UNIVERSITÀ DI PARMA

ARCHIVIO DELLA RICERCA

University of Parma Research Repository

Metallacrowns: controlling the assembly toward supramolecular constructs

This is the peer reviewd version of the followng article:

Original
Metallacrowns: controlling the assembly toward supramolecular constructs / Matteo, Tegoni; Corrado, Atzeri; Davide, Capucci; Maurizio, Remelli; Nicola, Marchetti; Vincent, L. PECORARO. - ELETTRONICO. - 4(2014), pp. 31-32. ((Intervento presentato al convegno ISMEC2014 - International Symposium on Metal Complexes tenutosi a Pavia nel 8-12 giugno 2014.

Availability:
This version is available at: 11381/2729717 since: 2015-12-11T12:47:23Z

Publisher:
ISMEC Group

Published
DOI:

Terms of use:
openAccess

Anyone can freely access the full text of works made available as "Open Access". Works made available

Publisher copyright

(Article begins on next page)

12 October 2022

Volume: 4
Year: 2014
Symposium Edition: XXV

ISMEC GROUP SERIES
http:// mat520.unime.it/ismecacta/
ISSN: 2239-2459

ISMEC2014

International Symposium on Metal Complexes (8/12 June - Pavia)

Acta of the International Symposia on Metal Complexes

Università degli Studi di Pavia (ITALY)

ISMEC2014

International Symposium on Metal Complexes (8/12 June - Pavia)

Acta of the International Symposia on Metal Complexes

Raffaela Biesuz, Editor
Dipartimento di Chimica, University of Pavia, Pavia, Italy
President of the Scientific Committee of ISMEC2014

Enrique García-España, Editor
ICMOL, Departamento de Química Inorgánica, University of Valencia, Spain
President of the ISMEC group

ISMEC GROUP SERIES
Volume: 4
Year: 2014
ISSN: 2239-2459
Symposium Edition: XXV

The **Acta of the International Symposia on Metal Complexes** (ISSN: 2239-2459) are published annually online by the ISMEC Group

Editors:

Raffaela Biesuz *(President of the Scientific Committee of ISMEC 2014)*
Dipartimento di Chimica
Università di Pavia
Via Taramelli, 12
27100 Pavia, ITALY
rbiesuz@unipv.it

Enrique García-España *(President of the ISMEC Group)*
Instituto de Ciencia Molecular (ICMOL), Departamento de Química Inorgánica
Universitat de Valencia
Catedrático José Beltrán Martínez, 2
46980 Paterna, Valencia, SPAIN
enrique.garcia-es@uv.es

Scientific Committee of ISMEC2014

Raffaela Biesuz	(University of Pavia, Italy)
Enrique García-España	(University of Valencia, Spain)
Guido Crisponi	(University of Cagliari, Italy),
Luigi Fabbrizzi	(University of Pavia, Italy)
Etelka Farkas	(University of Debrecen, Hungary)
Juan Niclós Gutierrez	(University of Granada, Spain)
Henryk Kozlowski	(University of Wroclaw, Poland)
Maurizio Remelli	(University of Ferrara, Italy)
Silvio Sammartano	(University of Messina, Italy)
Maria Amélia Santos	(Technical University of Lisbon, Portugal)

Copyright:
Authors retain the copyrights of their Acta, and their unrestricted use, distribution and reproduction in any medium are permitted, provided that the original work is properly cited. The use of general descriptive names, trade names, trademarks, and so forth in this publication, even if not specifically identified, does not imply that these names are not protected by the relevant laws and regulations. While the advice and information in this journal are believed to be true and accurate on the date of its going to press, neither the authors, the editors, nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher and the editors make no warranty, express or implied, with respect to the material contained herein.

Acta of the International Symposia on Metal Complexes
ISMEC GROUP SERIES
Volume: 4
Year: 2014
Symposium Edition: XXV
http://mat520.unime.it/ismecacta/
ISSN: 2239-2459

Foreword

The **International Symposium on Metal Complexes** (**ISMEC2014**), to be held in Pavia, Italy from 8th to 12th June 2014, is also the **XXV Italian-Spanish Congress on Thermodynamics of Metal Complexes**. The latter's internationalisation is the result of the ever-increasing proportion of contributions from other nations throughout the globe. With contributions from 27 countries belonging to 5 continents ISMEC2014 confirms this trend, which will facilitate the creation of many joint projects and will lead ISMEC into new cutting-edge areas, namely those relating to the most recent advances in metal complex applications in a wide range of diverse fields such as ecology and biomedicine.
In particular, the following topics, which focus on the chemistry and applications of metal complexes, will be presented and discussed in this year's congress:

- Solution equilibria and coordination chemistry
- Metal complexes of environmental interest
- Supramolecular chemistry
- Metal complex interactions with biomolecules
- Nanostructured metal complexes
- Metals in diseases: transport, homeostasis and toxicity
- Metal-based drugs: therapy and diagnosis
- Analytical methods and sensors based on metal complexes
- Computational modelling

ISMEC2014 has been organised by the University of Pavia's Chemistry Department. The organising team includes Prof. Raffaela Biesuz (Chairperson), Prof. Maria Pesavento and Dr. Giancarla Alberti.

Since 2011, immediately after each symposium, the publication "*Acta of ISMEC Symposia*" has and will continue to provide a comprehensive compendium of the most recent advances made by scientific research in the field of the thermodynamics of metal complexes. Each edition is edited by the relative Scientific Committee (President and Members) and by the President of the ISMEC Group.
In future additional publications relating to other events may be produced with the same aim of providing readily accessible, accurate information on basic aspects and/or new findings in the same field.

R. Biesuz
and
E. Garcia-España
June 2014

Scientific Committee

Raffaela Biesuz (University of Pavia, Italy)
Enrique García-España (University of Valencia, Spain)
Guido Crisponi (University of Cagliari, Italy),
Luigi Fabbrizzi (University of Pavia, Italy)
Etelka Farkas (University of Debrecen, Hungary)
Juan Niclós Gutierrez (University of Granada, Spain)
Henryk Kozlowski (University of Wroclaw, Poland)
Maurizio Remelli (University of Ferrara, Italy)
Silvio Sammartano (University of Messina, Italy)
Maria Amélia Santos (Technical University of Lisbon, Portugal)

Organizing Committee

Raffaela Biesuz (chair, University of Pavia, Italy)
Maria Pesavento (co-chair, Uniiversity of Pavia, Italy)
Giancarla Alberti (secretary & web maintenance, University of Pavia, Italy)
Antonella Profumo (University of Pavia, Italy)
Valeria Amendola (University of Pavia, Italy)
Roberta Colleoni (University of Pavia, Italy)
Greta Bergamaschi (University of Pavia, Italy)

Contacts

ISMEC2014 Organizing Committee
Dipartimento di Chimica, Università di Pavia
via Taramelli, 12
27100 Pavia
ITALY
Phone: +39 0382 987348
Fax: + 39 0382 528544
Congress website: http://ismec2014.org
Acta website: http://mat520.unime.it/ismecacta

CONFERENCE PROGRAMME

Sunday, 8th

18.00-20.30 *Registration and Welcome Reception (Broletto Palace)*

Monday, 9th

9.00-9.30 *Opening Ceremony*

Chairman: Luigi FABBRIZZI

9.30-9.50 **OC-1** Anion Recognition by Triethylbenzene-Capped Polyamine Macrobicyclic Receptors: Tuning Selectivity through Small Structural Changes.
Pedro MATEUS, Rita DELGADO

9.50-10.10 **OC-2** Metallacrowns: controlling the assembly toward supramolecular constructs
Matteo TEGONI, Corrado ATZERI, Davide CAPUCCI, Maurizio REMELLI, Nicola MARCHETTI, Vincent L. PECORARO

10.10-10.30 **OC-3** Copper(II) complexes of cyclams containing nitrophenyl substituents: push-pull behaviour and scorpionate coordination of the nitro group
Massimo BOIOCCHI, Carlo CIARROCCHI, Luigi FABBRIZZI, Carlo MANGANO

10.30-10.50 **OC-4** The Importance of Metal Ion Complexation in a Biphasic Solvent Extraction System
Travis S. GRIMES, Leigh R. MARTIN

10.50-11.20 *Coffee break*

Chairman: Enrique GARCÍA-ESPAÑA

11.20-12.00 **PL-1** Supramolecular Analytical Chemistry
Eric V. ANSLYN

12.00-12.20 **OC-5** New Kinetically Inert Cu(II)-Bispidine Complex for Nuclear Medicine and Diagnosis
Jérémy BRANDEL, Véronique Hubscher-Bruder, Amandine Roux, Aline Nonat, and Loïc Charbonnière

12.20-12.40 **OC-6** The role of side chains in the fine tuning of metal binding ability of peptides.
Katalin VÁRNAGY, Gizella CSIRE, Sarolta TIMÁRI

12.40-13.00 **OC-7** Insights on the coordination mode of phenolic compounds with Al(III) ion from a combined experimental and theoretical study**.**
Emilia FURIA, Tiziana MARINO, Antonio TAGARELLI, Nino RUSSO

13.00-15.00 *Lunch break*

13.00-15.00 *Chairman: Manuel VALIENTE*

15.00-15.15 ***Honoring Prof. Roberto Portanova*** *(Marilena TOLAZZI)*

15.15-15.45 **KN-1** Actinide carboxylate complexes in solution: a long travel among experiments and theory
Andrea MELCHIOR, Plinio DI BERNARDO, Marilena TOLAZZI

15.45-16.00 ***Honoring Prof. Vincenzo Romano*** *(Roberto ZINGALES)*

16.00-16.30 **KN-2** Generation of novel Au_mSe_n clusters via laser ablation synthesis. Laser desorption ionisation time-of-flight mass spectrometry
Lubomír PROKEŠ, Eladia Maria PEÑA-MÉNDEZ, Filippo AMATO, Milan ALBERTI, Pavel KUBÁČEK, Josef HAVEL

16.30-17.00 *Coffee break*

Chairman: Tarita BIVER

17.00-17.20 **OC-8** Some Research Results Accounting Professor Vincenzo Romano Teachings
Manuel VALIENTE

17.20-17.40 **OC-9** Weak complexes of sodium cation with negatively charged ligands
Silvia BERTO, Enrico CHIAVAZZA, Pier Giuseppe DANIELE, Gabriele LANDO, Enrico PRENESTI, Silvio SAMMARTANO

17.40-18.00 **OC-10** The Interaction of Scorpiand-type Polyazacylophanes with Single and Double-Stranded Polynucleotides Reveals Sequence Selectivity
Enrique GARCIA-ESPAÑA, Mario INCLÁN, Mª. Teresa ALBELDA

18.00-19.00 **Poster Session 1** *(from P1 to P30)*

21.30 **Live band music & dance entertainment**

Tuesday, 10th

Chairman: M. Amelia SANTOS

9.10-10.00 **PL-2 Iron chelators – novel therapeutic agents.**
Robert HIDER

10.00-10.20 **OC-11** Alarming use of chelation therapy
Guido CRISPONI, Valeria M. NURCHI, Joanna I. LACHOWICZ, Miriam CRESPO-ALONSO, M. Antonietta ZORODDU, Massimiliano PEANA

10-20-10.40 **OC-12** ^{68}Ga-labelled curcuminoids complexes: potential radiotracers for imaging of cancer and Alzheimer's disease
Erika FERRARI, Mattia ASTI, Stefania CROCI, Giulia ATTI, Sara RUBAGOTTI, Monica SALADINI

10.40-11.00 **OC-13** Kinetic study of copper(II) complexes of TETA-like macrocyclic ligands
Přemysl LUBAL, Romana ŠEVČÍKOVÁ, Jakub VANĚK, Petr HERMANN, Luís M.P. LIMA, Rita DELGADO

11.00-11.30 Coffee break

Chairman: Isabel VILLAESCUSA

11.30-12.00 **KN-3** Structural, thermodynamic, and kinetic chelation studies of f-elements by hydroxamic siderophores
Michel MEYER

12.00-12.20 **OC-14** Strategies for the Development of Novel Pt Anticancer Compounds: Shifting the Paradigms from Pt(II) to Pt(IV) Complexes
Mauro RAVERA, Elisabetta GABANO, Ilaria ZANELLATO, Ilaria BONARRIGO, Domenico OSELLA

12.20-12.40 **OC-15** Synthesis and asymmetric oxidations by chiral dinuclear copper complexes
Maria Lucia PERRONE, Eliana LO PRESTI, Luca PASOTTI, Enrico MONZANI, Laura SANTAGOSTINI, Luigi CASELLA

12.40-13.00 **OC-16** Reactivity of copper-α-synuclein peptide complexes relevant to Parkinson's disease
Simone DELL'ACQUA, Cecilia ANZANI, Valentina PIROTA, Michela M. ROCCO, Daniela VALENSIN, Enrico MONZANI, Luigi CASELLA

13.00-15.00 Lunch break

Chairman: Juan Niclós GUTIERREZ

15.00-15.20 **OC-17** The effect of the metal ions on the active centre of colicin E7 nuclease
Eszter NÉMETH, Gabriella SCHILLI, Csilla KONCZ, Anikó CZENE, Milan KOŽÍŠEK, Hans E.M. CHRISTENSEN, Kyosuke NAGATA, Béla GYURCSIK

15.20-15.40 **OC-18** Interaction of Silver Salts, Nanoparticles and Complexes with Bacterial and Yeast Cell Components
Iryna GONCHAROVA, Oleksiy LYUTAKOV , Marie URBANOVÁ

15.40-16.00 **OC-19** Surfaces modified with gold nanostars for a Near-IR switchable photothermal antibacterial action
Piersandro PALLAVICINI

16.00-16.20 **OC-20** The Peculiar Metal Ion-Coordinating Properties in Solution of the Antiviral and Cytostatic Nucleotide Analogue 9-[2-(Phosphonomethoxy) ethyl]-2-amino-6-dimethylaminopurine (PME2A6DMAP)
Astrid SIGEL, Helmut SIGEL

16.20-16.40 **OC-21** Synthesis, spectral characterization, anticancer activity and theoretical studies on some Schiff bases
Tiziana PIVETTA, Claudia FATTUONI, Federica TRUDU, Elisa VALLETTA, Elisa CARTA, Roberta MELIS, Alessandra PANI

16.40-17.00 Coffee break

Chairman: Plinio DE BERNARDO

17.00-17.20 **OC-22** *C,N*-chelated Organotin(IV) Pseudohalides: Synthesis, Characterization and Reactivity Studies
Petr ŠVEC, Zdeňka PADĚLKOVÁ, Aleš RŮŽIČKA

17.20-17.40 **OC-23** Structural Differences of Lithium Complexes Containing Hybrid Amino/Guanidinate Ligands
Jana NEVORALOVA, Zdenka PADELKOVA, Ales RUZICKA

17.40-18.00 **OC-24** Monomer or aggregate? Solution chemistry applications to today's problems
Tarita BIVER

18.00-19.00 **Poster Session 2** *(from P31 to P65)*

19.00-20.00 **GTC Meeting**

Wednesday, 11th

Chairman: Antonio BIANCHI

9.10-10.00 **PL-3** Stability Constants: Determination and Uses
Peter GANS

10.00-10.10 **OC-25** 5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one molecule as an intriguing tool in coordination and enzymatic studies
Joanna I. LACHOWICZ, Valeria M. NURCHI, Guadalupe J. PELAEZ, Leonardo TOSO, Miriam CRESPO-ALONSO, Peter GANS, M. Amelia SANTOS

10.20-10.40 **OC-26** Comprehensive modelling capability for aqueous solution thermodynamics: progress
Darren ROWLAND, Peter MAY

10.40-11.00 **OC-27** Naphthalenediimmides as Selective "Naked eye" Chemosensor for Copper(II) in Aqueous Solution
Filippo DORIA, Valeria AMENDOLA, Vincenzo GRANDE, Greta BERGAMASCHI, Mauro FRECCERO

11.00-11.30 *Coffee break*

Chairman: Guido CRISPONI

11.30-12.00 **KN-4** Is chemometric easy? I think so. For sure it is cheap
Riccardo LEARDI

12.00-12.20 **OC-28** Analysis of Phosphorus and Sulfur by QQQ-ICP-MS
Glenn WOODS, Peter PLANITZ, Sebastian SANNAC

12.20-12.40 **OC-29** Copper(II) Binding to (Tacrine-S-allyl)- and (Tacrine-S-propargyl)-cysteine as Potential Anti-Neurodegenerative Hybrid Drugs
Catarina QUINTANOVA, Rangappa S. KERI, Sílvia CHAVES, M. Amélia SANTOS

12.40-13.00 **OC-30** Cr(VI) removal by using exhausted coffee waste: from synthetic solutions to industrial effluents
Chang LIU, Núria FIOL, Marc BARTROLÍ, Jordi POCH, Isabel VILLAESCUSA

13.00-15.00 *Lunch break*

15.00-18.30 **Excursion**

20.30 **Social Dinner**

Thursday, 12th

Chairman: Matteo TEGONI

9.30-10.30 **PL-4** Metal Ions and Neuronal Peptides: Binding and Redox Reactivity
Luigi CASELLA

10.30-10.40 ***Pulidori Award – M. Remelli***

10.40-11.00 **OC-31 (Pulidori Award)**
Slawomir POTOCKI

11.00-11.10 ***Bertero Awards – R. Biesuz***

11.10-11.20 **PP1 (Bertero Award)** Phytate in aqueous solution: unveiling its microprotonation equilibria and coordination ability under physiological conditions
Nicolás VEIGA, Julia TORRES, Israel MACHO, Kerman GÓMEZ, Gabriel GONZÁLEZ, Carlos KREMER

11.20-11.30 **PP2 (Bertero Award)** Binding studies of a dicopper(II) cryptate with dicarboxylate anions
Catarina V. ESTEVES, Pedro MATEUS, Rita DELGADO

11.30-11.40 **PP3 (Bertero Award)** Biomonitoring of toxic element exposure by ICP-AES and ICP-MS analysis
Miriam CRESPO-ALONSO, Valeria M. NURCHI, Joanna I. LACHOWICZ, M. Guadalupe JARAQUEMADA-PELÁEZ, Gavino SANNA

11.40-12.00 *Coffee break*

Chairman: Maria PESAVENTO

11.30-12.00 **KN-5** Hydroxamates as useful tools for the construction of artificial siderophores and metallacrowns
Agnieszka SZEBESCZYK, Jenny BESSERGLICK, Evgenia OLSHVANG, Abraham SHANZER, Malgorzata OLEDZKA, Irina Golenya, Igor O. FRITSKY, and Elzbieta GUMIENNA-KONTECKA

12.30-13.00 Closing remarks & presentation of ISMEC 2015

PLENARY LECTURES

Supramolecular Analytical Chemistry

Eric V. ANSLYN

Department of Chemistry, The University of Texas at Austin, Anslyn@austin.utexas.edu

The use of synthetic and designed receptors for the analysis of complex analytes in real-life settings will be presented. Analytes in beverages, chiral mixtures, and blood/saliva have been targeted by mimicking the mammalian senses of taste and smell. The receptors derive from a combination of rational chemical design and modeling, with combinatorial synthesis techniques. Optical signaling derives either from indicator-displacement, or indicator-uptake, assays. It will be shown that a union of designed receptors targeted to a class of analytes, with combinatorial methods, gives fingerprints that differentiate between the individual members of the class. The strategy is to use a core-binding element that imparts a bias to each and every member of the library, ensuring affinity of the library members for the class of analytes being targeted. The design of this core derives from standard molecular recognition principles: preorganization, complementary, pair-wise interactions between receptor and analyte, and desolvation. Combinatorial techniques impart the differential behavior and cross-reactivity desired in an array sensing application. The fingerprints of the solutions are created using artificial neural networks, principle component analysis, and/or linear discriminate analysis. The technique represents a marriage of supramolecular chemistry and pattern recognition protocols.

Iron chelators – novel therapeutic agents

Robert HIDER

Institute of Pharmaceutical Science, King's College London, UK

robert.hider@kcl.ac.uk

Over the past 30 years iron chelators have been utilised for the selective removal of iron in patients that become iron overloaded due to regular blood transfusion. They are essential for the long term treatment of thalassaemia major and some forms of sickle cell anaemia. An important objective has been to identify orally active, non-toxic chelators. This presentation will discuss the underlying chemistry which has led to the identification of such compounds.

More recently the progression of various forms of neurodegeneration has been linked with elevated levels of brain iron. Currently there are ongoing clinical trials which are based on the use of iron chelators for the treatment of Parkinson's disease and Friedreich's ataxia. Again the presentation will discuss some of the chemical problems that need to be addressed for the successful treatment of these two neurodegenerative diseases.

Stability Constants: Determination and Uses

Peter GANS

Protonic Software, Leeds. U.K.
peter.gans@hyperquad.co.uk

Hyperquad, the current computer program for treating potentiometric data is the culmination of a long series of developments starting with mainframe programs written in FORTRAN and distributed as source code [1-3] and ending with Windows applications (Http://www.hyperquad.co.uk), distributed on the web. Programs for treating spectrophotometric [4], NMR[5] and calorimetric [6] data have also been developed.

The evolution of these programs for the determination of stability constants from experimental data has involved solving problems of both chemical and mathematical complexity. Within the structure of a non-linear least-squares refinement procedure the following questions have been addressed.

- How to obtain initial estimates of the stability constants of a chemical model
- Which parameters to refine
- How to set up the least-squares system
- Why a refinement may diverge
- How to protect refinements against divergence
- Why refinements can fail to converge
- How to select a chemical model

The presence of systematic errors in the data must be considered separately.

Other topics that will be discussed include: the concept of binding capacity of ligands, micro- and macro- constants, medium and ionic strength effects.

References:

[1] Sabatini, A; Vacca, A: Gans, P., MINIQUAD - a general computer program for the computation of formation constants from potentiometric data", T*alanta*, 1974, **21**, 53-77.

[2] Gans, P.; Sabatini, A; Vacca., A, SUPERQUAD - a new computer program for determination of stability constants of complexes by potentiometric titration, *Inorg. Chim. Acta,* 1983, **79**, 219.

[3] Gans, P.; Sabatini, A; Vacca, A., "Investigation of Equilibria in Solution. "Determination of Equilibrium Constants with the HYPERQUAD Suite of Programs, *Talanta*, 1996, **43**, 1739-1753.

[4] Gans, P.; Sabatini, A; Vacca, A., Determination of Equilibrium Constants from Spectrophotometric Data Obtained from Solutions of Known pH: the Program pHAB, *Annali di Chimica*, 1999, **89**, 45-49.

[5] Frassineti, C.; Alderighi, L.; Gans, P.; Sabatini, A.; Vacca, A.; Ghelli, S., Determination of protonation constants of some fluorinated polyamines by means of ^{13}C NMR data

processed by the new computer program hypnmr2000. Protonation sequence in polyamines", *Anal. Bioanal. Chem.*, 2003, **376**, 1041-1052.

[6] Gans, P.; Sabatini, A; Vacca, A., J., Simultaneous calculation of equilibrium constants and standard formation enthalpies from calorimetric data for systems with multiple equilibria in solution, *J. Solution Chem.*, 2008, **37**, 467-474.

Metal Ions and Neuronal Peptides: Binding and Redox Reactivity

Luigi CASELLA

Dipartimento di Chimica, Università di Pavia, Pavia, Italy
luigi.casella@unipv.it

The interplay between metal ions, oxidative stress and neurodegeneration is well established and documented for important pathologies such as Alzheimer's and Parkinson's diseases.[1] This finding motivated our main research interest in the last years, which focused on the consequences of the interaction between redox active metal ions and several neuronal peptides. Given our previous experience on copper and heme proteins involved in oxidative processes, a straightforward extension was to consider the significance of the same type of reactivity by the complexes of these metals with neuronal peptides. We have thus undertaken a systematic investigation of copper(II) and ferric heme (hemin) complexes with amyloid-β (Aβ) peptides, the R1 fragment of tau protein (R1τ), and α-synuclein (αS).

Free heme is highly toxic, because of its potential oxidizing properties and in particular for its ability to induce oxidative stress.[2] For these reasons, multiple control mechanisms maintain free heme concentration tightly controlled at low levels. Toxic heme effects are normally associated to pathological states resulting from severe hemolysis and vascular disorders, but several findings indicate that heme toxicity may have relevance also for neurodegenerative diseases.[3] Hemin has been recently described as a potential target for Aβ peptides,[4] and the resulting complexes appear to be more reactive towards hydrogen peroxide than free hemin.[5] The binding and reactivity of complexes of hemin with Aβ have been the subject of several other studies,[6] but the main features and especially the biological significance of this interaction remained poorly defined. We have recently demonstrated that hemin coordinates two Aβ16 peptides to form [hemin$(Aβ16)_2$], in which iron(III) is low-spin and six-coordinated, and this is in equilibrium with a five-coordinated high-spin [hemin(Aβ16)] species, the relative amount of which depends on the peptide concentration and on temperature.[7] As expected, hemin-Aβ complexes activate hydrogen peroxide, but we have found that the peroxidase activity towards exogenous substrates is extremely low and devoid of any biological significance. However, the reactivity towards the endogenous peptide is important, as upon reaction with H_2O_2 the hemin-Aβ16 complex produces dimerization of Aβ through the formation of a dityrosine cross-link at Tyr10. In addition, in the presence of nitrite, the same residue undergoes nitration.[7] Both modifications strongly enhance Aβ aggregation and plaque formation,[8] showing that heme binding to Aβ can indeed be a factor contributing to neuroinflammation and Aβ aggregation. Similar studies are in progress with the octadecapeptide R1τ and the 1-15 N-terminal fragment of αS, for which heme binding has never been investigated. Unlike Aβ, hemin only forms complexes in 1:1 ratio with both these peptides, and the resulting complexes exhibit weak peroxidase-like activity.

