.

The hydrolytic behavior of the Fe^{3+} has already been studied, and the mononuclear species are well known in very dilute solutions, owing to the low solubility of Fe(III) hydroxides limits the studies [1-3].

The aim of this study is to expand the knowledge of the hydrolytic behavior of Fe^{3+} in solutions with high metal concentrations (50 – 200 mmol L^{-1}), for the determination of the polynuclear species $Fe_n(OH)_m^{(n-m)+}$, in absence and with different ionic media as $NaNO_3$, NaCl and aqueous solutions with phosphate buffer, which simulates the serum environment. The solubility product of the $Fe(OH)_{3(s)}$, in different experimental conditions, has been determined.

The enhancement of hydrolysis by the formation of the hetero-metal hydrolytic species with a trivalent metal cation, Al^{3+}, has been another aspect studied.
The choose of Al^{3+} is due to high tendency to form polynuclear species, as it has also been evidenced for Fe^{3+}; the most important polynuclear species are: $Fe_2(OH)_2$, $Fe_3(OH)_4$ and $Fe_{12}(OH)_{34}$ species for Fe^{3+} and $Al_3(OH)_4$ and $Al_{13}(OH)_{32}$ ones for Al^{3+}.

By using usual criteria of selections, different speciation models were obtained for the different homo-metal and hetero-metal systems, Fe^{3+} and Fe^{3+}/ Al^{3+}, respectively.

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International Symposium on Metal Complexes 2019
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Macrocyclic Mn(II) complexes as potencial mri contrast agents: preparation and coordination chemical characterization

Tibor CSUPÁSZ, Attila SZABÓ, Ádám TANKÓCZI, Enikő MOLNÁR, Zoltán GARDA, Ferenc Krisztián KÁLMÁN, Imre TÓTH, Gyula TIRCSÓ

Department of Physical Chemistry, University of Debrecen, Egyetem tér 1., H-4032, Debrecen, Hungary
e-mail: csupasz.tibor@science.unideb.hu

A widely used technique of medical diagnostics is Magnetic Resonance Imaging (MRI), which utilize contrast agents (CAs) to increase the contrast of the image. The majority of the MRI CAs available on the market are complexes of paramagnetic Gd(III) ion formed with open-chain or macrocyclic amino-polycarboxylate ligands. A serious disease (NSF - Nephrogenic Systemic Fibrosis) has recently been discovered in patients with severe renal impairment after multiple examination with CAs, for which the gadolinium(III) ion released from the CAs can be responsible.[1,2] Moreover, it has recently been shown that gadolinium accumulation can also occur in various tissues (eg. brain, bones) in patients with healthy kidney function. Therefore, the actual research is focused on preparation of complexes containing essential paramagnetic metal ions (such as Mn(II), or high spin Fe(II), Fe(III) etc.) to substitute gadolinium(III) ion-based contrast agents (GBCAs).[3]

Our research group has long been engaged in the preparation and investigation of Mn(II) complexes. Our earlier results show how the thermodynamic stability and inertness of the complexes can be increased by selecting properly the structure (backbone) of macrocyclic ligands. Moreover, the physico-chemical properties of the Mn(II) complexes can be further improved by an appropriate selection of the metal binding pendant arms attached to the macrocyclic N-atoms. For this purpose, a promising new ligand family, carboxylate derivatives of the rigid 4-oxo-1,7-diaza-2,6-piridinophane (O-pyclene) macrocycle (i.e. OPC2A), has been proposed recently. The current study is the continuation of this research. We have replaced the acetate metal binding units in OPC2A by amides (OPC2AM^{PipCarb}) or alpha-methyl-acetate moiety (OPC2MA) with an aim of improving the inertness of their Mn(II) complexes.

The OPC2MA ligand is more basic than OPC2A as a result of hyperconjugative effect of the methyl substituent present on the alpha carbon atom of the sidearm. The given ligand forms Mn^{2+} complex of similar stability (log *K* as well as pMn values are slightly lower) to that of [Mn(OPC2A)], whereas the acid catalyzed dissociation of [Mn(OPC2MA)] occurs more slowly (nearly 2 times) than that of the parent chelate. The replacement of the acetate side arms by amide substituents results in a noticeable drop in the ligand basicity as well as in the stability of its Mn(II) complex. However when comparing the pMn value calculated for the [Mn(OPC2A2AM^{PypCarb})] complex with the one available for the [Mn(OPC2A)] complex only less pronounced drop is observed. The kinetic inertness of the [Mn(OPC2A2AM^{PypCarb})] complex has been accessed by studying the rate of metal exchange reaction occurring with Zn(II) ion at pH=6.0 as suggested by P. Caravan and coworkers.[4] The half-lives of dissociation of the [Mn(OPC2A2AM^{PypCarb})] complex under these conditions appears to be 3 to 4 orders of

magnitude greater than those of Gd(III)-based CAs prepared by using on open chain ligand platforms used in the clinics.

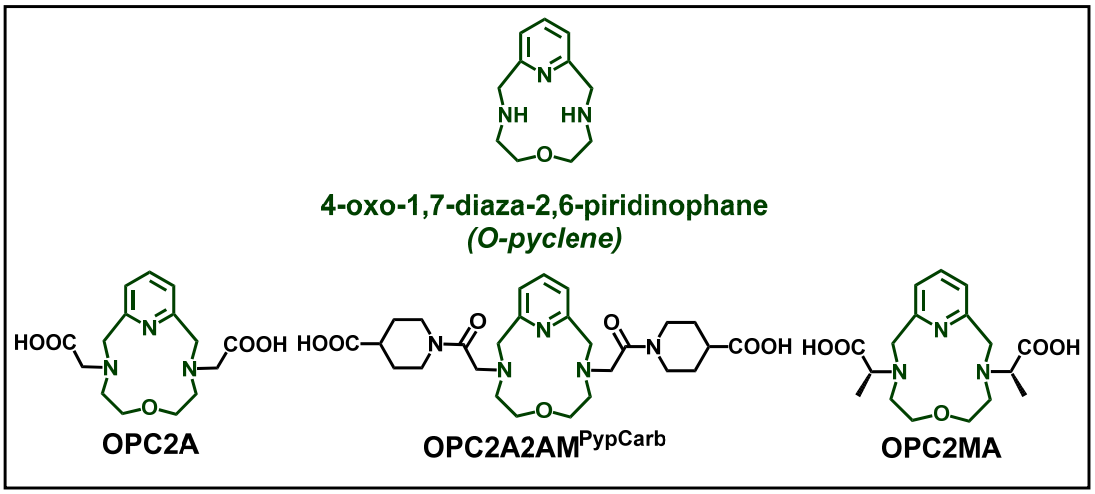

Figure 1: Formulae of the ligands prepared for Mn(II) complexation.

Acknowledgements: This research was funded by the GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004 projects supported by the EU and co-supported by the European Regional Development Fund. The authors are grateful for support granted by the Hungarian National Research, Development and Innovation Office (NKFIH K-120224 project) and for the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (Gy.T. and F.K.K.). The research was also supported by the ÚNKP-18-4 New National Excellence Program (Gy.T. and F.K.K.) of the Ministry of Human Capacities.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Solvent-free synthesis of several Rh-bis(NHC) complexes and utilization of them in several catalytic applications

Sourav DE, [a] Csilla CZÉGÉNI, [b] Antal UDVARDY, [a] Ferenc JOÓ [a],[b]

a) Physical Chemistry Department, University of Debrecen, Egyetem tér 1, 4032, Debrecen, Hungary
b) MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group, University of Debrecen, Egyetem tér 1, 4032, Debrecen, Hungary
e-mail: souravde@science.unideb.hu

N-heterocyclic carbenes (NHC) rank amongst the most powerful tools in today's chemistry because of their considerable potential and scope in coordination/organometallic chemistry, catalysis and materials science.[1–4] The aim of my work was to prepare unique NHC metal catalysts for water related applications. Synthesis of several chelating and bridging di-nuclear Rh(I) complexes of $(-CH_2-)_n$ bridged (n=1,4) benzylated imidazole were done without the use of any solvents in ball-mill with good yields. The target was to make the complexes water soluble by sulfonating the ligands, which has not yet been possible. However, the complexes were utilized as catalysts in several reactions like transfer hydrogenation of acetophenone, hydration of benzonitrile and polymerization of phenylacetylene. The complexes were responsive as catalysts in all the above-mentioned reactions. However, till now, the best results with almost full conversion were found for the bridging di-nuclear Rh(I) complexes of benzylated bis(imidazolyl)methane/butane for the polymerization reaction of phenylacetylene in chloroform.

Keywords: Bis N-heterocyclic carbene, catalysis, solvent-free, polymerization

Acknowledgement: The research was supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004. Author SD is thankful to Stipendium Hungaricum scholarship programme and Government of India for supporting his PhD study.

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International Symposium on Metal Complexes 2019
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Copper(II) binding within the N-terminal region of the Tau protein: the use of model peptides for the evaluation of metal ion binding preferences.

Giuseppe DI NATALE, [a] **Márton LUKÁCS,** [b] **Valeria LANZA,** [a] **Giovanni TABBI,** [a] **Tiziana CAMPAGNA,** [a] **Csilla KÁLLAY,** [b] **Giuseppe PAPPALARDO** [a]

[a] *CNR-IC Istituto di Cristallografia, via Paolo Gaifami 18, 95126, Catania, Italy*
[b] *University of Debrecen, Egyetem tér 1, 4032 Debrecen, Hungary*
e-mail: giuseppe.dinatale@cnr.it

Tau protein belongs to a family of microtubule-associated proteins (MAPs) specifically expressed in neurons.[1] Tau hyper-phosphorylation triggers toxic deposition of this protein, that in turn causes the formation of intracellular Tau paired helical filaments (PHF), which ultimately gather together to form the characteristic neurofibrillary tangles (NFT).[2,3] The formation of intracellular neurofibrillary tangles (NFT) and the accumulation of amyloid-beta (Aβ) within extracellular senile plaques, represent the most common clinical hallmarks in the brain of AD patients.[4,5]

There is evidence that some transition metals such as copper, zinc and iron might be implicated in the neurodegenerative process of the disease.[6] The role of transition metal ions in modulating Aβ's aggregation, fibrillogenesis and toxicity has exhaustively been reported.[7] By contrast, the association of metals with Tau protein has only recently become relevant to the pathogenesis of AD[8] even if their role in tauopathies is controversial.[9,10]

Several biophysical and structural studies have revealed binding of Cu^{2+} ions with full-length Tau protein[11] as well as short peptide comprising the first, second or third repeat of Tau microtubule domain.[12] Although increased levels of peptide fragments from the N-terminal portion of Tau protein have been detected in the cerebrospinal fluid (CSF) of AD patients,[13] only few work has been reported about the metal complexes with peptides derived from this region.[14] In particular, the Cu^{2+}-binding features of two peptide fragments, encompassing the 1–25 or 26–44 residues of the human Tau protein sequence were investigated. The overall results indicated that copper(II) can bind these peptides using the histidine residues 14 and 32, or the N-terminal amino group as anchoring sites.

With the aim to disclose the different metal coordination properties of the two histidines binding sites, in the present study we described the molecular features of copper(II) complexes of different peptides fragments belonging to N-terminal regions of Tau protein. The peptides synthetized in this work included the terminally blocked sequences of Tau(9-16) and Tau(26-33). The stoichiometry of the copper(II) complexes was determined by means of ESI-MS spectrometry. In addition, the EPR and far-UV CD studies were helpful for clarifying the coordination modes and conformational effect of the peptides studied respectively. In order to get complementary information about the key residues involved in the copper(II) coordination, we resorted to the tandem mass spectrometry. Interestingly, the study of the copper(II) complex species with the Tau(9-16) fragment revealed the formation of mononuclear and dinuclear complexes while only mononuclear species were observed in the case of the copper(II)-Tau(26-33) system. The study of the copper(II) complexes with the mutant Tau(9-16)His14Ala made

it possible to confirm the presence of a further copper(II) binding site, in addition to the two Histidine residues and the N-terminal amino group, in the N-terminal domain of Tau protein. The chimera peptide Tau(12-16)(26-33) was designed as a reliable model to evaluate the metal-binding affinity of the two histidines binding sites. The study of the mononuclear copper(II) complexes with this fragment revealed the higher affinity of the metal ion for the His32 binding site at physiological pH.

Acknowledgement: CNR-HAS joint research project is acknowledged for partial financial support. The authors thank the Hungarian Scientific Research Fund (K 115480) for the financial support. 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. The research was also supported by the UNKP-18-4 New National Excellence Program of the Ministry of Human Capacities and by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

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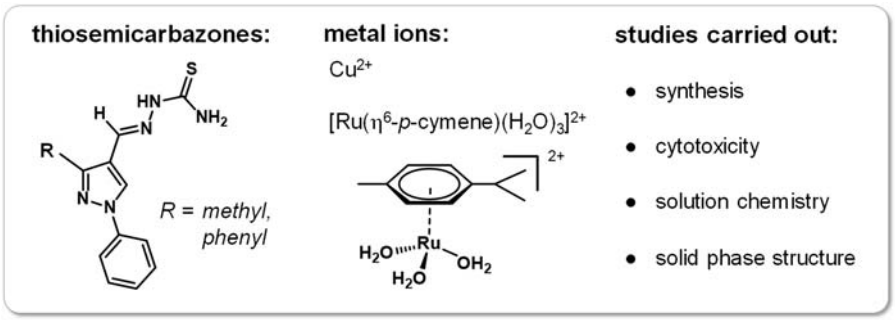
International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Studies on copper(II) and organoruthenium(II) complexes of pyrazolo-thiosemicarbazones: anticancer activity, structure and stability

Orsolya DÖMÖTÖR, [a] **, G. Tamás GÁL,** [b] **Nóra V. MAY,** [b] **Gabriella SPENGLER,** [c] **Márton A. KISS,** [d] **Éva FRANK,** [d] **Éva A. ENYEDY** [a]

[a] *Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary*
[b] *Research Centre for Natural Sciences Hungarian Academy of Sciences, Magyar tudósok körútja 2, H-1117 Budapest, Hungary*
[c] *Department of Medical Microbiology and Immunobiology, University of Szeged, Dóm tér 10, H6720 Szeged, Hungary*
[d] *Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720, Szeged, Hungary*
e-mail: domotor.o@chem.u-szeged.hu

Thiosemicarbazones (TSCs) have a broad range of activities, including anticancer and antibacterial properties, which are believed to be at least partly due to their ability to chelate versatile metal ions [1]. Triapine is the most prominent candidate among α-*N*-pyridyl-TSCs with anticancer activity. Triapine was found to be safe and effective against hematological malignancies, for example, leukemia in clinical phase I and phase II studies [2]. It is known, that Triapine and related TSCs are inhibitors of the enzyme ribonucleotide reductase (RNR), which catalyzes the reduction of ribonucleotides to the corresponding 2′-deoxyribonucleotides [3]. Although the actual mechanisms of action of these compounds are not fully understood yet, complex formation with iron(III)/(II) ions seems to be a key feature in their efficiency. Generally, complex formation with transition metal ions such as Cu(II) Ni(II), Pt(II) or Pd(II) often results in compounds with even higher cytotoxicity than that of the metal-free ligands [4].



Recently numerous TSCs with various structural features and their metal complexes were synthesized and tested against human cancer cells. Our interest turned to pyrazolo-TSCs, such as 3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehide-TSC and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehide-TSC (see figure). The Pd(II) bis complexes of both TSCs exerted antibacterial activity against Gram negative bacteria and were proved to be highly active against MCF-7 breast cancer cells (IC_{50} = 0.57-1.24 μM) [5].

In the present work complex formation of these TSCs with Cu(II) ion and [Ru(II)(η^6 *p* cymene)(H_2O)$_3$]$^{2+}$ is investigated in detail (see figure). The latter one is a half sandwich organometallic cation and forms so-called piano-stool type complexes with various ligands. Complexes of Ru(II)(η^6-*p*-cymene) bearing a bidentate ligand and one chlorido co-ligand are widely studied such the RAED complexes ([Ru(η^6-arene)(ethylenediamine)Cl]$^+$) [6]. Recently various organoruthenium complexes with TSC ligands were synthesized and tested against human cancer cells [7].

Generally, characterization of these type of TSC complexes in solid phase were performed, although knowledge of the actual chemical forms in the aqueous solutions strongly contributes to the structure-stability-activity relationship studies. Herein we report the synthesis and anticancer activity of the ligands and their Cu(II) and Ru(II)(η^6-*p*-cymene) metal complexes on multidrug resistant (Colo320) and non-resistant (Colo205) colon adenocarcinoma cells. Solid phase structure of the complexes is characterized by X-ray crystallography, and results on the solution chemistry of the ligands and their metal complexes are presented here as well.

Acknowledgements: National Research, Development and Innovation Office-NKFIA projects GINOP-2.3.2-15-2016-00038, FK 124240; Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT. The work was supported by the ÚNKP-18-2 (M.A.K.) and ÚNKP-4-Bolyai+ (É.A.E.) New National Excellence Program of the Ministry of Human Capacities.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Novel curcumin-based structure linked to bifunctional chelators as gallium-68 and scandium-44 labelled radiotracers.

Giulia ORTECA, [a] Jean-Philippe SINNES,[b] Sara RUBAGOTTI,[c] Michele IORI,[c] Pier Cesare CAPPONI,[c] Markus PIEL,[b] Frank ROESCH,[b] Mattia ASTI,[c] Erika FERRARI [a]

[a] Department of Chemical and Geological Sciences, University of Modena and Reggio Emilia, via G. Campi 103, 41125, Modena, Italy
[b] Institute of Nuclear Chemistry, Johannes Gutenberg-University of Mainz, D-55126 Mainz, Germany
[c] Radiopharmaceutical Chemistry Section, Nuclear Medicine Unit, Azienda USL-IRCCS Reggio Emilia, via Amendola 2, 42122, Reggio Emilia, Italy
email: erika.ferrari@unimore.it

Curcumin metal complexes showed widespread applications in medicine [1] and can be exploited as a lead structure for developing new tracers for nuclear medicine application [2]. The curcumin derivative obtained by derivatization with DOTA (DOTA-C21) was successfully labelled with gallium-68 and showed good water solubility and comparable uptake in HT29 cells with respect to the previous compounds. Although the stability was significantly enhanced with respect to [^{68}Ga]Ga-curcumin complexes, this still remains a concern and may be partially responsible for the biodistribution of [^{68}Ga]Ga-DOTA-C21 [3]. Herein, the synthesis, chemical characterization and radiolabeling with gallium-68 and scandium-44 of two new targeting vectors based on curcumin scaffolds and linked to chelators (namely NODAGA-C21 and AAZTA-PC21 – Figure 1, left), are reported.

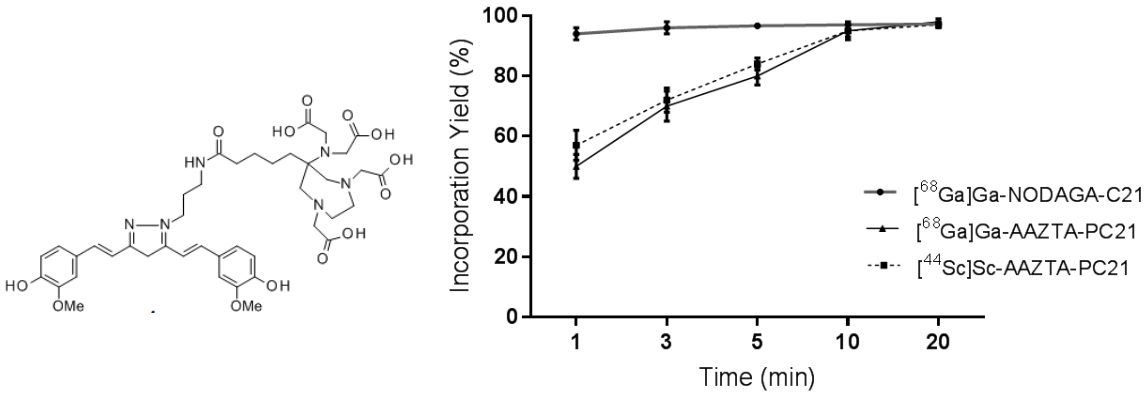

Figure 1.

Synthesis of the precursors could be achieved with a 13% and 11% yield and radiolabelling generally afforded rapid incorporation under mild conditions (> 95%), as reported in Figure 1, right. Stability in physiological media (~75% after 2 h in human blood for [^{68}Ga]Ga-/[^{44}Sc]Sc-AAZTA-PC21 and ~60% for [^{68}Ga]Ga-NODAGA-C21, respectively) and lipophilicity resulted in generally enhanced properties if compared to the previously radiolabelled analogues.

MS^n fragmentation experiments showed high stability of the AAZTA-PC21 structure mainly due to the pyrazole derivatization of the curcumin keto-enol moiety and a more feasible radiolabelling was noticed both with gallium-68 and scandium-44 mainly due to the AAZTA-chelator properties. [^{68}Ga]Ga-NODAGA-C21 showed the most favourable lipophilicity value (logD = 1.3). Due to these findings, both compounds appear to be promising candidates for the imaging of colorectal cancer, but further studies such as *in vitro* uptake and *in vivo* biodistribution experiments are needed.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

A "two birds with one stone" approach to the targeted treatment and imaging of tumors: vitamin B_{12}-functionalized metallotheranostic agents

Eirini FOTOPOULOU, Luca RONCONI

School of Chemistry, National University of Ireland Galway, University Road, Galway, Ireland
email: e.fotopoulou1@nuigalway.ie

Targeting and delivering are aspects of drug design that have been receiving much attention in recent years because of the potential for improving efficacy and reducing side-effects. Ideally, a pharmaceutical should be delivered and accumulate exclusively at the target site but rapidly cleared from the rest of the body.[1] Therefore, conjugated drugs incorporating a tumor-targeting group and a cytotoxic "smart bomb" are emerging as promising therapies for cancer treatment.[2]

Research efforts have been recently shifting from cytotoxic nonspecific chemotherapies to molecularly targeted rationally designed drugs. Targeted chemotherapies offer a great potential advantage owing to the avowed enhanced specificity of the pharmacological treatment which would lead to higher administered doses of drugs delivered directly into the target site. Anyway, this requires the identification of the relevant biomarkers that are over-expressed specifically by diseased cells but not in healthy tissue, so as to attain such selective targeted delivery.

In this context, vitamin B_{12} (cyanocobalamin) is currently under intense investigation.[3] In fact, cyanocobalamin is a vital nutrient characterized by extremely low bioavailability. Once taken up by the cell, it is converted into its biologically-active cofactors methylcobalamin (used to produce methionine) and adenosylcobalamin (used as coenzyme to enter the tricarboxylic acid cycle). Since rapidly growing tumor cells require higher amounts of energy and nutrients (including vitamin B_{12}) for their abnormal proliferation, the conjugation of therapeutic and/or diagnostic agents to cyanocobalamin turns out to be a very attractive approach.[4]

In particular, vitamin B_{12} derivatives functionalized with suitable fluorophores[5] can be conjugated to metallodrugs, so as to attain the site-specific delivery into the affected tissues. Such selective Trojan Horse-type metallotheranostics aim at improving therapeutic outcomes and reducing the side-effects.

We here report on the design and development of vitamin B_{12}-based potential metallotheranostics of the type [5'-(FLUO)-B12-Co(III)-CN-{M(dtc)}] in which the cyanocobalamin is functionalized at the 5'-hydroxo group of the ribose unit with a fluorophore (FLUO), whereas the cyano (CN) group is coordinated to the metal center of an anticancer metal-dithiocarbamato scaffold ({M(dtc)}; M = Au(III), Pt(II) / dtc = various dithiocarbamates). Such derivatives are expected to exhibit preferential accumulation of the overall metal-bioconjugate into tumor cells, so that the metallodrug would exert its anticancer activity only against diseased tissues without affecting healthy ones, and, at the same time, the attached fluorophore would allow the transport and biodistribution to be followed and assessed by fluorescence spectroscopy.

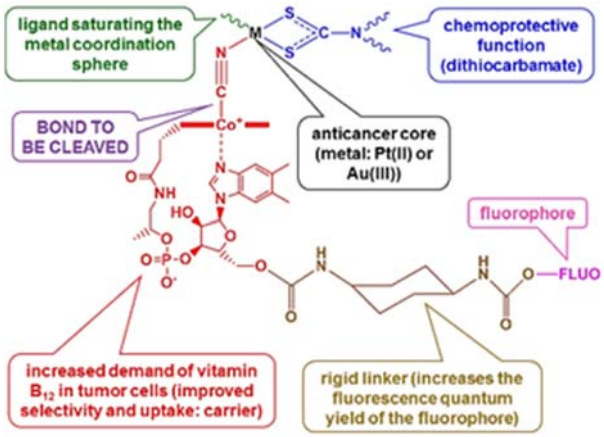

Figure 1: General structure of the fluorescent vitamin B_{12}-metaldithiocarbamato conjugates [5'-(FLUO)-B_{12}-Co^{III}-CN-{M(dtc)}] (FLUO = fluorophore; M = Au(III), Pt(II); dtc = various dithiocarbamates).