The association between copper and neuronal peptides has been extensively studied, starting from the observation of its relevance in prion-related diseases.[1,9] It is often assumed that binding of copper(II) ions by the peptides induces oxidative damage and

toxicity, and in the case of Aβ, even pseudoenzymatic monooxygenase and oxidase activities.[10] These ideas contrast other evidences showing that Cu-Aβ complexes are nontoxic and actually prevent aggregation. We have definitively shown that Cu-Aβ complexes bear neither monooxygenase nor superoxide dismutase activities, and that earlier claims were affected by experimental artefacts.[11] The same lack of significant oxidative activity characterizes copper complexes with R1τ and membrane-bound αS peptides.

References:

[1] (a) Brown, D. A., Brain proteins that mind metals: A neurodegenerative perspective. *Dalton Trans.* **2009**, 4069-4076; (b) Faller, P.; Hureau, C.; Berthomieu, O., Role of metal ions in the self-assembly of the Alzheimer's disease amyloid-β peptide. *Inorg. Chem.* **2013**, 52, 12193-12206; (c) Greenough, M. A.; Camakaris, J.; Bush, A. I., Metal dyshomeostasis and oxidative stress in Alzheimer's disease. *Neuerochem. Int.* **2013**, 62, 540-555.

[2] Kumar, S.; Bandyopadhyay, U., Free heme toxicity and its detoxification systems in human. *Toxicol. Lett.* **2005**, 157, 175-188.

[3] Kruer M. C., The neuropathology of neurodegeneration with brain iron accumulation. *Int. Rev. Neurobiol.* **2013**, 110, 165-194.

[4] Atamna, H.; Frey, W. H. II, A role for heme in Alzheimer's disease: Heme binds amyloid β and has altered metabolism. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101*, 11153-11158.

[5] Atamna, H.; Boyle, K., Amyloid-β peptide binds heme to form a peroxidase: Relationship to the cytopathologies of Alzheimer's disease. *Proc. Natl. Acad. Sci. U.S.A.* **2006,** *103*, 3381-3386.

[6] Pramanik, D.; Ghosh, C.; Mukherjee, S.; Dey, S. G., Interaction of amyloid β peptides with redox active heme cofactor: Relevance to Alzheimer's disease. *Coord. Chem. Rev.* **2013**, 257, 81-92.

[7] Thiabaud, G.; Pizzocaro, S.; Garcia-Serres, R.; Latour, J.-M.; Monzani, E.; Casella, L., Heme binding induces dimerization and nitration of truncated β-amyloid peptide Aβ16 under oxidative stress. *Angew. Chem. Int. Ed.* **2013**, 52, 8041-8044.

[8] Kummer, M. P.; Hermes, M.; Delakarte, A.; Hammerschmidt, T.; Kumar, S.; Tenwel, D.; Walter, J.; Pape, H.-C.; König, S.; Roeber, S.; Jessen, F.; Klockgether, T.; Korte, M.; Heneka, M. T., Nitration of tyrosine 10 critically enhances amyloid aggregation and plaque formation. *Neuron* **2011**, *71*, 833-844.

[9] Kepp, K. P., Bioinorganic chemistry of Alzheimer's disease. *Chem. Rev.* **2012**, 112, 5193-5239.

[10] da Silva, G. F. Z.; Ming, L.-J., Metallo-ROS in Alzheimer's disease: Oxidation of neurotransmitters by Cu-β-amyloid and neuropathology of the disease. *Angew. Chem. Int. Ed.* **2007**, 3337-.

[11] Ciregna, D; Monzani, E.; Thiabaud, G.; Pizzocaro, S.; Casella, L., Copper-β-amyloid exhibits neither monooxygenase nor superoxide dismutase activities. *Chem. Commun.* **2013**, 49, 4027-4029.

KEY NOTES

Actinide carboxylate complexes in solution: a long travel among experiments and theory

Andrea MELCHIOR,[a] Plinio DI BERNARDO,[b] Marilena TOLAZZI[a]

[a]Università di Udine, Dipartimento di Chimica Fisica e Ambiente, via del Cotonificio 108, 33100, Udine, Italy; [b]Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, 35131 Padova, Italy
andrea.melchior@uniud.it

The chemistry of the early actinide elements is of great importance from both fundamental and practical points of view[1]. Practical considerations arise from the use of actinides in nuclear energy and nuclear materials, where important issues as long-term storage of nuclear waste, environmental care, and actinide separation/recovery need to be addressed. Experimental and theoretical studies aimed at defining the stability, speciation and structure of actinide complexes in solution are fundamental, both to develop recovery systems and predict their behavior in the environment.

In the past century, pioneering investigations on the thermodynamics of complex formation between actinides and organic ligands have been carried out by several scientists as Ahrland [2] and Portanova [3-5]. In particular, Roberto spent a significant part of his career to study actinide hydrolysis and complex formation with mono- and polycarboxylic acids and neutral ligands (see for example refs. [3-6]).

Among the early actinide elements, uranium is certainly the most studied from a chemical point of view. Normally, U mobility in the environment is redox-controlled, with U(VI) species being highly soluble and mobile while U(IV) tends to form insoluble phases. U(VI), which is normally present in solution as uranyl cation (UO_2^{2+}), shows a marked tendency to form strong complexes with oxygen donor ligands, inorganic (e.g., carbonate, sulfate, phosphate) and organic (e.g., acetate, oxalate and phenols), commonly present in soil, especially in organic-rich deposits or in nuclear waste streams.

Among the carboxylate anions acetate received a special attention, since it can be considered a simplified general model for complex formation with organic matter and also because experimental studies demonstrated that acetate complexation may enhance the mobility of a wide range of metals in aqueous fluids.

The interaction of U(VI) with acetate in solution has been intensively investigated using both experimental [1-8] (and refs. therein) and theoretical [9-11] tools. It is generally accepted that in water U(VI) forms with acetate three successive mononuclear complexes which are mostly entropically-stabilized and enthalpically unfavored [7]. The complexation of uranyl ion with acetate has been predominantly studied in water, but also the complex formation in non-aqueous solvents has been investigated [6,8]. A recent work on UO_2^{2+}-acetate complexes in dimethylsulfoxide (DMSO) clearly showed the effect of the medium both on the thermodynamic parameters and structure of the species formed[8]. The main structural feature influenced by the medium is the binding mode of acetate, which can be either bi- or mono-dentate. A combination of DFT calculations and vibrational spectroscopy showed that in DMSO acetate behaves always as bidentate [8], differently from what previously found in

water by EXAFS spectroscopy [7] where the 1:3 complex was showing both types of coordination. Also, several theoretical and experimental studies in gas phase (absence of solvational effects) demonstrated that both types of acetate coordination in the 1:3 complex can exist, because of their small gap in energy [9-11]. On the other hand, the speciation and structure of uranyl-acetate complexes in water has been revised [12] on the basis of EXAFS and IR experiments and it has been concluded that the ligand is bidentate in all species. To get a clearer, and possibly definitive picture of the complex structure in water, Car Parrinello molecular dynamics simulations have been recently employed for the first time to study the solvated $[UO_2(CH_3COO)_3]^-$ complex.

References:

[1] Morss, L. R.; Edelstein, N. M.; Fuger, J. The Chemistry of the Actinide and Transactinide Elements; Springer Netherlands: **2011**

[2] Ahrland, S. , On the Complex Chemistry of the Uranyl Ion. IV. The Complexity of Uranyl Acetate. *Acta Chem. Scand.* **1951**, 5, 199-219

[3] Cassol, A; Magon, L.; Tomat, G.; Portanova, R., Relative stabilities of complexes of MO_2^{2+} (M = U, Np, and Pu) with monocarboxylate anions *Inorg. Chim. Acta.* **1969**, 3, 639–643

[4] Cassol, A.; Di Bernardo, P.; Portanova, R.; Magon, L. Interaction of MO_2^{2+} (M = U, Np, and Pu) with Dicarboxylate Ligands Containing Other Donor Atoms *Inorg. Chim. Acta*, **1973**, 7, 353-358

[5] Portanova, R.; Di Bernardo, P.; Cassol, A.; Tondello, E.; Magon, L. Thermodynamic Properties of Actinide Complexes. Part 1. Uranyl(VI) Monocarboxylate Complexes. *Inorg. Chim. Acta* **1974**, 8, 233-240

[6] Cassol, A.; Di Bernardo, P.; Portanova, R.;Tolazzi, M.;Tomat, G.; Zanonato, P.L. Complex Formation Reactions of Uranyl(VI) with Neutral N-Donors in Dimethyl-Sulfoxide - Influence of Small Amounts of Water Inorg. Chem. **1990**, 29(5), 1079-1084

[7] Jiang, J.; Rao, L. F.; Di Bernardo, P.; Zanonato, P.; Bismondo, A., Complexation of Uranium(VI) with acetate at variable temperatures. *J. Chem. Soc. Dalton Trans.* **2002**, (8), 1832-1838

[8] Di Bernardo, P.; Zanonato, P. L.; Benetollo, F.; Melchior, A.; Tolazzi, M.; Rao, L. F. Energetics and Structure of Uranium(VI)-Acetate Complexes in Dimethyl Sulfoxide. *Inorg. Chem.* **2012**, 51 (16), 9045-9055

[9] Groenewold, G. S.; de Jong, W. A.; Oomens, J.; Van Stipdonk, M. J., Variable Denticity in Carboxylate Binding to the Uranyl Coordination Complexes. *J. Am. Soc. Mass. Spectr.* **2010**, 21 (5), 719-727

[10] Vazquez, J.; Bo, C.; Poblet, J. M.; de Pablo, J.; Bruno, J., DFT studies of uranyl acetate, carbonate, and malonate, complexes in solution. *Inorg. Chem.*, **2003**, 42 (19), 6136-6141.

[11] De Jong, W. A.; Apra, E.; Windus, T. L.; Nichols, J. A.; Harrison, R. J.; Gutowski, K. E.; Dixon, D. A., Complexation of the carbonate, nitrate, and acetate anions with the uranyl dication: Density functional studies with relativistic effective core potentials., J. Phys. Chem. A, **2005**, 109 (50), 11568-11577

[12] Lucks, C.; Rossberg, A.; Tsushima, S.; Foerstendorf, H.; Scheinost, A. C.; Bernhard, G., Aqueous Uranium(VI) Complexes with Acetic and Succinic Acid: Speciation and Structure Revisited. *Inorg. Chem.* **2012**, 51 (22), 12288-12300

Generation of novel Au_mSe_n clusters via laser ablation synthesis. Laser desorption ionisation time-of-flight mass spectrometry

Lubomír PROKEŠ, [a,b,c] Eladia Maria PEÑA-MÉNDEZ,[d] Filippo AMATO, [a] Milan ALBERTI,[a,b,c] Pavel KUBÁČEK,[a] Josef HAVEL, [a,b,c]

[a] Department of Chemistry, Faculty of Science, Masaryk University, Kampus Bohunice, Kamenice 5/A14, 625 00 Brno, Czech Republic [b] Department of Physical Electronics, Faculty of Science, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic [c] CEPLANT, R&D Center for Low-cost Plasma and Nanotechnology Surface Modifications, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic, [d]Department of Chemistry, Faculty of Science, University of La Laguna, Campus de Anchieta, 38071 La Laguna, Tenerife, Spain; 389626@mail.muni.cz

Several gold selenium complexes are known (e.g., $[Au_2(Se_2)(Se_3)]^{2-}$, $[Au_2(Se_2)(Se_4)]^{2-}$ and $[Au_2Se_2(Se_4)_2]^{2-}$). Minerals such as fischesserite (Ag_3AuSe_2), kurilite ($(Au,Ag)_2(Te,Se,S)_2$) and petrovskite ((AuAg)(S,Se)) are found in nature.

Laser desorption ionisation time-of-flight mass spectrometry (LDI TOF MS) is powerful technique to generate and study clusters formed during laser ablation of various materials leading to metal chalcogenides [1] or gold carbides [2], for example.

The aim of this work is to study the generation of Au_mSe_n clusters *via* laser ablation synthesis (LAS) using mixtures of GNPs (or auric acid) with selenium in various molar ratios as precursors.

We have found that GNPs are chemisorbed on selenium surface leading to the formation of a kind of nano-composite as confirmed by scanning electron microscope (SEM) analysis. The LAS from various precursors and nano-composites leads to the generation of several series of Au_mSe_n clusters which stoichiometry was determined. Example of mass spectra showing some of the detected Au_mSe_n clusters is given in Fig. 1. Over 30 new gold selenide clusters were identified: $AuSe_2^-$, $AuSe_3^-$, $AuSe_4^-$, $AuSe_5^-$, $AuSe_6^-$, $AuSe_7^-$, $AuSe_8^-$, $AuSe_9^-$, $AuSe_{10}^-$, Au_2Se^-, $Au_2Se_2^-$, $Au_2Se_3^-$, $Au_2Se_4^-$, $Au_2Se_5^-$, $Au_2Se_6^-$, $Au_2Se_7^-$, $Au_2Se_8^-$, Au_3Se^-, $Au_3Se_2^-$, $Au_3Se_3^-$, $Au_3Se_4^-$, $Au_3Se_5^-$, Au_4Se^-, $Au_4Se_2^-$, $Au_4Se_3^-$, etc. Understanding the nature and chemistry of such clusters can inspire the development of novel routes for the synthesis of new compounds. Example of possible stabilization strategy has been reported for the $[NaAu_{12}Se_8]^{3-}$ complex [3].

Computed structures of selected gold selenides generated in this work via LAS are given in Fig. 2.

Concluding, (*i*) LAS is advantageous technique to generate novel un-usual gold selenides and (*ii*) the stoichiometry of Au_mSe_n clusters generated might inspire synthesis of new Au-Se materials with unique properties.

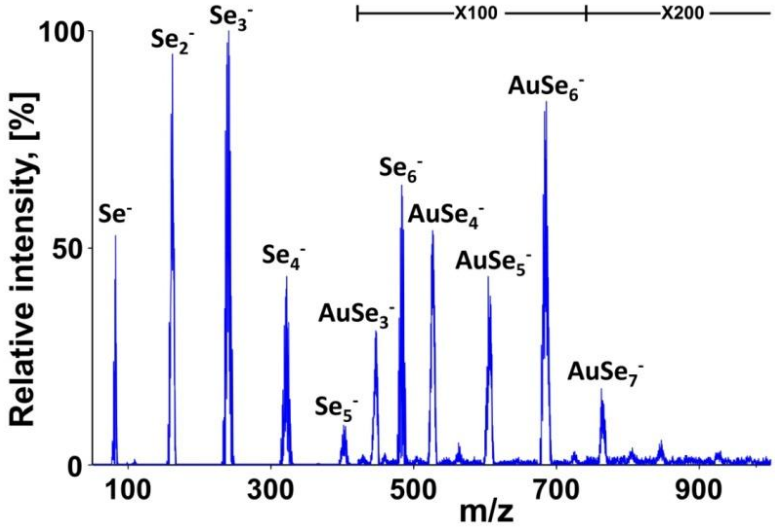


Fig. 1: Example of mass spectrum concerning LAS of clusters via laser ablation of GNPs-Se mixture in molar ratio 1:10.

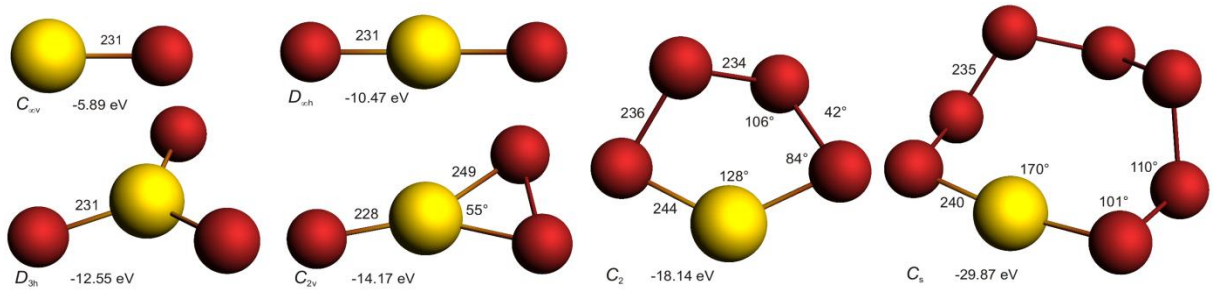


Fig. 2: Examples of anionic clusters ($AuSe^-$, $AuSe_2^-$, $AuSe_3^-$, $AuSe_4^-$, $AuSe_7^-$) as computed via DFT optimization using ADF® molecular modeling suite (symmetry, bonding energy, bond lengths and angles are given).

Acknowledgements
Support from GA of Czech Republic (Project No. 13-05082-S) and CEPLANT, "R&D center for low-cost plasma and nanotechnology surface modifications" CZ.1.05/2.1.00/03.0086 funding by European Regional Development Fund is acknowledged.

References:

[1] Švihlová, K.; Prokeš, L.; Skácelová, D.; Peña-Méndez, E. M.; Havel, J.; Laser ablation synthesis of new gold tellurides using tellurium and nanogold as precursors. Laser desorption ionisation time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* **2013**, 27, 1600-1606.

[2] Havel, J.; Peña-Méndez, E. M.; Amato, F.; Panyala, N. R.; Buršíková, V.; Laser ablation synthesis of new gold carbides. From gold-diamond nano-composite as a precursor to gold-doped diamonds. Time-of-flight mass spectrometric study. *Rapid Commun. Mass Spectrom.* **2014**, 28(3), 297–304.

[3] Huang, S. P.; Kanatzidis, M. G.; Synthesis and structure of the cluster $[NaAu_{12}Se_8]^{3-}$: an inorganic cryptand complex. *Angew. Chem. Int. Ed.***1992**, 31, 787-789.

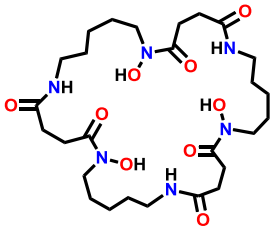
Structural, thermodynamic, and kinetic chelation studies of *f*-elements by hydroxamic siderophores

Michel MEYER [a)]

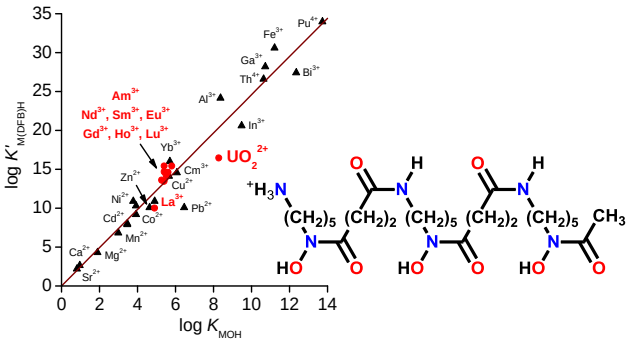
[a)] *Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB, UMR CNRS 6302), 9 avenue Alain Savary, BP 47870, 21078 DIJON Cedex, France*
michel.meyer@u-bourgogne.fr

Siderophores are ubiquitous, high-affinity iron(III) chelators excreted by virtually all bacteria and yeasts under iron-stress conditions. Their primary biological role is to supply the microorganisms 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.

Besides catecholates and (hydroxy)carboxylates, hydroxamates are common bidentate chelating groups found in many siderophores, some emblematic examples being desferrioxamines, desferrichromes, desferricoprogens, rhodotorulic acid… As all of these binders incorporate negatively-charged oxygen donor atoms, it is nowadays well established that their binding affinity correlates well with the Lewis acidity of the metal cation (see the figure below). Hence, they are expected to form even stronger complexes with tetravalent actinides than with iron(III). While desferrioxamines B and E are indeed able to dissolve $Pu(OH)_4$ [1], both ligands are moreover also able to efficiently mediate plutonium(IV) uptake by several bacterial strains [2].



Desferrioxamine E (H_3DFE)



Desferrioxamine B (H_4DFB^+)

As the concentration of desferrioxamines in soils is typically in the μg/kg range, it becomes obvious that they might significantly increase the solubility, migration rate, and bioavailability of highly-toxic actinides in case of environmental contamination [3]. It is therefore of outmost importance to gain a deeper understanding of their f-element coordination chemistry, in relation to the management and remediation of contaminated fields, or disposal of nuclear wastes in geological repositories. However, predicting and modeling the metal speciation in waters and soils requires an accurate knowledge of the thermodynamic

and kinetic parameters related to their complex formation and dissociation equilibria. Because such data are scarce and often unreliable in the case of the transuranium cations [4], considerable research efforts are still required.

By combining classical potentiometric and UV-vis spectrophotometric titration techniques with capillary zone electrophoresis, the speciation of desferrioxamine B in the presence of trivalent americium and lanthanides, taken as cold surrogates, and of hexavalent uranium (UO_2^{2+}) could be successfully unraveled. Relying on X-ray absorption and RAMAN spectroscopic data, structures for the various uranium complexes prevailing in solution will be presented. Finally, the proton-assisted step-by-step dissociation mechanism of the $[UO_2(DFB)H_2]^+$ complex, as established by stopped-flow spectrophotometry, will be discussed.

References:

[1] (a) Neu, M. P.; Matonic, J. H.; Ruggiero, C. E.; Scott, B. L., *Angew. Chem., Int. Ed.* **2000**, 39, 1442-1444. (b) Ruggiero, C. E.; Matonic, J. H.; Reilly, S. D.; Neu, M. P., *Inorg. Chem.* **2002**, 41, 3593-3595.

[2] John, S. G.; Ruggiero, C. E.; Hersman, L. E.; Tung, C. S.; Neu, M. P., *Environ. Sci. Technol.* **2001**, 35, 2942-2948.

[3] Neu, M. P.; Icopini, G. A.; Boukhalfa, H., *Radiochim. Acta* **2005**, 93, 705-714.

[4] Meyer, M.; Burgat, R.; Faure, S.; Batifol, B.; Hubinois, J.-C.; Chollet, H.; Guilard, R., *C. R. Chimie* **2007**, 10, 929-947.

Is chemometrics easy? I think so. For sure it is cheap

Riccardo LEARDI

Department of Pharmacy, University of Genoa; riclea@difar.unige.it

At present the analytical techniques allow to obtain a huge amount of data per sample in a relatively short time. It is therefore clear that, while since a few decades ago the main focus of the activity of the analytical chemist was in getting the experimental data, nowadays the main challenge is to correctly interpret them and to extract the maximum amount of information. This should have changed the attitude of the analytical chemist in what concerns the data analysis, with a greater emphasis on the use of multivariate data analysis tools.

Unfortunately, for the great majority of the researchers the univariate analysis is still by far the most used (not to say the only) approach. By looking at the data one variable at a time it is not possible to have a global overview of the data and to take into account the relationships among the variables.

So, why is chemometrics not as widespread as it should be?

In my opinion, the two major obstacles are the common idea that chemometrics is too difficult to be used by a non specialist and the need of a specific software.

About the first point, it is true that some methods are based on non trivial algorithms, but it has to be clear that in order to properly use them only a general, intuitive knowledge of what these algorithms do is required, in exactly the same way you do not need to know all the engineering details of a mobile phone to use it! What people must put their major effort into is instead a change of attitude, understanding and accepting the added value of a multivariate analysis compared with the standard univariate analyis.

About the second point, it is true that some commercial chemometric software is quite expensive, but nowadays also some free and open source tools can be used. During the present talk an R-based chemometric software developed by the Group of Chemometrics of the Division of Analytical Chemistry of the Italian Chemometric Society will be shown. This software is totally free and can be downloaded from the site gruppochemiometria.it. Though developed under R, it is menu-driven and does not require any knowledge of R. It will be shown how fast and easy performing a Principal Component Analysis is (it will be applied on environmental data).

The advantages of the multivariate analysis compared with the standard univariate approach will be evident, after which there will be no excuses not to apply chemometrics!

Hydroxamates as useful tools for the construction of artificial siderophores and metallacrowns

Agnieszka SZEBESCZYK,[a] Jenny BESSERGLICK,[b] Evgenia OLSHVANG,[b] Abraham SHANZER,[b] Malgorzata OLEDZKA,[a] Irina Golenya,[c] Igor O. Fritsky,[c] and Elzbieta GUMIENNA-KONTECKA[a]

[a] Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie, 50-383 Wroclaw, Poland
[b] Weizmann Institute of Science, 234 Herzl Street, 76100 Rehovot, Israel
[c] Department of Chemistry, National Taras Shevchenko University, 01601Kiev, Ukraine
presenting author e-mail: elzbieta.gumienna-kontecka@chem.uni.wroc.pl

Hydroxamic acids are multi donor ligands which biological activity stems from complexing capacity towards various metal ions. Diversity of coordination modes of these functions with metals makes them very promising ligands in coordination and bioinorganic chemistry.

Main directions in hydroxamic acids research undertaken by us in recent years include:

• studies of biomimetic analogues of siderophores as structural probes for microbial iron uptake processes - the research especially important at the time of increasing number of severe and often lethal infections caused by multiresistant bacterial and fungal strains [1];

• use of hydroxamate ligands for preparation of high nuclearity discrete coordination compounds, coordination polymers and metallacrowns as promising objects for molecular magnetism, functional fluorescent materials and probes, and metal complex catalysis [2-3].

The key information obtained in our recent studies will be presented in the view of their applications for various biological and inorganic purposes.

Acknowledgements:
The authors gratefully acknowledge the funding from the Polish National Science Centre (NCN, UMO-2011/03/B/ST5/01057) and EU FP7 (International Research Staff Exchange Scheme, FP7-PEOPLE-2013-IRSES, PIRSES-GA-2013-611488).

References:

[1] Shanzer, A.; Felder, C.E.; Barda, Y.; Natural and biomimetic hydroxamic acid based siderophores. In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Rapport, Z.; Liebman, J. F., Eds. A John Wiley & Sons, Chichester, **2009**, Vol. 2, pp 751-815.

[2] Golenya, I.A.; Gumienna-Kontecka, E.; Boyko, A.N.; Haukka, M.; Fritsky, I.O., Collapsed Cu(II)-Hydroxamate Metallacrowns, *Inorg. Chemistry* **2012**, 51, 6221-6227.

[3] Golenya, I.A.; Gumienna-Kontecka, E.; Boyko, A.N.; Haukka, M.; Fritsky, I.O., Encapsulation of a guest sodium cation by iron(III) tris-(hydroxamate)s, *Dalton Trans.* **2012**, 41, 9427-9430.

ORAL COMMUNICATIONS

Anion Recognition by Triethylbenzene-Capped Polyamine Macrobicyclic Receptors: Tuning Selectivity through Small Structural Changes.

Pedro MATEUS, [a] **Rita DELGADO** [b]

[a] *Instituto de Tecnologia Química e Biológica, UNL, Av. da República, 2780-157, Oeiras, Portugal; pmateus@itqb.unl.pt*

Polyamine macrobicyclic compounds have been used since the beginning of the Supramolecular Chemistry field and are among the most successful anion receptors in aqueous medium.[1-3] The macrobicyclic architecture and the properties of the amine functionality greatly contributes to the success of this family of compounds. Macrobicycles have well preorganized tridimensional cavities which are relatively easy to modify while amine groups can be protonated to provide the necessary positive charge to interact with anions, they can act both as hydrogen bond donors and acceptors and also help imparting water solubility.

Aiming to contribute to the field of anion recognition, we have explored triethylbenzene-capped polyamine macrobicyclic architectures as receptors for inorganic anions.[4-6]

In the present work we describe how small structural changes affect the selectivity pattern of these receptors.

References:

[1] Mateus, P.; Bernier, N.; Delgado, R.; Recognition of Anions by Polyammonium Macrocyclic and Cryptand Receptors. Influence of the Dimensionality on the Binding Behavior, *Coord. Chem. Rev.* **2010**, 254, 1726–1747.

[2] McKee, V.; Nelson, J.; Town, R. M.; Caged Oxoanions, *Chem. Soc. Rev.* **2003**, 32, 309–325.

[3] Kang, S. O.; Llinares, J. M.; Day, V. W.; Bowman-James, K.; Cryptand-like Anion Receptors, *Chem. Soc. Rev.* **2010**, 39, 3980–4003.

[4] Mateus, P.; Delgado, R.; Brandão, P.; Carvalho, S.; Félix, V.; Selective Recognition of Tetrahedral Dianions by a Hexaaza Cryptand Receptor, *Org. Biomol. Chem.* **2009**, 7, 4661–4637.

[5] Mateus, P.; Delgado, R.; Brandão, P.; Félix, V.; Polyaza Cryptand Receptor Selective for Dihydrogen Phosphate, *J. Org. Chem.* **2009**, 74, 8638–8646.

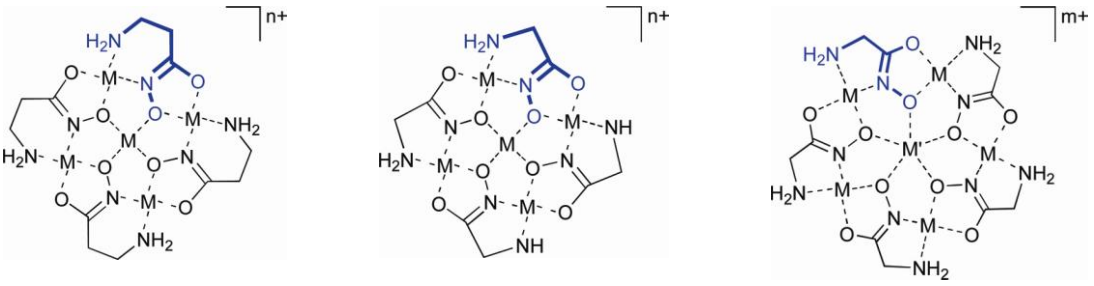
[6] Mateus, P.; Delgado, R.; unpublished work.

Metallacrowns: controlling the assembly toward supramolecular constructs

Matteo TEGONI, [a] Corrado ATZERI, [a] Davide CAPUCCI,[a] Maurizio REMELLI, [b] Nicola MARCHETTI,[b] Vincent L. PECORARO,[c]

[a] Department of Chemistry, University of Parma, Parco Area delle Scienze, 17, 43124 Parma, Italy [b] Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy; [c] Department of Chemistry, University of Michigan, Ann Arbor (MI) USA; matteo.tegoni@unipr.it

Metallacrowns (MC) are the inorganic analogues of crown ethers. These supramolecular aggregates have the capacity to self-assemble in a predictable way, giving rise to metallamacrocycles in which a large number of metal ions are confined into a small molecular scaffold [1]. Moreover, their planar arrangement forces the metal ions of the framework to possess unsaturated coordination positions which can be occupied by ancillary ligands. For these reasons metallacrowns have been explored in the field of single-molecule magnets and for the molecular recognition of anions and biomolecules. Recently, metallacrowns of Zn^{2+} and lanthanides have been reported as bright fluorescent NIR-emitters, and promising for the development of new dyes for fluorescence imaging *in vivo* [2].



Scheme 1: Representation of a 12-MC-4 of β- and α-aminohydroxamates (left and center), and of a 15-MC-5 of α-aminohydroxamates (right). M = Cu^{2+}, Ni^{2+}, Zn^{2+}; M' = Ca^{2+}, Ln^{3+}, UO_2^{2+}.

The theory of the metallacrowns formation is based on the *metallacrowns structural paradigm*: β-aminohydroxamate ligands are favoured to form 12-MC-4 complexes, while α-aminohydroxamates preferentially form the 15-MC-5 species (Scheme 1). However, we have demonstrated that stable 12-metallacrown-4 scaffolds are formed also in systems containing Cu^{2+} and α-aminohydroxamates, in disagreement with the structural paradigm (Scheme 1, center). For Cu^{2+}, the 15-MC-5 complexes with α-aminohydroxamates form only in the presence of a large cation which occupies the cavity, while Ni^{2+} showed an unexpected versatility allowing the assembly of metallacrowns of different nuclearities in solution.

In this communication we will present our most recent results in the study of the metallacrown assembly with Ni^{2+} as the peripheral cation, with the aim to rationalize the thermodynamics of the process of self-assembly of the 12-MC-4 and 15-MC-5 complexes in solution. In particular, we will discuss the simultaneous presence in solution of both

metallacrowns, and the role of the ionic medium. The study of the formation of metallacrowns with picolinehydroxamate and Cu^{2+}, Ni^{2+}, or Zn^{2+} in aqueous solution will be also presented.

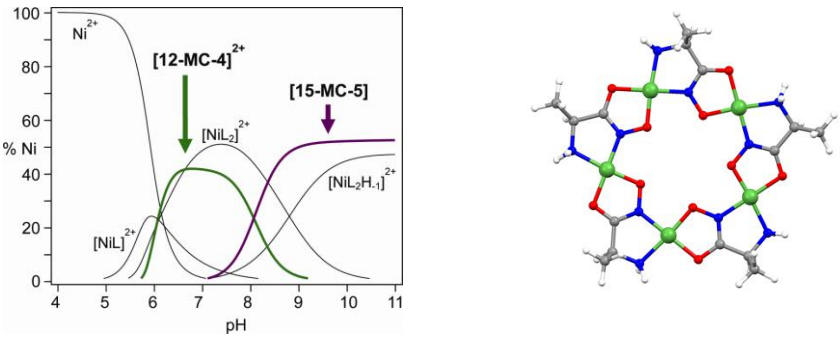


Figure 1: Left: Distribution diagram of the system Ni^{2+}/α-Alaha (Ni^{2+}/L = 1:1.5, C_{Ni} = 2.0 mM, I = 0.1 M (KCl)). Right: Calculated DFT structure of the Ni-containing 15-MC-5 of α-Alaha.

Our recent work in the context of the Marie Curie IRSES "Metallacrowns" project will be discussed, mainly the aspects related to the possibility to fine tune the formation of large 2D or 3D assemblies of metallacrown units by designing connecting units to promote their self-association of metallacrowns.

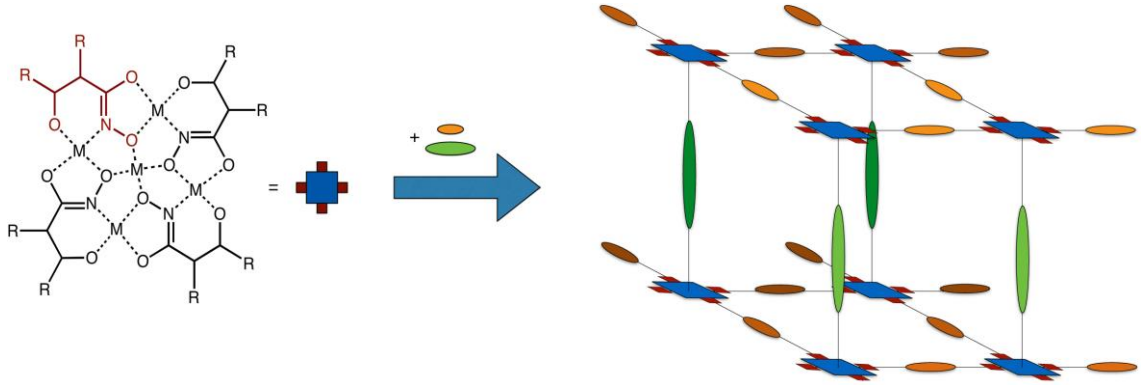


Figure 2: Schematic drawing of 3D assemblies using metallacrowns as building blocks. Orange and green ellipses indicate the connecting moieties needed to generate 2D layers and 3D assemblies.

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 611488.

References:

[1] Tegoni, M.; Remelli, M. Metallacrowns of copper(II) and aminohydroxamates: Thermodynamics of self-assembly and host–guest equilibria. *Coord. Chem. Rev.* **2012**, 256, 289–315.

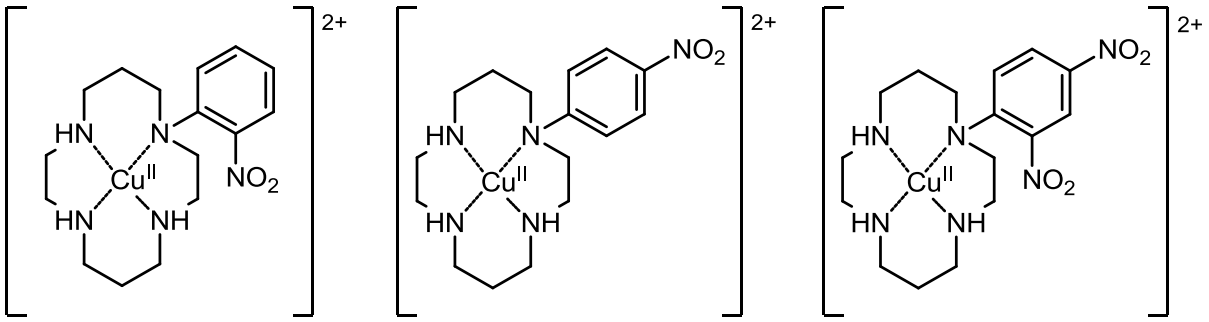
[2] Trivedi, E. R.; Eliseeva, S. V; Jankolovits, J.; Olmstead, M. M.; Petoud, S.; Pecoraro, V. L. Highly emitting near-infrared lanthanide "encapsulated sandwich" metallacrown complexes with excitation shifted toward lower energy. *J. Am. Chem. Soc.* **2014**, *136*, 1526–1534.

Copper(II) complexes of cyclams containing nitrophenyl substituents: push-pull behaviour and scorpionate coordination of the nitro group

Massimo BOIOCCHI, [a] Carlo CIARROCCHI, [b] Luigi FABBRIZZI, [b] Carlo MANGANO [b]

[a] Centro Grandi Strumenti, Università di Pavia, 27100 Pavia, Italy
[b] Dipartimento di Chimica, Università di Pavia, 27100 Pavia, Italy;
carlo.ciarrocchi01@universitadipavia.it

The design of molecular systems capable of selective interactions with anions plays an important role in supramolecular chemistry.[1, 2] In particular, coordinatively unsaturated metal complexes can bind anions at vacant coordination sites.[3] In multidentate ligands containing a push-pull chromophore huge shifts of the absorption band are observed upon coordination of a metal cation due to a change of the intensity of the dipole of the push pull-system.[4] A similar, but opposed shift may be induced by coordination of an anion to the complex, thus generating an easily detectable signal. In order to verify this hypothesis, three Cu(cyclam)$^{2+}$ derivatives bearing N-conjugated nitrophenyl moieties have been synthesized:



[Cu(1)]$^{2+}$ **[Cu(2)]$^{2+}$** **[Cu(3)]$^{2+}$**

Scheme 1: the three investigated compounds: **[Cu(1)](ClO$_4$)$_2$**, **[Cu(2)](ClO$_4$)$_2$** [4] and **[Cu(3)](ClO$_4$)$_2$**.

The behaviour of the three receptors was investigated through UV-vis spectroscopy titrations by monitoring the variations induced by anions in both the push-pull chromophore and Cu(II) d-d absorption bands.

Crystal structures evidenced in complexes **[Cu(1)](ClO$_4$)$_2$** and **[Cu(3)](ClO$_4$)$_2$**: (i) the presence of both *trans*-I and *trans*-III conformations of the cyclam skeleton; (ii) a scorpionate coordination of the closest nitro group of the phenyl substituent. A slow conformational change from *trans*-I to *trans*-III is observed in solution. The rate of the isomerisation is strongly influenced by the nature and concentration of added anions.

References:

[1] Gale, P. A.; Sessler, J. L.; Cho, W.-S., *Anion Receptor Chemistry*. The Royal Society of Chemistry: Cambridge, **2006**.

[2] Amendola, V.; Bonizzoni, M.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Sancenón F; Taglietti A., Some guidelines for the design of anion receptors. *Coord. Chem. Rev.* **2006,** 250, 1451-1470.

[3] Fabbrizzi, L.; Poggi, A., Anion recognition by coordinative interactions: metal–amine complexes as receptors. *Chem. Soc. Rev* **2013,** 42, 1681-1699.

[4] Boiocchi, M.; Fabbrizzi, L.; Licchelli, M.; Sacchi, D.; Vázquez, M.; Zampa, C., A two-channel molecular dosimeter for the optical detection of copper(II). *Chem. Comm.* **2003,** 15, 1812-1813.

The Importance of Metal Ion Complexation in a Biphasic Solvent Extraction System

Travis S. GRIMES, [a] **Leigh R. MARTIN** [a]

[a] *Aqueous Separations and Radiochemistry Department, Idaho National Laboratory, P.O. Box 1625, Idaho Falls, ID 83415-6150, U.S.A.; Travis.Grimes@inl.gov*

A key step in the development of a sustainable closed nuclear fuel cycle is transmutation of the long-lived minor actinides (Am^{3+} and Cm^{3+}). Transmutation of these elements is only achievable after they are separated from the fission product trivalent lanthanides (also found in used nuclear fuel). This separation is crucial, since the lanthanides (in particular Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}) have large thermal neutron capture cross sections that compete with the minor actinides for neutrons. In the U.S., TALSPEAK [1] (an acronym for Trivalent Actinide-Lanthanide Separations by Phosphorus reagent Extraction from Aqueous Komplexes) has received the most attention for accomplishing the aforementioned separation. Typically, TALSPEAK utilizes an aqueous medium with a high concentration of lactic acid (HL) buffer, typically ranging from 1.0-2.0 M (pH 3.0-4.0), containing diethylenetriamine-N,N,N',N",N"-pentaacetic acid (DTPA) as an aqueous "holdback" reagent for the actinides. The aqueous phase is contacted with an immiscible organic phase containing the monoacidic dialkyl bis(2-ethylhexyl)phosphoric acid extractant (HDEHP). During extraction DTPA selectively coordinates the actinides holding them in the aqueous phase as charged $AnDTPA^{2-}$ complexes, and HDEHP extracts the trivalent lanthanides to the organic phase. TALSPEAK balances the selective complexation of the actinides by DTPA against the electrostatic attraction of the lanthanides by the HDEHP extractant to achieve the desired trivalent lanthanide/actinide group separation. Although TALSPEAK has been proven successful at pilot plant scale, fundamental studies [2-4] have highlighted complex chemical interactions occurring in the aqueous and organic phases during the extraction process. Previous work [5] has attempted to model the traditional TALSPEAK system has shown thermodynamic models do not accurately predict the observed extraction trends in the $p[H^+]$ range 2.5-4.8.

Recent work [6] has demonstrated by substituting lactic acid (which has been shown to partition to the organic phase independent of metal ion at low metal ion concentrations,[3] and as an extracted mixed complex $ML(DEHP{\cdot}HDEHP)_2$ when organic phase metal concentrations exceed 0.020 M [3,6]) with a variety of amino acids (shown in

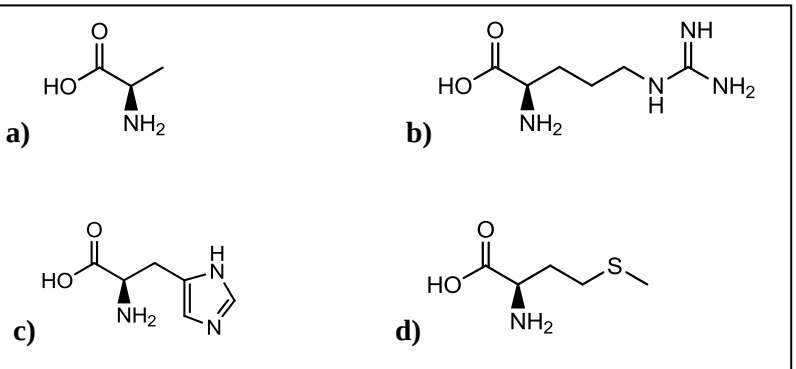


Figure 1. Amino acid buffers used in place of the lactic acid buffer in traditional TALPSEAK: a) L-alanine, b) L-arginine, c) L-histidine, d) L-methionine

figure 1), TALSPEAK was operated successfully at pH 2. It was proposed, operating TALSPEAK in a lower pH range and substituting the aromatic 1,4-diisopropylbenzene (DIPB) diluent with the aliphatic n-dodecane would create a more "ideal" solvent extraction system (one with limited solute partitioning and phase mixing) that could be modeled using thermodynamic data. A review of the literature has shown a limited number of stability constants available for Ln^{3+}/An^{3+}/amino acid complexes in acidic media. The thermodynamic data that is available varies greatly between different methods used for collection.

In this study, multiple analytical techniques have been used to determine the stability constants for Ln^{3+}/An^{3+} complexes with L-alanine, L-arginine, L-histidine, and L-methionine. The new stability constants will be used in a thermodynamic model to describe the extraction behavior in the aqueous-modified TALSPEAK separations process.

References:

[1] Weaver, B.; Kappelmann, F. A., TALSPEAK: A New Method of Separating Americium and Curium from the Lanthanides by Extraction from an Aqueous Solution of an Aminopolyacetic Acid Complex with a Monoacidic Organophosphate or Phosphonate. Oak Ridge National Laboratory, 1964; pp 1-61.

[2] Grimes, T. S.; Nilsson, M. A.; Nash, K. L., Lactic Acid Partitioning in TALSPEAK Extraction Systems. *Sep Sci Technol* **2010,** *45* (12-13), 1725-1732.

[3] Marie, C.; Hiscox, B.; Nash, K. L., Characterization of HDEHP-Lanthanide Complexes Formed in a Non-Polar Organic Phase Using 31P NMR and ESI-MS. *Dalton Trans.* **2012,** *41* (3), 1054-64.

[4] Grimes, T. S.; Jensen, M. P.; Debeer-Schmidt, L.; Littrell, K.; Nash, K. L., Small-Angle Neutron Scattering Study of Organic-Phase Aggregation in the TALSPEAK Process. *J. Phys. Chem. B* **2012,** *116* (46), 13722-30.

[5] Nilsson, M.; Nash, K. L. Trans-Lanthanide Extraction Studies in the TALSPEAK System: Investigating the Effect of Acidity and Temperature. *Solvent Extr. Ion Exch.* **2009**, 237(3), 354-377.

[6] Grimes, T. S.; Tillotson, R. D.; Martin, L. R. Trivalent Lanthanide/Actinide Separation Using Aqueous-Modified TALSPEAK Chemistry. *Solvent Extr. Ion Exch.* **2014,** In Print.

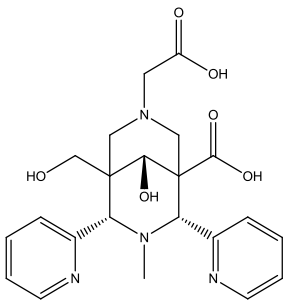
New Kinetically Inert Cu(II)-Bispidine Complex for Nuclear Medicine and Diagnosis

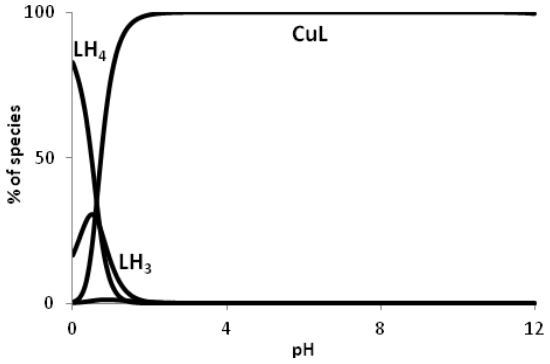
Jérémy Brandel,[a)] Véronique Hubscher-Bruder,[a)] Amandine Roux,[b)] Aline Nonat,[b)] and Loïc Charbonnière [b)]

[a] *Laboratoire de Reconnaissance et Procédés de Séparation Moléculaire (RePSeM)*
[b] *Laboratoire d'Ingénierie Moléculaire Appliquée à l'Analyse (LIMAA)*
IPHC- UMR7178-CNRS, ECPM, 25 rue Becquerel, 67087 Strasbourg; jbrandel@unistra.fr

Positron emission tomography (PET) is a powerful imaging technique that became, in recent years, one of the most important diagnostic tools in oncology. Among the possible radioisotopes, ^{64}Cu appears an ideal candidate for PET imaging and radiotherapy due to its very convenient half-time of 12.7 h compared to the presently used ^{18}F probes (109.8 min) and to its decay properties (β^+, 0.653 MeV, 17.8%; β^-, 0.579 MeV, 38.4%). The challenge of chemists lies in the design of Cu(II) chelators fulfilling all the requirements for *in vivo* imaging agents, i.e. fast complexation, high stability and inertia of the complexes, good selectivity of the ligand for Cu(II) against other biologically relevant cations, a reduction potential below the threshold for *in vivo* reduction and the availability of functionalities for the coupling to targeting vectors or molecular fragments for other imaging techniques. In depth knowledge of the solution behavior of potential ligands are thus crucial [1].

In this context we present a detailed physicochemical study of a new ligand, part of a bispidine series [2], showing promising qualities towards Cu(II) complexation in terms of thermodynamics, kinetics and electrochemistry.





References:

[1] Shokeen, M.; Anderson, C. J., Molecular Imaging of Cancer with Copper-64 Radiopharmaceuticals and Positron Emission Tomography (PET) *Acc. Chem. Res.* **2009**, 42(7), 832-841.

[2] Legdali, T.; Roux, A.; Platas-Iglesias, C.; re, L. J., Substitution-Assisted Stereochemical Control of Bispidone-Based Ligands. *J. Org. Chem.* **2012**, 77, 11167−11176.

The role of side chains in the fine tuning of metal binding ability of peptides

Katalin VÁRNAGY, Gizella CSIRE, Sarolta TIMÁRI

Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1, 4032 Debrecen, Hungary. varnagy.katalin@science.unideb.hu

It is well known that peptides have high metal binding affinity, but both the thermodynamic stability and the coordination geometry of peptide complexes are very much influenced by the amino acid sequence of the ligands. One field of our present research work is the synthesis and investigation of polypeptides containing various side chain donor groups, in which the coordination of side chain donor atoms comes to the front and their sequences serve as the models of different metalloproteins. These molecules include peptide fragments of Cu,Zn-superoxide dismutase enzyme, prion protein and β-amyloid peptide playing role in the neurodegenerative diseases. [1-3].

We synthesized such series of multihistidine peptides in which the systematic change of the amino acid sequence is carried out and the equilibrium, structural and electrochemical parameters of their complexes are determined. These molecules include oligopeptides built up from 4 to 12 amino acid residues containing 2 to 4 histidines among them. The thermodynamic, structural and electrochemical properties of these peptides are primarily determined by the number and location of histidyl residues. The presence of positively or negatively charged and polar or bulky side chains of other amino acids in the neighbourhood of the metal binding sites can, however, significantly contribute to the above mentioned parameters of these complexes. To understand the specific effects of these side chains aspartic acid, serine or phenylalanine are inserted into the sequence of the multihistidine peptides (Ac-(HisXaa)n-His, Xaa = Ala, Phe, Asp, Ser etc.) and copper(II), nickel(II) and zinc(II) complexes of these oligopeptides were studied by means of pH-potentiometry and spectroscopic techniques.

In this work we demonstrate through the studies of the above mentioned peptides those tendencies which finely regulate the equilibrium, structural and electrochemical parameters of metal complexes.