Fluorophores (FLUO) were chosen according to specific chemical (stability, solubility, reactivity toward conjugation) and photophysical (maximum absorption and emission wavelengths, Stokes shift, and quantum yield) properties. The choice of dithiocarbamato ligands is not accidental. In fact, the binding of a chelating dithiocarbamato scaffold (-NCSS) to metal centers in square-planar complexes (such as gold (III) derivatives) should make the coordination of additional S-donors trans to the -NCSS moiety less favorable because of the strong trans-influencing effect of the dithiocarbamato sulfur atoms. Consequently, further interaction of the metal with thiol-containing enzymes, commonly regarded as being responsible for heavy metals toxicity, should be avoided, thus reducing side-effects (i.e. acting as an intrinsic chemoprotectant).[6]

Acknowledgements: Financial support by NUI Galway (*Hardiman Research Scholarship 2016* to EF; *Millennium Fund Minor Project 2013* to LR), Irish Research Council (*Postgraduate Scholarship GOIPG/2017/1170* to EF), and COST Action CM1105 "Functional metal complexes that bind to biomolecules" (*STSM Grant*) is gratefully acknowledged.

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International Symposium on Metal Complexes 2019
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Structural investigation of diuretic Clopamide and its copper(II) complexes under different conditions (pH, solvent, counter ion)

Gyula Tamás GÁL,[a)] Nóra V. MAY,[a)] László TRIF,[b)] Petra BOMBICZ [a)]

[a)] Chemical Crystallography Research Laboratory, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2., 1117, Budapest, Hungary
[b)] Insitute of Materials and Environmental Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2., 1117, Budapest, Hungary
e-mail: gal.tamas@ttk.mta.hu

Clopamide (4-chloro-N-2,6-dimethylpiperidin-1-yl)-3-sulfamoylbenzamide, Figure 1) is an active pharmaceutical ingredient (API) categorized as a thiazide-like diuretic and is used against hypertension and oedema.[1,2] The carbonyl oxygen and the piperidine nitrogen of the clopamide molecule are able to coordinate to metal centres. The sort of coordination of the bioligand to metal ions can affect their biological properties. Despite of its medical application the structure of the clopamide molecule or any of its metal complexes has not been published so far.
Our primarily aim was to reveal the single crystal structure of clopamide. The outcome of several successful crystallization experiments allowed us to harvest single crystals of a series of clopamide containing compounds. It has opened up the way to determine how far the molecular conformation and the packing arrangement – isostructurality - can be preserved in respond to chemical changes to enrich the knowledge on the aspects which contribute to the development of materials with specific properties[3].

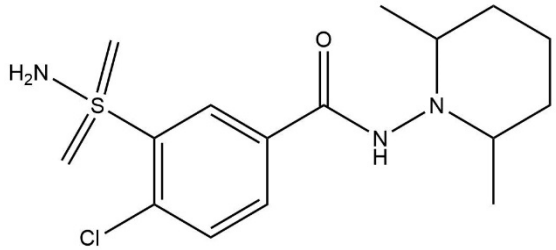

Figure 1. The structure of the investigated 4-chloro-N-(2,6-dimethylpiperidin-1-yl)-3-sulfamoylbenzamide (Clopamide).

We have studied the free ligand and its copper(II) complexes under different conditions (pH, solvent, counter ion) applying different techniques (single crystal X-ray diffraction (SXRD), electron paramagnetic resonance (EPR) spectroscopy, and thermoanalytical methods).
SXRD was used to determine the crystal structure of the free ligand and of the *bis*-ligand copper complexes obtained under different crystallization conditions. We succeeded to determine the crystal structure of both clopamide hemihydrate (C2/c) and ahnydrous clopamide ($P2_1/n$). The *bis*-ligand copper(II) complexes of clopamide have been crystallized from different pH's and solvents. 14 crystal structures have been determined so far obtained from different experimental conditions. The neutral [CuL_2] complex (Figure 2) which crystallized from different alcohols allowed us to fine tune the crystal lattice by inclusion of solvents with increasing size. Our goal was to investigate how far we can extend the unit cell and influence the system of supramolecular interactions[4] keeping isostructurality[5] before a structural change appears to

another solvatomorph. The methanol, ethanol, i-propanol and n-propanol solvent inclusion compounds resulted in *P*-1 crystals with increasing unit cell volume, while another crystal form crystallized with space group *R*-3 from apolar solvents. Protonated complexes $[CuL_2H]^+$ and $[CuL_2H_2]^{2+}$ have been crystallized with different counter ions (nitrate, sulphate and perchlorate) from alcohol solvents. Methanol and ethanol inclusion resulted in isostructural crystals however from n-propanol a different, solvent free crystal form was detected. The crystal structures were compared in respect to the conformation of the coordinated ligands and the secondary interactions with the solvent molecules or the counter ions.
Thermoanalytical methods (DSC, TG-MS) were used to determine the melting points of the crystals, the possible phase transitions and to detect the solvent content. The complex structures of the paramagnetic copper(II) complexes (S=1/2, I_{Cu}=3/2) in solution was studied by electron paramagnetic resonance spectroscopy (EPR) at room temperature and in frozen solution (77K). These results can contribute to the understanding and consequently to the controlling of the structural properties by gradual chemical change. We demonstrate how the well balanced spatial and electrostatic forces play role in the arrangement of packing motifs in the crystals.

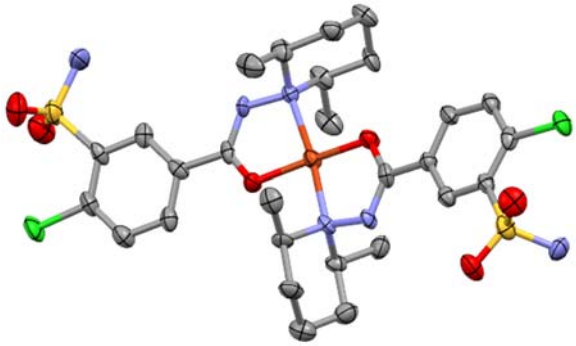

Figure 2. Molecular structure of a *bis*-clopamide Copper complex crystallised from dichloromethane. Displacement parameters are drawn at 50% probability level and hydrogens are omitted for clarity.

Acknowledgements: The support of the National Research, Development and Innovation Office – NKFIH through OTKA K115762 and K124544 are gratefully acknowledged**.**

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International Symposium on Metal Complexes 2019
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Synthesis, characterization and biological properties of half-sandwich complexes of ruthenium(II), rhodium(III) and iridium(III)

Agnieszka GILEWSKA,[a] Joanna MASTERNAK,[a] Barbara BARSZCZ,[a] Katarzyna KAZIMIERCZUK,[b] Eliza TURLEJ,[c] Joanna WIETRZYK[c]

[a] Jan Kochanowski University, Institute of Chemistry, Department of Inorganic Chemistry, 15G Świetokrzyska Str., 25-406 Kielce, Poland
[b] University of Technology, Faculty of Chemistry, Department of Inorganic Chemistry, 11/12 G. Narutowicza Str., 80-233 Gdańsk, Poland
[c] Polish Academy of Sciences, Institute of Immunology and Experimental Therapy, 12 Weigla Str., 53-114 Wrocław, Poland
e-mail: agnieszka5052@wp.pl

Actually the development of new anticancer drugs containing different transition-metal ions, for example, ruthenium, rhodium, iridium is a valid strategy in cancer treatment [1,2]. In this work we reported the synthesis (basing on precursors: $[(\eta^6\text{-}p\text{-cymene})Ru(\mu\text{-}Cl)Cl]_2$, $[CpRh(\mu\text{-}Cl)Cl]_2$, $[CpIr(\mu\text{-}Cl)Cl]_2$), spectroscopic, structural and biological properties of complexes of ruthenium(II), rhodium(III) and iridium(III) containing N,N-chelating ligand (2,2'-bisimidazole). These complexes were characterized by elemental analysis, UV-Vis and FT-IR spectroscopy, X-ray diffraction analysis. The complexes exhibit a typical pseudotetrahedral three-legged piano-stool geometry, in which the aromatic arene ring forms the seat of the piano-stool, while the bidentate 2,2'-bisimidazole and one chlorido anion form the three legs of the stool (Fig. 1).

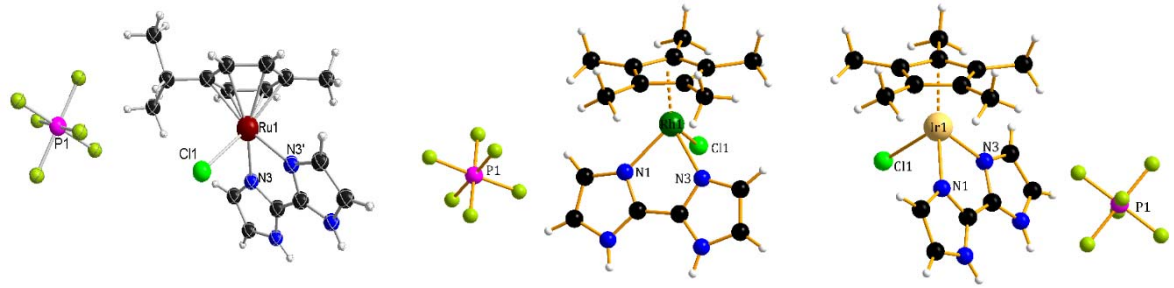

Figure 1. Molecular structures of $\{[RuCl(H_2biim)(\eta^6\text{-}p\text{-cymene})]PF_6\}_2 \cdot H_2O$ (**1**), $[(\eta^5\text{-Cp})RhCl(H_2biim)]PF_6$ (**2**) and $[(\eta^5\text{-Cp})IrCl(H_2biim)]PF_6$ (**3**).

The spectroscopy data (IR, UV-Vis) and elemental analysis correlate very well with molecular structures. Moreover, the cytotoxic activity of the complexes was carried out on human cancer cell lines: LoVo (colorectal adenoma), MV-4-11 (myelomonocytic leukaemia), MCF-7 (breast adenocarcinoma), HL-60 (promyelocytic leukaemia) and normal healthy mouse fibroblast BALB/3T3 cell lines. It is interesting to note that the investigated complexes show no cytotoxic effect towards the normal BALB/3T3 cell line, compared to cisplatin (IC_{50} 7.33 μM). Importantly, Ru(II) displayed the highest activity against HL-60 (IC_{50} 7.78 μM) (Fig. 2). To predict a binding mode, a potential interaction of metal complexes with calf thymus DNA (CT-DNA) has been explored using UV absorption and circular dichroism (CD). The spectroscopic

studies (hyperchromic effect) suggest that cationic arene-complexes bind to DNA through non-covalent interaction probably as external binding (on the outside of the helix).

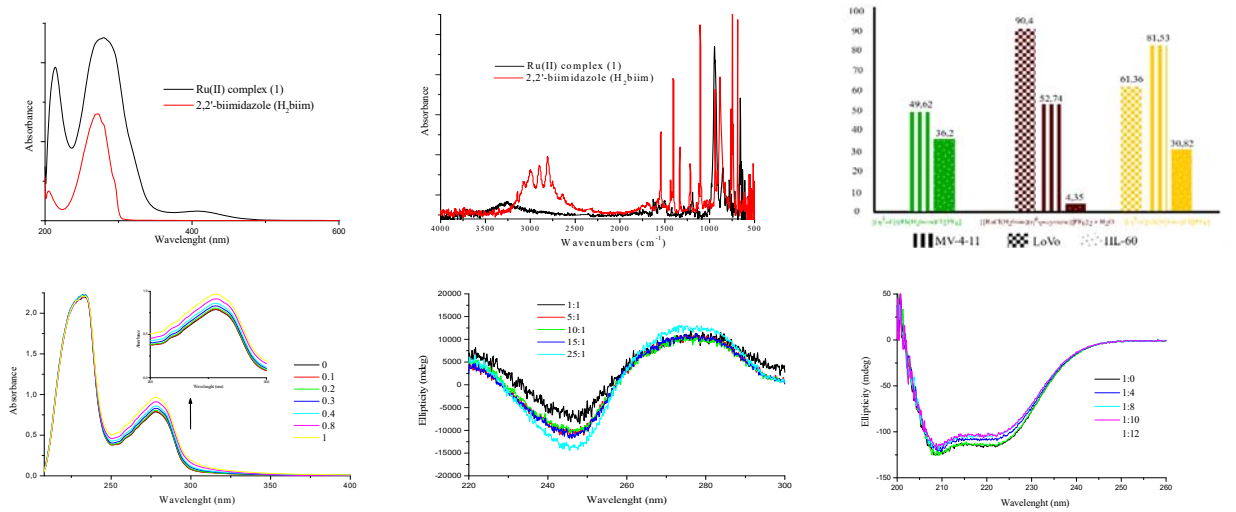

Figure 2. Selected spectra revealing the physicochemical and biological properties of the obtained complexes.

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International Symposium on Metal Complexes 2019
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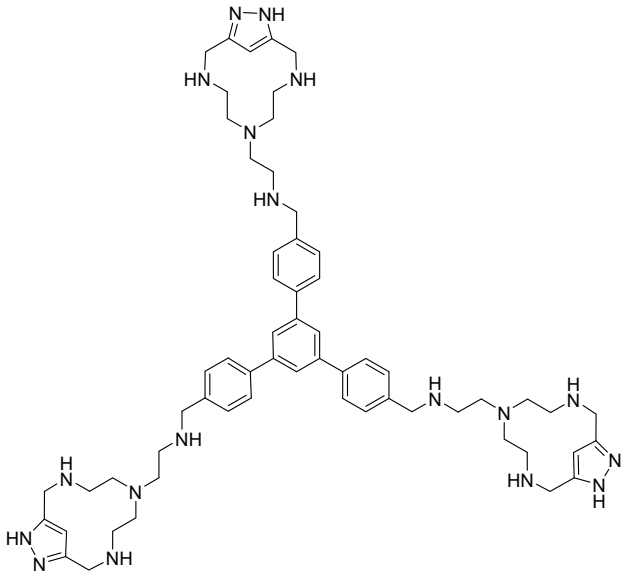
Synthesis and study of 1*H*-pyrazole-based azamacrocycles for G-quadruplex recognition

Ariadna GIL-MARTÍNEZ, Alberto LOPERA, Isabel PONT, Jorge GONZÁLEZ-GARCÍA, Enrique GARCÍA-ESPAÑA

ICMol, University of València, C/Catedrático José Beltrán 2, 46980, Paterna, Spain
email: agilmar4@alumni.uv.es

G-quadruplexes are secondary structures that can be found in guanine rich DNA sequences [1]. They can be naturally formed in telomeric and in transcriptional regulatory regions of multiple genes and oncogenes. Therefore, these structures have attracted attention as supramolecular targets for developing new antitumoral drugs [2]. Herein, we present the design, synthesis and characterisation of a novel tripodal polyamine derivative, which includes an aromatic core and three pending arms. The pending arms are based on polyamine macrocycles containing an 1*H*-pyrazole moiety as aromatic spacer that may provide an alternative interactions. The acid-base behavior in aqueous medium has been studied by means of potentiometric titrations and fluorescence emission spectroscopy. The interaction with canonical and G-quadruplex DNA models has been assessed by FID and FRET melting methods. As a preliminary result, a highly selective interaction for G-quadruplex over duplex B-DNA structures has been observed.



Scheme 1. Studied ligand.

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International Symposium on Metal Complexes 2019
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Effects of polar side chains on the formation of nickel(II), zinc(II) and cadmium(II) complexes of cysteine peptides

Ágnes GRENÁCS, [a] Norbert LIHI, [a), b)] Nikolett BODNÁR, [a)] Zsombor PATAKI, [a)] Dóra Csilla PÁLINKÁS, [a)] Márton LUKÁCS, [a)] Katalin VÁRNAGY [a)]

[a)] Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1., H-4032, Debrecen, Hungary
[b)] MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary
e-mail: grenacs.agnes@science.unideb.hu

Cysteine, as an anchoring residue of peptides and proteins plays a key role in various biological processes, such as metal ion transport, storage and activation/inhibition of redox reactions. In most cases thiolate function is not the exclusive binding site; imidazole ring(s) and/or carboxylate group(s) are also involved in the coordination to transition metal ions. In order to gain information on the species formed, smaller model peptides having the side chains mentioned above can be examined. Recent studies of our research group included the studies of coordination ability of N-terminally free oligopeptides with cysteine on the C-termini containing histidine [1,2], aspartic acid [3] or another cysteine [4] in different positions in the sequence. The results clearly show that the C-terminal cysteine behaves as an anchor for metal binding in competition with the N-terminal part of the molecules. This behavior results in the formation of

(i) stable macrochelated complexes with participation of thiolate donor atom
(ii) mononuclear complexes with coordination isomeric structures
(iii) dinuclear complexes

On the other hand the presence of two cysteine residues in the molecule is able to promote the zinc(II) and cadmium(II) induced amide nitrogen deprotonation due to the binding of C-terminal cysteine.

These results raised a new question: how does the C-terminal cysteine affect the metal binding ability of peptides, if the molecule does not contain other donor group with strong coordinating ability? Thus, in the continuation of this research, two hexapeptides having free N-terminal amino and a C-terminal cysteinyl functions as metal binding sites are introduced: AlaAlaAlaSerSerCys-NH_2 and AlaAlaGluAlaAlaCys-NH_2. The first ligand contains only serine residues in order to enhance the polarity of the molecule, while the second peptide has an additional carboxylate function in the sequence to show the influence of the carboxylate function of glutamic acid on the complex formation processes.

Affinity of nickel(II), zinc(II) and cadmium(II) ions towards the two binding sites and the structures of the complexes formed were described by the use of pH-potentiometry, UV-visible spectrophotometry, CD and NMR spectroscopy.

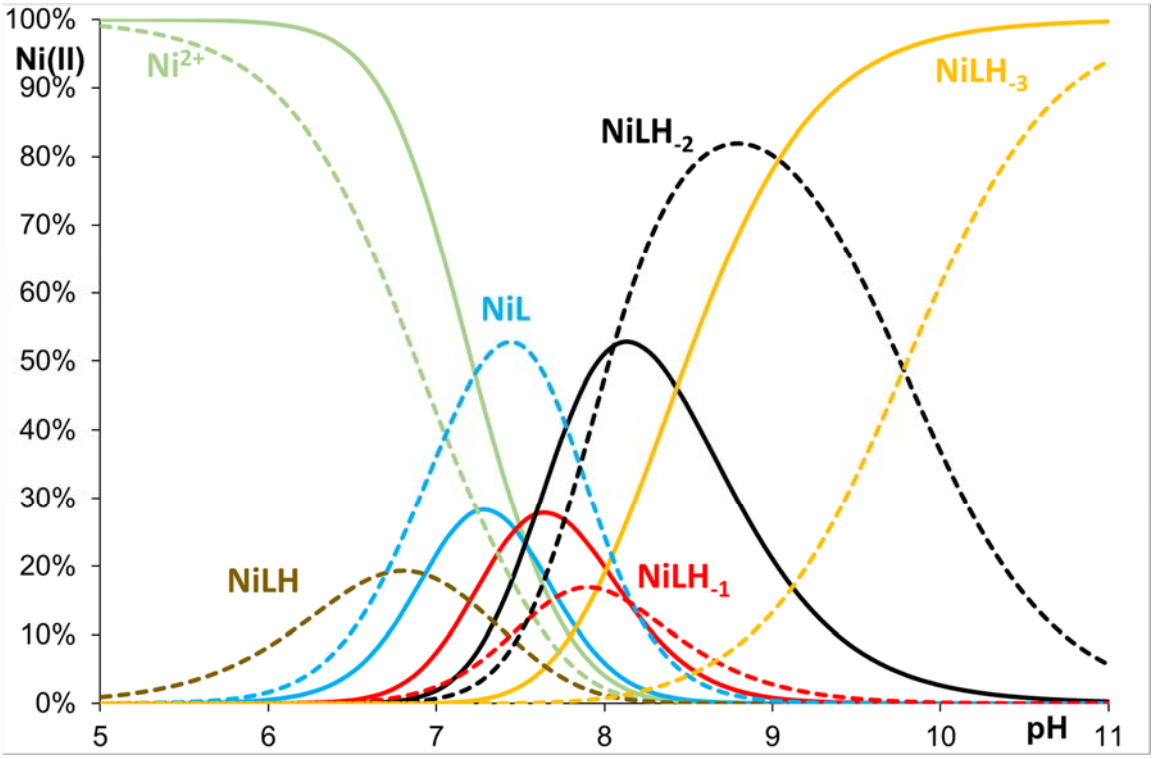

Figure 1. Complex distribution diagram between nickel(II) and the ligands (AAASSC-NH_2 – solid lines, AAEAAC-NH_2 – dashed lines) in equimolar solutions.

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 (K115480).

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International Symposium on Metal Complexes 2019
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Modulation of catalytic activity of the NColE7 metallonuclease

Heba A.H. ABD ELHAMEED, Bálint HAJDU, Béla GYURCSIK

Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary
e-mail: gyurcsik@chem.u-szeged.hu

NColE7 metallonuclease is used by E. coli to kill competing bacteria under stress conditions. This enzyme cleaves the DNA non-specifically resulting in its cytotoxicity. The extreme high catalytic activity is demonstrated by the fact that a single NColE7 molecule can kill the cell. For this reason the gene of the NColE7 metallonuclease can not be cloned into any commercial carrier DNA vector without the parallel cloning of the gene of its inhibitory protein: the minor leakage in the protein expression regulation disables bacteria to survive.

Recently we have developed a new strategy for protein purification by affinity chromatography on Ni(II)-NTA resin, in a system fusing a C-terminal hexahistidine protein tag to the target protein [1]. During the experiments we have observed that the affinity tag modulates the catalytic activity of the target metallonucleases. The genes of NColE7 as well as its less active mutants could be cloned into the newly constructed DNA vector. The reason for this can be multiple. (i) The DNA binding ability or the intramolecular allosteric activation mechanism of the enzyme may be sterically hindered by the prolonged C-terminal protein sequence. This would allow the regulation of the enzyme by shortening of the affinity tag or its removal from the protein through a suitably positioned hydrolytically sensitive amino acid sequence either by using a specific protease or by Ni(II)-induced cleavage. (ii) The metal ion containing active centre at the C-terminus of NColE7 is close enough to the hexahistidine sequence to allow its coordination to the free site of the catalytic Zn(II) ion. This event would also inhibit the nuclease action, as it prevents the metal ion coordination to the scissile phosphodiester group, which is an essential step of the DNA cleavage. In this case the enzyme could be reactivated by a metal ion, which can effectively compete with Zn(II) for the haxahistidine binding site, but does not replace Zn(II) in the active centre.

Based on the above considerations we have carried out catalytic experiments with the new NColE7 fusion proteins to learn more about the possibility of regulation of the enzyme. The latest results of this project will be presented.

Acknowledgements: This work has been supported by COST Action CA15126; GINOP-2.3.2-15-2016-00038; NKFIH K_16/120130.

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International Symposium on Metal Complexes 2019
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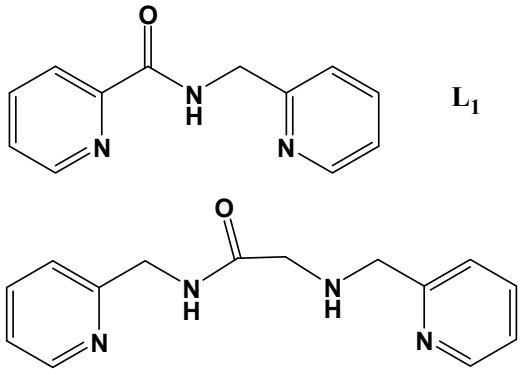
Characterization of copper(II) specific ligands: chelation therapy in Alzheimer's disease

Tamás JAKUSCH, Tamás KISS

Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary
email: jakusch@chem.u-szeged.hu

In an Alzheimer's disease affected brain copper is accumulated in senile plaques containing amyloid-β, while the total cellular copper levels are decreased.[1] An "artificial copper chaperon" is needed to return the copper(II) from plaques to brain cells, from β-amyloid to hCTR1. A potential chaperon can be a small molar mass ligand which affinity to copper(II) should be higher than β-amyloid (pM ~ 10)[2], but smaller than hCTR1[3].



Based on the Irving-Williams series Cu(II) always forms higher stability complexes than Zn(II). However, the Zn(II) (or free Zn(II)) concentration is usually significantly higher in biological fluids than Cu(II), so in order to avoid any competition, copper(II) specific ligand is needed.