Acknowledgement: The research was supported by the EU and co-financed by the European Social Fund under the project ENVIKUT (TÁMOP-4.2.2.A-11/1/KONV-2012-0043)

References:

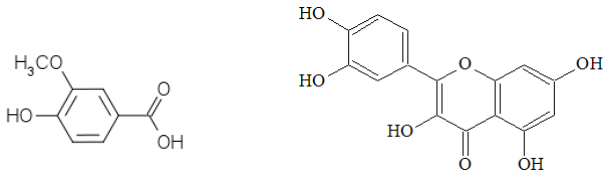
[1] Timári, S., Cerea, R., Várnagy, K., *J. Inorg. Biochem.*, **2011**, 105, 1009-1017
[2] Csire, G., Demjén, J., Timári, S., Várnagy, K., *Polyhedron*, **2013**, 61, 202-212.
[3] Kállay, C., Turi, I., Timári, S., Nagy, Z., Sanna, D., Pappalardo, G., De Bona, P., Rizzarelli, E., Sóvágó, I., in "*Metal Ions in Neurological Systems*", eds. W. Linert, H. Kozlowski, Springer-Verlag, Wien, **2012**

Insights on the coordination mode of phenolic compounds with Al(III) ion from a combined experimental and theoretical study

Emilia FURIA, Tiziana MARINO, Antonio TAGARELLI, Nino RUSSO

Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, via P Bucci, I-87036 Arcavacata di Rende, Italy; e.furia@unical.it

A variety of phenolic compounds are found in most vegetables. Second only to carbohydrates, they are the most abundant type of compounds in plants. The interest in these phenolic compounds lies in their known health benefits due to their antioxidant activity and ability as free-radical scavengers. These properties give them great potential as active principles in the pharmaceutical industry and as antioxidants in the food industry [1]. These compounds include one or more hydroxyl groups (polar part) attached directly to an aromatic ring (non-polar part) and are often found in plants as esters or glycosides, rather than as free molecules [2]. Phenolic compounds as antioxidants act as reducing agents, hydrogen donators and singlet oxygen quenchers. They are very important compounds due to their likely role in the prevention of several human diseases [3]. In this work, we have studied the complexation of vanillic acid and quercetin (Scheme 1) with Al(III) ion in solution by using a combination of experimental and computational tools in order to attain structural and electronic properties of the resulting complexes.



(a) **(b)**

Scheme 1: Chemical structure of vanillic acid (a) and quercetin (b)

Aluminium cation is the third most abundant element in the Earth's crust and often enters in the biotic cycle in many different ways [4]. The human exposure to aluminium is not fully explained but it is well known that it does not serve any essential function in human biochemistry. By contrary, Al(III) cation can enter in the brain where it persists for long time and a small increase seems sufficient to produce neurotoxicity [5]. For this reason, the presence of aluminium in the human brain has been associated to the Alzheimer's and other neurodegenerative diseases [6]. Chelation therapy with some ligands has been demonstrated to reduce some causes of aluminium toxicity. In this context, it is interesting to explore the ability of natural products to coordinate the Al(III) ion.

References:

[1] Boskou, D. Sources of natural antioxidants. *Trends in Food Science and Technology* **2006**, 17 (9), 505–512.

[2] Queimada, A.J.; Mota, F.L.; Pinho, S.P.; Macedo, E.A. Solubilities of biologically active phenolic compounds: Measurements and modeling. *Journal of Physical Chemistry B* **2009**, 113 (11), 3469–3476.
[3] Świsłocka, R.; Regulska, E.; Samsonowicz, M.; Lewandowski, W. Experimental and theoretical study on benzoic acid derivatives. *Journal of Molecular Structure* **2013**, 1044, 181–187.
[4] Exley, C. Human exposure to aluminium. *Environ. Sci.: Processes Impacts* **2013**, 15, 1807–1816.
[5] Yokel, R.A. The Pharmacokinetics and Toxicology of Aluminum in the Brain. *Curr. Inorg. Chem.* **2012**, 2, 54–63.
[6] Exley, C. A molecular mechanism of aluminium-induced Alzheimer's disease? *J. Inorg. Biochem.* **1999**, 76, 133–140.

Some Research Results Accounting Professor Vincenzo Romano Teachings

Manuel VALIENTE

Universitat Autònoma de Barcelona. Dept of Chemistry. Centre GTS.
Bellaterra (Barcelona), Spain

Professor Vincenzo Romano became a reference both scientifically and as a personal friend from our meetings at the Royal Institute of Technology, KTH, in Stockholm (Sweden) and later on in our ISMEC yearly meetings. He contributed to my learning of the importance of the basic science.

In this concern, the scientific methodology was one of the most appreciated teachings he provided to the international postgraduated students we were at the Inorganic Chemistry Department of KTH. This included relevant examples of how the purity of the ionic media could play a role on the stability of some non-stable chemical species, e.g, Ag2+ in perchlorate, or how to avoid salt bridge in potentiometric measurements.

Such teachings made some fruitful results when later on I tried to apply them to our research studies. In this communication, I will present some of these results that will include redox systems, i.e, Tl(III)/Tl(I), Se(IV)/Se(VI) and some other that have a critical importance in some systems of current development of industrial products and of environmental concern.

Weak complexes of sodium cation with negatively charged ligands

Silvia BERTO, [a] Enrico CHIAVAZZA, [b] Pier Giuseppe DANIELE, [a] Gabriele LANDO, [b] Enrico PRENESTI, [a] Silvio SAMMARTANO [a]

[a] Dipartimento di Chimica, Università di Torino, Via P. Giuria, 7 – 10125 Torino [b] Dipartimento di Chimica Inorganica, Chimica Analitica e Chimica Fisica dell'Università degli Studi di Messina, Viale Ferdinando Stagno d'Alcontres 31, I-98166 Messina
enrico.chiavazza@unito.it

The coordination chemistry in solution of alkali metal ions was relatively little investigated [1], in particular if compared with the great number of results reported in the literature for complexes of transition metal ions. Nevertheless, with the aim of correctly solving analytical problems, in building chemical speciation models for interpretation of natural chemical system behavior, the formation of alkali metal complexes cannot be neglected. According to the NEA authors [2], the existence of complexes with alkali metal ions "should not be considered as completely proven" by measurements carried out at different ionic strengths, because the results depend on the model used for activity coefficients. In this work the alkali metal complex formation with acetate, benzoate, malonate, phthalate, citrate, nitrilotriacetate, ethylenediaminetetraacetate [3], mellitate and 1,2,4-benzenetricarboxylate, has been investigated employing ISE-Na^+ potentiometry and working at strictly constant ionic strength (variation during the experiment < 5%). In these conditions the effects of the variation of activity coefficients on the potentials recorded is negligible and the formation of alkali metal complexes in solution has been evidenced unequivocally comparing the experimental values of free Na^+ ions with those of total sodium added for each point of titration curve. The electrode calibration procedure was performed in triplicate during each measuring day in order to avoid that the instability of the electrode response can affect the results. Moreover, in order to support the experimental evidence of the complex formation the pNa combined uncertainty was estimated. There are no doubts about the formation of alkali metal complexes in solution.

After detection, the formation constants were determined by the elaboration of potentiometric data taking into account the intrinsic content of Na^+ in the reagents used. The constant values obtained show a good agreement with those evaluated by pH-metric technique or by ISE-Na^+ potentiometry at variable ionic strengths, suggesting that also potentiometric techniques at variable ionic strengths can be used in the study of this topic with a good accuracy. Moreover, our results confirm the low stability of alkali metal complexes in aqueous solution, which is founded on coulomb interactions. In general, the values of stability constants depend not only on the number of charged oxygen donor groups, but also on the presence of amino donor(s) and hydroxyl groups.

References:

[1] Daniele, P.G.; Foti, C.; Gianguzza, A.; Prenesti, E.; Sammartano, S., Weak alkali and alkaline earth metal complexes of low molecular weight ligands in aqueous solution. *Coordination Chemistry Reviews* **2008**, 252,1093-1107.

[2] Anderegg, G.; Rao, L.; Puigdomenech, I.; Tochiyama, O., Chemical Thermodynamics of Compounds and Complexes of U, Np, Pu, Am, Tc, Se, Ni and Zr with Selected Organic Ligands. In *Chemical Thermodynamics 9*. Elsevier, Amsterdam, The Netherlands **2005**.

[3] Berto, S.; Daniele, P.G.; Lando, G.; Prenesti, E.; Sammartano S., Methodological aspects in the study of alkali metal ion weak complexes: an analytical approach. *International Journal of Electrochemical Science* **2012**, 7, 10976-10986.

The Interaction of Scorpiand-type Polyazacylophanes with Single and Double-Stranded Polynucleotides Reveals Sequence Selectivity

Enrique GARCÍA-ESPAÑA, Mario INCLÁN, M. Teresa ALBELDA.

Molecular Science Institute (ICMol), University of Valencia, C/Catedrático José Beltrán 2, 46980 Paterna, Spain. mario.inclan@uv.es

The studies performed a few years ago on the interaction of scorpiand-type polyamines [1] with calf thymus DNA provided evidence on the interesting possiblility of these ligands to modulate their interaction through pH or metal-driven molecular reorganizations, and how this modulation of the interaction could serve to increase or decrease the biological activity of these compounds [2]. These interesting results prompted us to continue with the research, in an effort to understand the mechanisms of the interaction, and to asses possible sequence selectivity. In a first approach, the recognition of individual mononucleotides by these ligands was studied. These work revealed selectivity between puric and pyrimidinic nucleobases; the ability of these ligands to efficiently discriminate, through different fluorescent outputs, between ATP and GTP; and the binding patterns of the interaction [3].

Taking another step forward in this investigation, here we present the most recent findings on the interaction of theses scorpiand-like ligands with single and double-stranded models of DNA and RNA. The results show again different ways of interaction and binding affinities depending on the base sequence and the secondary structure of the polynucleotides. The experimental data was obtained by means of UV-Vis and fluorescence titrations, CD and thermal denaturation measurements.

References:

[1] Pallavicini, P. S.; Perotti, A.; Poggi, A.; Seghi, B. ; Fabbrizzi, L. *J. Am. Chem. Soc.* **1987**, 109, 5139-5144.

[2] Inclán, M.; Albelda, M. T.; Frías, J.; Blasco, S.; Verdejo, B.; Serena, C.; Salat-Canela, C.; Díaz, M. L.; García-España, A.; García-España, E. *J. Am. Chem. Soc.* **2012**, 134, 9644-9656.

[3] Inclán, M.; Albelda, M. T.; Carbonell, E.; Blasco, S.; Bauzá, A.; Frontera, A.; García-España, E. *Chem. Eur. J.* **2014**, 20, 3730-3741.

Alarming use of chelation therapy.

Guido CRISPONI, [a] Valeria M. NURCHI, [a] Joanna I. LACHOWICZ, [a] Miriam CRESPO-ALONSO, [a] M. Antonietta ZORODDU, [b] Massimiliano PEANA [b]

[a] Dipartimento di Scienze Chimiche e Geologiche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy, [b] Dipartimento di Chimica e Farmacia, University of Sassari, Via Vienna 2, 07100, Sassari, Italy; crisponi@unica.it

Chelation therapy is a consolidated medical procedure used primarily to hinder the effects of toxic metal ions on human tissues [1]. Its application spans a broad spectrum of disorders, ranging from acute metal intoxication to genetic metal-overload. The use of chelating agents is compromised by a number of serious side effects, mainly attributable to perturbed equilibrium of essential metal ion homeostasis and dislocation of complexed metal ions to dangerous body sites. For this reason, chelation therapy has been limited to specific critical and otherwise untreatable conditions and needs to be monitored within an appropriate clinical context [2-3]. An alarming issue today is that fraudsters use the term "chelation therapy" to take advantage of and make profit from people with tragic health problems. We believe that scientists working in this field have the corollary obligation to deter these frauds and to inform the scientific community of the possible side effects and complications of chelation therapy. This duty is all the more important if we consider the detrimental and even life threatening consequences that can occur in subjects with no clear clinical and laboratory evidence of metal intoxication. The aim of this communication is to present how this "false chelation therapy" developed and in which diseases it is currently applied [4].

References:

[1] Crisponi, G.; Nurchi, V. M.; Crespo-Alonso, M.; Toso, L., Chelating Agents for Metal Intoxication. *Current Medicinal Chemistry* **2012,** 19, 2794-2815.

[2] Crisponi, G.; Nurchi, V. M.; Fanni, D.; Gerosa, C.; Nemolato, S.; Faa, G., Copper-related diseases: from chemistry to molecular pathology. *Coord. Chem. Rev.* **2010,** 254, 876-889.

[3] Crisponi, G.; Remelli, M., Iron chelating agents for the treatment of iron overload. *Coord. Chem. Rev.* **2008,** 252, 1225-1240.

[4] Crisponi, G.; Nurchi, V. M.; Lachowicz, I. J.; Crespo-Alonso,.M; Zoroddu, M. A.; Peana, M., Kill or Cure: Misuse of chelation therapy for human diseases**.** *Coord. Chem. Rev.* **2014,** accepted for publication.

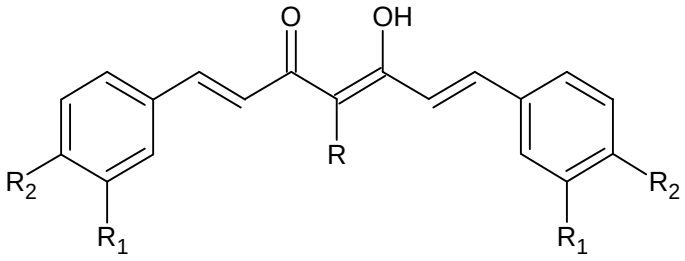
^{68}Ga-labelled curcuminoids complexes: potential radiotracers for imaging of cancer and Alzheimer's disease

Erika FERRARI,[a] Mattia ASTI,[b] Stefania CROCI,[c] Giulia ATTI,[b] Sara RUBAGOTTI [b] Monica SALADINI[a]

[a] Department of Chemical and Geological Sciences, University of Modena, via Campi, 183, 41125 Modena, Italy; [b] Nuclear Medicine Unit, Oncology and Advanced Technologies Department, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; [c] Clinical Immunology, Allergy, and Advanced Biotechnologies Unit, Diagnostic Imaging and Laboratory Medicine Department, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

erika.ferrari@unimore.it

Curcumin is a phyto-compound and dietary spice extracted from the rhizome of the herb *Curcuma longa* L., commonly known as turmeric. It is used in traditional medicines of eastern world countries thanks to its properties such as antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. In recent years, curcumin and curcuminoids complexes with metals, have been subjected to a large number of studies due to their interesting potential as therapeutics in varying diseases. Iron complexes of curcumin seem to have high potential in the treatment of cancer [1], while gallium complexes have remarkable antiviral effects on HSV-1 in cell culture [2]. Curcumin structure includes a heptadiene with two 3-methoxy, 4-hydroxy phenyl groups, and an α,β-diketone which is subjected to a keto-enol tautomerism, pH and solvent dependent, that also influences its metal-chelation capability [3]. The keto-enolic moiety of curcumin have also been exploited in the complexation of radioactive metals for synthesizing ^{99m}Tc-labelled radiopharmaceuticals where curcumin acts as OO bidentate ligand on a ^{99m}Tc-tricarbonyl core with the aim of projecting a target specific probes for potential diagnosis of Alzheimer's disease (AD) or cancer [4].



Compound	R	R_1	R_2
Curcumin	H	OCH_3	OH
DAC	H	OCH_3	OAc
bDHC	H	OCH_3	H
K2A21	CH_2COOH	OCH_3	OH
K2A23	CH_2COOH	OCH_3	H
K2T21	$CH_2COOC(CH_3)_3$	OCH_3	OH
K2T23	$CH_2COOC(CH_3)_3$	OCH_3	H

Figure 1

The aim of the present study is to investigate the feasibility of the labelling of curcuminoids with gallium-68 in order to obtain potential diagnostic tools for cancer and Alzheimer's disease.

For this purpose, different classes of curcuminoids (**Figure 1**) were selected and a complete characterization of the equivalent ^{nat}Ga-complexes structures and properties was performed by means of experimental and theoretical approach. Stoichiometry and formation of the curcuminoids complexes were investigated by MALDI-TOF-MS, NMR, UV-Vis, and Fluorescence

spectroscopy on the ^{nat}Ga-Curcuminoids complexes and their structure was computed by theoretical DFT calculations. The corresponding ^{68}Ga-labelled complexes with the most promising curcuminoids were then synthesized and characterized. The radiotracers were prepared by reacting $^{68}Ga^{3+}$ obtained from a ^{68}Ge/^{68}Ga generator with curcuminoids solutions. Reaction parameters (precursor amount, reaction temperature, and pH) were optimized in order to obtain high and reproducible radiochemical yield and purity. The complexes showed high stability in saline, human serum or when challenged with DTPA or with Fe^{3+}, Zn^{2+}, and Cu^{2+} for transchelation or transmetallation studies, respectively. In order to test the possibility to use ^{68}Ga-curcuminoids complexes as radiotracers for AD, a first evaluation of their affinity for Aβ(1-40) amyloid synthetic fibrils was here investigated *in vitro*. Finally study *in vitro* on lung cancer cells showed quite high level of cellular uptake of ^{nat}Ga-complexes (**Figure 2**), confirmed by ICP-MS spectrometry.

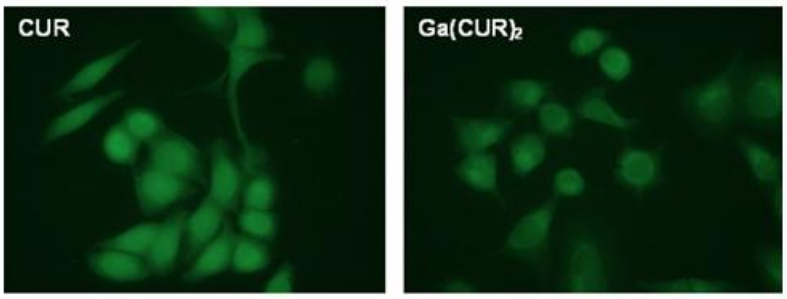


Figure 2

The obtained results are encouraging and shed new light on the potential use of curcuminoids as radiotracers for PET (positron emission tomography), in addition the intrinsic fluorescent emission of the Ga-curcuminoids complexes paves the way to the possibility of synthesizing a mixed radioactive/fluorescent pharmacophore that could be exploited as a dual-mode imaging tool.

References:

[1] Kovacevic, Z.; Kalinowski, S.D.; Lovejoy, B.D.; Yu, Y; Rahmanto, S. Y.; Sharpe, C.P.; Bernhardt, V. P.; Richardson, R. *Curr. Top. Med. Chem*. **2011**, 11, 483-499.

[2] Zandi, K.; Ramedani, E.; Mohammadi, K.; Tajbakhsh, S. ; Deilami, I.; Rastian, Z.; Fouladvand, M.; Yousefi, F.; Farshadpour, F. *Nat. Prod. Commun*. **2010**, 5, 1935-1938.

[3] Ferrari, E.; Asti, M.; Benassi, R.; Pignedoli, F.; Saladini, M. *Dalton Trans*. **2013**, *42*, 5304-5313.

[4] Sagnou, M.; Benaki, D.; Triantis, C.; Tsotakos, T. ; Psycharis, V.; Raptopoulou, C.P.; Pirmettis, I.; Papadopoulos, M.; Pelecanou. M. *Inorg. Chem.* **2011**, *50*, 1295–1303.

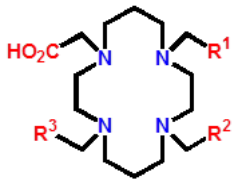
Kinetic study of copper(II) complexes of TETA-like macrocyclic ligands

Přemysl LUBAL,[a,b] Romana ŠEVČÍKOVÁ,[a] Jakub VANĚK,[a,b]

Petr HERMANN,[c] Luís M.P. LIMA,[d] Rita DELGADO[d]

a) Department of Chemistry, Masaryk University, Kotlářská 2, CZ-611 37 Brno, Czech Republic,e-mail:lubal@chemi.muni.cz
b) Central European Institute of Technology (CEITEC), Masaryk University, Kamenice 5, CZ-625 00 Brno, Czech Republic
c) Department of Inorganic Chemistry, Charles University, Hlavova 2030., CZ-128 40 Prague, Czech Republic
d) Instituto de Tecnologia Química e Biológica (ITQB), Avenida da República, P-2780-157 Oeiras, Portugal

Copper(II) complexes of tetraazamacrocyclic ligands exhibit both high thermodynamic stability as well as considerable kinetic inertness and, therefore, they are utilized in diagnosis (positron emission tomography - PET, ^{64}Cu with half-life 12.8 h) or in radio-immunotherapy (^{67}Cu with half-life 62 h). Ligands for copper(II) complexation are commonly used as bifunctional chelates (BFC's) having another reactive functional group used for covalent attachment of the ligand to a targeting vector (*e.g.* oligopeptides, antibodies, etc.) mostly *via* a linker while properties of BFC's and their complexes should be the same or better than those of the parent ligands [1, 2].



$R^1 = R^2 = R^3 = COOH$ **H_4teta**

$R^1 = R^2 = COOH$, $R^3 = P(O)(OH)_2$ **H_5te3ap**

$R^1 = R^2 = R^3 = P(O)(OH)_2$ **H_7tea3p**

Here, thermodynamic and kinetic properties of Cu(II) complexes with macrocyclic cyclam-based ligands where acetate pendant arm(s) were replaced by phosphonate arm(s) (H_4teta, H_5te3ap, H_7tea3p – see Fig. 1) [3, 4] are presented. In addition, the influence of substitution of one (H_4teta *vs.* H_5te3ap) and/or three acetate/phosphonate (H_4teta *vs.* H_7tea3p) pendant arms on kinetic inertness of Cu(II) complexes was studied. The impact of substitution of pendant arms attached to *cyclam* skeleton is less significant than on *cyclen*-like ligands [5,6]. The results will be compared with analogous *cyclam* derivatives containing one (H_2te1p) or two phosphonate pendant arms (H_4te2p) [7-9] as well as with corresponding *cyclen* derivatives [8, 9]. Results of this study will help in design of new bifunctional chelators for possible *in vivo* applications.

Acknowledgement:

Financial support from the Ministry of Education of the Czech Republic (grant MSM0021620857), Grant Agency of the Czech Republic (No. 13-08336S) and EU programs (TD 1004, CEITEC CZ.1.05/1.1.0/02.0068) are acknowledged.

References:

[1] Delgado, R; Félix, V; Lima, L.M.P., Price, D.W., Metal complexes of cyclen and cyclam derivatives useful for medical applications: a discussion based on thermodynamic stability constants and structural data. Dalton Perspective, *Dalton Trans.* **2007**, 2734-2745.

[2] Anderegg, G.; Arnaud-Neu, F.; Delgado, R.; Felcman, J.; Popov, K., Critical evaluation of stability constants of metal complexes of complexones for biomedical and environmental applications, *Pure App. Chem.* **2005** (77**)** 1445-1495.

[3] Lima, L.M.P.; Delgado, R.; Plutnar, J.; Hermann, P.; Kotek, J.; A New Tris(phosphonomethyl) Monoacetic Acid Cyclam Derivative: Synthesis, Acid-Base and Metal Complexation Studies, *Eur. J. Inorg. Chem.* **2011**, 527–538.

[4] Lima, L.M.P.; Delgado, R.; Drew, M.G.B.; Brandão, P.; Félix, V., Cyclam derivatives containing three acetate pendant arms: synthesis, acid-base, metal complexation and structural studies, *Dalton Trans.* **2008**, 6593-6608.

[5] Lima, L.M.P; Esteves, C.V.; Delgado, R.; Hermann, P.; Kotek, J.;Ševčíková, R.; Lubal P., Tris(phosphonomethyl) Cyclen Derivatives: Synthesis, Acid–Base Properties and Complexation Studies with Cu^{2+} and Zn^{2+} Ions, *Eur. J. Inorg. Chem.* **2012**, 2533-2547.

[6] Ševčík, R.; Vaněk, J.; Lubal, P.; Kotková, Z.; Kotek, J.; Hermann, P., Formation and dissociation kinetics of copper(II) complexes with tetraphosphorus acid DOTA analogs, *Polyhedron* **2014** (67), 449-455.

[7] Kotek, J.; Lubal, P.; Hermann, P.; Císařová, I.; Lukeš, I.; Godula, T.; Svobodová, I.; Táborský, P.; Havel, J., Unusually high thermodynamic stability and extraordinary kinetic inertness of copper(II) complexes with 1,4,8,11-tetraazacyclotetradecane-1,8-bis(methylphosphonic acid). Example of a rare isomerism between kinetically inert penta- and hexacoordinated Cu(II) complexes, *Chem. Eur. J.* **2003** (9), 233-248.

[8] Svobodová, I.; Lubal, P.; Plutnar, J.; Havlíčková, J.; Kotek, J.; Hermann, P.; Lukeš, I., Thermodynamic, kinetic and solid-state study of divalent metal complexes of 1,4,8,11-tetraazacyclotetradecane (cyclam) bearing two *trans* (1,8-)methylphosphonic acid pendant arms, *Dalton Trans.* **2006,** 5184-5197.

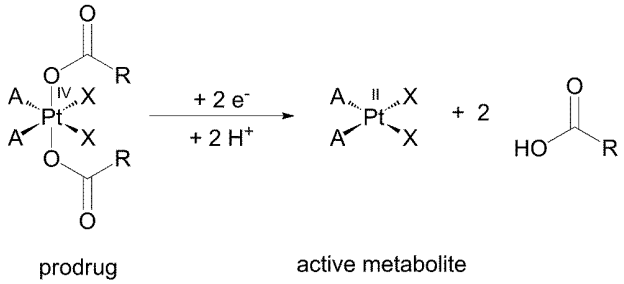
[9] Svobodová, I.; Havlíčková, J.; Plutnar, J.; Lubal, P.; Kotek, J.; Hermann, P., Metal Complexes of 4,11-Dimethyl-1,4,8,11-tetraazacyclotetradecane-1,8-bis (methyl phosphonic acid) – Thermodynamic and Formation/Decomplexation Kinetic Studies, *Eur. J. Inorg. Chem.* **2009,** 3577-3592.

Strategies for the Development of Novel Pt Anticancer Compounds: Shifting the Paradigms from Pt(II) to Pt(IV) Complexes.

Mauro RAVERA, Elisabetta GABANO, Ilaria ZANELLATO, Ilaria BONARRIGO, Domenico OSELLA

Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, Viale Teresa Michel 11, 15121 Alessandria (Italy); mauro.ravera@unipmn.it

Since the discovery of the antitumor activity of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, the search for platinum complexes as antiproliferative agents has been the most active area of research in bioinorganic chemistry. Platinum(IV) compounds represent an alternative class of potential prodrugs that are of considerable interest. They are believed to be reduced in vivo to their active Pt(II) metabolite in the hypoxic, reducing and acidic tumor milieu, leading to lower systemic toxicity and unwanted side reactions and can be administered *per os*[1].



In general, Pt(IV) complexes show a striking cytotoxic effect (in the sub-micromolar range) on various human carcinoma cell lines. A judicious choice of the six ligands around Pt centre is necessary in order to optimize the physicochemical properties of complexes (in particular lipophilicity and reduction potential) and, hence, their biological activity (bioavailability, cellular uptake, activation, and cytotoxicity).

In this framework, *i)* the cytotoxicity of Pt(IV) complexes will be related to their structure (quantitative structure-activity relationship, QSAR) [2], *ii)* the selectivity between cancer and healthy cells and the activity on cancer cell lines intrinsically resistant or made resistant to the traditional Pt(II) drugs [3] will be discussed.

References:

[1] Hall, M. D.; Mellor, H. R.; Callaghan, R.; Hambley, T. W., Basis for design and development of Platinum(IV) anticancer complexes. *J. Med. Chem.* **2007**, 50 (15), 3403-3411.

[2] Ermondi, G.; Caron, G.; Ravera, M.; Gabano, E.; Bianco, S.; Platts, J. A.; Osella, D., Molecular interaction fields vs. quantum-mechanical-based descriptors in the modelling of lipophilicity of platinum(IV) complexes. *Dalton Trans.* **2013**, 42 (10), 3482-3489 and references therein.

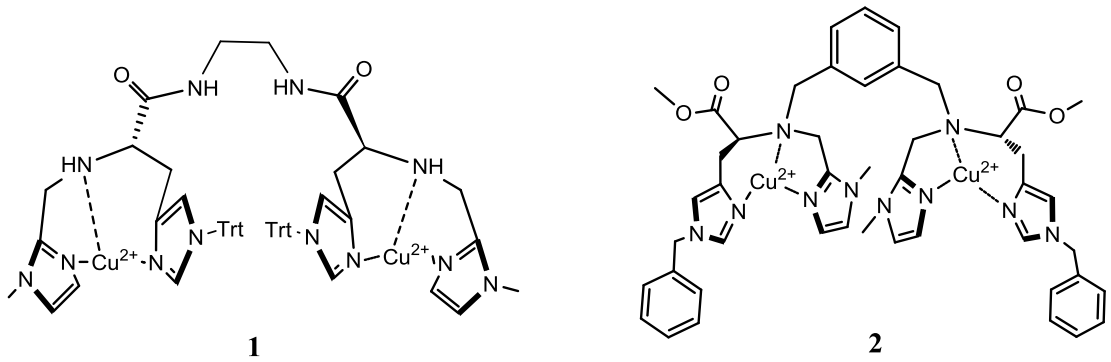
[3] Zanellato, I.; Bonarrigo, I.; Gabano, E.; Ravera, M.; Margiotta, N.; Betta, P. G.; Osella, D., Metallo-drugs in the treatment of malignant pleural mesothelioma. *Inorg. Chim. Acta* **2012**, 393, 64-74.

Synthesis and asymmetric oxidations by chiral dinuclear copper complexes

Maria Lucia PERRONE, [a] Eliana LO PRESTI, [a] Luca PASOTTI, [a,b] Enrico MONZANI, [a] Laura SANTAGOSTINI, [c] Luigi CASELLA [a]

[a] Dipartimento di Chimica, Università di Pavia, viale Taramelli 12, 27100 Pavia, Italy; [b] Noxamet Srl, Sede operativa di Pavia, Via Taramelli 12, 27100 Pavia, Italy; [c] Dipartimento C.I.M.A. Lamberto Malatesta, Università di Milano, via Venezian 21, 20133Milano, Italy; perrone.marialucia@gmail.com

The dicopper enzyme tyrosinase continues to be an important source of inspiration for biomimetic chemists interested in developing effective catalysts for oxygenation reactions.[1-3] Indeed, recent reports described the first examples of catalytic phenol hydroxylation,[4,5] and sulfoxidation[6] by dinuclear copper complexes in the presence of dioxygen. Spectroscopic and structural studies have shown that three types of copper-dioxygen intermediates are competent to perform oxygen transfer reactions to the substrates:[1-3] the μ-η^2:η^2-peroxodicopper(II), bis(μ-oxo)dicopper(III) or *trans*-μ-η^1:η^1-peroxodicopper(II) species. An important development for synthetic applications of biomimetic tyrosinase models would be the possibility to perform catalytic stereoselective oxidations, through the design of chiral complexes, capable of reproducing the nature of active site and the nuclearity of the original model.



1 **2**

Scheme 1: chiral copper complexes synthesized. **1**: **enHI 2**: **mXHI**

We have synthesized two chiral dinuclear copper complexes including polydentate nitrogen ligands and typically containing a set of six donor nitrogens, with synthetic accessible chiral centres, provided by L-histidine. The ligand environment of the pair of copper ions is provided by tridentate amino-bis(imidazole) residues, while the spacer has been varied in order to optimize the performance of the resulting dicopper complexes in terms of catalytic efficiency and recognition ability. For complex **1** we have used an ethylendiammide bridge, replaced by a m-xylenic portion in complex **2**.

The catecholase activity was studied for a set of chiral catechol pairs,[7,8] so as to test the enantiodifferentiating capacity and to provide mechanistic insight into the substrate

binding mode. For a similar purpose the monophenolase activity was investigated towards a set of phenol pairs.[9]

References:

[1] (a) L. Que, Jr., W.B. Tolman, *Nature* 2008, 455, 333-340; (b) S. Itoh, in *Copper-Oxygen Chemistry*, K. D. Karlin, S. Itoh Eds, Wiley, Hoboken, N. J., 2011, pp.225-282; (c) M. R. Halvagar, D. J. Salmon, W. B. Tolman, in *Comprehensive Inorganic Chemistry II*, Volume 3, J. Reedijk, K. Poeppelmeier Eds., Elsevier, 2013, pp. 455-486.

[2] (a) L. Q. Hatcher, K. D. Karlin, *Adv. Inorg. Chem.* 2006, 58, 131-184; (b) G. Battaini, A. Granata, E. Monzani, M. Gullotti, L. Casella, *Adv. Inorg. Chem.* 2006, 58, 185- 233.

[3] M. Rolff, J. Schottenheim, H. Decker, F. Tuczek, *Chem. Soc. Rev.*, 2011, 40, 4077-4098.

[4] M. Rolff, J. Schottenheim, G. Peters, F. Tuczek, *Angew. Chem. Int. Ed.* 2010, 49, 6438-6422.

[5] A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rübhausen, O. Troeppner, I. Ivanović-Burmazović, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, *Angew. Chem. Int. Ed*. 2013, 52, 5398-5401.

[6] I. Gamba, S. Palavicini, E. Monzani, L. Casella, *Chem. Eur. J*. 2009, 15, 12932-12936.

[7] (a) L. Santagostini, M. Gullotti, R. Pagliarin, E. Monzani, L. Casella, *Chem. Commun.* 2003, 2186-2187; (b) M. Gullotti, L. Santagostini, R. Pagliarin, S. Palavicini, L. Casella, E. Monzani, G. Zoppellaro, *Eur. J. Inorg. Chem.* 2008, 2081-2089.

[8] (a) M. C. Mimmi, M. Gullotti, L. Santagostini, G. Battaini, E. Monzani, R. Pagliarin, G. Zoppellaro, L. Casella, *Dalton Trans.* 2004, 2192-2201; (b) F. G. Mutti, M. Gullotti, L. Casella, L. Santagostini, R. Pagliarin, K. Kristoffer Andersson, M. F. Iozzi, G. Zoppellaro, *Dalton Trans.* 2011, 40, 5436-5457; (c) F. G. Mutti, G. Zoppellaro, M. Gullotti, L. Santagostini, R. Pagliarin, K. Kristoffer Andersson, L. Casella, *Eur. J. Inorg. Chem.* 2009, 554-566.

[9] A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rübhausen, O. Troeppner, I. Ivanović-Burmazović, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, *Angew. Chem. Int. Ed.* 2013, 52, 5398-5401.

Reactivity of copper-α-synuclein peptide complexes relevant to Parkinson's disease

Simone DELL'ACQUA, [a] Cecilia ANZANI, [a] Valentina PIROTA, [a] Michela M. ROCCO, [a] Daniela VALENSIN, [b] Enrico MONZANI, [a] Luigi CASELLA [a]

a) Dipartimento di Chimica, Università di Pavia, via Taramelli 12, Pavia, Italy
b) Dipartimento di Chimica, Università di Siena, Via A. De Gasperi 2, Siena, Italy
simone.dellacqua@unipv.it

Parkinson's (PD) disease is a neurodegenerative disorder characterized by the presence of abnormal α-synuclein (αSyn) deposits in the brain. [1]. At the same time, alterations in metal ion homeostasis and metal-induced oxidative stress and the related formation of reactive oxygen species (ROS) may play a crucial role in the progression of αSyn amyloid assembly and pathogenesis of PD.

ROS formation is indeed accelerated in the presence of redox-active metals such as copper and iron, and there is much evidence that abnormal metal homeostasis has a significant impact on the development of age-related neurodegenerative diseases. Therefore, it is essential to clarify binding of metals in different oxidation states to these proteins and the reactivity related to the metal-bound complexes.

Here, we present the oxidase reactivity of Cu(II) complexes with αSyn1-15 and αSyn1-6 peptides towards phenolic and catecholic substrates. As for Cu-Aβ, the activity is promoted by the reducing agent MBTH [2]. The oxidation proceeds with a biphasic behavior, with a fast initial step followed by a slower turnover rate compared to free Cu(II) ion. This behavior is likely due to a structural rearrangement in the coordination sphere of Cu(II) and Cu(I). We have recently shown by NMR and CD spectroscopy that αSyn is bound to Cu(I) and the isoelectronic Ag(I) in a linear two-coordinate mode with two Met residues [3] (Figure 1).

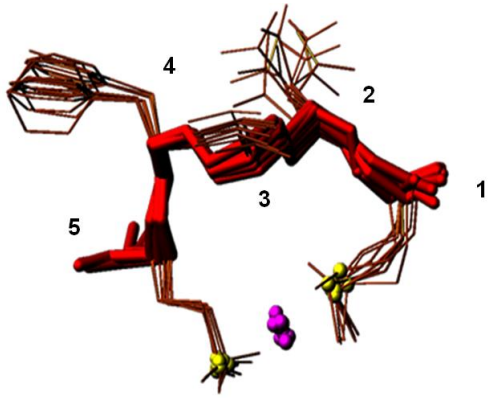


Figure 1 – Superimposition of the first 10 structures obtained for the $\alpha S_{1\text{-}15}$-Ag(I) complex. The structures are fitted on the 1-5 backbone residues (MDVFM). The model structures were obtained by integrating NMR signals with Cara program and converted with CALIBA of the program package DYANA. The sulfur donor atoms of Met 1 and Met 5 are shown as yellow spheres. The silver ion is shown as a magenta sphere.

Moreover, reactivity studies have been also performed in sodium dodecyl sulfate (SDS) micelles as a membrane-mimetic environment. In this case, different reactivity is due the structural rearrangement of the unstructured 1-15 peptide to an α-helix conformation. In particular, the oxidation of catecholic substrates is quenched in the presence of the micelles due to the formation of stable Cu(I)-peptide complex. Structural characterization of this complex and potential implications in the pathogenesis of PD will be discussed.

References:

[1] M.G.Spillantini, M.L.Schmidt, V.M.Y.Lee, J.Q.Trojanowski, R.Jakes, M.Goedert, α-Synuclein in Lewy bodies. *Nature* , 1997, 338, 839-840

[2] D.Ciregna, E.Monzani, G.Thiabaud, S.Pizzocaro, L.Casella, Copper-amyloid-□ peptide(1-16) exhibits neither monooxygenase nor superoxide dismutase activities. *Chem.Comm*., 2013, 49, 4027-4029

[3] F.Camponeschi, D.Valensin, I.Tessari, L.Bubacco, S.Dell'Acqua, L.Casella, E.Monzani, E.Gaggelli, G.Valensin, Copper (I)-α-Synuclein interaction: structural description of two independent and competing metal binding sites. *Inorg.Chem*., 2013, 52, 1358-1367

The effect of the metal ions on the active centre of colicin E7 nuclease

Eszter NÉMETH, [a] Gabriella SCHILLI, [a] Csilla KONCZ, [a] Anikó CZENE, [a] Milan KOŽÍŠEK [b] Hans E.M. CHRISTENSEN, [c] Kyosuke NAGATA, [d] Béla GYURCSIK [a]

[a] Department of Inorganic and Analytical Chemistry and MTA-SZTE Bioinorganic Chemistry Research Group, University of Szeged, Dóm tér 7, H-6720 Szeged, Hungary. [b] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Gilead Sciences and IOCB Research Center, Flemingovo namestí 2, 166 10 Prague 6, Czech Republic. [c] Department of Chemistry, Technical University of Denmark, Kemitorvet, Building 207, 2800 Kgs. Lyngby, Denmark. [d] Nagata Special Laboratory, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Japan.
e-mail: gyurcsik@chem.u-szeged.hu

Colicin E7 is a bacterial toxin released by *Escherichia coli*. Its nuclease domain (NColE7) enters the foreign bacterial cell and digests its nucleic acids nonspecifically. The host cell is protected by the Im7 immunity protein, blocking the binding site of the substrate. The catalytic centre of the nuclease consists of a Zn^{2+}-binding HNH motif at the C-terminus. The metal ion is coordinated by three His residues, H544, H569 and H573 and it is required for the catalytic activity [1]. However, it was found, that the enzyme is active in the presence of other transition metal ions, as well [2]. Also, for other HNH motif containing nucleases different metal ions were suggested to build up the active centre. In order to learn more about the role of the transition metal ions in the active centre of nucleases we have expressed and purified the NColE7 protein, N-terminally truncated mutants with 4 or 25 amino acids deleted [3] and one flexible point mutant exerting T454A/K458A/W464A amino acid changes (Figure 1).

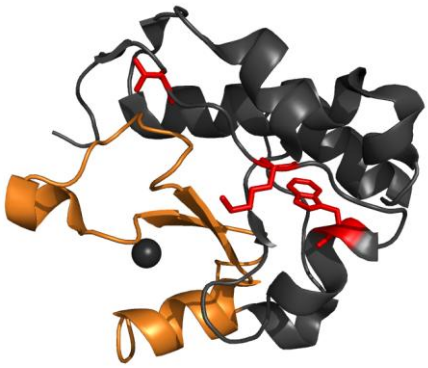


Figure 1. *The crystal structure of Zn^{2+}-bound NColE7 (PDB Id:1M08) with the HNH motif in gold, and the mutated amino acids in red.*

With these proteins we have performed metal ion binding studies by means of various techniques, such as circular dichroism spectroscopy, mass spectrometry and isothermal calorimetric titrations to check the stability and the structural effect of the metal ions on the active centre and the whole protein. The shorter truncated protein and the point mutant

showed impaired zinc(II)-binding and the structure of these proteins significantly differed from the native NColE7 enzyme. The results may allow us to conclude structure-activity relationships for NColE7 and in general for the HNH nucleases in the context of the metal ion exchange in the active centre. The recent results of this project will be presented.

Acknowledgement: Financial support of OTKA-NKTH CK80850, JSPS and TÁMOP 4.2.4.A/2-11-1-2012-0001 'National Excellence Program' is greatly acknowledged.

References:

[1] Doudeva, L.; Huang, D.; Hsia, K.; Shi, Z.; Li, C.; Shen, Y.; Cheng, Y.; Yuan, H. *Protein Sci.* **2006,** 15, 269-280.
[2] Ku, W.; Liu, Y.; Hsu, Y.; Liao, C.; Liang, P.; Yuan, H.; Chak, K. *Nucl. Acids Res.* **2002,** 30, 1670-1678.
[3] Czene, A.; Németh, E.; Zóka, IG.; Jakab-Simon, NI.; Körtvélyesi, T.; Nagata, K.; Christensen, HEM.; Gyurcsik, B. *J. Biol. Inorg. Chem.* **2013,** 18, 309-321.

Interaction of Silver Salts, Nanoparticles and Complexes with Bacterial and Yeast Cell Components

Iryna GONCHAROVA[a], **Oleksiy LYUTAKOV**[b], **Marie URBANOVÁ**[c]

[a] *Department of Analytical Chemistry Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic,* ***gonchari@vscht.cz***
[b] *Department of Solid State Engineering, Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic*
[c] *Department of Physics and Measurement, Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic*

The origin of the bioactivity of Ag(I) compounds is currently unknown. The fact that silver compounds do not destroy mammalian cells makes them prospective agents in drug design.

The antibacterial effects and mechanism of action of silver were investigated for *Escherichia coli* and *Saccharomyces cerevisiae* by analysing the morphology and ultrastructure of the cells that were grown on PMMA matrix contained various silver compounds (Ag(I) complexes of amino- and hydroxyacids, Ag(I) salts and Ag nanoparticles). Release of the Ag^+ ions and Ag(0) nanoparticles and their interactions with the cells and their components were studied by combination of circular dichroism, absorption and fluorescence spectroscopies. Transmission electron microscopy showed considerable changes in both the cell membranes and intracellular structures and two ways of the antimicrobial activity of the studied Ag compounds were tested.

In the first case, interactions with the bacterial cell wall components (peptidoglycans, polysaccharides and proteins) were studied. In the second case, a systematic chiroptical study on Ag(I) complexes interactions with nucleotides, RNA, and DNA was made. In the case of DNA, strong coordination of Ag(I) to G-C pair was observed. It was also found, that even in the case of nucleotides, the formation of the Ag(I)-mediated base pairs and their self-assembles were observed in wide pH range. Based on the obtained data, in the first time, the formation of the Ag(I)-mediated self-assembled species of cytidine and its derivatives with a structure similar to the i-motif structure in DNA was proposed.

Acknowledgements
The work was supported by the Grant agency of the Czech Republic (P205/12/P584)

Surfaces modified with gold nanostars for a Near-IR switchable photothermal antibacterial action

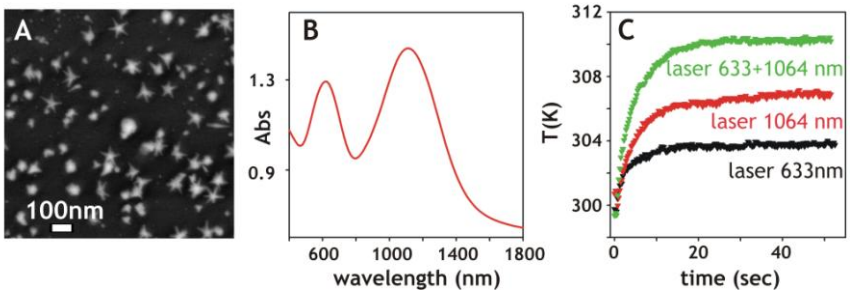
Piersandro PALLAVICINI,[a]* Simone BASILE,[a] Giacomo DACARRO,[a] Alice DONÀ,[a] Giuseppe CHIRICO,[b] Laura SIRONI,[b] Andrea FALQUI,[c],Pietro GRISOLI[d]

[a)]Department of Chemistry, University of Pavia - Italy; [b)]Department of Physics "G.Occhialini", University Milano Bicocca - Italy; [c)]IIT, Istituto Italiano di Tecnologia, Genova – Italy; [d)]Department of Pharmacological Sciences, University of Pavia – Italy

piersandro.pallavicini@unipv.it

Coating of surfaces with monolayers of gold nanostars (GNS) produces materials with microgram/cm^2 quantities of Au. These are capable of efficient local heating by photothermal conversion of laser radiation at wavelengths matching the GNS plasmon resonances (LSPR). When LSPRs are placed in the Near-IR window in which blood and tissues are semitransparent, GNS monolayers may be used on protheses as biolfilm eradicators in non invasive laser treatments.[1]

We recently described a new type of GNS with a regular five-branched shape, featuring three LSPRs,[2] two of which are positioned at will in two NIR ranges, 650-900nm ($LSPR_1$) and 1000-1600 nm ($LSPR_2$). We have now found that these five-branched GNS form monolayers on glass slides, pre-coated with a grafted PEI-silane layer. Adhesion takes place by immersion in the GNS colloidal solutions and the density of the GNS monolayer is kinetically regulated by dipping time. Gold surface concentrations in the 2.25-6.32 μg/cm^2 are obtained (calculated by aqua regia etching + ICP OES analysis). Partially coated slides can be prepared (SEM image, Figure A, absorption spectrum Figure B). The photothermal properties of the coated slides are remarkable: laser irradiation on $LSPR_1$ or $LSPR_2$ produces ΔT proportional to GNS surface density and to the laser power (eg ΔT_1 = +4 and ΔT_2 = +6 °C for dilute coating, laser power 30 mW, λ_1 633 nm, λ_2 1064 nm, thermograms in Figure C). Simultaneous irradiation of $LSPR_1$ and $LSPR_2$ yields a total T increase equal to $\Delta T_1 + \Delta T_2$, introducing the interesting case of a surface where the spot hit by the laser beams can be switched among three levels of temperature. Moreover, free surface areas can be filled with Ag nanoparticles, yielding mixed surfaces displaying both the intrinsic antibacterial effect of Ag NP and the photothermal antibiofilm action of GNS. Finally, metal complexes with further antibacterial action can be grafted on the upper, free surface of the metal nanoparticles, adding a synergic activity.



References:

[1] P.Pallavicini et al., *Chem. Commun.*, **2014**, 50, 1969-1971;

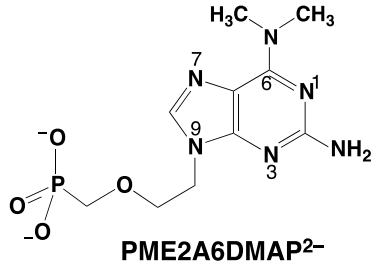
[2] P. Pallavicini et al., *Chem. Commun.*, **2013**, 49, 6265-6267

The Peculiar Metal Ion-Coordinating Properties in Solution of the Antiviral and Cytostatic Nucleotide Analogue 9-[2-(Phosphonomethoxy)ethyl]-2-amino-6-dimethylaminopurine (PME2A6DMAP)

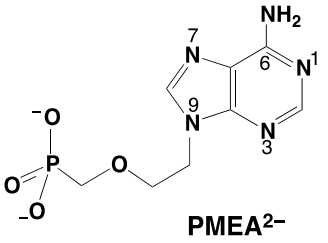
Astrid SIGEL, Helmut SIGEL

Department of Chemistry, Inorganic Chemistry, University of Basel, Spitalstrasse 51, CH-4056 Basel, Switzerland; e-mail: Helmut.Sigel@unibas.ch

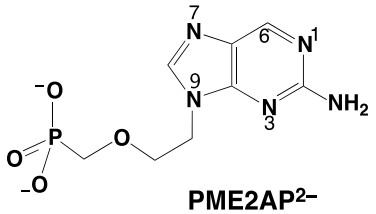
The metal ion-binding properties of the acyclic nucleotide analogue PME2A6DMAP have been studied and it was shown [1] that the (C2)NH_2 and (C6)$N(CH_3)_2$ substituents suppress any metal ion interaction of the purine residue with a phosphonate-coordinated divalent metal ion (M^{2+}). This is different for the previously studied [2, 3] and also antivirally active [3, 4] 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), where the (C6)NH_2 group screens N1 and to some extent N7, but allows a metal ion interaction with N3 via the ether oxygen of the "aliphatic" chain [5]. On the other hand, the PMEA isomer 9-[2-(phosphonomethoxy)ethyl]-2-aminopurine (PME2AP), which lacks biological activity (apparently due to the absence of a C6 substituent [6, 7]) but has a (C2)NH_2 unit, which screens N3 (and N1), but not N7, allows the phosphonate-coordinated M^{2+} to form a macrochelate with N7 [8, 9].