Two ligands (see figure) containing amide bond were synthesized, and their Cu(II) and Zn(II) complexes were studied by pH-potentiometry, UV-VIS- and EPR spectroscopy. At millimolar concentration level (and pH = 7.4) unexpectedly both ligands partly or completely coordinates to Zn(II) through deprotonated amide nitrogen. However in therapeutic conditions ($c(L) \sim 10^{-5}$ mol/dm^3) the Zn(II) complex formation are negligible in both cases.

The two ligands form stable enough complexes with Cu(II) to remove Cu(II) from its $A\beta_{1-16}$ complex. Addition of one of the ligands to Cu(II)/$A\beta_{1-16}$/ascorbate system reduces/terminates ROS production even at the presence of high excess of Zn(II).

Acknowledgement: This work was supported by the National Research, Develop-ment and Innovation Office-NKFIH through project GINOP-2.3.2-15-2016-00038.

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International Symposium on Metal Complexes 2019
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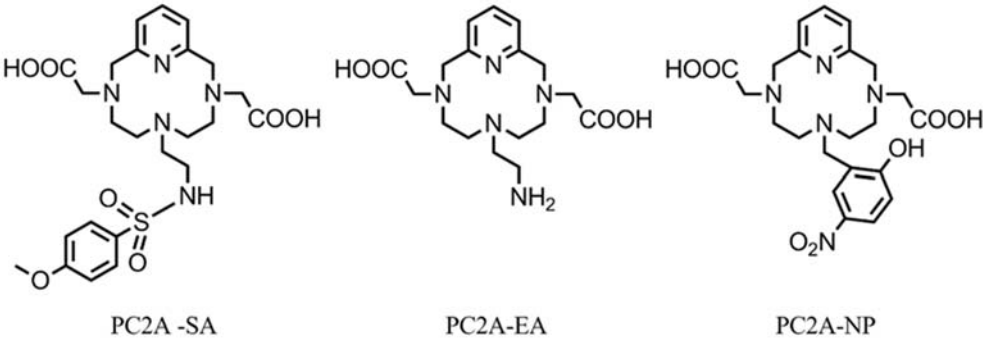
Mn(II)-based, pH-sensitive MRI contrast agent candidates for *in vivo* applications.

Ferenc K. KÁLMÁN, [a] Richárd BOTÁR, [a] Katinka TARNÓCZI, [a] Enikő MOLNÁR, [a] Viktória NAGY, [a] Zoltán GARDA, [a] Balázs VÁRADI, [a] György TRENCSÉNYI, [b] Éva JAKAB-TÓTH, [c] Gyula TIRCSÓ [a]

[a] Department of Physical Chemistry, Faculty of Science and Technology, University of Debrecen, Egyetem tér 1., H-4032, Debrecen, Hungary
[b] Division of Nuclear Medicine, Medical Imaging Department, Faculty of Medicine, University of Debrecen, Nagyerdei Krt. 98., H-4032, Debrecen, Hungary
[c] Centre de Biophysique Moléculaire, Rue Charles Sadron, CS 80054, 45071, ORLEANS CEDEX 2, CNRS, France
e-mail: kalman.ferenc@science.unideb.hu

In the last decades the Magnetic Resonance Imaging (MRI) has proved its capability to deliver excellent anatomical images of the human body with or without using the so called contrast agents (Gd(III)-based complexes). However, the MRI technique also provides the opportunity to investigate the biochemical processes on molecular level. The molecular imaging - instead of anatomical imaging - requires special molecular imaging probes which can give adequate response for the change of the investigated parameter. The benefit of these methods would be the deeper understanding of biochemical abnormalities for earlier diagnosis.[1]

Here, we report the results of the detailed investigation of three newly synthesized PC2A derivative ligands, namely the PC2A-SA, PC2A-EA and PC2A-NP (Scheme 1.). The solution equilibrium of the ligands and their metal complexes was investigated by means of pH-potentiometry, spectrophotometry and ^{1}H relaxometry.



Scheme 1. Structure of the ligands.

The stability constants (log K_{MnL}) of the [Mn(PC2A-SA)], [Mn(PC2A-EA)] and [Mn(PC2A-NP)] were found to be 17.96, 19.01 and 18.05, respectively. For the better comparison, the pMn values (-log[Mn(II)]$_{free}$, c_{lig}=$c_{Mn(II)}$=0.01 mM, pH=7.4) of the Mn(II) complexes were calculated and those are 9.77, 9.67 and 9.27 for the [Mn(PC2A-SA)], [Mn(PC2A-EA)] and [Mn(PC2A-NP)], respectively. The values show that the complex formation in all system is practically 100% at pH 7.4 which is good for the *in vivo* applications.

The pH-dependence of the relaxivity of the complexes was also investigated by using ^{1}H relaxometry. These results showed that only the [Mn(PC2A-EA)] complex has a significant (~1.5 unit) decrease in its relaxivity in the pH range of 6.0-8.0 due to the deprotonation and coordination of the primer amine group (log K_{MnLH}=6.88(2)). Neither the extent nor the pH range of the given pH response was affected by Human Serum Albumin (HSA). For the [Mn(PC2A-SA)] and [Mn(PC2A-NP)] complexes, the protonation constants of the sulfonamide and nitrophenyl moieties are 8.77 and 4.58 which make those unsuitable for *in vivo* pH sensing.

The inertness of the complexes was studied by means of metal exchange reactions occurring between the Mn(II) complex and a suitable metal ion such as Cu(II) or Zn(II). Owning to the rate constants characterizing the dechelation of the Mn(II) complexes the half-lives of the dissociation ($t_{1/2}$) for the complexes have been calculated. The $t_{1/2}$ values (at 25 °C) are 1.0×10^3, 8.0×10^3 and 7.0×10^3 hours for the PC2A-SA, -EA and -NP complexes, respectively. Based on the results gained for Gd(III) complexes we can assume that the decomplexation reactions of Mn(II) complexes occur circa 5 times faster at 37 °C. Furthermore, considering the fact that the $t_{1/2}$ of the renal excretion of the complexes injected intravenously is about 1.6 h, the amount of the released Mn(II) can be calculated. The result shows that circa 0.1% of the total Mn(II) would be released from the [Mn(PC2A-EA)] which is more than acceptable for a Mn(II)-based compound.

The efficacy of pH-sensing of [Mn(PC2A-EA)] complex was studied by MRI technique using 1 T magnetic field. As it is shown in Figure 1., phantom samples were prepared and measured. One can clearly conclude that the signal intensity of the samples was pH dependent.

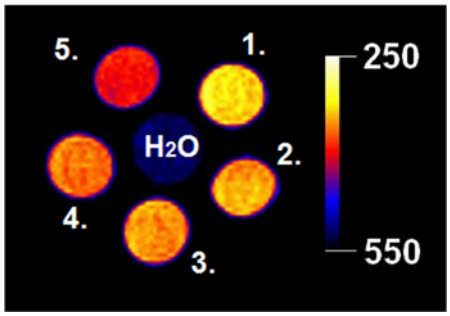


Figure 1. 1 T MRI image of the [Mn(PC2A-EA)] complex solutions at different pH values. The pH of the phantoms were 6.43, 6.70, 7.01, 7.33 and 7.95 from sample 1 to 5. The concentration of the [Mn(PC2A-EA)] complex was 1 mM and the unit of the T_1 relaxation time presented in the figure is msec.

Acknowledgements: This research was funded by the Hungarian Scientific Research Fund (NKFIH K-120224 projects) and the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (Gy.T. and K.F.K.). The research was also supported in a part by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004. The project was supported by the ÚNKP-18-4 new national excellence program of the Ministry of Human Capacities (Gy.T. and K.F.K.).

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Binding of radionuclide cations by picolinate-containing ligands

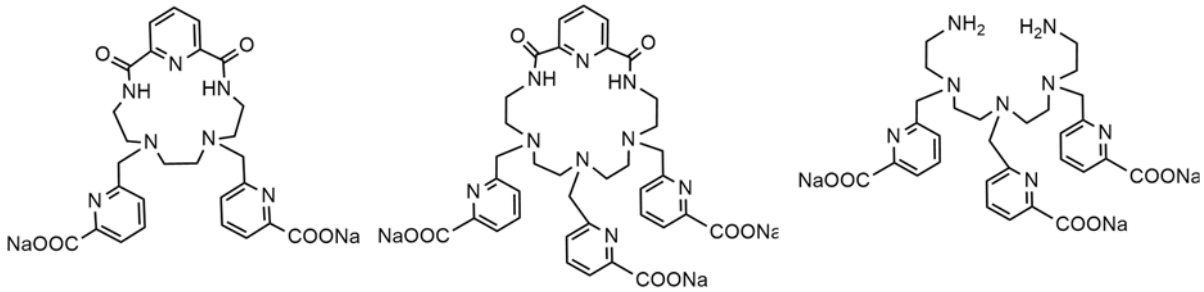
Taisia KALMYKOVA, [a] Likhosherstova DARIA, [a] Bayirta EGOROVA, [a] Sinenko IRINA, [a] Anastasia ZUBENKO, [b] Olga FEDOROVA, [a,b,c] Stepan KALMYKOV [a]

[a] Department of Chemistry, Lomonosov Moscow State University, Moscow, Russia
[b] A. N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Moscow, Russia
[c] Mendeleev University of Chemistry and Technology of Russia, Moscow, Russia
e-mail: taisia2906@rambler.ru

At the present time the complexation of cations by known macrocyclic ligands (DOTA and its analogs) used in nuclear medicine occurs either at elevated temperatures [1], which is often not acceptable for biological vectors, or requires a long reaction time [1], that can cause to significant losses due to radioactive decay. Complexes with known acyclic ligands (DTPA and its derivatives) dissociate fast under *in vivo* conditions which leads to accumulation of free cations of radionuclides in healthy tissues [2-4].

Thus, it is necessary to find such ligands that would form a stable complex with radionuclides for a short time and at low temperatures.

One approach to improve the kinetics of binding by macrocyclic ligands of metals is the addition of picolinate fragments [5], which demonstrate a strong coordination ability of the binding of transition metals in macrocyclic and acyclic ligands due to their ability to provide O, N donor atoms in strong mutual arrangement. These ligands have the same backbone as common polyamines studied for radiopharmaceuticals like cyclen, cyclam and acyclic derivatives. Studied here acyclic ligand L3 is characterized by acyclic structure similar to the DTPA derivatives, as L2 possesses the same backbone but hardened by closing into macrocycle via bisamide moiety and L1 similar to L2 but with less size of cavity and number of basic sites respectively (Fig.1). Bisamide moiety provides open cavity for complexation of cations although decreases overall protonation of ligands.



L1 L2 L3

Figure 1. Studied ligands.

In this work, the binding of Cu^{2+} and Bi^{3+} by new picolinate containing acyclic (L3) and macrocyclic (L1, L2) ligands was studied.

The protonation constants of these ligands were determined by potentiometric titration. Stability constants of Cu-L1, Cu-L2, Cu-L3, Bi-L1 and Bi-L3 complexes were calculated by

potentiometric titration as well as bismuth complexation was verified by solvent extraction technique (Table 1) [6].

Table 1. Calculated stability constants of complexes

Ligand	$\log K_{CuL}$	$\log K_{BiL}$
L1	10.42±0.06	-
L2	14.6±0.1	19.6±0.6
L3	18.7±0.4	27.69±0.04

The conditions for the formation of complexes were studied using thin layer chromatography (TLC) combined with autoradiography and measurement of radioactivity by γ spectrometry for quality and quantity control.

The optimal conditions for complexes under which the maximum degree of labeling is achieved at the minimum concentration of ligand were determined.

In vitro serum stability studies of the radiolabeled complexes in excess of fetal bovine serum (FBS) have been conducted.

Acknowledgements: This work is supported by RFBR project №18-33-20152.

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Investigation of the catalytic activity of immobilized Na_2[Ir(cod)(emim)(*m*tppts)] in a flow reactor

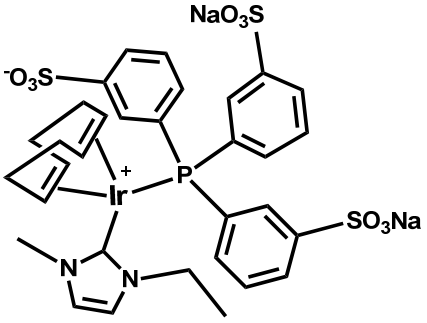
Henrietta KOVÁCS, [a] **Gábor PAPP,** [a] **Ferenc JOÓ,** [a),b)] **Henrietta HORVÁTH** [b]

a) Physical Chemistry Department, University of Debrecen, Egyetem tér 1, 4032, Debrecen, Hungary
b) MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group, University of Debrecen, Egyetem tér 1, 4032, Debrecen, Hungary
e-mail: kovacshenrietta@science.unideb.hu

The viability of safe and reversible hydrogen storage utilizing [Ir(NHC)(phosphine)] complexes and continuous flow reactors is one of our main areas of research. [Ir(NHC)(phosphine)] complexes are highly active catalysts of numerous organic and aqueous phase hydrogenation and dehydrogenation reactions. [1] Using these complexes, we have previously studied the formate-bicarbonate catalytic interconversion as a potential process for hydrogen storage. We successfully proved that the catalytic cycle is feasible in a homogeneous phase reaction under flow conditions. [2]

In order to fully utilize the unique advantages of a flow reactor, it's necessary to immobilize an active complex catalyst on a solid surface. Ideally, after loading the heterogenized catalyst into a catalyst holder, and placing the catalyst in the flow reactor, it's possible to recycle the catalyst without the extra step of filtration after a reaction.

We attempted the immobilization of Na_2[Ir(cod)(emim)(*m*tppts)], a highly active hydrogenation catalyst in organic and aqueous phase reactions, on numerous types of commercially available anion exchange resins. We have investigated the stability of the heterogenized catalysts under acidic and basic conditions, and their catalytic properties in hydrogenation test reactions in an H-Cube® hydrogenation microreactor.



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The effect of lead(II) lone electron pair and non-covalent interactions on the supramolecular assembly and fluorescence properties of Pb(II)-pyrrole-2-carboxylato polymer

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

[a] *Institute of Chemistry, Jan Kochanowski University in Kielce, 15 G Świętokrzyska 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] *Shupyk National Medical Academy of Postgraduate Education, 9 Dorogozhytska Str., 04112 Kyiv, Ukraine*
[d] *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*
e-mail: mateuszkowalik.86@gmail.com

Recently, the growing interest of chemists in metal–organic coordination polymers (MOCPs) is primarily derived from their intriguing structures and potential applications in catalysis, gas storage, molecular sensing, ion exchanges, nonlinear optics, luminescence, etc. Currently, we are devoting considerable effort to finding the proper method of synthesizing new coordination polymers containing S- or N-heteroaromatic carboxylates as linkers and characterizing the obtained Pb(II) compounds according to their structural diversity, luminescence and thermal properties. The choice of Pb(II) as the central ion of MOCPs was motivated by several reasons mentioned in the literature: i) a large ionic radius allowing for a wide range of coordination numbers, ii) the stereoactivity of the $6s^2$ lone electron pair leading to a hemidirected or holodirected geometry, iii) a flexible coordination environment, and iv) the possibility to form secondary bonds and unusual non-covalent interactions, such as classic hydrogen bonds and π···π stacking interactions, as well as nonconventional hydrogen bonds and rarely reported tetrel bonds, Pb(lone pair)···π interactions, C–H···Pb agostic-type interactions or hydrogen bonds, and chelate ring stacking interactions. Moreover, the construction of coordination polymers requires the selection of proper ligands acting as linkers, because we are looking for materials exhibiting different network topologies and fluorescence properties, which point to potential applications [1–3].

The reaction of $Pb(NO_3)_2$ with 1*H*-pyrrole-2-carboxylic acid (2prCOOH) leads to the formation of a new four-nuclear Pb(II) polymer, $[Pb_4(2prCOO)_8(H_2O)]_n$ (Fig. 1), which has been characterized by CHN, FT-IR, TG, PL and single-crystal X-ray diffraction methods. In view of the primary Pb–O bonds, Pb1 and Pb3 show hemidirected pentagonal pyramidal geometries, while Pb2 and Pb4 display hemidirected octahedral geometries. The topology of the strongest Pb–O bonds was determined as the $(4{\cdot}8^2)$ fes topology. Taking the secondary Pb–O bonds into account, the coordination number of Pb centres increased, Pb1 exhibited a hemidirected monocapped pentagonal pyramidal geometry, Pb2 and Pb4 exhibited a

holodirected tricapped trigonal prismatic geometry, and Pb3 exhibited a holodirected bicapped trigonal prismatic geometry. Moreover, the Pb(II) lone pair stereoactivity was confirmed by DFT calculations. The 2D structure was expanded into 3D by the existence of non-covalent O/C–H···π and Pb···π interactions, which was confirmed by the Hirshfeld surface analysis.

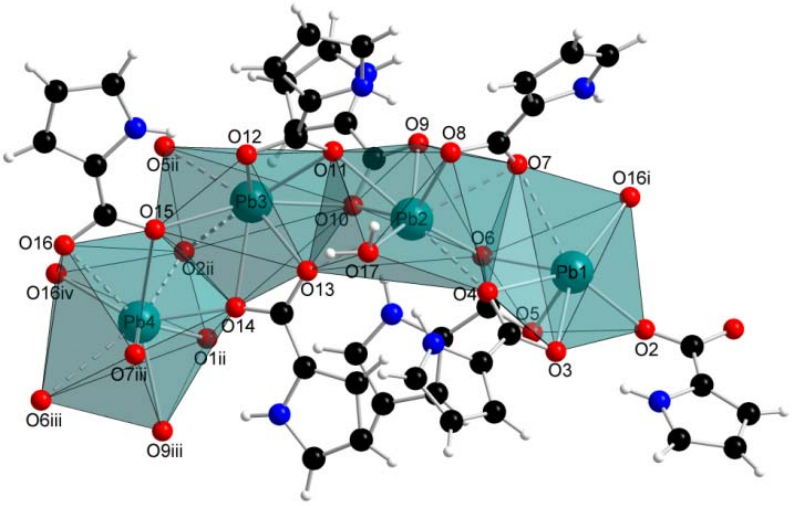

Figure 1. The molecular structure of the $[Pb_4(2prCOO)_8(H_2O)]_n$ polymer.

The above mentioned interactions improve the rigidity of the structure and facilitate the charge and energy transfer between metal centres, making the polymer a promising luminescent compound. The complex displays green fluorescence ca. 520 nm (λ_{ex} = 375 nm) and greenish yellow ca. 540 nm (λ_{ex} = 468 nm). The large Stokes shift (145 nm) of the first band reveals that the ground and excited states are significantly distorted to each other. Such an effect is observed in s^2-metal complexes when $s \rightarrow p$ metal-centred (MC) transitions occur, and associated with the elimination of the ground-state distortion in the excited state. The DFT calculations pointed to some orbitals localized on Pb(II) centres with significant contribution of s orbitals, which confirmed the appearance of MC transitions. The second emission band should be attributed to ligand-to-metal charge transfer (LMCT) transitions between the delocalized π-bonds of pyrrole-2-carboxylates and the unoccupied valence *p* orbitals of Pb(II) centres.

Acknowledgements: Polish Ministry of Science and Higher Education (Projects No. 612060 and 612415).

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Co(III) and Bi(III) complexes of retrohydroxamate-based antibacterial compounds

Máté KOZSUP, [a] **Darren GRIFFITH,** [b] **Brendan TWAMLEY,** [c] **Donal M. KEOGAN,** [b] **Etelka FARKAS,** [a] **Péter BUGLYÓ** [a]

[a] *Department of Inorganic and Analytical Chemistry, University of Debrecen, H-4032 Debrecen, Egyetem tér 1, Hungary*
[b] *Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin*
[c] *Trinity College Dublin, The University of Dublin, Dublin*
e-mail: kozsup.mate@science.unideb.hu

After cancer therapy the antibacterial treatment of the patient is necessary. Higher efficiency of the method can be gained by transporting the antibacterial agent directly to the treated area. Chaperoning of the drug molecule to the site of action in an inactive form and activation of it at the site is one of the known approaches. [1-3]

The hypoxic character of the cancer cells provides highly reductive environment in the tumor, which is an important difference to normal cells, and can be useful for activating the pro-drugs. The large difference in lability between the complexes of cobalt(III) and cobalt(II) makes this metal preferred to construct hypoxia-selective pro-drug complexes. After the selective reduction of these Co(III) complexes the bioligand could only be released in the tumor cells.

Tripodal 4N-donor ligands, tris(2-methylpyridyl)amine (tpa) and tris(2-aminoethyl)amine (tren) were selected to synthesize chaperons with stabilized 3+ oxidation state of the central metal ion, while the coordination sphere was completed with drug molecules, having biological activity.

For drug molecules, the retrohydroxamate-based GSK1322322 molecule and its model N-hydroxy-N-phenylformamide (HFA) were selected, which are potential chelating bioligands, having antibacterial activity. Bi(III) complex of the HFA was also synthesized as a reference for the biological studies due to the antibacterial activity of the bismuth ion. In our work, synthesis, characterizations with different analytical techniques and biological screening of the compounds have been carried out.

This contribution will highlight the details of the characterization of the compounds together with the most important findings regarding their biological activity.

Acknowledgement: 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).

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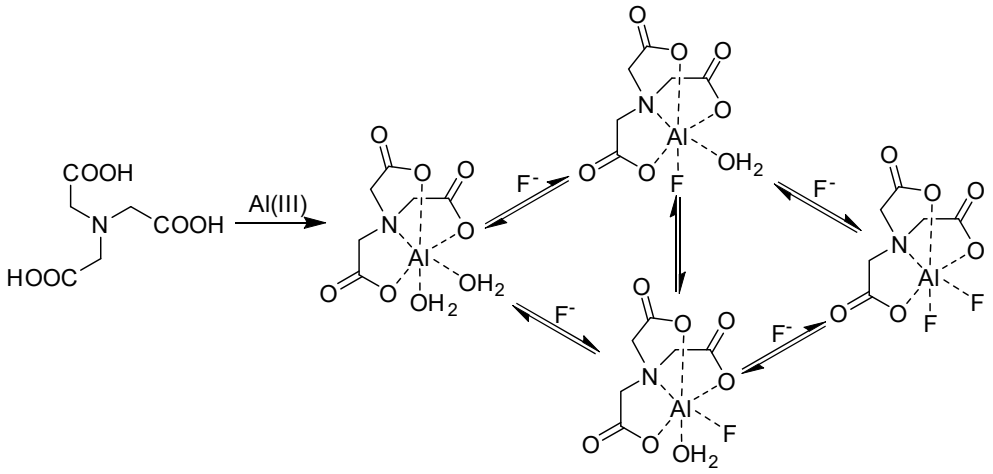
[Al(nta)] complex as a fluoride carrier

Eliška HACAPERKOVÁ, Vojtěch KUBÍČEK, Jan KOTEK, Petr HERMANN

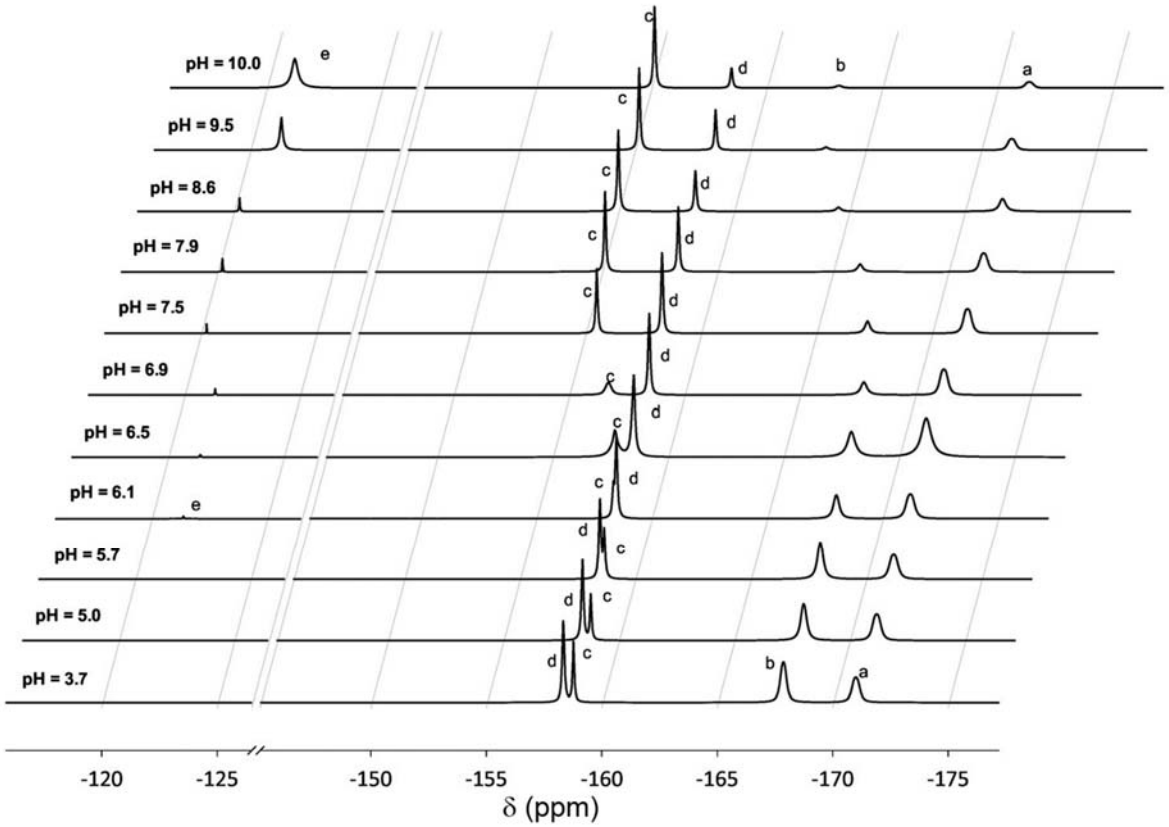
Charles University, Faculty of Science, Department of Inorganic Chemistry, Hlavova 8, 128 40, Prague, Czech Republic
e-mail: kubicek@natur.cuni.cz

Positron Emission Tomography (PET) is a common medical non-invasive diagnostic technique. The technique utilizes positron emitters. The most common PET radioisotope is ^{18}F. The isotope is mostly administered bound in organic compounds such as ^{18}F-fluorodeoxyglucose. However, syntheses of fluorine bearing organic compounds are often laborious or reaction rates and yields are insufficient. Thus, alternative routes have been investigated. One of the promising directions is ^{18}F-fluoride binding to Al(III) ion. However, Al(III) cannot be administered in a free form. The metal ion must be bound in a thermodynamically stable and kinetically inert complex to avoid its non-specific deposition in tissues. The most common way of labeling is treatment of ^{18}F-fluoride with free Al(III) aquaion followed immediately by complexation by stabilizing multidentate ligand. However, this strategy results in a mixture of species that must be separated prior to the administration. The alternative strategy is synthesis of Al(III) complex with unsaturated coordination sphere. Such complex can be labeled with ^{18}F-fluoride in the final step. Albeit this strategy is promising, it attracted only limited attention and there is not enough data in the literature to allow design of suitable ligand-metal-fluoride ternary systems for practical application.

To gather the basic data on thermodynamic and kinetic behavior of such ternary systems, we have investigated substitution reactions of water and fluoride in the coordination sphere of Al(III) complex with nitrilo-triacetic acid (H_3nta). The ligands is a simple symmetrical model ligand forming stable Al(III) complex. As the ligand is tetradentate, there are two remaining positions in the coordination sphere that are occupied by water molecules. These water molecules can be replaced by fluorides. The ligand exchange in the Al(III) coordination sphere is slow in the NMR timescale and, thus, individual species and isomers show separate signals. It allows for detailed investigation of the ternary system. The two unoccupied positions on [Al(nta)] complex are non-equivalent and they show significantly different properties in terms of basicity of the coordinated water molecule, preferential binding of fluoride anions and their chemical shifts in ^{19}F NMR.



Fluoride binding and dissociation was further studied with fluoride ion selective electrode. Fluorides are effectively bound in the weakly acidic or neutral solutions. Increasing concentration of hydroxide anions in alkaline solutions leads to preferential formation of hydroxido species. Competition with various anions showed that acetates or carbonates do not replace fluorides in the coordination sphere. On the contrary, fluorides are partially replaced by phosphates; however, only under a high phosphate excess. All the mentioned substitution reactions are fast, so that the exchange of ligands in the Al(III) coordination sphere is completed in less than three seconds in all experiments.



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Transformation of calcium oxalate dihydrate to monohydrate crystallites

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

Centre Grup de Tècniques de Separació en Química (GTS), Departament de Química, Universitat Autònoma de Barcelona, Facultat de Ciències. Edifici CN. 08193, Bellaterra, Barcelona, Spain
e-mail: montserrat.lopez.mesas@uab.cat

Calcium oxalate hydrates are present in the nature forming three crystallographic species: the thermodynamically stable calcium oxalate monohydrate (whewellite, COM), the kinetically favorable calcium oxalate dihydrate (weddellite, COD), and calcium oxalate trihydrate (caoxite, COT), which is rarely observed.[1] Crystallites of those minerals are easily found on sediments, animals and plants, which make them the focus of study of different research areas. As an example, the study of calcium oxalate films is a hot topic in the field of cultural heritage since those have been found on the surface of ancient monuments.[2] Moreover, on the medical field, calcium oxalate represent 70% of all urinary calculi in the Western countries.[3]

Whewellite (COM) stone/crystals are the most commonly found since, as mentioned before, it is the stable specie. Regarding weddellite (COD), crystallites suffer a transformation to the monohydrated specie due to its low stability,[2,4,5] process that could be caused by the loss of one water molecule, known as zeolitic water,[6] forming a monohydrated phase, named TRA. Since COM and TRA are chemically the same, it is not possible to differentiate them by the most common techniques of characterization, such as infrared spectroscopy (IR) and X-ray diffraction (XRD).[7] This transformation process and the stability of COD under thermal treatment and with different degrees of humidity has been studied and described in mineral system and in vitro by several authors.[8-10]

The most remarkable feature of this oxalocalcic species is that, even being highly instable in humid conditions, COD crystals are found in the surface of monuments (which are never in dry conditions),[4] and in kidney stones (which media is urine).[11] It has been observed that COD renal calculus usually have depositions of hydroxyapatite (HAP) between crystals,[11] meanwhile those without depositions are most likely to be found with several degrees of transformation.

In order to understand the stability of COD under non-ideal conditions, the transformation process has been studied in vitro simulating the human urine medium. To do so, a series of artificial human urine (AHU) with different degrees of calcium oxalate relative supersaturation (RSS) and different promotors/inhibitors ratios were designed. The designed AHUs have a composition inside the normal range for humans, considering the RSS of healthy as well as stone formers subjects. Synthetic microcrystals of COD were placed on the different AHUs mediums at 37ºC for an appropriate period of time. Samples were filtered and measured by ATR-FTIR. The transmission spectra were treated with a Savitzky-Golay second derivative, followed by a maximum normalization on the region of interest (between 1000-800 cm^{-1}). The obtained results were treated by Multivariative Curve Resolution (MCR) and the obtained

sigmoidal curve fitted. With this data treatment, the half-time ($t_{1/2}$) for all the conditions was obtained (fig. 1).

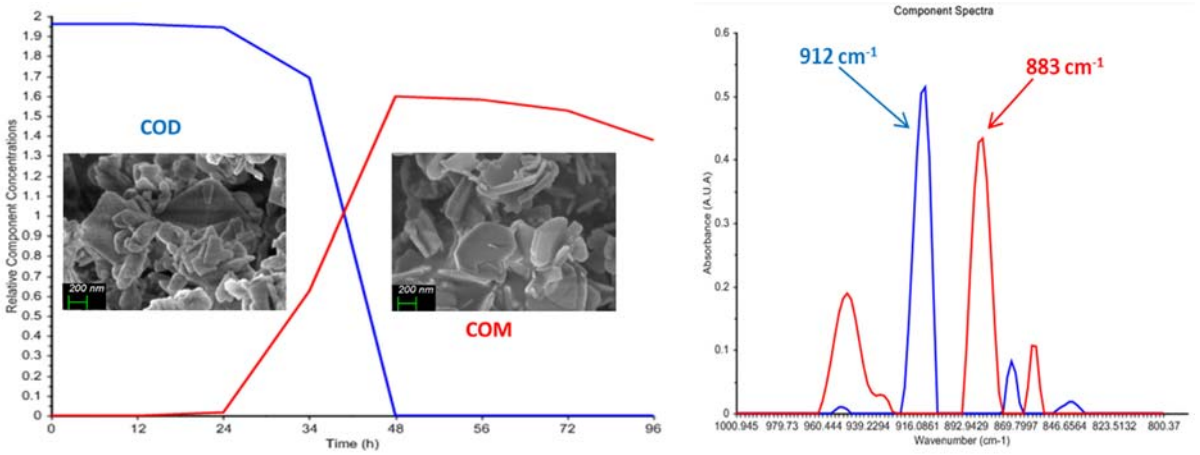

Figure 1. Example of the MCR data treatment of one AHU. On the left, the relative component concentrations of the two determined components (912 cm^{-1} for COD and 883 cm^{-1} for COM) showed on the right. Moreover, SEM images are placed to observe the differences on the crystallites morphology before and after the transformation (left).

From this research, it can be concluded that the transformation/stability of the dihydrate specie do not only depend on the humidity conditions, or in the presence of calcium oxalate promotors, but also on the presence of inhibitors that helps on the stabilization of the zeolitic water, such as phosphates and citrates.

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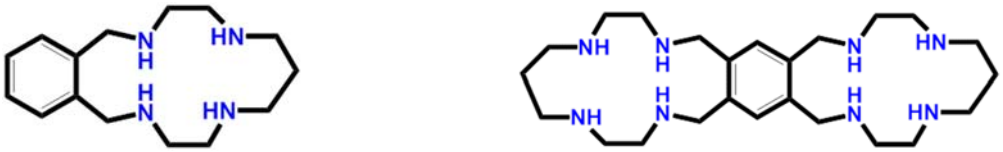
Kinetic study of Cu(II) complexes of mono- and bis-tetraazamacrocyclic ligands

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

[a] *Department of Chemistry, Masaryk University, Kamenice 5, CZ-625 00 Brno, Czech Republic*
[b] *Department of Organic Chemistry, University of Chemistry and Technology, Technická 5, CZ-166 28 Prague 6, Czech Republic*
e-mail: 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].



Scheme 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/1359/2018) and the Ministry of Education of the Czech Republic is acknowledged.

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International Symposium on Metal Complexes 2019
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Metal ion binding ability of the free N-termini of tau protein: appraisal of preference by solution equilibrium study

Márton LUKÁCS,[a)] Györgyi SZUNYOG,[a)] Ágnes GRENÁCS,[a)] Giuseppe DI NATALE,[b)] Giuseppe PAPPALARDO,[b)] Katalin VÁRNAGY,[a)] Imre SÓVÁGÓ[a)]

[a)] Department of Inorganic and Analytical Chemistry, Egyetem tér 1., H-4032, Debrecen, Hungary
[b)] CNR-IC Istituto di Cristallografia, Via Paolo Gaifami 18., I-95126, Catania, Italy
e-mail: lukacs.marton@science.unideb.hu

Nowadays, neurodegenerative diseases, such as Alzheimer's (AD) and prion disease, represent a serious medical and social concern. The number of people living with dementia worldwide is estimated to 45 million, which is expected to increase to more than 130 million people by 2050. AD is by near the most common form of dementia; [1] thus, the investigation of its molecular background is crucial.

The gross atrophy of the cortex and hippocampus is the neuropathology hallmark of AD. During the course of the disease, the accumulation of characteristic proteinaceous fibrillary substances (senile plaques made of amyloid-beta or neurofibrillary tangles made of tau), is increased in the human brain. [2] Tau is well established as a microtubule-associated protein in neurons; it binds to microtubules thus stabilizing and making them rigid. After an aberrant phosphorylation step (or post-translational altering), hyperphosphorylated tau molecules are formed in cytosol. These are not able to bind to microtubules anymore; thus, free tau concentration is multiplied in cells. The exact steps during the aggregation are not known, however, it is clear that the process begins with an accumulation of the aforementioned substance. Some toxic effects of neurofibrillary tangles may arise from the relatively large size of tangles which accumulate inside the neurons causing disruption in the healthy molecular transport and in the healthy cell-other molecule interaction. [3]

Studies support a sensitive interaction between the proteins implicated in the pathogenesis of AD and brain metal concentrations. [4] Tau is able to bind Al(III), Fe(III), Cu(II), Zn(II), Cd(II), Hg(II) and Cu(II), and all ions may contribute to the tau aggregation. [5]

The aim of our investigation is a comprehensive study on the copper(II), nickel(II) and zinc(II) complexes of two peptide fragments and their various mutants from the N-terminal region of human tau protein. The octapeptide Tau(9-16) (Ac-EVMEDHAG-NH_2) contains H14 residue of the native protein. Another octapeptide (Tau(26-33) (Ac-QGGYTMHQ-NH_2) and its mutants (Ac-KGGYTMHK-NH_2, KGGATMHK-NH_2) provide information on the binding ability of H32 residue of the native protein. To compare the binding ability of H14 and H32 in a single molecule a model decapeptide Tau(12-16,30-34) (Ac-EDHAG-TMHQD-NH_2) has also been synthesized and studied.

The techniques used were pH-potentiometry, UV-visible and circular dichroism spectroscopy. The results have shown that the presence of more carboxylate groups enhances the stability of [CuL] and [NiL] complexes while the deprotonation of peptide N donors is shifted into the slightly alkaline pH range. The formation of the amide coordinated species with

(N_{im},N^-,N^-,N^-) binding mode changes the metal ion preference and the complexes formed with the peptides containing H32 residue predominate over those of H14 in alkaline samples. (Figure 1.).

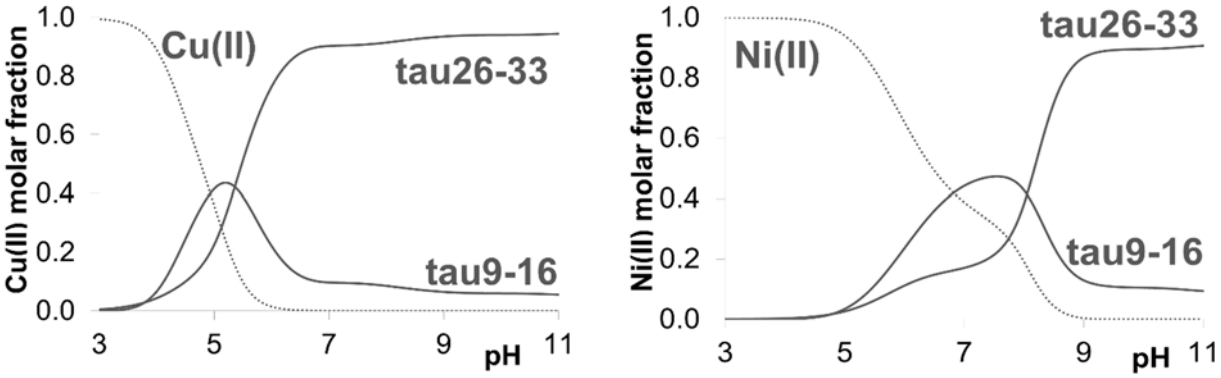

Figure 1. Concentration distribution of Ni(II)and Cu(II) ion in a model system containing Ni(II)/Cu(II) and the peptides Tau(9-16) and TauQ26K-Q33K in equimolar concentration (c(L)= 0.001 M).

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International Symposium on Metal Complexes 2019
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Investigation on the Alcian Blue-tetrakis(methylpyridinium) chloride reactivity in presence of DNA, RNA, G-quadruplex structures and BSA

Francesca MACII,[a)] Cristina PÉREZ ARNAIZ,[b)] Natalia BUSTO,[b)] Begoña GARCÍA RUIZ,[b)] Tarita BIVER [c),a)]

[a)] Department of Chemistry and Industrial Chemistry, University of Pisa, via G. Moruzzi 13, 56124, Pisa, Italy
[b)] Departamento de Quimica, Universidad de Burgos, Plaza Misael Bañuelos, 09001, Burgos, Spain
[c)] Department of Pharmacy, University of Pisa, Via Bonanno 6, 56126, Pisa, Italy
e-mail: francesca.macii@dcci.unipi.it

Phtalocyanines have the potential to act as anticancer drugs, thanks to their interactions with proteins and polynucleotides [1]. Their strong and specific interaction with G-quadruplex structures may be responsible for inhibiting cancer cells proliferation [2]. Phtalocyanines are excellent macrocyclic ligands for transition metals and metal coordination deeply modulates their chemical and photophysical properties.

We focused our attention on Alcian Blue-tetrakis(methylpyridinium) chloride (ABTP), a commercially-available Cu(II)-phtalocyanine complex with promising features. The binding properties in presence of several polynucleotides and a protein were investigated at physiological conditions through spectrophotometric and spectrofluorometric techniques, thermal denaturation tests and calorimetric measurements. The measurements were repeated at different temperatures and ionic strengths in order to obtain information on the binding modes. The thermodynamic parameters were evaluated as well.

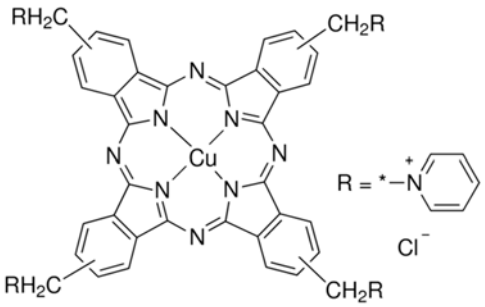

Figure 1. Molecular structure of Alcian Blue-tetrakis(methylpyridinium) chloride (ABTP).

The UV-vis absorption titrations suggested that an interaction does occur with calf thymus DNA, telomeric DNA G-quadruplex (Tel23), double stranded RNA (polyA·polyU) and triple stranded RNA (polyA·2polyU). The results were confirmed by the appearance of induced signals in the circular dichroism spectra. The isothermal titration calorimetry also corroborated

the interactions and provided the thermodynamic parameters for the bindings. On the other hand, ABTP does not seem to interact with bovine serum albumin at all.
The Foster Resonance Energy Transfer (FRET) was exploited in Real Time Quantitative PCR measurements in order to evaluate the binding's effect on double helix DNA and G-quadruplex structures. Although the previous measurements indicate that ABTP has a strong affinity for the biosubstrates, it does not affect the stability of the polynucleotides.
The overall results suggest an external binding mode, with partial intercalation of the substituents. This hypothesis does agree with the dimension and geometry of the system.

The obtained results are encouraging and further investigations will be performed in order deepen the mechanistic details of the processes. Furthermore, quantum chemistry studies are still in progress and will be refined.

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International Symposium on Metal Complexes 2019
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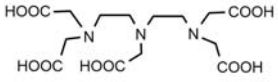
Complex of Bi^{3+} and new aza-crown ligand: fast formation and high stability

Ekaterina MATAZOVA, [a] Bayirta EGOROVA, [a] Ekaterina KONOPKINA, [a] Gleb ALESHIN, [a] Anastasia ZUBENKO, [b] Anna PASHANOVA, [b] Olga FEDOROVA, [b] Stepan KALMYKOV [a]

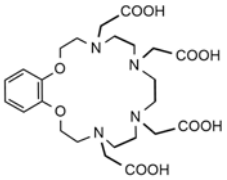
[a] Department of chemistry, Lomonosov Moscow State University, Build. 3, Leninskie Gory 1, 119991, Moscow, Russian Federation
[b] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova 28, Moscow 119991, GSP-1, Russia
email: ek.matazova@yandex.ru

^{212,213}Bi are known as a promising α-emitting radionuclides for application in targeted alpha therapy (TAT) of cancer [1]. For this purpose complex with fast formation kinetics and stability is required. For nuclear medicine a limited number of ligands for binding radionuclide is used but none of them possesses both fast kinetics and high inertness. So, macrocyclic chelators like **H_4DOTA** shows high complex stability *in vitro* and *in vivo* in comparison with the linear analogues **H_5DTPA**, **H_4EDTA** and their derivatives but inferior in the rate of complex formation and commonly demand heating up to 100°C which limits use of **H_4DOTA** with many biological vectors for target delivery [2]. Simple enlargement of the cavity size does not always increase the rate of complexation but also reduces stability of the complex [3]. Thus development of new chelators with appropriate characteristics remains a challenge.

H_4DOTA



H_5DTPA



H_4L

In our work complex of Bi^{3+} with the new aza-crown ligand (**H_4L**) was studied. Firstly, protonation constants of ligand and stability constants of the complexes using potentiometric titration were determined. We observed two dominant forms of the complex (**H_3BiL^{2+}** and **H_2BiL^{+}**) in a wide range of pH and their stability constants are significantly higher than the one reported for **$BiDOTA^{-}$** (log K_{BiDOTA} = 30.3) [4]. In our work we optimized radiolabeling conditions for **H_4L** and it was shown that in presence of 1.0 μM of **H_4L**, no significant difference in the labeling efficiency of **H_4L** with $^{207}Bi^{3+}$ at room temperature and upon heating to 80°C after 1 hour incubation was observed. Moreover obtained data show formation of final complex at 1-2 minutes after mixing of components. Labelling efficiency reached 97±4% at pH 6.1 and 0.1 mM of **H_4L**. This value wasn't affected by variation of buffer systems such as MES, PBS, bicarbonate- and acetate-buffer which allows to use any of this buffer system if necessary.

According to TLC complex of **H$_4$L** with ^{207}Bi is stable in isotonic solution (at least for 2 days) and in presence of excess of biological cation Ca^{2+}, Mg^{2+}, Zn^{2+} and Cu^{2+} (at least for 1 day) during *in vitro* experiment. In addition, using protein precipitation technique it was discovered that complex of **H$_4$L** with ^{207}Bi does not dissociate in the medium of competitive serum proteins (1:100 dilution) as **H$_4$DOTA** does.

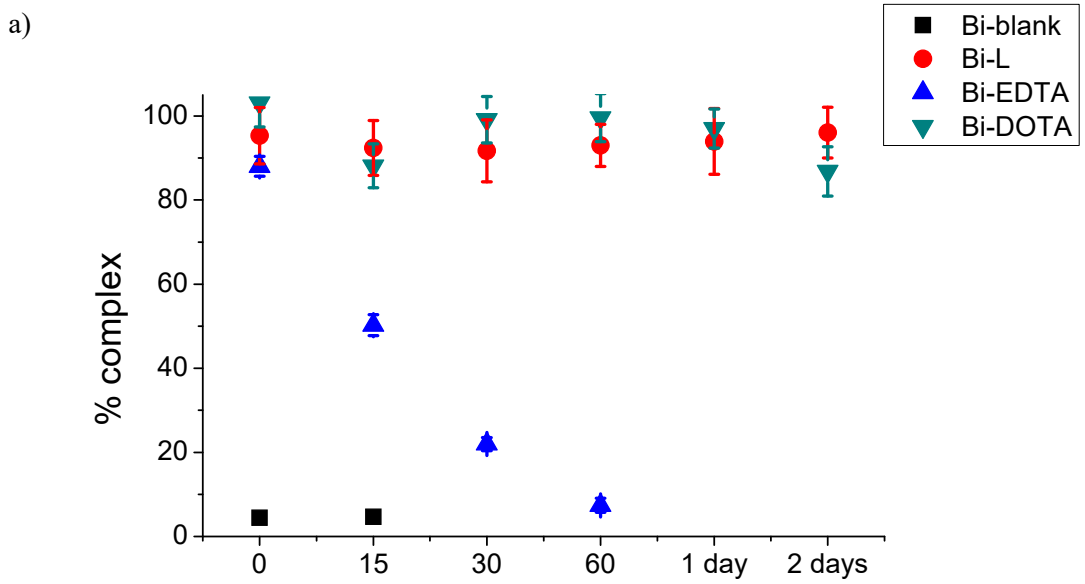


Figure 1. a) Percentage of the **H$_4$L**·^{207}Bi^{3+} after precipitation of the serum protein; b) TLC of the supernatant after 2 days of incubation (95% of the complex).

Due to such promising results biodistribution experiments in normal mice were performed. It was shown that the major accumulation of radioactivity achieves only 3.0±0.5% ID/g in 1 hour after injection that is the same order as for BiDOTA complex (1.6±0.2% ID/g). Furthermore complex is quickly cleared from the body: after 6 h radioactivity in kidneys decreases to 2.0±0.1% ID/g and radioactivity of other organs was less than 0.11% ID/g.

Acknowledgements: This work was supported by RSF project №18-73-10035.