PME2A6DMAP^{2-}

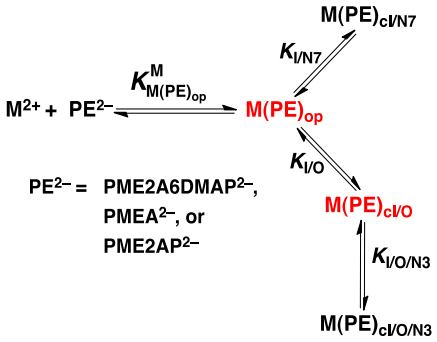


PMEA^{2-}



PME2AP^{2-}

All the indicated isomers are summarized in the equilibrium scheme (1). The various isomers are: $M(PE)_{op}$ = M^{2+} coordinated at the phosphonate group only; $M(PE)_{cl/N7}$ = macrochelate of the PO_3^{2-}-coordinated M^{2+} with N7; $M(PE)_{cl/O}$ = 5-membered chelate (see Eq 2); $M(PE)_{cl/O/N3}$ = next to the 5-membered chelate also a 7-membered one is formed involving N3.



$$K^{M}_{M(PE)_{op}} = [M(PE)_{op}]/([M^{2+}][PE^{2-}]) \qquad (1a)$$

$$K_{I/N7} = [M(PE)_{cl/N7}]/[M(PE)_{op}] \qquad (1b)$$

$$K_{I/O} = [M(PE)_{cl/O}]/[M(PE)_{op}] \qquad (1c)$$

$$K_{I/O/N3} = [M(PE)_{cl/O/N3}]/[M(PE)_{cl/O}] \qquad (1d)$$

The two isomers given in the equilibrium scheme in RED are the important ones for the M(PME2A6DMAP) complexes. This conclusion is based on the stability constants of the M(H;PME2A6DMAP)$^+$ and M(PME2A6DMAP) complexes (M^{2+} = Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} or Cd^{2+}), which were determined by potentiometric pH titrations

in aqueous solution (25°C; I = 0.1 M, $NaNO_3$) [1]. The application of previously determined straight-line plots of log $K^{M}_{M(R\text{-}PO_3)}$ *versus* p$K^{H}_{H(R\text{-}PO_3)}$ for simple phosph(on)ate ligands, R-PO_3^{2-}, where R represents a residue that does not affect metal ion binding [2, 10], proves that all the M(PME2A6DMAP) complexes have larger stabilities than is expected for a sole phosphonate coordination of M^{2+}. Comparison with previous results obtained for M(PME-R) complexes [11, 12], where R is a non-coordinating residue at the (phosphonomethoxy)ethane chain, R–CH_2–CH_2–O–CH_2–PO_3^{2-}, allows the conclusion [1] that the increased stability of all the M(PME2A6DMAP) complexes is due to the formation of 5-membered chelates (Eq 2) involving the ether-oxygen atom: The formation degrees of these $M(PME2A6DMAP)_{cl/O}$ chelates [1], which occur in intramolecular equilibria (Eq 2) for the mentioned metal ions, vary between about 20% (Sr^{2+}, Ba^{2+}) and 50% (Zn^{2+}, Cd^{2+}), going up to 67% (Cu^{2+}) in the maximum.

(2)

Furthermore, the "unique" non-coordinating properties of the 2-amino-6-dimethylaminopurine residue [in contrast to the 2-amino- ($PME2AP^{2-}$) and 6-aminopurine residue ($PMEA^{2-}$)] allow the formation of monoprotonated $M(H;PME2A6DMAP)^{+}$ complexes in which the proton *and* the metal ion are located at the phosphonate group [1]. This is a further very important result because it reflects the metal ion-binding properties of a single-negatively charged phosphoryl diester bridge in a nucleic acid.

Supported by the Department of Chemistry of the University of Basel.

References:

[1] Gómez-Coca, R. B.; Sigel, A.; Operschall, B. P.; Holý, A.; Sigel, H., *Can. J. Chem.* **2014**, 92, in press (issue in honor of Barry Lever).
[2] Sigel, H., *Coord. Chem. Rev.* **1995**, 144, 287-319.
[3] Sigel, H., *Chem. Soc. Rev.* **2004**, 33, 191-200.
[4] De Clercq, E.; Holý, A., *Nature Rev. Drug Discovery* **2005**, 4, 928-940
[5] Gómez-Coca, R. B.; Kapinos, L. E.; Holý, A.; Vilaplana, R. A., Gonzalez-Vilchez, F.; Sigel, H., *J. Chem. Soc., Dalton Trans*. **2000**, 2077-2084.
[6] Holý, A.; Günter, J.; Dvořáková, H.; Masojídková, M.; Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E., *J. Med. Chem.* **1999**, 42, 2064-2086.
[7] Holý, A., *Antiviral Res.* **2006**, 71, 248-253.
[8] Fernández-Botello, A.; Operschall, B. P.; Holý, A.; Moreno, V.; Sigel, H., *Dalton Trans.* **2010**, 39, 6344-6354.
[9] Sigel, A.; Operschall, B. P.; Sigel, H., *Coord. Chem. Rev*. **2012**, 256, 260-278.
[10] Sigel, H.; Kapinos, L. E., *Coord. Chem. Rev.* **2000**, 200-202, 563-594.
[11] Blindauer, C. A.; Holý, A.; Sigel, H., *Coll. Czech. Chem. Commun.* **1999**, 64, 613-632.
[12] Fernández-Botello, A.; Griesser, R.; Holý, A.; Moreno, V.; Sigel, H., *Inorg. Chem.* **2005**, 44, 5104-5117.

Synthesis, spectral characterization, anticancer activity and theoretical studies on some Schiff bases

Tiziana PIVETTA,[a] Claudia FATTUONI,[a] Federica TRUDU,[a] Elisa VALLETTA,[a] Elisa CARTA,[b] Roberta MELIS,[b] Alessandra PANI,[b]

[a] Dipartimento di Scienze Chimiche e Geologiche, [b] Dipartimento di Scienze Biomediche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato CA - ITALY; tpivetta@unica.it

The Schiff bases and their metal complexes exhibit wide applications in biological systems and are of great interest in the fields of coordination chemistry and material sciences [1-3]. In the last years, these molecules have received a particular attention for their pharmacological properties, soft-hard donor character and coordination ability.

Although the solution equilibria of the Schiff bases are widely studied in literature [4-5], a direct comparison of the reported data and then of their chemical and physicochemical properties, is difficult because different experimental conditions (solvent, temperature, ionic strength) have been used. Moreover, the possible presence of tautomeric equilibria makes problematic the study of the protonation constants (macro and micro).

In this work, the use of IR-ATR spectroscopy, together with NMR, Uv-Vis and potentiometry measurements, was investigated on some Schiff bases with the aim to collect useful information on the species actually formed. Theoretical studies were also performed. As preliminary data, results of the solution studies of the compounds reported in Table 1 and their cytotoxic activity on some human cancer-derived cell lines, are presented. In Figure 1 some Uv-Vis spectra recorded during the potentiometric titration of **3** are reported.

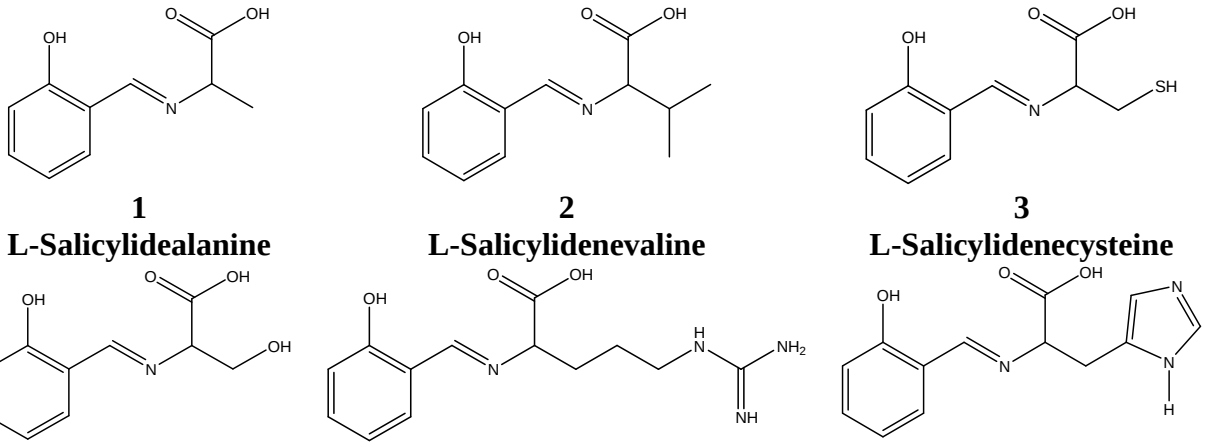


Table 1. Formulas, names and acronyms of the compounds studied in this work.

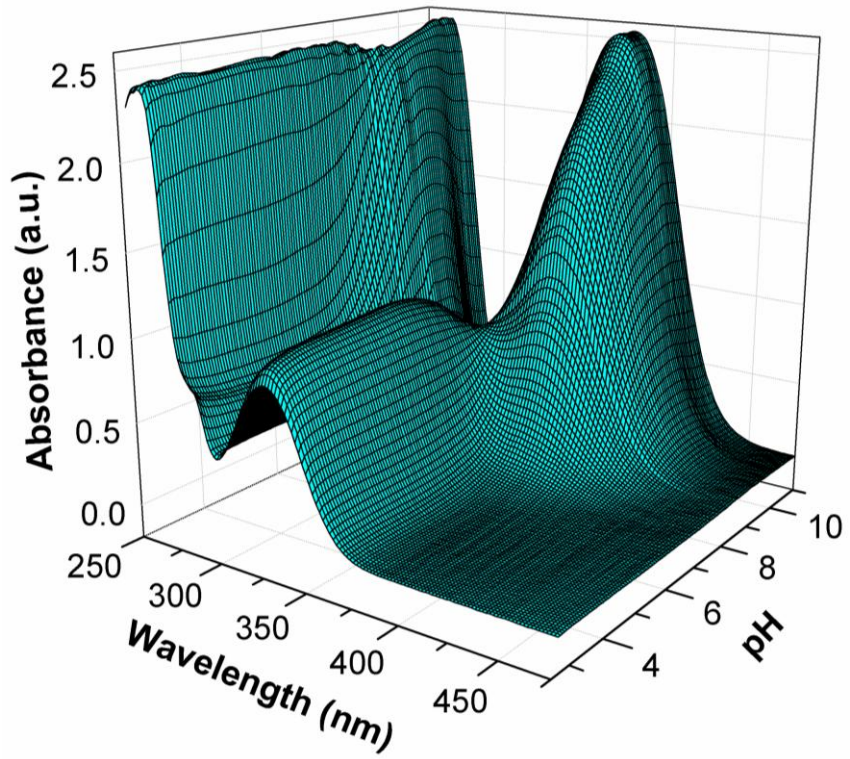


Figure 1. UV-Vis spectra recorded during the potentiometric titration of **3** ($8.0 \cdot 10^{-4}$ mol/L, 25 °C, 0.1 M NaCl, l = 1cm).

References:

[1] Dudek, G.O.; Dudek, F.P., Spectroscopic Studies of Keto-Enol Equilibria. IX. N15-Substituted Anilides. *J. Am. Chem. Soc*. **1966**, 88, 2407-2412

[2] Cohen, M.D.; Flavian, S., Topochemistry. Part XXV. The Absorption Spectra of Some N-Salicylideneanilines and Related Anils in Solution. *J. Chem. Soc. (B)* **1967**, 317-328

[3] J. Costamagna, J. Vargas, R. La Torre, A. Alvarado, G. Mena, Coordination compounds of copper, nickel and iron with Schiff bases derived from hydroxynaphthaldehydes and salicylaldehydes. *Coord. Chem. Rev.* **1992**, 119, 67–88

[4] Khouba, Z.; Benabdallah, T.; Maschke, U., Spectrophotometric investigation of interaction between iodine and pentadentate Schiff base ligands, *Spectrochimica Acta - Part A: Mol. and Biomol. Spectroscopy* **2014**, 61-66

[5] Kołodziej, B; Grech, E.; Schilf, W.; Kamieński, B.; Pazio, A.; Woźniak, K., The NMR and X-ray study of l-arginine derived Schiff bases and its cadmium complexes. *Journal of Molecular Structure* **2014**, 145-152

C,N-chelated Organotin(IV) Pseudohalides: Synthesis, Characterization and Reactivity Studies.

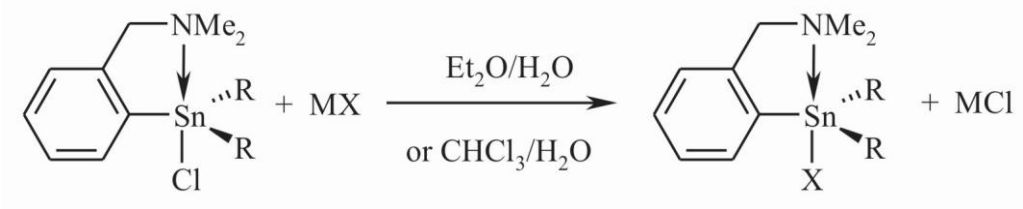
Petr ŠVEC,[a] Zdeňka PADĚLKOVÁ,[a] Aleš RŮŽIČKA [a]

a)Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, Pardubice, Czech Republic, CZ-532 10.
E-mail: petr.svec2@upce.cz

Organotin(IV) species bearing the 2-(N,N-dimethylaminomethyl)phenyl- moiety as a C,N-chelating ligand (LCN) are studied since seventieth of the last century.[1] Significant intramolecular contact between tin and nitrogen atoms is the typical phenomenon for this class of compounds. Both structure and reactivity of C,N-chelated organotin(II and IV) species has been studied thoroughly at our department, too.[2]

Recently, we have prepared and structurally characterized some organotin(IV) azides bearing either C,N-chelating or bulky bis(trimethylsilyl)amido ligands.[3] These compounds were prepared by the oxidative addition of trimethysilylazide towards the corresponding stannylenes.

Now we report on the synthesis of some novel C,N-chelated organotin(IV) pseudohalides (e.g. azides, cyanates, isothiocyanates, cyanides, and selenocyanates). These species can be prepared simply by the reaction of starting C,N-chelated organotin(IV) halide with excess of corresponding metal pseudohalide in a biphasic system (Scheme 1).



Scheme 1: Synthesis of some *C,N*-chelated organotin(IV) pseudohalides (M = K or Na; R = *n*-Bu or Ph; X = SCN, OCN, CN or SeCN)

Preparation, structural characterization and some reactivity studies of these novel species will be discussed in detail.

Acknowledgement: The authors would like to thank the Czech Science Foundation (grant no. P207/12/0223) for the financial support.

References:

[1] Jastrzebski, J. T. B. H.; Van Koten, G.; Intramolecular Coordination in Organotin Chemistry. *Adv. Organomet. Chem.* **1993**, 35, 241-294 and references cited therein.

[2] For example see: a) Švec, P.; Růžička, A.; Use of *C,N*-chelated triorganotin(IV) fluoride for fluorination of organic compounds, coordination compounds, phosphines, silanes and stannanes. *Main Group Met. Chem.* **2011**, 34, 7-25. b) Růžička, A.; Padělková, Z.; Švec, P.; Pejchal, V.; Česlová, L.; Holeček, J.; Quest for triorganotin(IV) compounds containing three *C,N*- and *N,C,N*-chelating ligands. *J. Organomet. Chem.* **2013**, 732, 47-57. c) Padělková, Z.; Švec, P.; Pejchal, V.; Růžička, A.; Activation of E-Cl Bonds (E = C, Si, Ge and Sn) by a *C,N*-chelated Stannylene. *Dalton Trans.* **2013**, 42, 7660–7671.

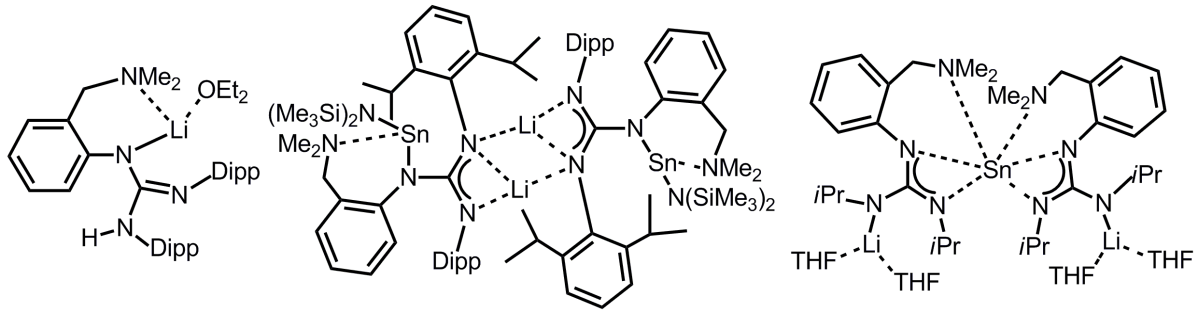
[3] Švec, P.; Padělková, Z.; Alonso, M.; De Proft, F.; Růžička, A.; Comparison of Reactivity of *C,N*-chelated and Lappert's Stannylenes with Trimethylsilylazide. Can. J. Chem. *accepted*.

Structural Differences of Lithium Complexes Containing Hybrid Amino/Guanidinate Ligands

Jana NEVORALOVA,[a] Zdenka PADELKOVA,[a] Ales RUZICKA[a]

[a] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentska 573, CZ-532 10, Pardubice, Czech Republic.
e-mail: ales.ruzicka@upce.cz

Complexes of metals, from nearly whole the Periodic Table, containing amidinate/guanidinate ligands, or its variations, are frequently tested as catalysts of various organic chemistry transformations in the present time.[1, 2] Moreover the application of these complexes as precursors of new materials [3] together with stabilization of unusual[4], generally lower, oxidation states of metals in its complexes opened new areas of chemistry. The essential step of synthesis of metal guanidinates is the preparation of lithium guanidinate



precursors, which in contrary to the target compounds are rarely described in the literature.[5].

Figure 1 – Schematic view of some compounds studied.

Synthesis, structure and applications in catalysis of various hybrid guanidinate lithium, dilithium and tin (as a model of oxidisable and reducible metal center with ambiphilic Lewis character) complexes with an extra donating amino group(s) will be presented (Fig. 1) along with the reactivity of these compounds with different metal halides and amides.

Acknowledgement: The financial support of the Czech Science Foundation (Project no. P207/12/0223) is gratefully acknowledged.

References:

[1] (a) Edelmann, F. T., Lanthanide amidinates and guanidinates: from laboratory curiosities to efficient homogeneous catalysts and precursors for rare-earth oxide thin films, *Chem. Soc. Rev.*, **2009**, 38, 2253-2268; (b) Collins, S., Polymerization catalysis with transition metal amidinate and related complexes, *Coord. Chem. Rev.*, **2011**, 255, 118-138.

[2] for some recent references see: (a) Yu, Z.-T.; Yuan, Y.-J.; Cai, J.-G.; Zou, Z.-G., Charge-Neutral Amidinate-Containing Iridium Complexes Capable of Efficient Photocatalytic Water Reduction, *Chem. Eur. J.*, **2013**, 19, 1303 – 1310; (b) Kratsch, J.; Kuzdrowska,

M.; Schmid, M.; Kazeminejad, N.; Kaub, C.; Oña-Burgos, P.; Guillaume, S.M.; Roesky, P.W., Chiral Rare Earth Borohydride Complexes Supported by Amidinate Ligands: Synthesis, Structure, and Catalytic Activity in the Ring-Opening Polymerization of rac-Lactide, *Organometallics*, **2013**, 32, 1230–1238.

[3] for example: Krasnopolski, M.; Hrib, C.G.; Seidel, R.W.; Winter, M.; Becker, H.-W.; Rogalla, D.; Fischer, R.A.; Edelmann, F.T.; Devi, A., Homoleptic Gadolinium Amidinates as Precursors for MOCVD of Oriented Gadolinium Nitride (GdN) Thin Films, *Inorg. Chem.*, **2013**, 52, 286–296.

[4] for example: (a) Jones, C., Bulky guanidinates for the stabilization of low oxidation state metallacycles, *Coord. Chem. Rev.*, **2010**, 254, 1273–1289; (b) Sen, S.S.; Khan, S.; Nagendran, S.; Roesky, H.W., Interconnected Bis-Silylenes: A New Dimension in Organosilicon Chemistry, *Acc. Chem. Res.*, **2012**, 45, 578–587; (c) Inoue, S.; Epping, J. D.; Irran, E.; Driess, M.; Formation of a Donor-Stabilized Tetrasilacyclobutadiene Dication by a Lewis Acid Assisted Reaction of an N-Heterocyclic Chloro Silylene, *J. Am. Chem. Soc.*, **2011**, 133, 8514–8517; (d) Chlupatý, T.; Padělková, Z.; Lyčka, A.; Brus, J.; Růžička, A., Reactivity of lithium n-butyl amidinates towards group 14 metal(II) chlorides providing series of hetero- and homoleptic tetrylenes, *Dalton Trans.*, **2012**, 41, 5010-5019.

[5] Chlupaty, T.; Olejnik, R.; Ruzicka, A., In: F.L. Tabarés, Ed., Lithium: Technology, Performance and Safety, Chapter 4, Nova Science Publishers, Inc., Hauppauge NY, **2013**.

Monomer or aggregate? Solution chemistry applications to today's problems

Tarita BIVER,[a,b] Francesco CRISCITIELLO,[a] Amanda DA SILVA,[a] Andrea PUCCI,[a,b] Izadora RAMOS LIMA,[a] Fernando SECCO,[a] Marcella VENTURINI [a]

[a] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy. Tel: +39 0502219270; fax: +39 0502219320; [b] INSTM, Unità di Ricerca di Pisa, Via Risorgimento 35, 56126 Pisa, Italy; tarita.biver@unipi-it

Solution chemistry and reliable equilibria analysis can non-negligibly contribute to recent challenges, even using relatively simple experiments and approaches.

Studies aimed to analyse if a molecule is present in the form of a monomer or undergoes auto-aggregation processes, depending on different surroundings conditions, can deserve interest and find practical applications. For instance, analysis of the micelle formation process of amphiphilic block copolymers, dependent on external parameters such as temperature or pH, deserves high interest in connection to the applications in diverse areas as for instance enhanced oil recovery. [1]

We will present some aspects of the analysis of small molecules aggregation that we are dealing with in our group.

Thioflavin-T (4-(3,6-dimethyl-1,3-benzothiazol-3-ium-2-yl)-N,N-dimethylaniline, TFT) is a fluorescent emicyanine dye (Figure 1) which acts as a molecular rotor.[2]

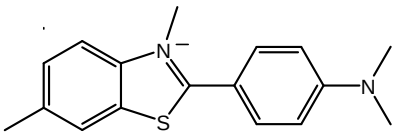


Figure 1. Molecular structure of Thioflavin-T (TFT).

The interest on TFT molecule stays on its peculiar photophysical properties, which can find application in biochemistry and medicine. TFT has been used as common marker in biomedical research over the last 50 years but, more recently, TFT has become a major tool to recognise amyloid fibrils, both in vivo and in vitro.[2,3] The ability to selectively bind to the fibrils, in particular at the level of β-sheet and at hydrophobic amino acid residues, is also correlated to the tendency to auto-aggregate. Therefore, we have analysed, by a thermodynamic and kinetic approach, the mechanistic details of TFT auto-aggregation process and TFT binding to natural DNA.

Carbon nanotubes (CNTs) are well known allotropes of carbon that are nowadays widely studied as their unique (thermal, electrical) properties can find application in materials science and frontier technologies.[4] However, both single walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) being hydrophobic, these tend to agglomerate, deeply limiting their performances.[5,6] It is therefore important to stabilise the CNTs dispersions either by chemical modification of their surface or by interaction with species that are bound

to the surface by van der Waals forces (π–π stacking interactions). In the frame of the study of the optical, metal ion binding, and dispersing properties of different types of perylene dye derivatives,[7] we have analysed if the Pery-MeI dye (Figure 2) could efficiently disperse MWNT solutions.

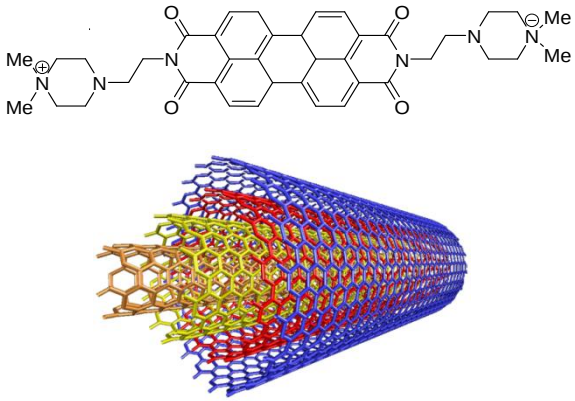


Figure 2. Perylene dye (Pery-MeI, above) used for MWNTs (below) stabilisation.

References:

[1] Raffa, P.; Brandenburg, P.; Wever, D. A. Z.; Broekhuis, A. A.; Picchioni, F., Polystyrene−Poly(sodium methacrylate) Amphiphilic Block Copolymers by ATRP: Effect of Structure, pH, and Ionic Strength on Rheology of Aqueous Solutions. *Macromolecules*, **2013**, 46, 7106−7111.

[2] N. Amdursky, N.; Erez, Y.; Huppert, D., Molecular rotors: what lies behind the high sensitivity of the thioflavin-T fluorescent marker. *Accounts of Chemical Research*, **2012**, *45*, 1548-1557.

[3] Ban, T.; Hamada, D.; Hasegawa, K.; Naiki, H., Goto, Y., Direct observation of amyloid fibril growth monitored by thioflavin T fluorescence. *Journal of Biological Chemistry*, **2003**, 278, 16462-16465.

[4] Park, H. G.; Jung, Y., Carbon nanofluidics of rapid water transport for energy applications. *Chemical Society Reviews*, **2014**, 43(2), 565-576.

[5] Zhu, S.-E.; Li, F.; Wang, G.-W., Mechanochemistry of fullerenes and related materials. *Chemical Society Reviews*, **2013**, 42(18), 7535-7570.

[6] Adeli, M.; Soleyman, R.; Beiranvand, Z.; Madani, F., Carbon nanotubes in cancer therapy: a more precise look at the role of carbon nanotube-polymer interactions. *Chemical Society Reviews*, **2013**, 42(12), 5231-5256.

[7] Donati, F.; Pucci, A.; Ruggeri, G., *Physical Chemistry Chemical Physics*, **2009**, 11, 6276-6282.

5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one molecule as an intriguing tool in coordination and enzymatic studies.