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International Symposium on Metal Complexes 2019
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Insight into the *cis/trans* geometric isomers of *bis*-hydroxypyridinecarboxylic acid - copper(II) complexes

Nóra V. MAY,[a] Kevin NYS,[b] H.Y. Vincent CHING,[b] G. Tamás GÁL,[a] Judit MIHÁLY,[a] Valerio DI MARCO,[c] Sabine VAN DOORSLAER[b]

[a] Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2., 1117, Budapest, Hungary
[b] Department of Physics, University of Antwerp, Universiteitsplein 1, 2610, Antwerp, Belgium
[c] Department of Chemical Sciences, University of Padova, via Marzolo 1, 35131 Padova, Italy
email: may.nora@ttk.mta.hu

Metal complexes of small biomolecules are frequently used as bioactive compounds in diverse fields of clinical practices. The structure and physico-chemical properties such as solubility and stability of these functional metal complexes are usually fine-tuned in order to optimize the bioavailability and bioactivity. Hydroxypyridinecarboxylic acids (HPCs) have been synthesized as possible iron chelators based on deferiprone (3-hydroxy-1,2-dimetyl-4(1*H*)-pyridone), a drug used world-wide in chelation therapy.[1] *In vitro* studies showed that Cu(II) is the most competing metal ion which affects considerably the complex formation of deferiprone with Fe(III).[2,3] The design of non-toxic but metal-selective ligands is extremely difficult and it must fulfil several chemical properties, such as high stability of the complexes formed under physiological conditions, fast formation kinetics, high selectivity for the specified ion, good bioavailability, and low toxicity. Since different structural isomers of the metal-ligand complexes often coexist in solution, a key research step in the design of new chelating agents involves the investigation of these complex equilibrium systems under near physiological conditions (aqueous solution and room temperature) with spectroscopic methods. The investigation of coexisting *cis/trans* geometric isomers is challenging with spectroscopic techniques, since the difference between the individual spectra of the isomers are usually small and the deconvolution of the superimposed spectra is not always possible, although the stereochemistry is expected to have a huge impact on the biological activity. The most known example is the widely used chemotherapy drug cisplatin (*cis*-diamminedichloroplatinum(II)) for which its *trans* isomer has no significant anticancer effect. In this study, the structure of *bis*-ligand copper(II) complexes of 3-hydroxy-1-methyl-4-pyridinecarboxylic acid (L1), 3-hydroxy-1,2,6-trimethyl-4-pyridinecarboxylic acid (L2), 4-hydroxy-1-methyl-3-pyridinecarboxylic acid (L3), 4-hydroxy-1,6-dimethyl-3-pyridinecarboxylic acid (L4) have been studied both in solid and solution phases (Figure 1). The bidentate [O^-_{carb}, O^-] [O^-_{carb}, O^-] coordination mode of the ligands have been found preferentially with *cis* arrangements in the single crystals of L1 and L2 and *trans* arrangements in L3 and L4 using single crystal X-ray diffraction (SXRD) method. In order to investigate these paramagnetic copper(II) complexes (S=1/2, I_{Cu}=3/2) in solution, electron paramagnetic resonance spectroscopy (EPR) was used.

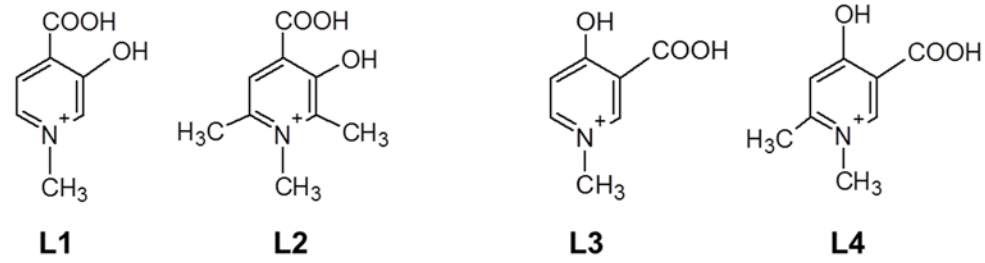

Figure 1. Structure of the investigated ligands

The continuous wave (CW) EPR spectra recorded at room temperature or frozen solution did not allow the distinction of the two possibly coexisting *cis/trans* isomers, owing to the small spectral differences expected for the two species and limited resolution of the X-band CW EPR spectra. For this, we applied pulsed EPR techniques[4-6] (Mims ENDOR) wich led to a further detailed analysis of the hyperfine interactions of the unpaired electrons with the surrounding magnetic nuclei, facilitating an in-depth characterization of the different molecular structures. With this technique the orientation of ligand protons versus the copper centre can be determined. In order to interpret our results, density functional theory (DFT) calculations have been performed using the ORCA program[7]. The simulations suggested that the Cu(II) complexes of L1 and L2 exist predominantly in their *trans* form in solution. However for the Cu(II) complexes of L3 and L4 the spectra were broader and more complex, which suggests the coexistence of both *cis* and *trans* forms. Infrared spectra have also been measured for the complex solutions (after evaporation of the solvent) to support these observations.

Acknowledgements: The support of the National Research, Development and Innovation Office – NKFIH through OTKA K115762 and J. Bolyai Research Scholarship (NVM) for Hungarian Academy of Sciences, and international collaboration program grant (PROJEKT2017-16, VS06718N) for HAS and FWO are gratefully acknowledged.

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International Symposium on Metal Complexes 2019
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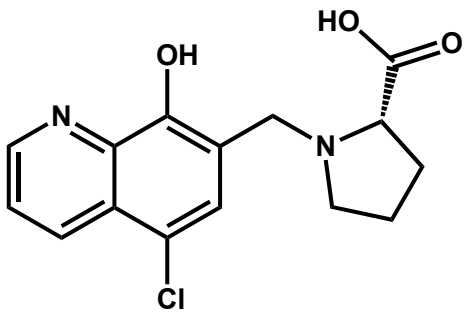
A novel 8-hydroxyquinoline derivative with multidrug resistance selectivity and its half-sandwich Ru and Rh complexes

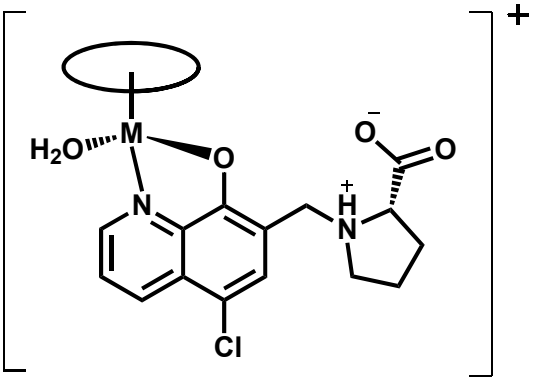
<u>János P. MÉSZÁROS</u>,[a] Jelena M. POLJAREVIĆ,[b] István SZATMÁRI,[c] Ferenc FÜLÖP,[c] Gabriella SPENGLER,[d] Éva A. ENYEDY[a]

[a] Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720 Szeged, Hungary
[b] University of Belgrade - Faculty of Chemistry, Studentski trg 12-16, 11000 Belgrade, Serbia
c) Institute of Pharmaceutical Chemistry and Stereochemistry Research Group of Hungarian Academy of Sciences, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary
d) Department of Medical Microbiology and Immunobiology, University of Szeged, Dóm tér 10, H-6720 Szeged, Hungary
email: meszaros.janos@chem.u-szeged.hu

Development of effective new compounds against cancer cells is a hard task; however targeting the special properties of the tumor environment such as hypoxia [1], lower pH [1] and higher concentration of oncometabolites [2] can increase the drug selectivity. One of the most severe problems of traditional chemotherapeutics is the acquired resistance against a wide range of drugs, which is called multidrug resistance (MDR). P-glycoproteins (Pgp-s) are connected to this resistance, since they cause a high efflux of toxic components and drugs as well [3]. There are several Pgp inhibitors, *e.g.* verapamil and cyclosporine A, but their use caused unwanted side effects [3]. Szakács *et al.* showed a group of anticancer compounds including 8-hydroxyquinolines which are more cytotoxic against MDR cancer cells than non-resistant cancer cells [4].



HQ-Pro



[ML]⁺ complexes, where
⬭=toluene, *p*-cymene, $C_5Me_5^-$
M=Ru or Rh and L=HQ-Pro

Herein we report the design and synthesis of a new 8-hydroxyquinoline derivative (HQ-Pro, see in the figure) with good water solubility. It was found to be selectively cytotoxic against MDR cancer cells. The reference compounds 8-hydroxyquinoline and 5-chloro-8-hydroxiquinoline have fairly low water solubility and do not show MDR selectivity. HQ-Pro is

a (N,O) donor ligand similarly to 8-hydroxyquinoline and 5-chloro-8-hydroxiquinoline. The combination of 8-hydroxyquinolines with half-sandwich ruthenium and rhodium cations might results in increased cytotoxicity. Numerous drug candidates containing *e.g.* the organometallic Ru(*p*-cymene) moiety show promising *in vitro* and/or *in vivo* bioactivity such as RAED and RAPTA complexes [5] or the complexes of various 8-hydroxyquinolines [6].

The solution chemical properties of these metal complexes are essential to know, since these compounds may transform to biologically or kinetically inert species. Their complex formation (log *K* [ML]), deprotonation of the coordinated water molecule in the complex (pK_a[ML]), the exchange of this water molecule to a chloride ion (log *K'* (H_2O/Cl^-)) and lipophilicity (log $D_{7.4}$) are worth to investigate. In our previous works the listed types of equilibrium constants were reported for several half-sandwich Ru and Rh complexes bearing (N,O) donor ligands like 2-picolinic acid and oxine derivatives [6,7].

In this work we investigated the proton dissociation processes of HQ-Pro and its complex formation with $Rh(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$, $Ru(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ and $Ru(\eta^6\text{-toluene})(H_2O)_3]^{2+}$ by the combined use of pH-potentiometry, UV-Vis spectrometry and ^{1}H NMR spectroscopy. Our results revealed prominent complex solution stability in all cases. The lipophilicity of the complexes was found to be increased with the chloride ion concentration which is a result of the formation of neutral [MLCl] complexes from positively charged $[ML]^+$ aqua complexes.

Antiproliferative and cytotoxic effect of HQ-Pro and its Ru, Rh complexes were measured *in vitro*. The ligand and its Rh complex were more effective against the MDR Colo205 adenoma carcinoma human cell lines compared to the sensitive counterpart cell lines.

This work was supported by National Research, Development and Innovation Office, (Hungary) through project FK 124240 and Ministry of Human Capacities (Hungary) grant 20391-3/2018/FEKUSTRAT. J. P. M. thanks support from the National Young Talent Scholarship (NTP-NFTÖ-18-B-0404).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Investigation of the SAAP and clavanin complexes - potential new antimicrobial agents

Adriana MILLER, Magdalena ROWIŃSKA – ŻYREK

Univeristy of Wrocław, Faculty of Chemistry, F. Joliot-Curie 14, 50-383 Wrocław;
e-mail: adriana.miller@chem.uni.wroc.pl

The growing number of drug-resistant bacterial strains is becoming an increasingly serious problem of current medicine. Therefore, new antibiotics are being sought for more and more intensively.

Antimicrobial peptides (AMPs) are promising candidates to use as a new therapeutics. They are present in all multicellular organisms and act as a part of innate immune systems. Despite the fact of presence in those organisms for millions of years, pathogens show almost no resistance for AMPs. [1-3] So far, more than 3000 peptides have been deposited in the AMP databases. [4]

In this work, we aim to find the relationship between metal coordination ability, structure, function and biological activity of several metal-AMP complexes, focusing on two peptide families – SAAPs and clavanins.

SAAPs, isolated from ovine pulmonary surfactant, are anionic peptides, composed of 7 amino acids, mainly aspartic acid residues. The SAAP family consists of three members and each of them is active against many Gram positive and Gram negative bacteria. Their antimicrobial mode of action is based on intracellular damage. What is noteworthy, the peptides are active only when bound with a zinc(II) ion. [5-7]

Clavanins are His-rich cationic peptides, which naturally occur in tunicates (*Styela clava).* There are five types of those peptides, signed as a clavanin A, B, C, D and E. They consist of 23 amino acids, with four (or in clavanin E - three) His residues and show an alpha-helical structure. Like SAAPs, they are active against a broad spectrum of pathogens, but their antimicrobial activity relies not only on causing intracellular damage, but also on the cell membrane disruption. Interestingly, zinc(II) ions increase bactericidal properties of clavanin A up to 16 times. [8-10]

In this poster, we will show the results of research of clavanin-Zn(II), clavanin-Cu(II) and SAAP-Zn(II) complexes, which provides information about their stoichiometry, geometry and thermodynamic properties. The long-term plan of experiments and used methods will also be presented.

Acknowledgements: Financial support by the National Science Centre (UMO-2017/26/A/ST5/00364) is gratefully acknowledged.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Biosynthesis of SmtB - a zinc-sensing, mycobacterial transcriptional regulator from ArsR family. Zinc coordination abilities of metal-binding domains

Karolina MOJSA, [a] **Elżbieta GUMIENNA-KONTECKA,** [a] **Damian TROJANOWSKI,** [b] **Joanna ZAKRZEWSKA-CZERWIŃSKA,** [b] **Joanna HOŁÓWKA,** [b] **Sławomir POTOCKI** [a]

[a] *Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50383 Wroclaw, Poland.*
[b] *Faculty of Biotechnology, University of Wroclaw, F. Joliot-Curie 14a, 50383 Wroclaw, Poland.*
e-mail: karolina.mojsa@chem.uni.wroc.pl

Tuberculosis (TB) is one of the top 10 reasons of death worldwide caused by the bacterium *Mycobacterium tuberculosis* (MTB). In 2017, 10 million people fell ill with this disease and 1.6 million died. WHO reported 558 000 new cases with resistance to the most effective first-line drug - rifampicin, of which - 82% had multidrug-resistant Tuberculosis (MDR-TB). [1] The lack of new antibiotics development, forces scientific world to look for the new strategies in fighting against pathogens, thus metal-based antimicrobial therapy has now gained pace. [2]

M. tuberculosis is a facultative intracellular pathogen that thrives inside host macrophages. A key trait of *M. tuberculosis* is to exploit and manipulate metal cation trafficking inside infected macrophages to ensure survival and replication inside the phagosome. The mammalian immune system responds to infections with *M. tuberculosis* by overloading the phagosome with copper and zinc, two metals which are essential nutrients in small quantities but toxic in excess. [3,4] That breakthrough information has been an inspiration to start ArsR-family proteins related research.

ArsR-family proteins, which are bacterial transcriptional regulators, directly sense zinc and other divalent metal ions excess to induce efflux genes expression. The exact mechanism of this process is still unknown. Below, the general model mechanism of action of ArsR-SmtB family proteins is presented (Fig.1)

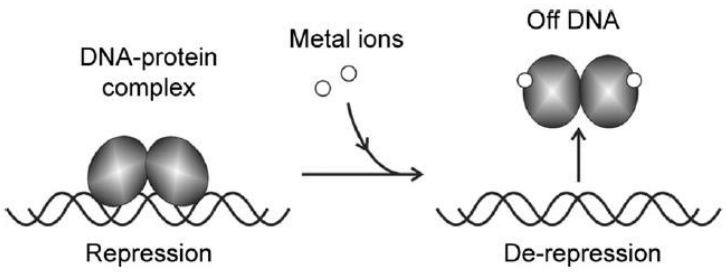

Figure 1. Model of the mechanism of gene regulation by the members of the ArsR–SmtB family.

Our research is focused on: (i) SmtB from *M. tuberculosis* and (ii) BigR4 – a recently identified by us SmtB homologue from *M. smegmatis* - a non-pathogenic model organism commonly used to study the biology of tubercle bacilli. The main goal is to understand the interaction of Zn(II) with these "metal-sensing" mycobacterial transcriptional regulators and to explore their biological role in the zinc homeostasis, together with the involvement in regulation of genes transcription in mycobacteria. Combination of two complementary approaches, coordination chemistry and genetic engineering methods will allow us to create comprehensive picture of Zn-dependent SmtB metal-sensing machinery in *Mycobacterium*.

Here we present our latest results concerning expression and purification of SmtB and BigR4 proteins in *E. Coli* cells. Proteins has been obtained using pMal c2x TEV and pET21 oligo strep vector systems respectively. Plasmids were isolated from DH5α *E. coli* cells (convenient strain for genetic manipulation) and were transformed into BL21(DE3)-RIL (expressive strain) by heat shock transformation. Affinity chromatography was used as a major technique to purify proteins. We were able to biosynthesize around 6-9 mg of protein from 1 l of culture. CD, UV-Vis and ITC studies are being carried out on both, Zn(II)-protein as well as on Zn(II)-metal binding domain complexes.

Protein mutants with the lack of particular His residues in α5 domain lose their metal-induced derepression function. [5] We investigated Zn(II) complexes of wild type His-containing α5 domains and their His-missing Ala mutants. We observed surprising binding modes and stabilities, what may have significant biological implication.

Acknowledgements: The financial support from the Polish National Science Centre (NCN, nr UMO-2017/26/D/ST5/00372) is gratefully acknowledge.

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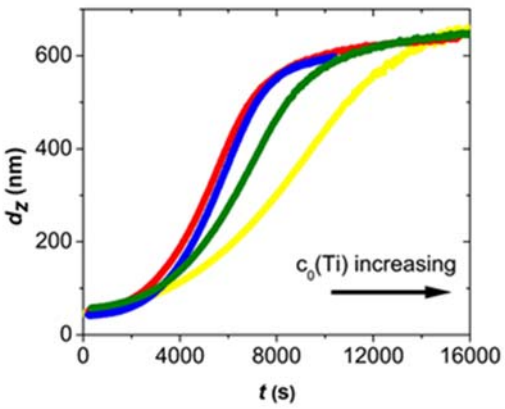
International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Kinetic model for hydrolytic nucleation and growth of TiO_2 nanoparticles

Attila FORGÁCS, [a] Krisztián MOLDOVÁN, [a] Petra HERMAN [a]
Edina BARANYAI, [a] István FÁBIÁN, [a] Gábor LENTE, [b] József KALMÁR [a]

[a] Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1., 4032, Debrecen, Hungary
[b] Department of General and Physical Chemistry, University of Pécs, Ifjúság útja 6, 7624, Pécs, Hungary
e-mail: moldovan.krisztian@science.unideb.hu



Crystalline nanoparticles of titania (TiO_2) with different size has a growing interest in the past few years, due to their varied applications (e.g. photocatalysis, hydrogen production and storage). Nanocrystalline, monodisperse TiO_2 are prepared in aqueous solution from a stable precursor Ti(IV)-bis(ammonium-lactate)-dihydroxide. [1]

The formation of nanoparticles was followed by dynamic light scattering (DLS) and UV-vis spectrometric methods. The turbidity (i.e. the apparent absorbance at 500 nm) of a stable TiO_2 suspension is shown to be proportional to the TiO_2 concentration at constant particle size and proportional to the size at constant Ti concentration. The compilation of the DLS and UV-vis data yields characteristic sigmoid shaped kinetic curves for the evolution of particle size.

A kinetic model with 3 reaction steps is postulated which provides an excellent fit to the experimental data. First, the rapid hydrolysis of the precursor takes place to give primary particles for the subsequent steps. The dimerization of 2 primary particles is slow and this is followed by the formation of larger particles in the step-by-step addition of subsequent primary units. An integrated rate equation was developed to predict the time-dependent mean particle size as the function of the initial precursor concentration. An important feature of the model is that a simple continuous function describes the temporal evolution of average particle size up to d = 600 nm. [2]

Acknowledgements: The authors thank the Hungarian Science Foundation (OTKA: FK_124571) for financial support.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Coordination chemical properties of Gd^{3+} complexes of macrocyclic ligands bearing picolinate pendant arms: equilibrium and kinetics

Enikő MOLNÁR, [a] Ferenc K. KÁLMÁN, [a] Mariane LE FUR, [b] Maryline BEYLER, [b] Olivier FOUGÈRE, [c] David ESTEBAN-GÓMEZ, [d] Carlos PLATAS-IGLESIAS, [d] Nicolas LEPAREUR, [e] Olivier ROUSSEAUX, [c] Raphaël TRIPIER, [b] Gyula TIRCSÓ [a]

[a] Department of Physical Chemistry, Faculty of Science and Technology, University of Debrecen, Egyetem tér 1., H-4032, Debrecen, Hungary
[b] Université de Bretagne Occidentale, UMR-CNRS 6521, IBSAM, UFR des Sciences et Techniques, 6 avenue Victor le Gorgeu, C.S. 93837, 29238 BREST Cedex 3, France.
[c] Groupe Guerbet, Centre de Recherche d'Aulnay-sous-Bois, BP 57400, 95943 Roissy CdG Cedex, France.
[d] Departamento de Química, Facultade de Ciencias & Centro de Investigaciones Científicas Avanzadas (CICA), Universidade da Coruña, 15071 A Coruña, Spain.
[e] Département de Médecine Nucléaire, Centre Eugène Marquis, INSERM U1241, Avenue de la Bataille Flandres, Dunkerque CS 44229, 35042 Rennes Cedex, France
e-mail: molnar.eniko@science.unideb.hu

In recent years many problems have been described (positive Gd^{3+} anomaly [1], Nephrogenic Systemic Fibrosis (NSF) disease [2,3], Gd^{3+}-retention in different tissues [4,5]) concerning contrast agents (CAs) used in Magnetic Resonance Imaging (MRI). In 2017 the European Medicine Agency recommended the suspension of three commercialized products based on open-chain ligand platforms (Magnevist, Optimark and Omniscan) and restricted the use of the Multihance agent. These problems have spurred new research aiming to design and characterize safer CA candidates. On this avenue one possible solution can be the design and synthesis of ligands forming Gd^{3+} complexes with exceptionally high stability and inertness.

The inertness of the complexes formed with macrocyclic ligands is expected to increase when rigidifying the backbone (cyclic entity) of the ligands, therefore our attention was devoted to the pyridine containing macrocyclic chelators (pyclen derivatives, e.g. PCTA). The carboxylic groups of the PCTA ligand were gradually replaced by picolinate groups resulting in PC2A1PA (containing two acetates and one picolinate pendants) and the PC1A2PA (containing one acetate and two picolinate metal binding moieties) chelators. In both ligands the pendant arms could be attached to the macrocycle in symmetric and asymmetric arrangements, returning altogether four ligands. Our aim was to investigate the physico-chemical parameters of the Gd^{3+} complexes formed with these four complexons, $PC2A1PA^{sym}$, $PC2A1PA^{asym}$, $PC1A2PA^{sym}$ and $PC1A2PA^{asym}$ (Figure 1.).

The results of thermodynamic and dissociation kinetic studies revealed that the stability constants and the inertness of the complexes are higher when two picolinate and one acetate groups are attached to the pyclen macrocyclic platform. Our result also confirm that the non-symmetric arrangement of the pendant arms is more favorable for Ln(III) ion complexation than the symmetric one which can be explained in terms of "labile capping bond effect" evidenced recently in Ln(III) complexes causing faster water exchange rate and higher

relaxivity in the Gd^{3+} complex formed with non-symmetric $PC2A1PA^{asym}$ ligand. Altogether, the $Gd(PC2A1PA^{asym})$ complex possesses the most attractive parameters as far as the MRI applications are concerned.

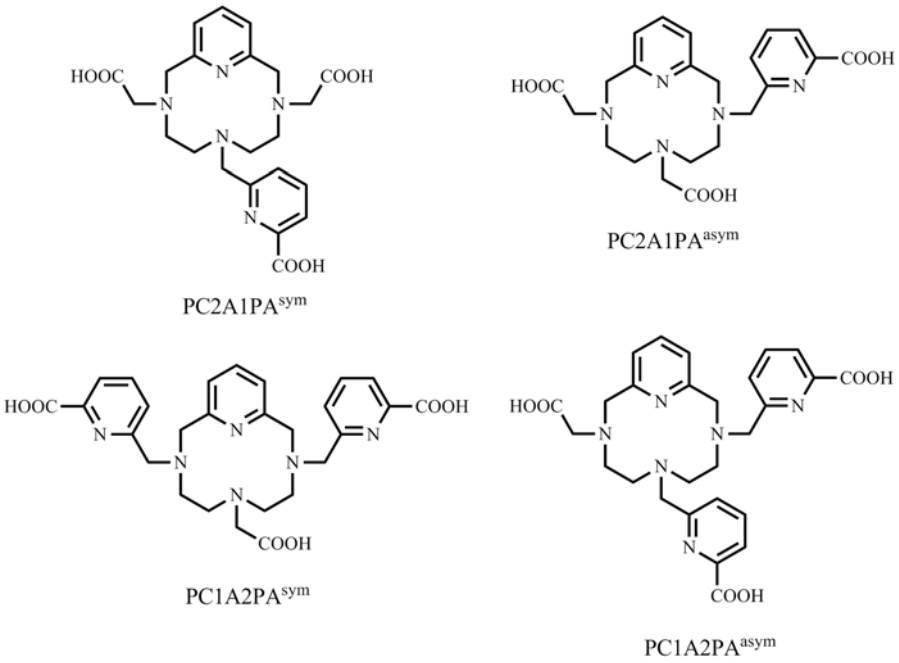

Figure 1. Structure of the investigated ligands.

Acknowledgements: This research was funded by the GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004 projects supported by the EU and co-supported by the European Regional Development Fund. The authors are grateful for support granted by the Hungarian National Research, Development and Innovation Office (NKFIH K-120224 project) and for the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (Gy.T. and F.K.K.). The research was also supported by the ÚNKP-18-4 New National Excellence Program (Gy.T. and F.K.K.) of the Ministry of Human Capacities.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Iron and gallium complexes of novel siderophores analogues.

Andrzej M. MULAR, Henryk KOZŁOWSKI, Elżbieta GUMIENNA-KONTECKA

Faculty of Chemistry, University of Wroclaw, Wroclaw, Poland
e-mail: andrzej.mular@chem.uni.wroc.pl

Almost 100 years have passed since Alexander Fleming discovered penicillin, the very first antibiotic. Since 1928 antibiotics became saviors of humanity and helped contain diseases that haunted our race. But since then more and more microbes started to develop resistivity and now we need to face another threat – pathogens immune to antibiotics. That is why we aim to find other way to fight this grave threat [1].

Novel treatments and ways to specifically deliver them to drug resistant bacteria and invasive mycoses are being actively sought. We aim to find pathogen-specific therapeutics that will not cause severe side-effects in patients.

Those properties are presented by wide group of microbe-produced low molecular weight compounds – metalophores, which are used by bacteria, fungi and some plants to acquire metals that are crucial for their viability . Although pathogen-selective targets are scarce, what arises from the fact that bacteria and fungi share essential metabolic pathways with humans there is at least one significant difference between the microbial and mammalian cells: the transport of transition metal ions.

In our recent studies [2,3,4] we focus on the transport of biologically indispensable metal ion – Fe(III) .Its effective acquisition is often considered as a virulence factor. Bacteria and fungi have developed highly efficient transport systems, which rely on metallophores – metal chelating molecules which are excreted outside the pathogen in order to efficiently bind a given metal ion. This can serve either as metal acquisition or as a way of protecting themselves against the toxic excess of metal ions. On the other hand, vertebrate hosts have developed mechanisms which restrict the bioavailability of metal ions for pathogens via a process called nutritional immunity [5].

We also aim to incorporate Ga(III) to our research due to its potential role in treatment and nuclear imaging. Gallium(III) and iron(III) ions have similar coordination chemistry because of their comparable ion radius and electronegativity. We aim to introduce ^{68}Ga ions to siderophores which should distribute radioactive gallium into bacteria cell via iron transport mechanism. This will allow us to visualize metal transportation pathways in pathogens applying ^{68}Ga as radioprobe [6].

To fully understand mechanisms of those processes and later utilize them we need to examine thermodynamics and coordination chemistry of matalophores and corresponding metal ions.

Another aspect of our work is to modify naturally occurring siderophores and improve their properties. Those biological ligands can be functionalized by incorporating various side groups into their structure which could give them new properties, such as antimicrobial or cytostatic [7].

Here we will present current advancements in research concentrated on coordination properties of novel analogues of siderophores towards Fe(III) and Ga(III) ions.

Acknowledgements: The financial support from the Polish National Science Centre (NCN UMO-2017/26/A/ST5/00363) is gratefully acknowledged.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Synthesis, characterization and biological studies of heterobimetallic complexes as candidates for hypoxia-activation

Imre NAGY, [a] **Jana KASPARKOVA,** [b] **Hana KOSTRHUNOVA,** [c] **Etelka FARKAS,** [a] **Péter BUGLYÓ** [a]

[a] *Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary*
[b] *Department of Biophysics, Palacky University, Slechtitelu 27, 78371 Olomouc, Czech Republic*
[c] *Institute of Biophysics, Czech Academy of Sciences, Kralovopolska 135, CZ-61265 Brno, Czech Republic.*
email: nagyimre@science.unideb.hu

Chemotherapeutic agents used in the treatment of cancer are mostly harmful to the normal cells too. These side effects often decrease the quality of patient's life. An important difference among normal and cancerous cells is the hypoxic environment. This disparity is capable of increasing selectivity and efficiency. To apply this potential recently we have synthesized Co(III) complexes assuming that their likely reduction takes place in hypoxic tumors with the subsequent formation of Co(II) complexes having decreased stability. The cathodic peak potential of these complexes is tunable and allows reaching the reduction potential range of hypoxic tumors which is lower than ca. -300 mV. [1]

Recently four SAHA containing drugs have been granted FDA approval for cancer treatment relying on their potent HDAC inhibitory effect. In order to widen the activity of the SAHA ligand numerous derivatives were also synthesized. Very recently the phenanthroline conjugate of SAHA was reported to form complexes with half-sandwich platinum metal ions and it was found that they maintained their proper HDAC inhibitory effects *in vitro*. [2]

In this work we have carried out the synthesis of heterobimetallic complexes of the phenanthroline SAHA conjugate ligand using $[Co(tripodal\text{-}tetraamine)]^{3+}$ and $[(\eta^6\text{-}p\text{-}cym)RuCl]^{+}$ cores. In these complexes the half-sandwich ruthenium ion coordinates to the (N,N) donor atom set of the phenanthroline part of the ligand while the Co(III) entity binds to the hydroxamate moiety of the ligand. The tren and tpa tripodal ligands were applied because of the different nitrogen donors of them in order to fine tune the redox properties of the new complexes. The compounds were characterized by NMR, CHN, mass spectrometry and cyclic voltammetry. Biological studies were also carried out to test the anticancer property of the novel complexes. This contribution will present our results achieved in this field.

Acknowledgements: The research was also supported 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).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Maltol and deferiprone containing ternary Co(III) complexes

Sándor NAGY,[a] Attila MAKAI,[a] István KACSIR,[b] Etelka FARKAS,[a] Attila Csaba BÉNYEI,[c] Péter BUGLYÓ[a]

[a] Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary
[b] Department of Organic Chemistry, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary
[c] Department of Physical Chemistry, University of Debrecen, Egyetem tér 1, H-4032, Debrecen, Hungary
e-mail: nagy.sandor@science.unideb.hu

Although no metal-containing chemotherapeutic agents have been developed since cisplatin and its newer derivatives recently hypoxia-activated prodrugs have shown promising preliminary results. By the use of cobalt(III) complexes, for instance, it is likely that they would get activated only in tumor cells so they would exert their effects selectively.[1]

Previous results have shown that in octahedral Co(III) complexes the 4N+2O donor atom set provides a reduction potential close to that of the biologically relevant one. The excessive stability of some of the complexes containing tripodal 4N donors can be optimized by the use of 2x2N donors instead. In our previous works we have shown how chelate size and type of N donor influence the redox properties of these type ternary Co(III) complexes.[2]

After bioreduction, the (O,O) donor drug molecules are released from the less stable cobalt(II) complexes and may hinder the growth of cancer cells directly or indirectly. During an indirect inhibition the required nutrients like Fe(III) are complexed by the released molecule thus inhibiting the growth of the cancer cells.

One type of the (O,O) donor ligands could be maltol and their derivatives. Maltol is an organic compound and an FDA approved food additive. It is known that its Fe(III), Ga(III), Al(III) and V(IV)O^{2+} binding capability is high so it might be used as an aluminium(III) chelator in the human body.[3] The hydroxypiridinone derivative (deferiprone, HDHP) also has high affinity for iron(III) and currently used as a drug in thalassaemia major.[4] These ligands can suppress the increased Fe(III) uptake of cancer cells, therefore inhibiting the growth.

Based on these properties of the ligands we have synthesized and characterized novel cobalt(III) complexes, which the general formulae of $[Co(4N)(O,O)]X_n$ and $[Co(N,N)_2(O,O)]X_n$ using maltol and deferiprone as (O,O) donors. The structures have been studied by NMR, IR, MS and SCRD, and the redox properties have been explored using cyclic voltammetry. This contribution will summarize the results.

Acknowledgements: The research was also supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00004, GINOP-2.3.2-15-2016-00008 and the Hungarian Scientific Research Fund (OTKA K112317).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Characterization and separation of structural isomers of 1,10-phenanthroline-mono-*N*-oxides

Ferenc NAJÓCZKI,[a)] Gábor BELLÉR,[a)] Antal UDVARDY,[b)] Mária SZABÓ,[a)] István FÁBIÁN[a) c)]

[a)] *University of Debrecen,* Department of Inorganic and Analytical Chemistry
[b)] *University of Debrecen,* Department of Physical Chemistry
[c)] *MTA-DE Redox and Homogeneous Catalytic Reaction Mechanizm research group*
e-mail:najoczki.ferenc@science.unideb.hu

The oxidation products of 1,10-phenanthroline and its derivates (phen-s) find widespread applications in various fields of chemistry. However, only limited information is available on the details of these oxidation reactions in the literature. In general, the oxidation of phen-s frequently leads to dezaromatization or breaking the aromatic rings. The *N*-oxidation of these compounds occurs only with peroxide type oxidizing agents. First, H_2O_2 was used for this purpose leading to the formation of only mono-*N*-oxide (phenO) in 1946.[1] Almost 50 years later, Dayan and Rozen were the first to synthetize 1,10-phenanthroline-di-*N*-oxide ($phenO_2$) by bubbling elemental fluorine through the solution of phen in a mixture of acetonitrile and H_2O.[2] Peroxomonosulphate ion (PMS) is a strong oxidant and often used to substitute H_2O_2 in the corresponding reactions. In 2016, our research group successfully used PMS to produce $phenO_2$ under ambient conditions, i.e. in neutral aqueous solution.[3] Our ultimate goal is to explore the chemistry of mono- and di-*N*-oxides of phen-s. As part of this project, now we report our results on the formation of mono-*N*-oxides.

Prior to the synthetic work, detailed kinetic studies were performed on the formation of mono-*N*-oxides. These overall second order reactions are first order in phen-s as well as in PMS. The pH dependence of the rate constants was interpreted by considering the acid – base equilibria of the reactants. The temperature dependence of the rate constants were studied in the 10 - 70 ºC range, and the activation parameters were estimated using the Eyring-Polányi equation. The large negative activation entropies ($\Delta S^{\ddagger} \sim -130$ $Jmol^{-1}K^{-1}$) are consistent with oxygen atom transfer mechanism.

The acid-base properties of the phen-s and their phenO derivates were studied using various experimental methods such as pH-potentiometric, UV-Vis spectrophotometric and ^{1}H-NMR titrations. The acid dissociation constants (pK_a) were estimated by fitting the data on the basis of the appropriate expressions using non-linear least squares routines. It was concluded that the mono-*N*-oxides are weaker acids (by 1,5 – 2,5 pK_a units) than the corresponding parent compounds. The correlation between the logarithm of the rate constant and the pK_a can primarily be interpreted in terms of electronic effects, however, in the case of the 2,9-dimethyl-derivative, steric hindrance also plays an important role.

During the synthesis, nearly stoichiometric amounts of PMS were used and the mono-*N*-oxides were prepared with high yields under acidic conditions. At appropriately high pH (depending on the pK_a of the mono-*N*-oxides), further oxidation occurs and di-*N*-oxides form.

It is important to note, that there are four non-symmetrical starting materials, 4-methyl-1,10-phenanthroline (4MP), 5-methyl-1,10-phenanthroline (5MP), 5-chloro-1,10-phenanthroline (5CP) and the 5-nitro-1,10-phenanthroline (5NP). The *N*-oxidation of these compounds yields two isomers. In principle, the two reaction paths are characterized with different rate constants, but, independent direct determination of these parameters is not feasible. This indicates that the two products form via the same reaction path.

The products were purified and the isomers were separated. For the characterization of these species, conventional methods (APCI-MS, ^{1}H and ^{13}CNMR, UV-Vis) and the X-ray diffraction technique were used in solution and solid phases, respectively. The structures of phenO [4] and 2,9-dimethyl-1,10-phenanthroline-mono-*N*-oxide (DMPO) were published earlier.[5] The structures of 3,4,7,8-tetramethyl-1,10-phenanthroline-mono-*N*-oxide (TMPO), 5-chloro-1,10-phenanthroline-mono-*N*-oxide (5CPO) and 6-chloro-1,10-phenanthroline-mono-*N*-oxide (6CPO) are reported here for the first time.

Acknowledgement: The authors thank the Hungarian Science Foundation (OTKA) under grant No. K-124983 and NKFI-FK128333 for financial support. 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 GINOP-2.3.3-15-2016-00004.

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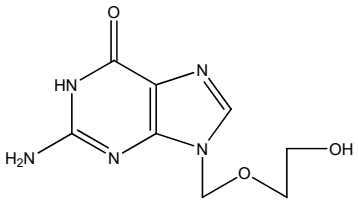
International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Unveiling the nature of the X-H···O6 interligand interaction in the molecular recognition between the Cu(II)-N-(2-hydroxyethyl)-ethylenediamine chelate and acyclovir

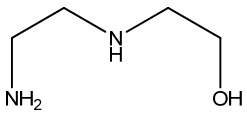
Elisabet MUELA, [a] Alicia DOMÍNGUEZ-MARTÍN, [a] Duane CHOQUESILLO-LAZARTE, [b] María Eugenia GARCÍA-RUBIÑO, [a] Alfonso CASTIÑEIRAS, [c] Juan NICLÓS-GUTIÉRREZ [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain
[c] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
e-mail: jniclos@ugr.es

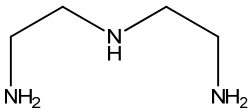
As a part of our research program on molecular recognition between Cu^{II}-polyamine chelates and acyclovir (acv), [1-4] now we investigate the molecular recognition between this synthetic purine nucleoside and the dien analogue N-(2-hydroxyethyl)-ethylenediamine (hen).



acv



dien



hen

To this purpose we have successfully synthesized and determined the crystal structure of $[Cu(hen)acv)(H_2O](NO_3)_2$ (110 K, monoclinic, $P2_1/c$, final R_1 0.068). The asymmetric unit (figure 1) contains the mixed-ligand cationic complex and two nitrate anions (one of them disordered over two positions with a 0.7:0.3 ratio). The Cu(II) center exhibits a 4+1 distorted square planar coordination, with aqua as apical-distal ligand. Molecular recognition between the Cu(hen) moiety and acv consists of the Cu1-N27 bond (2.010(5 Å) and the rather short intra-molecular interligand interaction O4(ol)-H···O26(acv) (2.648(6) Å, 130.7º). Indeed this is the shortest H-bond in the crystal.

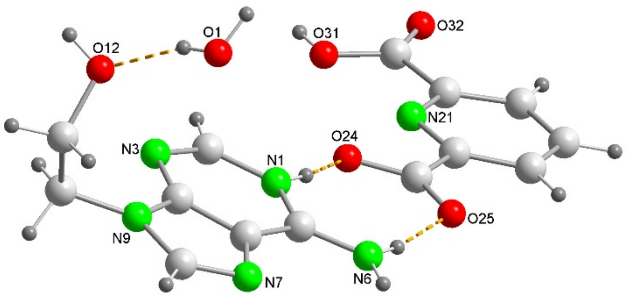


Figure 1. Asymmetric unit in the crystal of $[Cu(hen)acv)(H_2O](NO_3)_2$.

The crystal is built via multi-π,π-stacked chains, along the c axis, between six-membered guanine moieties from anti-parallel acv ligands (figure 2-A). These chains are reinforced by (amino)N6-H···O(ol,acv) and (aqua)O-H···O6(acv) inter-molecular H-bonds (figure 2-A). Additional H-bonds with O-nitrate acceptors accomplish the crystal architecture (figure 2-B).

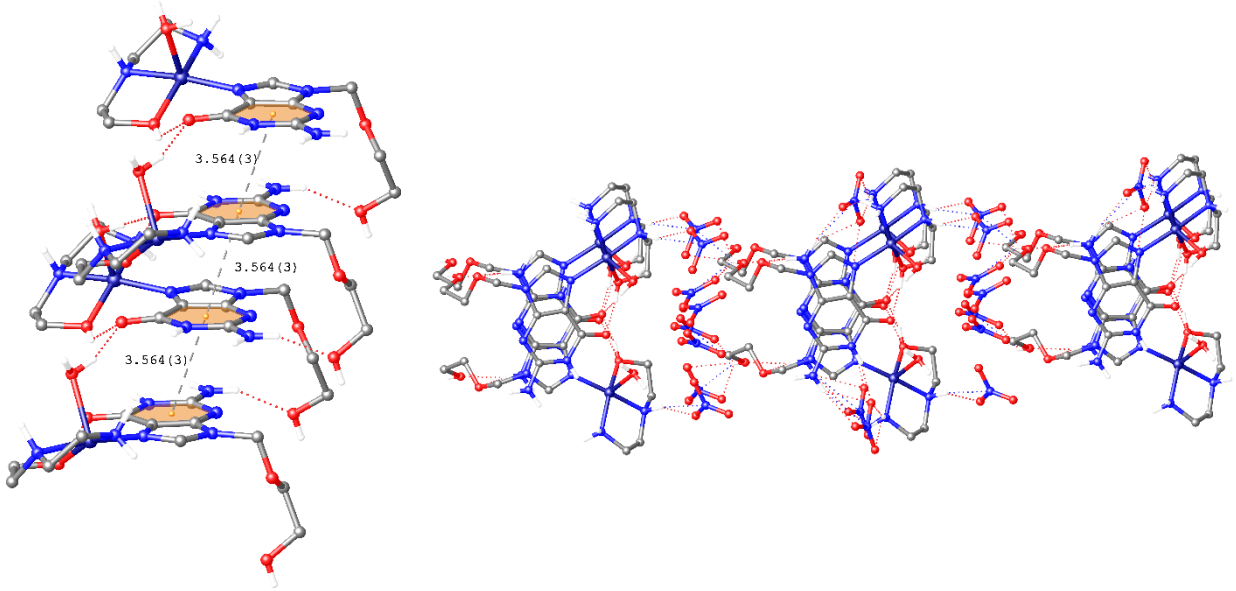


Figure 2. A) Multi-π,π-stacked chains of complex cations. B) Detail of crystal network.

It seems clear that the (hen)O-H···O6(acv) interligand interaction is preferred against other possibilities such as (hen)N-H···O6(acv) involving the primary $–NH_2$ or secondary –NH- amino groups of hen. Thus we conclude that the highest polarity of the terminal of –O-H in hen favours its implication in the molecular recognition between acv and the $Cu(hen)^{2+}$ chelate.

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International Symposium on Metal Complexes 2019
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The influence of pH and buffer on ligation at the heme distal site of a B-class dye-decolorizing peroxidase from *K. pneumoniae*

Kevin NYS, [a] **Jeroen ROEFS,** [a] **Vera PFANZAGL,** [b] **Christian OBINGER,**[b] **Sabine VAN DOORSLAER** [a]

[a] *Department of Physics, University of Antwerp, Universiteitsplein 1, 2610, Antwerp, Belgium*
[b] *Division of Biochemistry, BOKU – University of Natural Resources and Life Sciences, Muthgasse 18, 1190, Vienna, Austria*
e-mail: kevin.nys@uantwerpen.be

EPR or electron paramagnetic resonance is the perfect tool to study the catalytic site of heme proteins. The unpaired electron of the heme iron is hereby used as a spy and provides information on the spin state and ligands of the paramagnetic centre.

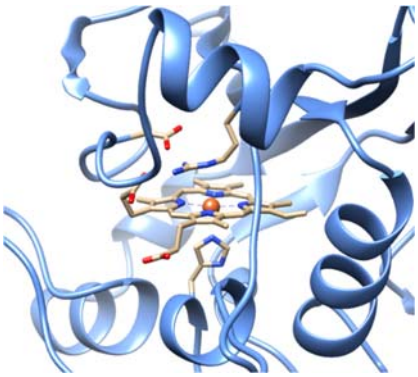

Fig. 1. *X-ray structure of wt KpDyP [pdb:6FKS]*

Here, low-temperature EPR was used to study *Kp*DyP, a dye-decolorizing peroxidase from the human pathogen *Klebsiella pneumoniae*, recombinantly expressed in *E. coli*. These so-called DyPs are presumed to degrade bulky textile dyes and lignin, making them interesting for biotechnological applications such as waste water treatment and biofuel production. However, kinetic rate constants show a fairly low peroxidase activity with conventional substrates compared to other peroxidases, challenging the physiological function of this family.

In an earlier report, we have shown the effect of site-directed mutations of the heme distal site residues, Asp143 and Arg232 [1]. Stopped-flow spectroscopy and X-ray crystallography indicated significant changes in peroxidase activity and in heme pocket architecture. These differences, although not directly involving the heme iron, were also sensed by EPR. In the present study we show the effect of pH and buffer. Increasing the acidity, typically results in a hydroxo-ligated heme. However, this appears to be very case-specific for DyPs. Moreover, there is an important role for glycerol, which is currently used as a cryoprotectant.

A comprehensive comparison is presented including the hypothesis of the first observation of a glycine-ligated heme with EPR.

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International Symposium on Metal Complexes 2019
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Synthesis of environment-friendly products based on BPA-free epoxy materials for stone conservation: New analytical methodologies to optimize their curing process

Olivia GÓMEZ-LASERNA, [a] Pablo IRIZAR, [a] Paola CARDIANO, [b] Irantzu MARTINEZ-ARKARAZO, [a] Ilaria COSTANTINI, [a] Leire KORTAZAR [a], Luis Ángel Fernández, [a] Marian OLAZABAL [a]

[a] Department of Analytical Chemistry, University of the Basque Country (EHU/UPV), BarrioSarriena s/n, E-48940, Bilbao, Spain.
[b] Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University ofMessina, Viale F. Stagnod'Alcontres 31, I-98166, Messina, Italy
e-mail: marian.olazabal@ehu.eus

The development of stone conservation products has attracted industry attention to achieve environment-friendly long-term stone treatments with consolidating and hydrophobic properties. In this sense, novel products derived from Bisphenol A (BPA)-free epoxy resins have become increasingly appealing due to the easy tailoring of their physical, thermal and chemical properties coming from their combination with compatible inorganic precursors and/or their nano-reinforcement [1].
Thus, the aims of this work were: a) The synthesis of a BPA-free epoxy resin, based on a diglycidyl ether of a substituted cycloaliphatic diol, with minor associated health and environmental concerns than phenolic-based ones. b) The development of a new spectroscopic methodology to monitor and optimize the synthesis and curing processes.
Accordingly, the synthesis of 2,2,4,4-tetramethyl-1,3-cyclobutanediol diglycidyl ether (CBDO-DGE) was carried out from the reaction of 2,2,4,4-tetramethyl-1,3-cyclobutanediol (CBDO), 2-(chloromethyl)oxirane (EHC) and sodium hydroxide (NaOH) in the presence of a phase transfer catalyst, tetra-n-butylammonium bromide (TBAB) (Fig.1) [2].

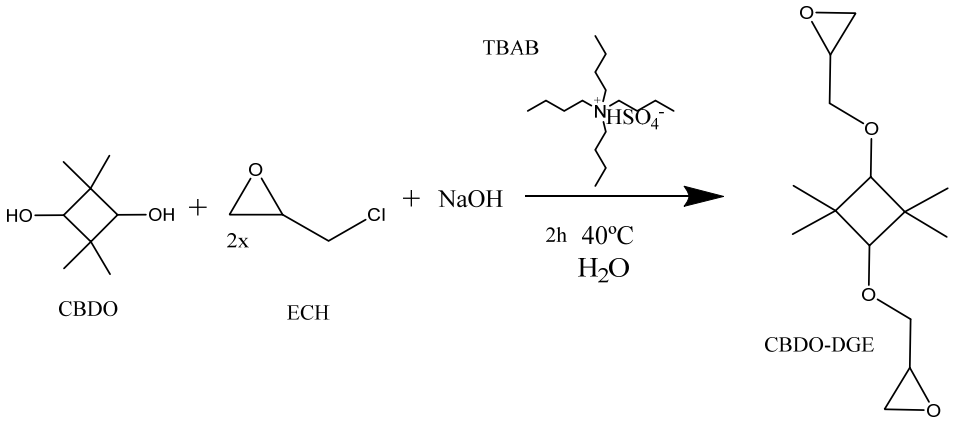

Figure 1. Reactants employed for the epoxy synthesis.

The crude purification method was monitored by FT-IR and Raman spectroscopies whereas the characterization of the expected compound was carried out by ^{1}H-NMR and ^{13}C-NMR measurements. Then, the epoxy-amine ratio used for its UV cure was optimized by a combination of Raman imaging measurements and a specific Multivariate Linear Regression

approach (MLR) software (PALME) [3]. Finally, the thermal behavior of the most promising product was investigated by means of Raman spectrometry coupled with a temperature controlled stage camera, thermogravimetric (TGA) and differential scanning calorimetry (DSC) analysis.

Acknowledgements: This work has been financially supported by the project PHETRUM (**CTQ2017-82761-P**) from the Spanish Ministry of Economy and Competitiveness (**MINECO**) and by the European Regional Development Fund (**FEDER**). O. Gómez-Laserna gratefully acknowledges her post-doctoral contract from the University of the Basque Country (UPV-EHU).