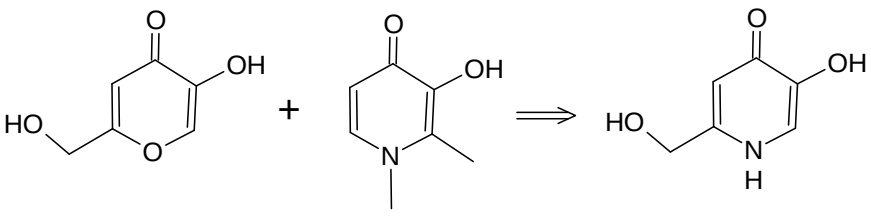
Joanna I. LACHOWICZ, [a] Valeria M. NURCHI, [a] Guadalupe JARAQUEMADA PELAEZ, [a] Leonardo TOSO, [a] Miriam CRESPO-ALONSO, [a] Peter GANS, [b] M. Amelia SANTOS, [c]

[a] Dipartimento di Scienze Chimiche e Geologiche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy, [b] Protonic Software, Leeds, U.K. [c] Centro Quimica Estrutural, Instituto Superior Tecnico, Universidade de Lisboa, Av. Rovisco Pais,1049-001 Lisboa, Portugal; lachowicz@unica.it

Chelation therapy is practiced to remove excess iron from the body in patients suffering from iron overload or iron toxicity. Since the seventies of last century the drug desferal (desferrioxamine) was used very successfully for this purpose, despite its limitations: it is expensive, has a short half-life inside the body and cannot be administered orally. Deferiprone (1,2- dimethyl-3-hydroxy-4-pyridinone), introduced in 2000, is both cheaper and can be administered orally, even if it cannot totally replace desferal [1]. The dose required with deferiprone is rather high compared to desferal and this chelator may have adverse side effects in patients [2]. A major reason for the limited efficacy of deferiprone is that it is quite quickly metabolized in the liver [3].

In previous studies we reported the complex formation equilibria of Fe(III) and Cu(II) with deferiprone [1] and of Fe(III) and Al(III) with kojic acid [4]. In the framework of our research, we have now synthesized a new ligand, 5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one, which combines properties of both kojic acid and deferiprone.

Complex formation of this ligand with Fe(III), Al(III), Zn(II) and Cu(II) has been studied by means of potentiometry, spectrophotometry and NMR. Equilibrium data have been processed with the use of the latest versions of HypNMR, Hyperquad2013 and HypSpec2014 [5]. The speciation was confirmed by electrospray ionization-mass spectrometry (ESI-MS), and quantum chemical calculations. We obtained intriguing results that give new regard on complex formation of pyridinone complexes.



Scheme showing the relation of 5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one with kojic acid and deferiprone.

Both kojic acid and deferiprone have been studied as tyrosinase inhibitors [6,7]. It has been suggested that their inhibitory activity is connected with the formation of copper-

containing coordination complexes [6]. 5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one has been found to be a useful tool for the study of the mechanism of tyrosinase inhibition.

References:

[1] Nurchi, V.M.; Crisponi, G.; Pivetta, T.; Donatoni, M.; Remelli, M., Potentiometric, spectrophotometric and calorimetric study on iron (III) and copper (II) complexes with 1, 2-dimethyl-3-hydroxy-4-pyridinone. *Journal of Inorganic Biochemistry* **2008**, 102, 684-692.

[2] Brittenham, G.M., Development of iron-chelating agents for clinical use. *Blood* **1992**, 80, 569-574.

[3] Liu, Z.D.; Khodr, H.H.; Liu, D.Y.; Lu, S.L.; Hider, R.C., Synthesis, physicochemical characterization, and biological evaluation of 2-(1'-hydroxyalkyl)-3-hydroxypyridin-4-ones: Novel iron chelators with enhanced pFe3+ values. *Journal of medicinal chemistry* **1999**, 42, 4814-4823.

[4] Nurchi, V.M.; Crisponi, G.; Lachowicz, J.I.; Murgia, S.; Pivetta, T.; Remelli, M.; Rescigno, A.; Niclós-Gutíerrez, J.; González-Pérez, J.M.; Domínguez-Martín, A., Iron (III) and aluminum (III) complexes with hydroxypyrone ligands aimed to design kojic acid derivatives with new perspectives. *Journal of Inorganic Biochemistry* **2010**, 104, 560-569.

[5] http://www.hyperquad.co.uk.

[6] Battaini, G.; Monzani, E.; Casella, L.; Santagostini, L.; Pagliarin, R., Inhibition of the catecholase activity of biomimetic dinuclear copper complexes by kojic acid. JBIC *Journal of Biological Inorganic Chemistry* **2000**, 5, 262-268.

[7] Liu, Z.D.; Lockwood, M.; Rose, S.; Theobald, A.E.; Hider, R.C., Structure–activity investigation of the inhibition of 3-hydroxypyridin-4-ones on mammalian tyrosine hydroxylase. *Biochemical pharmacology* **2001**, 61, 285-290.

Comprehensive modelling capability for aqueous solution thermodynamics: progress

Darren ROWLAND, [a] **Peter MAY** [a]

[a] *Chemistry, Murdoch University, Western Australia; d.rowland@murdoch.edu.au*

At the present state-of-the-art, the modelling of equilibria occurring in concentrated reactive electrolyte mixtures remains problematic: the theoretical deficiencies related to calculating the activity of species in multicomponent solutions seem unlikely to be overcome soon. However, thermodynamic data for reactive systems, e.g. solubility values, are widespread in the chemical literature and need to be better utilised.

A key challenge for storing this information is expressing the complete chemistry of a large number of potentially complicated solutions – such as phosphate and borate buffers – in a compact, and ultimately machine-processable, form. The approach taken to date (e.g. [1]) records only the analytical concentrations of well-defined components. We are seeking to build the data repository which will be required in future to parameterise theoretical solution chemistry frameworks estimated to involve at least five million experimental data values.

A major issue is that existing databases do not store information relating to the chemical behaviour of the solution components that is needed for processing experimental data. We find that defining all solution species and the set of allowed reactions is necessary and sufficient for describing the chemistry of the solution.

A database system implementing this design is in development building upon our existing chemical reaction [2] and physicochemical property [3] databases. Accordingly, the new database can store a vast range of properties including solubility, pH, density, mean activity coefficients and equilibrium constants. Methods to harmonise these data, which is a preliminary step prior to extracting reliable thermodynamic parameters for modelling, are described.

References:

[1] IUPAC-NIST Solubility Database (Online), http://srdata.nist.gov/solubility/index.aspx

[2] May, P.M.; Murray, K., Database of Chemical Reactions Designed to Achieve Thermodynamic Consistency Automatically. *J. Chem. Eng. Data* **2001**, 46, 1035-1040.

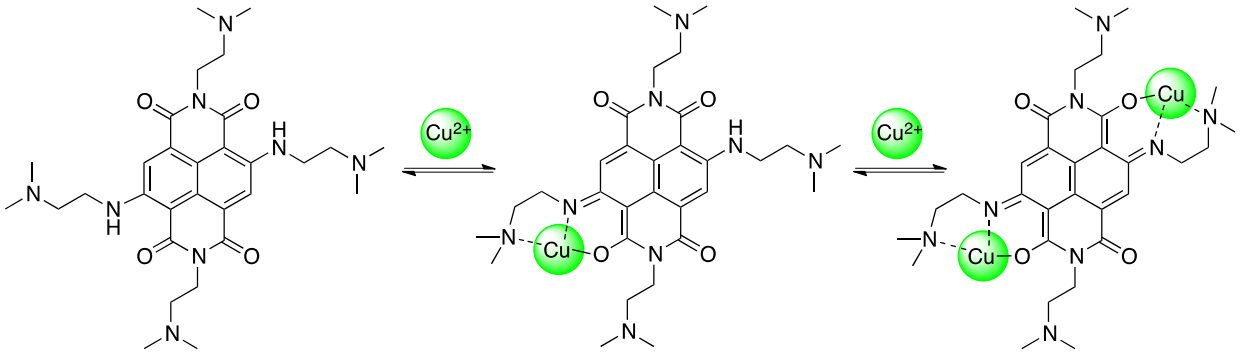
[3] May P.M.; Rowland D.; Königsberger E.; Hefter G., JESS, a Joint Expert Speciation System - IV: A Large Database of Aqueous Solution Physicochemical Properties with an Automatic Means of Achieving Thermodynamic Consistency. *Talanta* **2010**, 81, 142-148.

Naphthalenediimmides as Selective "Naked eye" Chemosensor for Copper(II) in Aqueous Solution.

Filippo DORIA, Valeria AMENDOLA, Vincenzo GRANDE, Greta BERGAMASCHI, Mauro FRECCERO.

Dipartimento di Chimica Università di Pavia; filippo.doria@unipv.it

Recently, we have studied the synthesis and the reactivity of a large family of engineered naphthalene diimide (NDI) exhibiting interesting photophysical properties [1, 4]. The present study reports synthesis and characterization of two novel colorimetric chemosensor based on naphthalene diimide (NDI) core, for a selective detection of copper ions in 100% aqueous solution. Receptors **1** and **2** are able to detect Cu^{2+} ions by a remarkable colour change with a fast response time. Moreover, we were able to determine a certain range of pH simply by observing the color change of receptors in the presence of Cu^{2+} ions. In addition, the NDI **2** is one of the few example of multisite-coordinating colorimetric sensor. In a physiological pH range it is possible to discriminate with naked eye, free ligand, the mono- and the di-nuclear complexes.



References:

[1] Doria, F.; Gallati, CM.; Freccero, M. Hydrosoluble and solvatochromic naphthalene diimides with NIR absorption. *Org Biomol Chem.* **2013,** Vol. 11, pp. 7838-42.

[2] Doria, F.; Manet, I.; Grande, V.; Monti, S.; Freccero, M. Water-soluble naphthalene diimides as singlet oxygen sensitizers. *J Org Chem.* **2013,** Vol. 78, pp. 8065-73.

[3] Doria, F.; Nadai, M.; Sattin, G.; Pasotti, L.; Richter, SN.; Mauro, Freccero. Water Soluble Extended Naphthalene Diimides as pH Fluorescent Sensors and G-Quadruplex Ligands. *Org. Biomol. Chem.*, **2012,** Vol. 10, pp. 3830-3840.

[4] Doria, F.; Di Antonio, M.; Benotti, M.; Verga, D.; Mauro, Freccero. Substituted Heterocyclic Naphthalene Diimides with Unexpected Acidity. Synthesis, Properties, and Reactivity". *J. Org. Chem.* **2009,** Vol. 74, pp. 8616–8625.

Analysis of Phosphorus and Sulfur by QQQ-ICP-MS

Glenn Woods, [a] Peter Planitz, [b] Sebastian Sannac, [c]

[a] Agilent Techn. UK
[b]Agilent Techn. Germany [c]Agilent Techn. France; peter_planitz@agilent.com

Phosphorous and Sulphur are not easily accessible by ICP-MS. A number of prominent interferences from solvent elements will compromise the achievable detection limits. This presentation will describe the merits of a commercially available ICP-Ms/Ms instrumentation for the analysis of these and a number of other elements.

Collision/Reaction Cell (CRC) technology is essential for modern ICP-MS to resolve spectroscopic interferences and to achieve sufficiently low Detection Limits (DL) or Background Equivalent Concentrations (BEC). While collision mode, using helium, offers ease of use and versatility, reaction mode can achieve superior DL/BEC in some applications. However application of reaction mode has been severely limited since chemical reactions in the cell of conventional single quadrupole ICP-QMS are so complex and unreliable that the analytical performance is often poor.

The Agilent 8800 Triple Quadrupole ICP-MS (ICP-QQQ) with MS/MS mode resolves these problems and permits reaction chemistry to be applied to the most complex and challenging interference problems 1). MS/MS mode, which is unique to ICP-QQQ, controls which ions enter the reaction cell, offering ideal reaction cell conditions 2).The reaction of S and P with O_2 is exothermic as shown below hence both elements can be measured using the reaction product ions: SO^+ and PO^+.

$S^+ + O_2 \rightarrow SO^+ + O \quad \Delta H_r = -0.34eV$

$P^+ + O_2 \rightarrow PO^+ + O \quad \Delta H_r = -3.17eV$

In addition the now available correct isotopic information for Sulphur allows the observation of isotopic spiked species as well as their transformation in chemical or biological reactions.

References:

[1] J. T. Rowan and R. S. Houk, Applied Spectroscopy, vol.43, 976, 1989
[2] Agilent 8800 Triple Quadrupole ICP-MS: Understanding oxygen reaction mode in ICP-MS/MS, Agilent technical note, 5991-1708EN

Copper(II) Binding to (Tacrine-*S*-allyl)- and (Tacrine-*S*-propargyl)-cysteine as Potential Anti-Neurodegenerative Hybrid Drugs

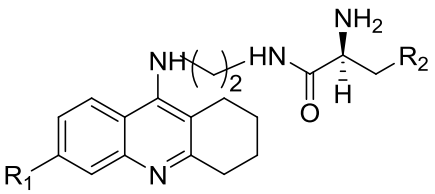
Catarina QUINTANOVA, Rangappa S. KERI, Sílvia CHAVES, M. Amélia SANTOS

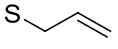
Centro de Química Estrutural, Instituto Superior Técnico, Universidade Técnica de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal; masantos@ist.utl.pt

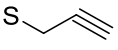
Alzheimer´s disease (AD) is a progressive neurodegenerative age-linked disease associated to dementia, cognitive deficit and memory loss, which can lead to incapacitation and dead. The AD brain shows several typical pathological features, such as accumulation of misfolded amyloid-*β* (A*β*), metal ion (Cu, Zn, Fe) dyshomeostasis and elevated oxidative stress. Moreover, metal ions, such as Cu and Zn, bind to A*β* peptides enabling their aggregation, as well as dysregulated redox active metal ions, Cu(I/II) and Fe(II/III), promote overproduction of reactive oxygen species (ROS) with consequent disruption of biological molecules such as proteins, DNA and lipids. Due to the multifactorial nature of AD and to the potential interconnection of various factors in its pathogenesis, there is still absence of a drug for AD cure. Tacrine (TAC) was the first drug approved for AD that demonstrated improvement on the cholinergic system and on memory loss due to inhibition of acetylcholine esterase (AChE) [1], even though some limitations associated to its therapeutic use abolished this drug from clinical application.

To overcome TAC drawbacks, this compound has been used as an inspiration for the development of multi-target analogues in conjugation with moieties such as melatonin, hydroxyquinoline or thioflavine, in order to combine the AChE inhibition with antioxidant properties, metal-binding capacity and/or inhibition of Aβ aggregation.

Continuing our research on the development of multifunctional heterocyclic compounds with potential application in AD [2-4], and taking also in account the recent interest on the neuro-protective role of some natural products, two hybrid compounds containing TAC and also *S*-allyl-cysteine (SAC, garlic constituent) or *S*-propargyl-cysteine (SPRC, attenuator of spatial learning and memory impairment [5]) moieties were designed and studied.



Tacrine-SAC R_1 = Cl R_2 = 

Tacrine-SPRC R_1 = H R_2 = 

Based on the hypothesis that AD brains suffer from metallostasis, it has been world widely accepted that metal chelators can interfere in metal-induced Aβ aggregation and neurotoxicity, and so, beyond the assessment of several biological properties of TAC-SAC and TAC-SPRC, these compounds were also studied in terms of their acid-base behavior as well as chelating capacity towards Cu(II). We report herein the results of those studies, which involved various techniques such as UV/Vis spectrophotometry, ^{1}H NMR and potentiometry. Both compounds showed a moderate chelating power towards Cu(II), analogous to that of cysteine (pCu = 6.3), and also that, at the physiological pH and micromolar metal concentration ($C_L = 10 \times C_M$), CuL is the predominant complex species. The reasonable effect of compounds on the inhibition of Cu-induced Aβ aggregation seems slightly more relevant for the allylic derivative (TAC-SAC) which might be rationalized by some apparent differences on the coordination modes. The anti-oxidant and biological activities (AChE inhibition, neuroprotection) of both compounds were also assessed and reported herein, providing an insight on their potential mechanism as anti-neurodegenerative drug candidates.

References:

[1] Giacobini, E., Invited Review Cholinesterase inhibitors for Alzheimer's disease therapy: from tacrine to future applications. *Neurochem. Int.* **1998**, 32(5-6), 413-419.

[2] Keri, R.S.; Quintanova, C.; Marques, S.M.; Esteves, A.R.; Cardoso S.M.; Santos, M.A., Design, synthesis and neuroprotective evaluation of novel tacrine-benzothiazole hybrids as multi-targeted compounds against Alzheimer's disease. *Bioorg. Med. Chem.,* **2013**, 21(15), 4559-4569.

[3] Nunes, A.; Marques, S.M.; Quintanova, C.; Silva, D.F.; Cardoso, S.M.; Chaves, S.; Santos, M.A., Multifunctional iron-chelators with protective roles against neurodegenerative diseases. *Dalton Trans.*, **2013**, 42, 6058-6073.

[4] Sebestík, J.; Marques, S.M.; Falé, P.L.; Santos, S.; Arduíno, D. M.; Cardoso, S. M.; Oliveira, C.R.; Serralheiro, M.L.; Santos, M.A., Bifunctional phenolic-choline conjugates as anti-oxidants and acetylcholinesterase inhibitors. *J. Enzyme Inhib. Med. Chem.*, **2011**, 26(4), 485-497.

[5] Gong, Q.H.; Wang, Q.; Pan, L.L.; Liu, X.H.; Xin, H.; Zhu, Y.Z., S-propargyl-cysteine, a novel hydrogen-sulfide modulated agent, attenuates lipopolysaccharide-induced spatial learning and memory impairment: involving of TNF signaling and NF-kB pathway in rats. *Brain Behav. Immun.* **2011,** 25 (1), 110-119.

Cr(VI) removal by using exhausted coffee waste: from synthetic solutions to industrial effluents

Chang LIU,[a] Núria FIOL,[a] Marc BARTROLÍ,[a] Jordi POCH,[b] Isabel VILLAESCUSA[a]

[a] Chemical Engineering Department, Escola Politècnica Superior, Universitat de Girona, Avda. Lluís Santaló, s/n, 17071 Girona (Spain)
[b] Applied Mathematics Department, Escola Politècnica Superior, Universitat de Girona, Avda. Lluís Santaló, s/n, 17071 Girona (Spain);
chang.liu@udg.edu

During the last decade our research group has been investigating the potential application of vegetable wastes for water treatment. Sorption performance of several materials such as olive stones, cork, grape stalks, yohimbe bark [1] and exhausted coffee [2] has been evaluated. Exhausted coffee waste (EC) generated in soluble coffee production resulted to be effective for the removal of Cr(VI) in the presence of divalent metal ions [3]. The objective was to develop a sustainable technology based on EC as sorbent for the treatment of wastewater with a special emphasis in those contaminated with hexavalent chromium. In this work, we present the results and goals achieved in the treatment of synthetic solutions first and the application of the technology to industrial effluents.

In order to evaluate the efficiency of the sorbent to remove Cr(VI) in binary mixtures, 4 synthetic solutions with different mixtures of Cr(VI) and Cu(II) (0.6 mM Cr(VI)-0.4 mM Cu(II), 0.4 mM Cr(VI)-0.6 mM Cu(II), 6 mM Cr(VI)-2 mM Cu(II) and 6 mM Cr(VI)-4 mM Cu(II)) were prepared. All the sorption studies were performed in a 5 L stirred batch reactor under continuous agitation (350 rpm) at 20±2^{o}C using 27 g of EC (0.5-1.0 mm) until equilibrium was reached. Sampling was performed at interval times to determine Cr(VI), Cr(III) and Cu(II) concentrations in order to obtain the corresponding kinetics profile. Afterwards the filtered solution was discharged to another reactor to proceed with metal ions precipitation by the addition of flocculating agents to eliminate the remaining metal ions in solution. Two different flocculating agents $FeCl_3$ and $Al_2(SO_4)_3 \cdot 18H_2O$ were used. Once the overall process conditions were established the technology was applied to the treatment of industrial effluents from an electroplating industry which contain metal ions and other compounds.

The results proved the efficiency of the proposed technology based on exhausted coffee for the treatment of industrial wastewater containing Cr(VI), other metal ions and other compounds. Higher than 99% of Cr(VI) can be removed by EC sorption/reduction step from both synthetic solutions and industrial effluents. In the precipitation step, the formed Cr(III) accounting for 15%-30% of the initial Cr(VI) at equilibrium together with other metal ions can be almost totally eliminated by using $FeCl_3$ which resulted to be the most efficient flocculating agent. After the overall water treatment process, metal ions concentrations were far below the regulated discharge limits.

The proposed technology based on exhausted coffee waste biosorption appears to be sustainable and promising for the detoxification of industrial effluents containing hexavalent chromium.

References:

[1] Fiol, N.; Villaescusa, I.; Martínez, M.; Miralles, N.; Poch, J.; Serarols, J., Biosorption of Cr(VI) using low cost sorbents. Environmental Chemistry Letters 2003, 1 (2), 135-139.
[2] Fiol, N.; Escudero, C.; Villaescusa, I., Re-use of exhausted ground coffee waste for Cr(VI) sorption. Separation Science and Technology 2008, 43 (3), 582-596.
[3] Pujol, D.; Bartrolí, M.; Fiol, N.; de la Torre, F., Villaescusa, I.; Poch, J., Modelling synergistic sorption of Cr(VI), Cu(II) and Ni(II) onto exhausted coffee wastes from binary mixtures Cr(VI)-Cu(II) and Cr(VI)-Ni(II). Chemical Engineering Journal 2013, 230 (15), 396-405.

Acknowledgements:
This work has been financially supported by the Spanish Ministry of Economy and Competitiveness, Spain, Project CTM2012-37215-C02-01. A Ph.D fellowship from Chinese Scholarship Council was attributed to Chang Liu.

The specificity of Zn^{2+}, Ni^{2+}, Cd^{2+}, Cu^{2+} and Bi^{3+} ions interactions with the unstructured domains of ZIP transporters

Slawomir POTOCKI, [a] **Daniela VALENSIN,** [b] **Henryk KOZLOWSKI** [a]

[a] *Faculty of Chemistry, University of Wroclaw, ul. Joliot-Curie 14, 50-383 Wroclaw, Poland*
[b] *Department of Biotechnology, Chemistry and Pharmacy, via Aldo Moro 2, 53100 Siena, Italy;*
slawomir.potocki@chem.uni.wroc.pl

ZIP proteins are transmembrane metal transporters. They are built of 6 - 8 transmembrane domains (TMDs) and intra/extracellular loops. Their function is to increase divalent metal ions concentration, e.g. Zn^{2+}, Fe^{2+}, Mn^{2+} and even Cu^{2+} within the cell cytoplasm [1,2]. Not much is known about the mechanism of their action till now. Moreover, they are evolutionarily related and have structural similarities to a prion proteins [1], what make them extremely interesting to study.

The metal complexes of different ZIP proteins domains have been thoroughly investigated. Among studied unstructured domains we may list: (i) multi-cysteine N- terminus of ZIP13 [3] (Fig.1), (ii) metal selectivity loop of IRT1 protein (between II and III TD) [4] and (iii) metal binding multi-histidine loop (between III and IV TD) of TjZNT1 ZIP family transporter [5]. Metal complexes with these protein fragments revealed very interesting behavior, sometimes even surprising. The stability of the ZIP13 complexes formed in solution changes in the series Bi^{3+} >> Cd^{2+} > Zn^{2+} > Ni^{2+}, the strongest being for bismuth and the weakest for nickel. An interesting coordination mode has been proposed for the IRT1-Zn^{2+} complex, in which imidazoles from two histidines (His-96 and His-116), a cysteine thiolate (Cys-109) and one of a glutamic acid carboxyl group are involved. The stability of multi-histidine loop of TjZNT1 complexes increase in the series Ni^{2+} < Zn^{2+} << Cu^{2+}; for Zn^{2+} ions high specificity toward studied sequence have been observed.

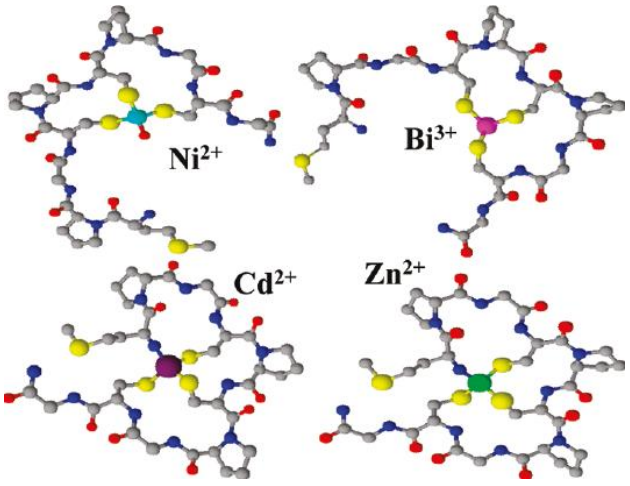


Fig. 1. ZIP13 N-terminus complexes with Ni^{2+}, Zn^{2+}, Cd^{2+} and Bi^{3+}.

References:

[1] Kozlowski, H.; Potocki, S.; Remelli, M.; Rowinska-Zyrek, M.; Va lensin, D., *Coord. Chem Rev.* **2013**, 257(19-20), 2625-2638.
[2] Potocki, S.; Rowinska-Zyrek, M.; Witkowska, D.; Pyrkosz, M.; Szebesczyk, A.; Krzywoszynska, K.; Kozlowski, H., *Curr. Med Chem.* **2012**, 19, 2738-2759.
[3] Potocki, S.; Rowinska-Zyrek, M.; Valensin, D.; Krzywoszynska, K.; Witkowska, D.; Luczkowsk, M.; Kozlowski, H., *Inorg. Chem.* **2011**, 50, 6135-45.
[4] Potocki, S.; Valensin, D.; Camponeschi, F.; Kozlowski, H., *J. Inorg. Chem.* **2013**, 127, 246-252.
[5] Potocki, S.; Valensin, D.; Kozlowski, H., *Dalton Trans.* **2014**, submitted.