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International Symposium on Metal Complexes 2019
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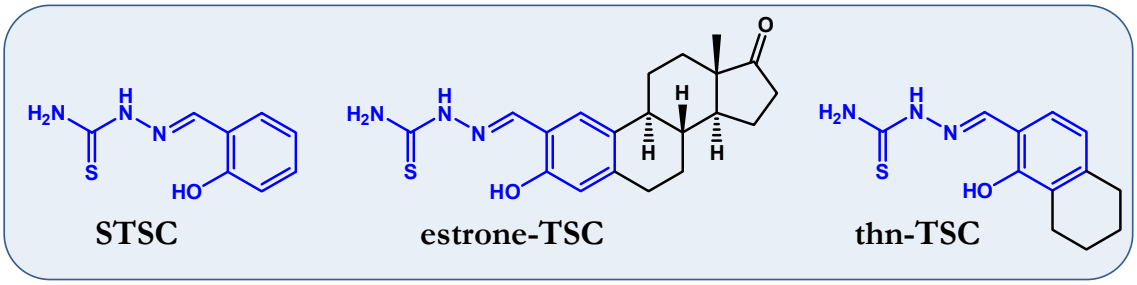
Copper(II) complexes of salicylaldehyde thiosemicarbazone and its structurally-related analogs: solution stability, redox properties and cytotoxicity

Tatsiana PETRASHEUSKAYA, [a] Orsolya DÖMÖTÖR, [a] Gabriella SPENGLER, [b] Annamária KINCSES, [b] Márton A. KISS, [c] Éva FRANK, [c] Éva A. ENYEDY [a]

[a] *Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary*
[b] *Department of Medical Microbiology and Immunobiology, University of Szeged, Dóm tér 10, H-6720, Szeged, Hungary*
[c] *Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720, Szeged, Hungary*
e-mail: petrashevtanya@gmail.com

Thiosemicarbazones (TSCs) possess a broad range of biological properties including antitumor, antimalarial and antimicrobial activity. Three α-*N*-pyridyl derivatives (Triapine, Coti-2, DpC) have been evaluated as anticancer agents in multiple clinical phase I/II trials in the last decades showing promising results [1]. Triapine is a very potent inhibitor of the iron-containing ribonucleotide reductase (RNR), and its mechanism of action is associated with its strong iron(II/III) chelation effect via the tridentate ($N_{pyridyl}$,N,S) donor set. On the contrary salicylaldehyde thiosemicarbazone (**STSC**, see figure) exhibits only low cytotoxic activity against tumor cells [2]. This ligand coordinates via an ($O_{phenolate}$,N,S) donor set resulting in a higher iron(III) preference over iron(II) which is not advantageous for the RNR inhibition [3]. In general, the cytotoxicity of copper(II) complexes formed with STSC and its derivatives exceeds that of the free ligands suggesting a different mechanism of action compared to α-*N*-pyridyl TSCs.



Numerous 2-substituted estrone derivatives display significant antitumor effect with negligible hormonal action [4]. In order to improve the anticancer activity of STSC and its copper(II) complex, we designed and synthesized a novel steroidal TSC derivative, **estrone-TSC** (see figure). A simpler structurally-related bicyclic compound, a new 5,6,7,8-tetrahydro-1-naphtol-based molecule (**thn-TSC**), was also prepared and studied.

In vitro cytotoxicity of STSC, estrone-TSC and thn-TSC and their copper(II) complexes was measured in doxorubicin-sensitive (Colo 205) and multidrug resistant (Colo 320) human colonic adenocarcinoma cell lines, in a breast cancer cell line (MCF-7) in addition to normal

human embryonal lung fibroblast cells (MRC-5). Both novel derivatives were more active than the reference compound STSC, and all the ligands showed strong synergism with copper(II). To understand better the differences between the biological activities of these ligands and complexes, a detailed comparative study was performed on their solution chemical and redox properties. Herein we characterized the lipophilicity, membrane permeability of the studied compounds and the proton dissociation processes of the ligands. We determined the stoichiometry and stability of the copper(II) complexes in pure aqueous solution or in a 30% (v/v) DMSO-H_2O solvent mixture by UV-visible titrations. In addition, the direct redox reaction of the complexes with the physiological reductants L-glutathione and ascorbate was also monitored under anaerobic conditions spectrophotometrically.

Acknowledgements: National Research, Development and Innovation Office-NKFIA projects GINOP-2.3.2-15-2016-00038, FK 124240; Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT. The work was supported by the ÚNKP-18-2 (M.A.K.) and ÚNKP-4-Bolyai (É.A.E.) New National Excellence Program of the Ministry of Human Capacities.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Acid-base properties and sequestering abilities towards toxic metal ions of cyclodextrin-calixarene co-polymers

Salvatore CATALDO, [a] Antonella DI VINCENZO, [b] Paolo LO MEO, [b] Nicola MURATORE, [a] Alberto PETTIGNANO [a]

[a] Dipartimento di Fisica e Chimica,Università di Palermo, viale delle scienze,I-90128, Palermo, Italy
[b] Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali Università di Palermo, viale delle scienze,I-90128, Palermo, Italy
email: alberto.pettignano@unipa.it

Smart materials with stimuli-responsive properties represent an interesting research area considering both their potential applications and the conceptual issues implied. They might be successfully employed in various fields, such as drug carrier/delivery devices to sensors, environment remediation, active packaging [1-2]. In this contest, we have recently synthesized various pH-responsive pre- and post-modified cyclodextrin-calixarene nanosponges (**CyCaNS**s) with 1,2,3-triazole linker units (**ACNS**s) able to vary their sequestering abilities towards organic and inorganic compounds. In particular, their adsorption properties were varied changing the molar ratio between the co-monomers, and the substituent groups present on each co-monomer scaffold and introducing ionizable groups by chemical post-modification.
A representation of the synthesized nanosponges is reported in the following Figure.

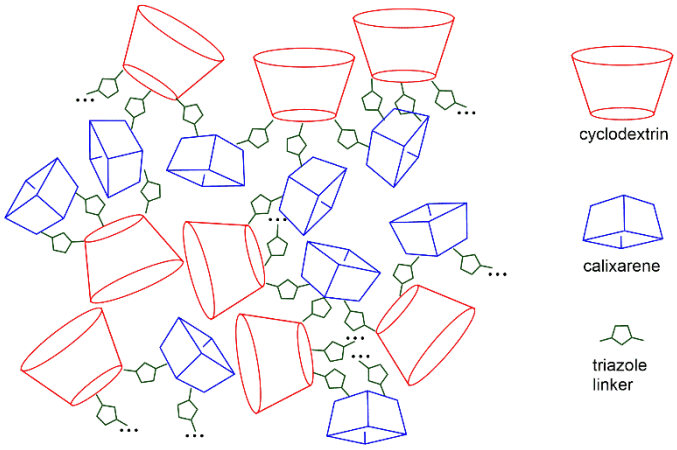

Figure 1. Cyclodextrin-calixarene nanosponges [3]

The experimental results showed that a fair pH-tunability was possessed even by non-modified materials, and this behavior was tentatively attributed to the presence of the triazole linkers, which may act as weak bases. This hypothesis, however, implies that triazole linkers should largely increase their basic strength (up to several orders of magnitude), due to their insertion in the polymeric network.
With the aim of clarifying the latter point, in the present work we perform a systematic study on the acid-base properties and on the sequestration abilities of nanosponges towards a series

of toxic metal ions. In particular, a panel of fifteen materials previously characterized (FT-IR, $^{13}C\{^{1}H\}$ CP-MAS solid state NMR, thermogravimetry) [3-4] was taken into account. Their acid-base behavior was investigated by means of ISE-H^+ potentiometric titrations, whereas their adsorption abilities were tested on a set of metal ions measuring their concentrations in the solutions by differential pulse anodic stripping voltammetry. ISE-H^+ potentiometric data were analyzed assuming the existence of different units, one for each type of functional group in the polymer. Protonation constants of functional groups of each unit were calculated by using different models already tested on others polymeric substances [5].

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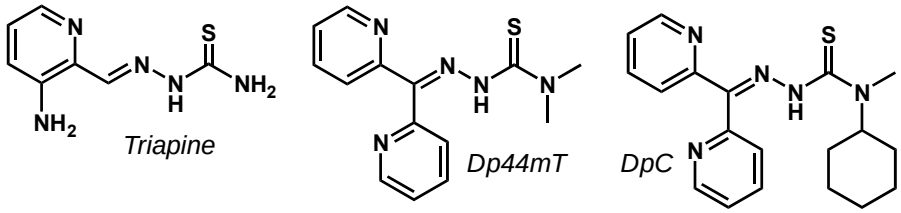
International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Redox properties and solution stability of copper complexes formed with various methylated Triapine derivatives

Vivien PÓSA, [a] Sonja HAGER, [b), c)] Veronika F.S. PAPE, [d), e)] Gergely SZAKÁCS, [b), d)] Bernhard K. KEPPLER, [c), f)] Christian R. KOWOL, [c), f)] Petra HEFFETER, [b), c)] Éva A. ENYEDY [a)]

[a)] Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre, University of Szeged, Dóm tér 7, H-6720, Szeged, Hungary
[b)] Institute of Cancer Research, Medical University of Vienna, Borschkeg. 8a, A-1090 Vienna, Austria
[c)] Research Cluster 'Translational Cancer Therapy Research', University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria
[d)] Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar Tudósok körútja 2, H-1117 Budapest, Hungary
[e)] Department of Physiology, Faculty of Medicine, Semmelweis University, , H-1094 Budapest, Tűzoltó utca 37-47, Hungary
[f)] Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria
e-mail: posavivien@gmail.com

Numerous thiosemicarbazones were clinically developed for a variety of diseases such as tuberculosis, malaria, viral infections and cancer in the last decades. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) as the most prominent representative of the α-*N*-pyridyl thiosemicarbazones is currently undergoing phase I/II trials acting as a highly efficient inhibitor of the enzyme Ribonucleotide Reductase [1]. To improve thiosemicarbazone-based therapy, several new derivatives, such as Dp44mT and DpC, have been developed in the last years resulting in compounds with much higher cytotoxicity than Triapine [1,2]. Dpc has been recently entered human clinical trials.



Various *N*-mono/dimethylated derivatives of Triapine were synthesized systematically in our previous work [3] representing versatile cytotoxicity and synergism or antagonism with copper(II) ions. Herein we characterized the solution stability and redox activity of the copper complexes of these methylated Triapine derivatives in addition to Dp44mT and DpC by UV-visible spectrophotometric titrations in aqueous solution. The number and position of the methyl substituents have a significant impact on the pK_a values of the ligands and the stability constants of the copper(II) complexes. The direct redox reaction of the copper(II) complexes

with the physiological reductants L-glutathione and ascorbate was investigated under anaerobic conditions spectrophotometrically. The obtained reaction rates show considerable differences depending on the mode of substitution. The *in vitro* cytotoxicity of the ligands and their copper complexes was measured against sensitive and multidrug resistant human uterine sarcoma cell lines (MES-SA/MES-SADx5) in addition to the detection of reactive oxygen species (ROS) using the DCF-DA fluorescence assay.

Acknowledgements: National Research, Development and Innovation Office-NKFIA through projects FK 124240 and GINOP-2.3.2-15-2016-00038. Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT.

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International Symposium on Metal Complexes 2019
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A computational study of Pb(II) complexes with tetraazamacrocyclic ligands

Viktorie REICHOVÁ, Přemysl LUBAL

Department of Chemistry, Faculty of Science, Masaryk University, Kamenice 5, CZ-625 00 BRNO, Czech Republic
e-mail: reichova.viki@gmail.com

$^{203/212}$Pb(II) complexes with macrocyclic ligands have potential in cancer theranostics as cytotoxic α-emitters [1,2]. In order to utilize these ligands for sufficient complexation of Pb(II) ions *in vivo* and/or for analytical/environmental applications, their behavior in various experimental conditions must be understood.

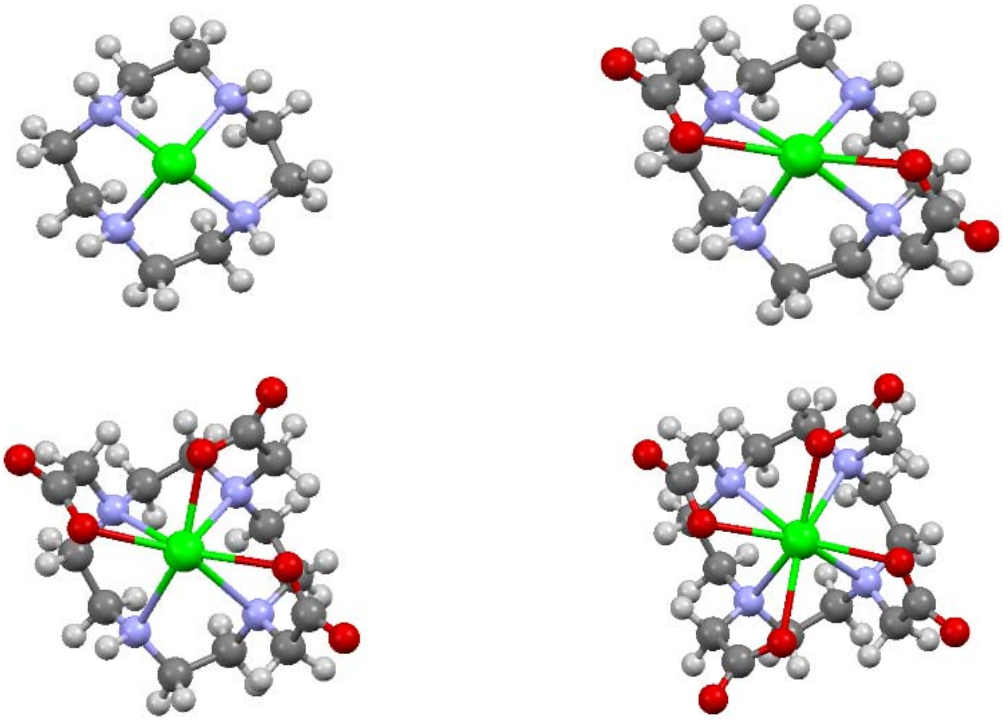

Figure 1. The molecular structures of Pb(II) complexes with tetraazamacrocyclic ligands estimated by DFT calculations.

This work is focused on the theoretical computational study of Pb(II) complexes with tetraazamacrocyclic-based ligands in order to understand their thermodynamic and kinetic properties. Density functional theory (DFT) calculations using the PBE0 functional with the Def2TZVP basis set were used to optimize the geometries of the Pb(II) complexes and calculate structural parameters (*e.g.* bond length, angle, *etc.*). The AIMAll program was also used to calculate the delocalization indexes of the Pb(II) complexes. These values were then correlated with experimentally available thermodynamic and kinetic data for Pb(II) complexes (*e.g.* stability constants, rates of formation/dissociation, *etc.*) and certain trends were observed. For

example, complexes with longer Pb-N bond lengths and lower energies have faster rates of formation, while complexes with longer Pb-O bond lengths and a higher delocalization index have enhanced kinetic inertness and a larger stability constant. These results can be used for the rational design of ligands having desired thermodynamic and kinetic properties for the specific applications of interest.

Acknowledgments: This study was supported by the Ministry of Education of the Czech Republic and Masaryk University (MUNI/A/1359/2018).

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International Symposium on Metal Complexes 2019
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Synthesis, characterization and biological investigations of ruthenium(II)-arene complex with 1-H-benzimidazole-2-carboxylic acid

Patrycja ROGALA, [a] Barbara BARSZCZ, [a] Katarzyna KAZIMIERCZUK, [b] Agnieszka JABŁOŃSKA-WAWRZYCKA, [a] Joanna WIETRZYK, [c] Justyna TRYNDA, [c] Agnieszka GILEWSKA [a]

[a] Institute of Chemistry, Jan Kochanowski University in Kielce, 15G Świętokrzyska 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) Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Weigla 12, 53-114 Wrocław, Poland
e-mail: patrycja.rogala@ujk.edu.pl

Organometallic half-sandwich Ru(II) complexes are currently the subject of interest as a result of their anticancer and antimicrobial activity [1-3]. Compounds of this type possess a pseudo-octahedral three-legged piano-stool geometry, in which three coordination positions are occupied by an aromatic arene ring binding in a η^6-manner (the seat), while three other coordination sites are filled by a various mono- or bidentate ligands (the legs). Among organometallic ruthenium complexes, Ru(II)-arene RAPTA-type compounds are widely investigated for their therapeutic properties. These complexes offer numerous ways to tune its structural parameters and electronic property. The change in the arene moiety or any of the other ligands is expected to influence reactions of the complex, thus altering the biological activity and redox property [4]. Apart from the phosphine complexes of the RAPTA family [5], mononuclear arene ruthenium complexes containing imidazole ligands have also been reported as anticancer agents. [2].

Therefore, we focused our studies on the synthesis of arene ruthenium compound with benzimidazole derivative – 1-H-benzimidazole-2-carboxylic acid (2-bimcH) as a potential N,O-chelating ligand. The obtained compound has been characterized using analytical and spectroscopic (CHN, ^{1}H and ^{13}C NMR, IR and UV-Vis) methods. Cyclic voltammetry and magnetic study were also performed. The structure of the complex was obtained from single-crystal X-ray diffraction studies. The complex exhibits a pseudo-octahedral three-legged piano-stool geometry, in which three “legs” are occupied by one chloride ion, one nitrogen atom and one oxygen atom of the chelating ligand. The spectroscopic results confirmed the composition of the complex. In turn, electrochemical and magnetic data show that the metal in complex has an oxidation state of +2.

In addition, the biological studies of the complex, such as cytotoxicity, lipophilicity and interactions with DNA were performed. Cytotoxic activity was probed versus tumour cell lines: myelomonocytic leukaemia (MV-4-11), colon adenocarcinoma (LoVo) as well as on normal mice fibroblast cells (BALB/3T3). Cisplatin was used as a reference drug. The complex demonstrated a moderate antiproliferative activity against the cell lines tested. The activity of complex as antibacterial agent against four pathogenic bacterial strains (*Staphylococcus aureus*,

Escherichia coli, *Pseudomonas aeruginosa* PAO1 and *Pseudomonas aeruginosa* LES B58) was also evaluated. Obtained results suggest that the ruthenium complex has bacteriostatic activity toward *Pseudomonas aeruginosa* strains.

Acknowledgements: Polish Ministry of Science and Higher Education (Projects No. 612415 and 666038).

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

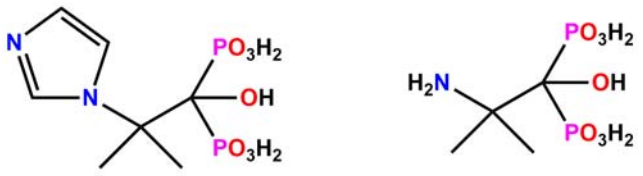
The analysis and comparison of supramolecular organization of Co(II) coordination polymers based on the new structurally diversified bisphosphonate ligands

Tomasz ROJEK, [a] **Waldemar GOLDEMAN**, [a] **Katarzyna ŚLEPOKURA**, [b] **Ewa MATCZAK-JON** [a]

[a] *Faculty of Chemistry, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370, Wrocław, Poland*
[b] *Faculty of Chemistry, University of Wrocław, F. Joliot-Curie 14, 50-383, Wrocław, Poland*
e-mail: tomasz.rojek@pwr.edu.pl

Bisphosphonic acids are a class of compounds which main application is associated with antiresorptive properties and high affinity for cations, and for that reason have been successfully used in clinical treatment of diseases such as osteoporosis or Paget disease.[1] Apart from interest of pharmaceutical industry and medical sciences, this class of compounds have been an object of interest of supramolecular chemistry due to their ability to form highly complex hydrogen-bonded networks resulting from the tetrahedral geometry of phosphonate and phosphonic groups and their donor/acceptor potential. This, combined with the presence of multiple donor atoms, allows them to create with metal ions structures such as isolated coordination units (0D), one-dimensional (1D) chain coordination polymers, two-dimensional (2D) layers or even three-dimensional (3D) coordination networks with promising properties and potentially wide range of applications.[2, 3] A specific architecture of final product is determined by various factors such as structural requirements of the ligand, the degree of protonation of the phosphonate groups as well as the charge and geometrical preferences of the central atom.

In this presentation we show the synthesis and crystal structures of new α,α-disubstituted analog of zoledronic acid (**1**) and its derivative with the imidazole ring replaced by an amino group (**2**). Furthermore we discuss the effect of this structural modification on the supramolecular architecture of their Co(II) coordination polymers.



1 2

Figure 1. The α,α-disubstituted analog of zoledronic acid (**1**) and its derivative (**2**).

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International Symposium on Metal Complexes 2019
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Donepezil based multi-target hybrids as metal chelating agents for potential Alzheimer´s disease therapy

Marina COSTA, [a] Romane JOSSELIN,[a] Diana SILVA, [b] Sandra M. CARDOSO, [b], [c] Sílvia CHAVES, [a] M. Amélia SANTOS [a]

[a] Centro de Quimica Estrutural, Instituto Superior Tecnico, Universidade de Lisboa, Av, Rovisco Pais 1, 1049-001, Lisboa, Portugal
[b] CNC – Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal
[c] Institute of Molecular and Cell Biology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
e-mail: masantos@tecnico.ulisboa.pt

Alzheimer´s disease (AD) is the most common form of dementia in the elderly population, but drugs so far developed only demonstrate palliative effects and/or temporary symptomatic reliefs [1]. The complex and multifactorial nature of this disease requires the development of drugs able to hit different pathophysiological targets, such as cholinergic dysfunction, deposits of amyloid-β peptide (Aβ), oxidative stress and metal dyshomeostasis [2,3].

To pursue the engineering of new anti-AD multi-target compounds based on a strategy of repositioning already approved palliative drugs with acetylcholinesterase (AChE) inhibitory capacity, namely donepezil [4,5], a hydroxyphenyl-benzimidazole (BIM) chelating unit was attached to a benzylpiperidine mimetic of donepezil (DNP) moiety. A series of five positional isomers were developed as DNP-BIM hybrids, corresponding to different attachment points at the BIM portion as well as at the benzylpiperidine group within the DNP moiety (see Fig. 1).

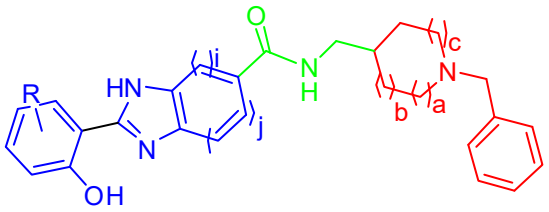
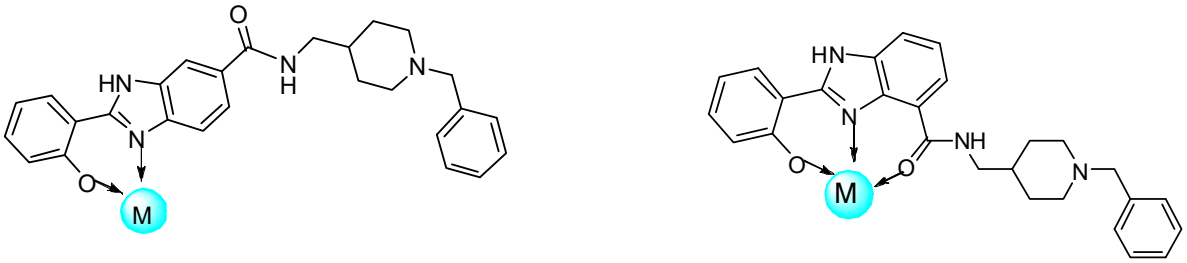


Figure 1. Novel multi.target DNP-BIM hybrids.
(i,j = 1,1; 3,0; a,b,c = 1,1,1; 0,1,2; 0,0,3; R = H,F)

The compounds were evaluated in terms of their potential multiple properties, namely inhibition of AChE (low micromolar range) and Aβ self-aggregation and under the co-effect of copper (moderate/good), as well as their capacity for the modulation of misplaced metal ions, well known as age triggers of AD (formation of redox active species and/or promotion of Aβ aggregation). The copper and zinc chelation were studied for representative hybrid compounds and it was found a good chelating capacity towards Cu(II) (pCu ~ 11-14) and moderate towards Zn(II) in a 50% w/w DMSO/water medium, involving complex species with metal coordination through the phenolic oxygen and the imidazole nitrogen N(3) of the BIM moiety. In the case of

L4, with the BIM unit *ortho*-attached to the benzylpiperazinic moiety, a higher copper(II) capacity, as compared with the *para*-analogue (**L1**), should be explained by the possible formation of a (N,O,O) tridentate chelate, involving the BIM moiety and the adjacent carbonyl oxygen atom (see Fig. 2). The metal binding results can also rationalize the generally improved inhibitory activity found for Cu-induced aggregation versus self-aggregation.



L1:M **L4:M**

Figure 2. Proposed metal coordination core for two DNP-BIM hybrids.

The neuroprotective effect of the compounds in neuroblastoma cells subjected to AD stressors, as Aβ-induced toxicity, was also evaluated.

Overall, the set of obtained results are discussed in terms of positional isomerization and structure-activity relationships, providing indications of the most promising compounds as potential multi-target anti-AD drug candidates.

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International Symposium on Metal Complexes 2019
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Synthesis and study of tumor-targeted photosensitizers for one- and two-photon photodynamic therapy

Angélique SOUR, [a] **Sébastien JENNI,** [a] **Valérie HEITZ,** [a] **Frédéric BOLZE,** [b] **Barbara VENTURA** [c]

[a] *LSAMM, Institut de Chimie de Strasbourg, CNRS/UMR 7177, Université de Strasbourg, 4, rue Blaise Pascal, 67070 Strasbourg, France*
[b] *CAMB, Faculté de Pharmacie, CNRS/UMR 7199, Université de Strasbourg, 74, route du Rhin, 67401 Illkirch, France*
[c] *Istituto ISOF-CNR, Via P. Gobetti 101, 40129 Bologna, Italy*
e-mail: a.sour@unistra.fr

Photodynamic therapy (PDT) is a light-activated medical treatment with several advantages such as low side effects, lack of treatment resistance and temporal and spatial selectivity inherent to the light activation of the drug.[1,2] It uses a non-toxic photosensitizer which should ideally be water-soluble, accumulate in the region of interest, it should be activated by irradiation in the near infrared region, and produce toxic reactive oxygenated species.[3,4] Finally, it should also be eliminated from the body relatively rapidly. We will report new targeted photosensitizers for tumor-targeting PDT, they consist of a pi-delocalized diketopyrrolopyrrole-porphyrin conjugate linked to folic acid or to biotin. They show promising in vitro properties related to PDT such as intense absorption following one-photon excitation in the red or two-photon excitation in the near-infrared and also good singlet oxygen production. Cellular studies demonstrated that both targeted photosensitizers induced one-photon phototoxicity at 660 nm. Moreover, two-photon excitation at 920 nm also resulted in efficient cell death with the folate-targeted PS.

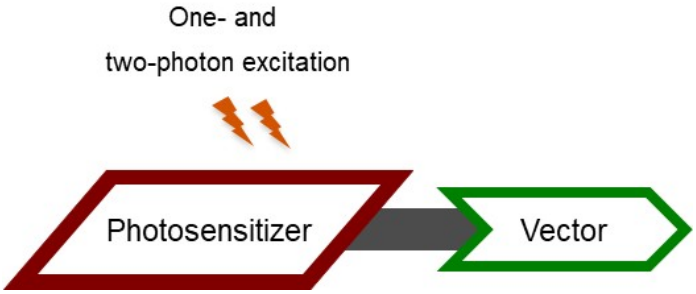

Figure 1. Targeted photosensitizer for photodynamic therapy.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

The decomposition of *N*-chloro-leucine, -isoleucine and -valine

Vivien BÍRÓ, [a] Fruzsina SIMON, [a] Mária SZABÓ, [a] István FÁBIÁN [a], [b]

[a] University of Debrecen, Department of Inorganic and Analytical Chemistry, Egyetem tér 1., H-4032, Debrecen, Hungary
[b] MTA-DE Homogeneous Catalysis and Reaction Mechanisms Research Group, Egyetem tér 1., H-4032, Debrecen, Hungary
e-mail: szabo.maria@science.unideb.hu

In recent years, *in vivo* processes and environmental aspects have generated massive interest in the reactions of chlorine and hypochlorous acid with amines, amino acids and peptides. These reactions lead to the formation of various *N*-chlorinated amines under various conditions. The formation of *N*-chloramines in biological systems has outstanding importance because these molecules can penetrate into the cells and cause oxidative stress which ultimately leads to the death of the cells. We investigated the decomposition of the mono-*N*-chloro derivatives of three essential amino acids: leucine, isoleucine and valine. These compounds are known as branched chain amino acids (*BCAA*) and due to their biological significance (e.g. anticatabolic and anabolic effect), they are very popular in the health-industry.

Upon mixing hypochlorous acid with BCAA-s the chloramines are formed in very reactions. These overall second order processes are first-order for HOCl and the fully deprotonated form of the amino acid. The rate constants are typically several times 10^7 M^{-1} s^{-1}. The *N*-chloro amino acids of BCAA-s undergo slow decomposition which can be monitored by spectrophotometric methods at the characteristic absorption maximum of these compounds (λ_{max} ~ 255 nm). The decomposition reactions show very similar kinetic features. In all cases, two competing paths are operative in these systems and the pseudo-first-order reaction can be expressed as follows:

$$k_{obs} = k + k_{OH}$$

Via the pH independent and the [OH^-]–dependent paths, the primary product of the decomposition is the same aldehyde in accordance with the following stoichiometry.

$$R\text{-}CH(NHCl)COO^- + H_2O = R\text{-}CHO + CO_2 + NH_3 + Cl^-$$

Under alkaline conditions, the corresponding Schiff-base is formed with the excess of amino acid in a fast, subsequent reaction.

We present a detailed common mechanism for these reactions which is supported by the kinetic, ^{1}H NMR and MS experimental results.

Acknowledgements: The research was supported by the Hungarian Scientific Research Fund: OTKA K-124983. The research was also supported by the EU and co-financed by the European Regional Development Fund under the project GINOP-2.3.2-15-2018-00008 and by the ÚNKP-18-3 New National Excellence Program of the Ministry of Human Capacities.

International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Solution chemical and cytotoxic study on copper(II) complexes of three naturally occurring flavonoids

Attila SZORCSIK, [a] **Eszter BEZZEG,** [b] **Nóra V. MAY,** [c] **Attila HUNYADI,** [b] **Gabriella SPENGLER,** [d] **Tamás GAJDA** [a]

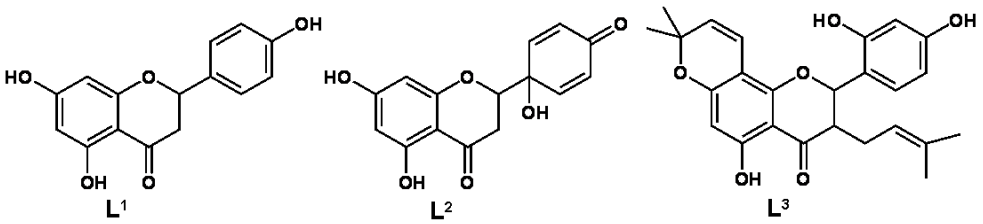
[a] *Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720 Szeged, Hungary*
[b] *Institute of Pharmacognosy, Faculty of Pharmacy, University of Szeged, 6720 Szeged, Eötvös utca 6, Hungary*
[c] *Research Centre for Natural Sciences HAS, Magyar tudósok körútja 2, 1117 Budapest, Hungary*
[d] *Department of Medical Microbiology and Immunobiology, Faculty of Medicine, University of Szeged,Dóm tér 10, 6720 Szeged, Hungary*
e-mail: szorcsik@chem.u-szeged.hu

Flavonoids are among the most important phytochemicals due to their wide-ranging pharmacological and therapeutic effects, that include anticancer, anti-inflammatory, antiatherosclerotic, antioxidant, antidiabetic, antimutagenic, antithrombotic, vasodilatory and antiviral activities. Here we report our results on copper(II) complexes of three, structurally rather different flavonoids.

Apigenin is a common dietary flavonoid that is abundantly present in many fruits, vegetables and Chinese medicinal herbs and serves multiple physiological functions, such as strong anti-inflammatory, antioxidant, antibacterial and antiviral activities and blood pressure reduction. Therefore, apigenin has been used as a traditional medicine for centuries. Recently, apigenin has been widely investigated for its anti-cancer activities and low toxicity. Apigenin was reported to suppress various human cancers in vitro and in vivo by multiple biological effects, such as triggering cell apoptosis and autophagy, inducing cell cycle arrest, suppressing cell migration and invasion, and stimulating an immune response. [1]

Protoapigenone is a member of protoflavones and the most deeply studied among them. This compound has been shown to exert strong cytotoxic activity in a wide variety of cancer cells including breast, ovarian, cervical, prostate, lung, liver, etc. [2]

Morusin is an isoprenylated flavone, which was isolated from Morus alba. It is known, that the plant possesses antimicrobial, antioxidant, anticancer, neuroprotective and antidepressant etc. activities. The anticonvulsant activity of morusin has been widely studied.



Scheme 1. Structures of the investigated flavonoids
(**L**[1] = apigenine, **L**[2] = protoapigenone, **L**[3] = morusin)

The interaction of flavonoids with endogenous redox active metal ions play a major role in the biological behavior and medicinal applications of flavonoids. In addition, several studies have been reported that flavonoid–metal complexes exhibit improved anticancer effects when compared with the parent flavonoid. [3] Nevertheless, complete solution equilibrium study on metal complexes of flavonoids are very rare in the literature [4], mainly due to the low solubility of these compounds and their metal complexes in aqueous solution. For these reasons, we aimed to characterize the copper(II) complexes of the three above mentioned flavonoid ligands in solution state, using pH-potentiometric, UV-Vis and EPR techniques. Due to the aforementioned low solubility, we performed our study in 80% (w/w) dmso-water mixture. According to our results, the three systems show similar behavior. Below the neutral pH the formation of CuHL és CuH_2L_2 complexes were detected. Their basicity corrected stability constants are nearly equal for the three ligands, which together with the spectroscopic data indicate similar {C5-O^-,C4=O} type coordination in these species, which was also confirmed by the spectroscopic data. Above neutral pH the further deprotonations do not alter the coordination mode, they take place without metal-ion assistance. Although, at room temperature the EPR spectra indicate the presence of mononuclear complexes, at 77 K refer to dimerization of bis complexes via π-π interactions (possibly supplemented with axial coordination of O-donors). The typical aromatic π − π interaction between parallel planes results in a distance of 3.3-3.8 Å, which is consistent with the 4 Å copper-copper distance calculated from the D = 330 G dipolar coupling constant of these complexes. In the copper(II)-protoapigenone system above pH 10 copper(II) promoted degradation of the ligand was observed, coupled with the formation of 1,4-benzosemiquinone radical, as indicated by the hyperfine structure of its EPR spectrum.

The cytotoxicity of the *bis*-complexes and the corresponding free ligands was determined by MTT assay against three human cancer cell lines, including Colo205, Colo320 and MRC5, with oxorubicin as a positive control. Although, the IC_{50} values of the complexes were lower in all cases, only the $Cu(apigenine)_2$ complex showed synergistic effect.

Acknowledgement: The research was supported by the National Research, Development and Innovation Office-NKFIH through project GINOP-2.3.2-15-2016-00038.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Nickel(II) complexes of peptides containing cysteinyl residues

Györgyi SZUNYOG, Dóra Csilla PÁLINKÁS, Katalin VÁRNAGY

University of Debrecen, Egyetem tér 1, 4032, Debrecen, Hungary
e-mail: szunyog.gyorgyi@science.unideb.hu

Nickel is an essential element for a lot of plants and bacteria. It plays a role in the metabolism of higher organisms [1]. For nickel(II), the terminal amino group and side chain imidazole-N, thiolate-S and carboxylate-O of proteins serve as main binding sites in the metalloproteins.

In our previous research we have synthesized and studied the zinc(II), cadmium(II) and lead(II) complexes of a series of peptides containing two cysteine residues [2, 3]. One group of the ligands have a free N-terminal amino group and an amide group on the C-termini: Ser-SerCysSerSerAlaCysSer-NH_2 (SSCSSACS-NH_2), AlaCysSerSerAlaCysSer-NH_2 (ACSSACS-NH_2) and CysSerSerAlaCysSer-NH_2 (CSSACS-NH_2), while the other group of consists of terminally protected peptides: Ac-AlaAlaAlaCys-NH_2 (Ac-AAAC-NH_2), Ac-SerAlaAlaCys-NH_2 (Ac-SAAC-NH_2) and Ac-CysSerSerAlaCysSer-NH_2 (Ac-CSSACS-NH_2).

We have continued this work with the investigation of nickel(II) complexes of aforementioned peptides and completed them with the terminally protected tetrapeptides containing cysteine on the N-termini: Ac-Cys-GlyAlaAla-NH_2 (Ac-CGAA-NH_2), Ac-CysGlyAlaLys-NH_2 (Ac-CGAK-NH_2), Ac-CysGlyAlaAsp-NH_2 (Ac-CGAD-NH_2) and Ac-CysGlyAlaHis-NH_2 (Ac-CGAH-NH_2).

The stoichiometry and stability constants of the metal complexes were determined by potentiometry, while their structures were supported by means of CD-, UV-Vis, MS- and NMR-spectroscopy.

In the case of three peptides containing free terminal amino group, the N-terminal part of the molecules is the primary binding site and (NH_2, S^-), (NH_2, N^-, S^-) or (NH_2, N^-, N^-, S^-) donor sets coordinate the metal ion, but the coordination of C terminal cysteine-S^- contributes to the formation of stable complexes. At high pH-range, however, the C terminal thiolate group is able to behave as an anchor group, and coordination isomers are present in equimolar solution, while dinuclear species were detected at excess of nickel(II) ion (**Figure 1.**).

In the case of the terminally protected tetra- and hexapeptides, the C-terminal thiolate and the amide groups are the primary binding sites. For tetrapeptides containing cysteine on the N-termini the thiolate group is the primary binding site only, when there are no side chain donor groups with strong coordination ability in the peptide (Ac-CGAA-NH_2, Ac-CGAK-NH_2 and Ac-CGAD-NH_2).

The presence of C-terminal histidine in the Ac-CGAH-NH_2 peptide however, takes over the role of primary binding site, and the (N^-,N^-,N^-, N_{Im}) coordinated nickel(II) complexes are formed.

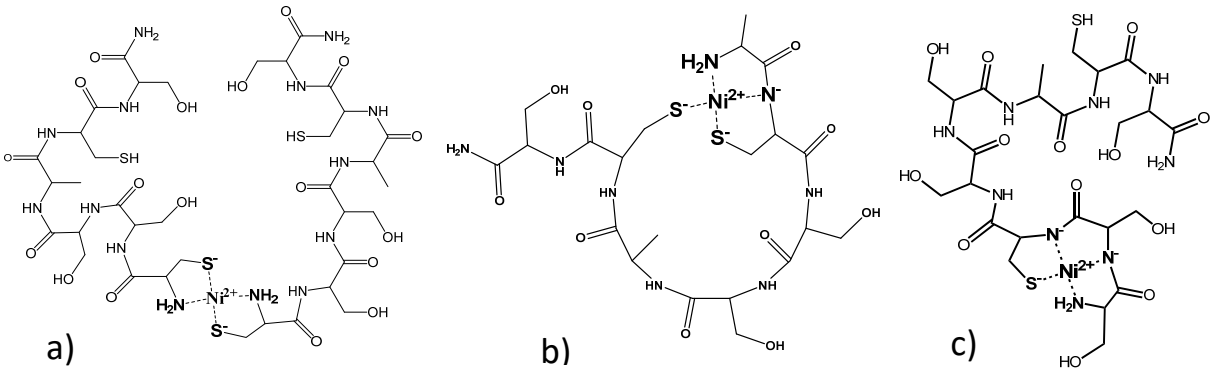

Figure 1. The sematic structures of $[NiH_2L_2]$ complex (L = CSSACS-NH_2) (a), $[NiH_{-1}L]^-$ complex (L = ACSSACS-NH_2) (b) and $[NiH_{-2}L]^{2-}$ complex (L = SSCSSACS-NH_2) (c).

Acknowledgements: This work was supported by the Hungarian Scientific Research Fund (K115480) and EU and co-financed by the European Regional Development Fund under the project GINOP-2.3.2-15-2016-00008.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Interaction between Aβ42 and KLVFF peptide conjugated with metallated porphyrins: a potential route toward the discovery of theranostic agents in Alzheimer's disease.

Rita TOSTO, Giuseppe DI NATALE, Tiziana CAMPAGNA, Francesco BELLIA, Giuseppe PAPPALARDO

Institute of Crystallography (IC) CNR , Via Paolo Gaifami 18, 95126, Catania, Italy
e-mail: ttstt.rita@live.it

Alzheimer's disease (AD) is the most common cause of dementia, in the elderly that affect more than 24 million people worldwide. Unfortunately, there is no cure for AD and the precise etiology of the disease remains unclear at present time.
The disease is characterize by the aggregation of amyloid β peptide (Aβ) into amyloid fibrils. The formation of β-sheet-rich amyloid fibrils is a complex multistep process involving the assembly of various oligomers aggregated species.[1] An increasing amount of studies indicate that diffusible oligomers of Aβ are responsible for synaptic dysfunction in the brains of AD patients. However, if small diffusible aggregation products are suspected as the toxic species in AD, accelerating nucleation and/or increasing the size of the aggregates, altering possibly their morphology, may represent one valid strategy to cancel out the Aβ oligomers' neurotoxicity.[2]
In this context, use of di-functional systems capable of synergic and/or additive actions to counteract the adverse effects of Aβ aggregated forms[3]. The compound generally consist of a known Aβ recognition group combined to other moieties able to explicate additional or complementary functions, including antioxidant, metal chelation or aggregates disassembly.
Recent experimental work uses porphyrins and conjugates thereof as suppressors of Aβ aggregation and cytotoxicity[4]. Porphyrins have been used as pioneering agents not only for diagnostic imaging[5], but also for therapy[6].
We synthesized a conjugated between a cationic metallic-porphyrin and the well-known Aβ-recognizing KLVFF amino acid sequence. Peptide conjugation to porphyrin macrocyclic was previously accomplished via amide bonds using standard coupling reagents. A second generation of this bifunctional peptide conjugated was obtained in good yields via click chemistry approach (Fig 1).

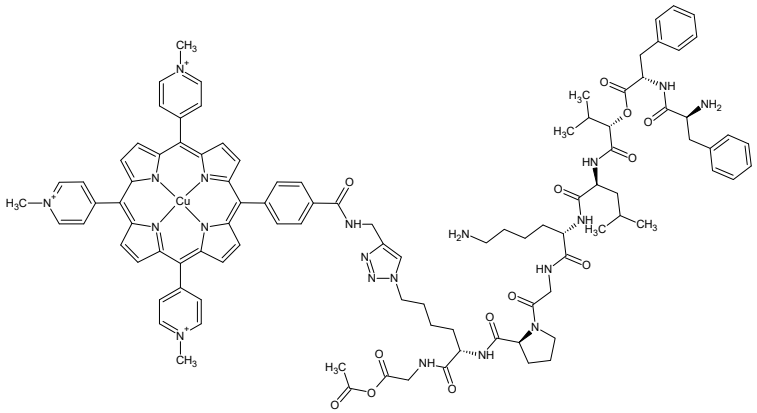

Figure 1. Scheme of structure obtained with click chemistry.

In this communicated we describe the capability of the metallic ion (Zn, Cu and Co) to be coordinated by the histidine residues located within the N-terminal region of Aβ42 peptide. This, in award disease would increasis the binding affinity of the hybrid system toward the Aβ core region while enhancing porphyrin binding at the Aβ N-terminus.
The interaction between the peptide conjugate and Aβ was studied by using an array of different biophysical techniques including Dynamic Light Scattering (DLS), far-UV, Circular Dicroism (CD), Fluorescence spectroscopy and MALDI-TOF-MS.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Silver(I) complexes with amino acids as potential antibacterial and anticancer agents

Zuzana VARGOVÁ, [a] Michaela RENDOŠOVÁ, [a] Gabriela KUZDEROVÁ,[a] Danica SABOLOVÁ, [b] Róbert GYEPES, [c] Daniela HUDECOVÁ,[d] Petra OLEJNÍKOVÁ,[d] Martin KELLO, [e] Dagmar MUDROŇOVÁ [f]

[a] Department of Inorganic Chemistry, Faculty of Science, P. J. Šafárik University, Moyzesova 11, 041 54 Košice, Slovak Republic
[b] Department of Biochemistry, Faculty of Science, P. J. Šafárik University, Moyzesova 11, 041 54 Košice, Slovak Republic
[c] Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030, 128 00 Prague, Czech Republic
[d] Department of Biochemistry and Microbiology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovak Republic
[e] Department of Pharmacology, Faculty of Medicine, P. J. Šafárik University, Trieda SNP 1, 040 01, Košice, Slovak Republic
[f] Department of Microbiology and Immunology, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovak Republic
e-mail: zuzana.vargova@upjs.sk

For thousands of years, silver in ionic or metal form has been used in the medical field for the treatment of burns, ulcers and bacterial infections because it has antimicrobial effects and it accelerates wound healing [1]. Over the last decades, it has been found that antimicrobial silver(I) ions need to be appropriately coordinated with ligands to develop more stable antimicrobial and anticancer compounds. Silver(I) complexes are extensively studied with NHC- ligands, N-, P-donor ligands, carboxylate ligands or with mixed ligands [2, 3].

The aim of our experimental work is the preparation and solid-state characterization of new stable silver(I) coordination compounds based on the amino acids. Their antibacterial, antifungal and anti-yeasts activity is studied and compared with commercially-used drug, silver sulfadiazine. Moreover, cytotoxic activity against different cell lines is evaluated and DNA binding to calf thymus DNA through UV-Vis and fluorescence quenching experiments is investigated.

Acknowledgements: This work was financially supported by Slovak grant agencies VEGA 1/0016/18, KEGA 008UPJŠ-4/2018, Pavol Jozef Safarik University VVGS-PF-2018-799 and Slovak Research and Development Agency under the contract No. APVV-15-0520.

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International Symposium on Metal Complexes 2019
Debrecen Hungary 11-14 June

Complexes of Bi^{3+}, Eu^{3+}, Sc^{3+}, Y^{3+} with conjugates of short somatostatin analogues for the diagnosis and therapy of cancer

Anzhelika YAKUSHEVA, [a] Bayirta EGOROVA, [a] Ekaterina MATAZOVA, [a] Stepan Kalmykov, [a] Dmitry AVDEEV, [b] Vasily OSIPOV, [c] Derenik KHACHATRYAN [d]

[a] Lomonosov Moscow state university, Leninskiye gory 1, 119991, Moscow, Russia
[b] National Medical Research Center for Cardiology, 3rd Cherepkovskaya Str.15A, 121552, Moscow, Russia
[c] «N.N. Blokhin National Medical Research center of oncology» of the Health Ministry of Russia, Kashirskoe sh. 2, 115478, Moscow, Russia
[d] NRC «Kurchatov Institute» - IREA, Bogorodskiy Val 3, 107076, Moscow, Russia
e-mail: angie.chem.msu@gmail.com

Among the oncological diseases, there are neuroendocrine tumors that have high expression of somatostatin receptors on their surface. For diagnosis and therapy of such diseases, a number of peptide analogues of the somatostatin hormone have been developed [1]. In order to maintain the activity of such peptides the presence of following sequence of amino acids Phe – D-Trp – Lys – Thr is required. It is suggested that peptides containing this sequence have cytotoxic and antitumor activity [2].

For this work two new short tetra- (P1) and pentapeptide (P2) conjugates were synthesized for the first time (Fig.1).

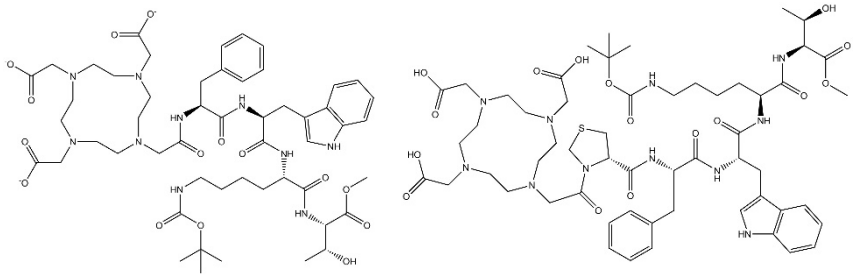

Figure 1. The structure of DOTA-P1 and DOTA-P2 conjugates.

For the complexation radionuclides ^{207}Bi and ^{152}Eu were selected as the long-lived analogues of ^{213}Bi [3] and other radionuclides of rare earth elements, which can be potential radiation sources in radiopharmaceuticals. ^{44}Sc is potential radionuclide for positron emission tomography (PET) [4] and ^{90}Y is therapeutic radionuclide [5]. DOTA is well-known macrocyclic ligand, which is widely used in radiopharmaceuticals, but it has a slow kinetics of complexation at room temperature [6]. All these metals mentioned above form stable complexes with DOTA.

Labeling was carried out varying different factors: conjugate concentration, temperature, pH and time of reaction. Quenching of labeling reactions in kinetic experiments was achieved by addition of DTPA.

The resulting complexes were analyzed by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The appropriate conditions for the formation of M-DOTA-P1 (where M = Eu, Bi, Sc, Y) were found. It is established that the preparation of the M-DOTA-P2 complexes is possible only at low temperature for several days, so it is difficult to use such pentapeptide conjugate in the synthesis of radiopharmaceuticals. All resulting complexes have high stability in serum, isotonic solution and in the excess of biogenic cations (Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}).

Acknowledgements: This work was supported by RFBR project №18-03-00891.

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