POSTER COMMUNICATIONS

Metallacrowns: Metallacrowns-based innovative materials and supramolecular devices

Matteo TEGONI,[a] Elżbieta GUMIENNA-KONTECKA,[b] Stéphane PETOUD,[c] Talal MALLAH,[d] Igor FRITSKY,[e] Vincent L. PECORARO,[f]

[a] Department of Chemistry, University of Parma, Parco Area delle Scienze 17, 43124 Parma, Italy [b] Faculty of Chemistry, University of Wroclaw, Wroclaw, Poland [c] Centre de Biophysique Moléculaire, CNRS, Orléans, France [d] Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université Paris-Sud 11, Orsay, France [e] Department of Chemistry, National Taras Shevchenko University, Kiev, Ukraine [f] Department of Chemistry, University of Michigan, Ann Arbor (MI),United States; matteo.tegoni@unipr.it

In 2013, the Marie Curie project "METALLACROWNS" has been funded by the Research Executive Agency – EU as an International Research Staff Exchange Scheme (IRSES).[1,2] The objective is to support the mobility of the researchers which are involved in the design of innovative functional magnetic or fluorescent materials and probes based on metallacrown complexes.

The project involves six research groups from five countries (Italy-Coordinator, Poland, France, Ukraine and USA) with complementary expertises and the common aim to devise new metallacrown complexes with novel magnetic, photophysical and structural properties be used as tools in bio- or nanotechnological devices. In particular, the development of a common platform to promote and strengthen our joint activities will be promoted through the support of the temporary mobility of the staff members, both permanent and non-permanent (post-docs and graduate students). Through this network, we will carry out collaborative research, and we will train young researchers at the early stage of their career.

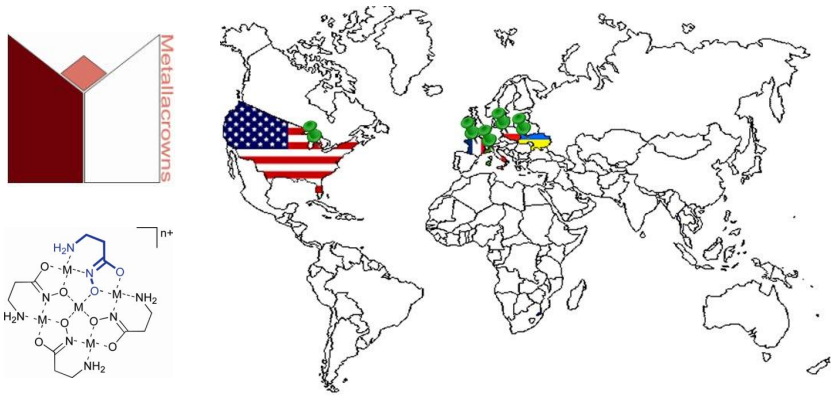


Figure 1: The IRSES Metallacrowns logo, a representation of a 12-metallacrown-4 (left), and the map of the partner countries (right).

Training aspects will be considered in the project activities: graduate students and early career scientists will significantly improve their skills and expertise through their secondments to other laboratories, while the hosting institutions will benefit from visits of

senior scientists and collaborators. Regular workshops and seminars delivered at the hosting institutions by the seconded researchers will also increase the visibility of the project: the next meeting is scheduled for 2015 and will be held at the University of Wroclaw (PL).

The duration of the Metallacrowns project is 4 years, and is organized into six work packages: design and synthesis of metallacrowns; physical methods for MC characterization; X ray structures and large MC assemblies; metallacrowns as hosts, and cytotoxicity; Luminescent probes and surfaces; magnetic MC-based materials.

This IRSES project eventually aims to establish and support multilateral transfer of knowledge and expertise among the involved EU and Extra-EU research teams. On one hand this will stimulate the aggregation of scientists into an EU to worldwide network on the research on functional materials and molecular devices, increasing in turn the competitiveness of ERA and its attractiveness to foreign researchers. On the other hand, this network will promote the set-up of new future research projects and new long-term collaborations between the partners.

References:

[1] Metallacrowns project website: https://sites.google.com/site/metallacrowns/project.
[2] http://first.aster.it/_aster_/viewNews?ID=29746.

Evidences for the biomedical applicability of supramolecular nano-capsules – structure and anticancer activity

Anife AHMEDOVA,[a] **Denitsa MOMEKOVA**,[b] **Georgi MOMEKOV**,[b] **Masahiro YAMASHINA**,[c] **Michito YOSHIZAWA** [c]

[a] *Faculty of Chemistry and Pharmacy, University of Sofia, 1, J. Bourchier blvd., Sofia 1164, Bulgaria;*

[b] *Faculty of Pharmacy, Medical University, 2 Dunav Street, 1000 Sofia, Bulgaria;*

[c] *Chemical Resources Laboratory, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan.*

presenting author e-mail: ahmedova@chem.uni-sofia.bg

The design and synthesis of anthracene based coordination capsules **1** have recently been reported [1,2]. The capsules have an M_2L_4 composition and provide large, hydrophobic cavity with an average volume of ~580 $Å^3$ (Fig. 1). Among the seven isostructural capsules, the Pd(II) and Pt(II) ones have been proved as ideal hosts for encapsulating a variety of organic molecules [3,4]. Guest encapsulation takes place in mixed organic-aqueous solutions and is governed by hydrophobic and aromatic interactions. The formed host-guest complexes are easily characterized by NMR and MS measurements.

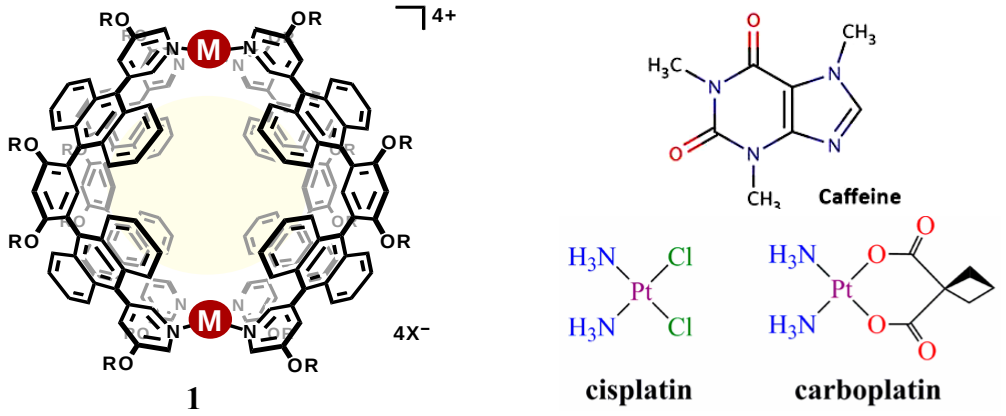


Figure 1. Structure of the coordination capsules **1** where (M = Pd(II) or Pt(II), and R = $CH_2CH_2OCH_3$) and some of the tested guest molecules

The synergistic effect of caffeine (our best guest molecule) to the cis-DDP activity is reported in the literature. Accordingly, we set up our cytotoxicity experiments on three types of cancer cell lines (HL-60, SKW and t-24) so that the potential application of the Pt-capsule for drug delivery can be estimated. In our experimental conditions the caffeine itself does not affect the cis-DDP activity. However, the Pt-capsule, empty or loaded with caffeine, does increase the anticancer activity of cis-DDP by almost twice (Fig. 2). The results on the anticancer activity of the empty Pt-capsule **alone** shows that it has activity comparable to that of cis-DDP. Analysis of the results suggests that the effect of the Pt-capsule on the cis-DDP anticancer activity is not a simple additive increase but some synergism is also operative. A

possible explanation could be a capsule-facilitated transport of the drug through the cancer cells membrane.

Our recent results on the anticancer activity against cis-platin resistant cell lines indicated additional positive effect of the Pt-capsule. While cis-DDP shows no activity when treated alone or with caffeine, a very good cytotoxicity was obtained when treated together with the Pt-capsule. These results show that the Pt-capsule not only increases the cis-DDP activity (against the non-resistant cancer cells) but it also helps the drug to overcome the aquired cis-DDP-resistance retaining its cytotoxicity. The obtained data are very promising for removing the shortcomings in the cis-DDP-based chemotherapy (e.g. high general toxicity and side effects) that imply strict dose limitations, and therefore will be further elaborated.

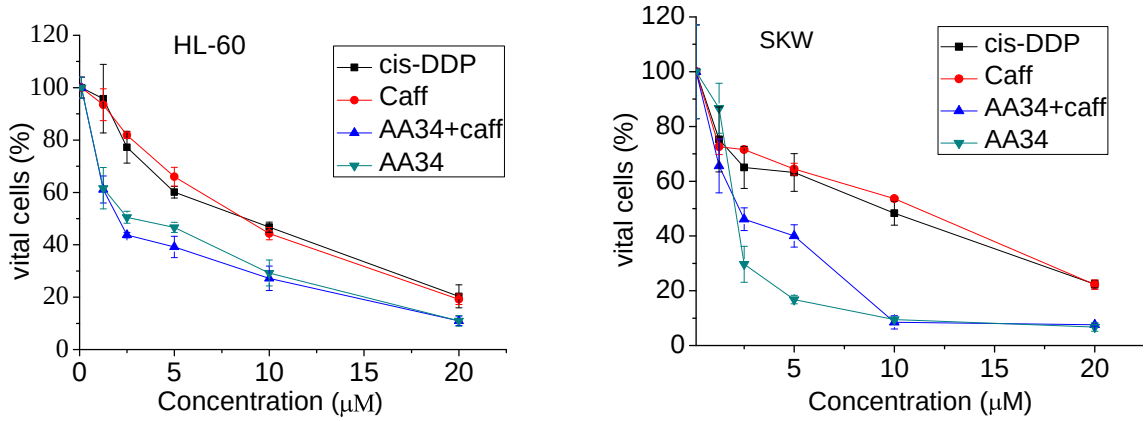


Figure 2. Concentration dependent cytotoxicity against human cancer cell lines HL-60 and SKW of the platinum drug cis-DDP in presence of equivalent amounts of caffeine, Pt-capsule (AA34) and Pt-capsule loaded with caffeine (AA34+caff).

Acknowledgements:
A.A. is grateful to The Matsumae International Foundation for the financial support of her research activities in Japan.

References:

[1] Li, Z., Kishi, N., Yoza, K., Akita, M., Yoshizawa, M., Isostructural M_2L_4 Molecular Capsules with Anthracene Shells: Synthesis, Crystal Structures, and Fluorescent Properties. *Chem. Eur. J.,* **2012**, 18, 8358–8365.

[2] Li, Z., Kishi, N., Hasegawa, K., Akita, M., Yoshizawa, M., Highly Fluorescent M_2L_4 Molecular Capsules with Anthracene Shells. *Chem. Commun.*, **2011**, 47, 8605–8607

[3] Kishi, N., Li, Z., Sei, Y., Akita, M., Yoza, K., Siegel, J. S., Yoshizawa, M., Wide-Ranging Host Capability of a Pd(II)-Linked M_2L_4 Molecular Capsule with an Anthracene Shell. *Chem.–Eur. J.,* **2013**, 19, 6313–6320.

[4] Kishi, N., Li, Z., Yoza, K., Akita, M., Yoshizawa, M., An M_2L_4 Molecular Capsule with an Anthracene Shell: Encapsulation of Large Guests up to 1 nm. *J. Am. Chem. Soc.,* **2011**, 133, 11438–11441;

Advances in Amino-Maltolic derivatives: Calcium vs. Magnesium Selectivity, Anion Binding and Biological Activity of Metal Complexes

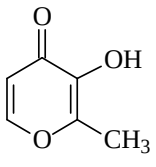
Gianluca AMBROSI, [a] Stefano AMATORI, [b] Mirco FANELLI, [b] Mauro FORMICA, [a] Vieri FUSI, [a] Luca GIORGI, [a] Eleonora MACEDI, [a] Mauro MICHELONI, [a] Paola PAOLI, [c] Patrizia ROSSI [c]

[a] Department of Basic Sciences and Fundamentals, University of Urbino, P.za Rinascimento 6, I-61029 Urbino, Italy; [b] Molecular Pathology and Oncology Lab. 'PaoLa', Department of Biomolecular Sciences, University of Urbino, Arco d'Augusto 2, I-61032 Fano (PU), Italy; Department of Industrial Engineering, University of Florence, Via S. Marta 3, I-50139 Florence, Italy; eleonora.macedi@uniurb.it

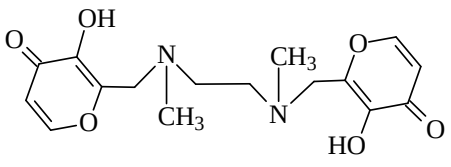
Metal complexes form the base of the most common receptor systems, finding multiple applications due to their intriguing properties. In this view, metallo-receptors are normally used to interact with anions or neutral species, exploiting the coordination properties of the metal center, although positively charged guests can also be hosted. In this case, the metal ion mainly serves to pre-organize the hosting area and is usually not directly involved in the interaction with the guest.

Recently, we developed a class of molecules based on two 3-hydroxy-2-methyl-4-pyrone units (Maltol) linked to a polyamine scaffold that exhibits anti-neoplastic activity *in vitro* and *in vivo* [1].

Some compounds of this class also show coordination properties towards M^{2+} transition metal ions which are stabilized by the polyamine functions and by the deprotonated hydroxyl oxygen atom of each maltol function [2]. The involvement of both maltol units in the coordination of the transition M^{2+} ion brings them to converge the four oxygen atoms forming an electron-rich area that allows the transition metal complexes to bind hard metal ions. Among these, the alkaline earth series (AE) is significant and, from a biological point of view, calcium and magnesium are the most important as they are cofactors in many enzymes and cover a wide spectrum of functions. On the other hand, their discrimination and recognition in solution is quite difficult, due to their chemical similarity. As a consequence, the selective detection and recognition in the series, in particular magnesium *vs* calcium, is a challenging and important target of research.



Maltol



Malten

Here, we extended the binding studies of the complex formed with Cu^{2+} by Malten compound and its capacity to behave as metallo-receptor for the series of alkaline earth metal ions. Malten forms the highly stable $[CuH_{-2}\mathbf{L}]$ species in water which was used as a metallo-receptor for the alkaline earth series (AE) in aqueous solution at physiological 7.4 pH. This species is able to bind all of the main metal ions of the series (Ca^{2+}, Sr^{2+} and Ba^{2+}), with the exception of Mg^{2+}, exhibiting the

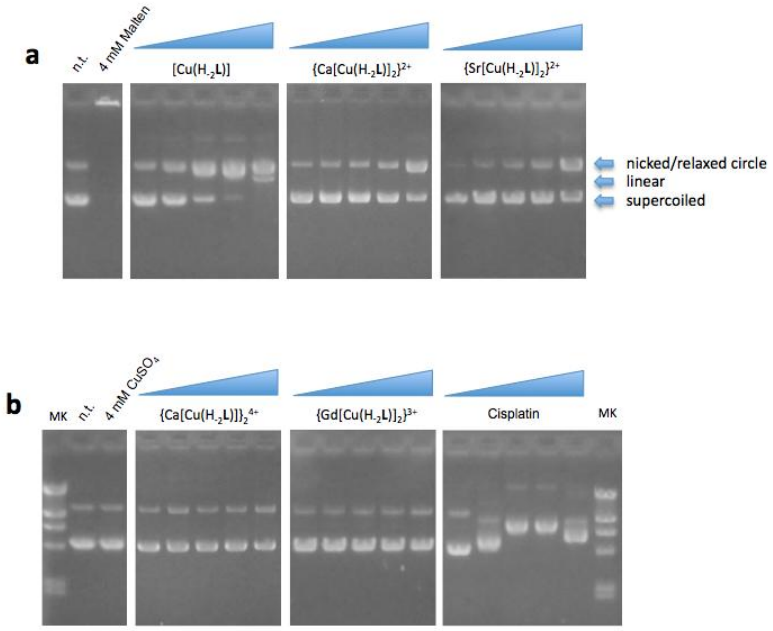
important property to selectively discriminate Ca^{2+} versus Mg^{2+} in water. The binding of the AE ion is visible to the naked eye.

The stability constant values of the tri-nuclear $\{AE[Cu(H_{-2}\mathbf{L})]_2\}^{2+}$ species formed reach the maximum for Ca^{2+}.

Ca^{2+} also forms a tetra-nuclear $\{Ca[Cu(H_{-2}\mathbf{L})]\}_2^{4+}$ species at high Ca^{2+} concentration. Tri- and tetra-nuclear calcium complexes show blue and pink colored crystals, respectively.

The tetra-nuclear complex was further investigated as a chemosensor for anions.

Finally, we also reported the biological potential of all of the up to now characterized metal complexes of Malten in terms of the ability to induce DNA structural alterations. The latter are compatible with the hydrolytic cleavages of the DNA.



References:

[1] a) Amatori, S.; Bagaloni, I.; Fanelli, M.; Formica, M V. Fusi, V.; Giorgi, L.; Macedi, E. *Brit. J. Cancer.*, **2010**, *103*, 239-248; b) Amatori, S.; Ambrosi, G.; Fanelli, M.; Formica, M.; Fusi, V.; Giorgi, L.; Macedi, E.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P. *J. Org. Chem.*, **2012**, *77*, 2207-2218; c) Guerzoni, C.; Amatori, S.: Giorgi, L.; Manara, M. C.; Landuzzi, L.; Lollini, P.-L.; Tassoni, A.; Balducci, M.; Manfrini, M.; Pratelli, L.; Serra, M.; Picci, P.; Magnani, M.; Fusi, V.; Fanelli, M.; Scotlandi, K. *BMC Cancer* **2014**, *14*,137.

[2] a) Borgogelli, E.; Formica, M.; Fusi, V.; Giorgi, L.; Macedi, E.; Micheloni, M.; Paoli, P.; Rossi, P. *Dalton Trans.* **2013**, *42*, 5848–5859; b) Benelli, C.; Borgogelli, E.; Formica, M.; Fusi, V.; Giorgi, L.; Macedi, E.; Micheloni, M.; Paoli, P.; Rossi, P. *Dalton Trans.* **2013**, *42*, 2902–2912.

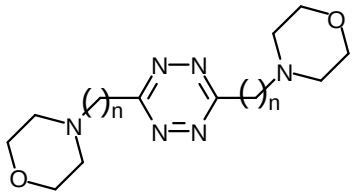
Anion Complexes with Tetrazine-based Ligands

Carla BAZZICALUPI, [a] Antonio BIANCHI, [a] Celeste GARCÍA,[b] Claudia GIORGI,[a] Manuel MELGUIZO GUIJARRO,[b] Maria Dolores LÓPEZ de la TORRE,[b] Fabio PICHIERRI, [c]

[a] Department of Chemistry "Ugo Schiff", University of Florence, via della Lastruccia 3, 50019 Sesto Fiorentino, Italy [b] Department of Inorganic and Organic Chemistry, University of Jaen, Campus las Lagunillas, 23071 Jaen, Spain [C] Department of Applied Chemistry, Graduate School of Engineering, Tohoku University, Sendai, Japan; Antonio.bianchi@unifi.it

Anion coordination chemistry, that is the binding of anionic species by natural and synthetic receptors, is a maturing aspect of supramolecular chemistry. Electrostatic attractions, hydrogen bonding and anion-dipole interactions, are the main non-covalent forces involved in anion binding. Very recently, it has been recognized that also the interactions between electron-deficient aromatic systems and anions, the so called "anion-π interactions" may play important roles in such association processes [1-3].

We report here some preliminary results of a solution, solid state and computational study on the interaction between two new symmetric tetrazine-based ligands, L1 and L2, containing two morpholine moieties, and a group of anions of different geometry such as F^-, NO_3^-, SO_4^{2-}, ClO_4^- and PF_6^-.



n = 1, L1
n = 2, L2

The synthesis of L1 and L2 was performed following a classical Pinner-type scheme in which a carbonitrile carrying the N-alkyl substituted morpholine moiety is reacted with hydrazine hydrate in the presence of N-acetyl-cysteine (catalyst), at room temperature under argon atmosphere, to afford a 3,5-disubstituted dihydro-1,2,4,5-tetrazine intermediate that is readily oxidized by atmospheric oxygen to yield the corresponding fully aromatic tetrazine.

The determination of thermodynamic parameters (log*K*, ΔH°, TΔS°), performed by means of potentiometric titration and isothermal titration calorimetric (ITC) experiments in aqueous 0.1M NMe_4Cl solution, at 298.1 K, showed that protonated forms a the ligands, and in several cases even the neutral ligands, give rise to fairly stable anion complexes. The stability of these complexes is mainly determined by favourable entropic contributions.

The crystal structures of the $[H_2L(ClO_4)]^+$ and $[H_2L(PF_6)]^+$ (L = L1, L2) complexes showed that, in the solid state, the interacting partners form strong anion-π interactions in addition to CH:::anion and, in the case of L2, salt-bridge contacts (Figure 1).

Density functional theory calculations (DFT, M06-2X/DGTZVP level of theory with the inclusion of solvent effects), performed starting from the experimental structures, indicate that besides the strong coulombic interaction that is operative in these complexes, anion binding is achieved through CH:::anion and anion-π interactions. Furthermore, the conformational properties of the free ligand, which can adopt a boat-like or chair-like conformation, also play a role in the anion binding process.

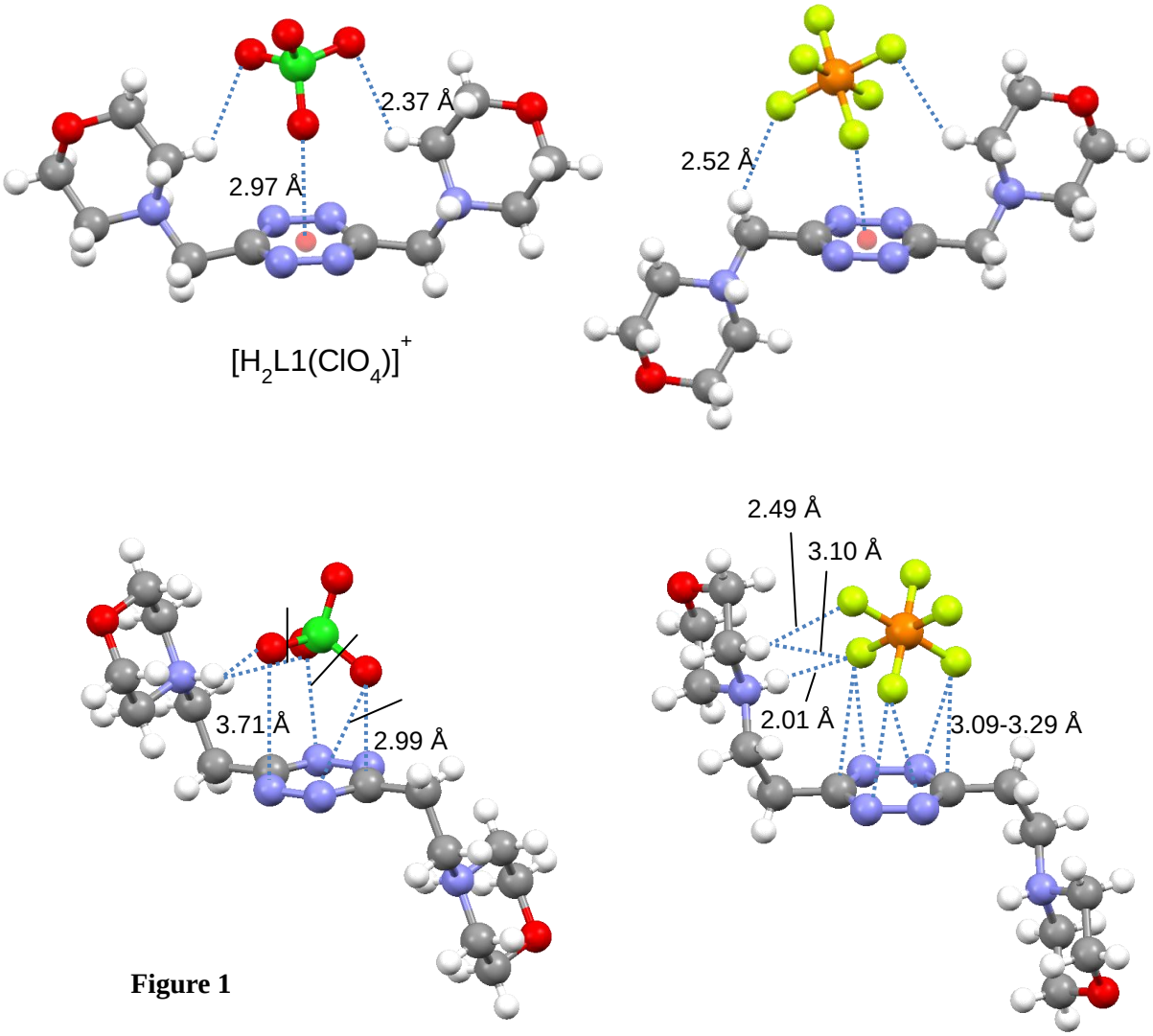


Figure 1

References:

[1] Bowman-James, K.; Bianchi, A.; Garcia-España, E. (Eds.), *Anion Coordination Chemistry*, Wiley-VCH, New York, **2012**.

[2] Sessler, J.L.; Gale, P.A.; Cho, W.S., *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, **2006**.

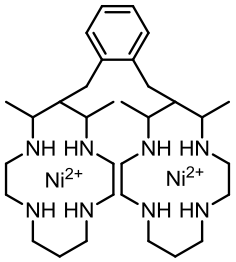
[3] Bianchi, A.; Bowman-James, K.; Garcia-España, E. (Eds.), *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, **1997**.

Solution behaviour and solid-state structures of dinickel(II) complexes with ligands containing face-to-face cyclam subunits

Massimo BOIOCCHI, [a] Luigi FABBRIZZI, [b] Nadia FUSCO, [b] Michele INVERNICI [b]

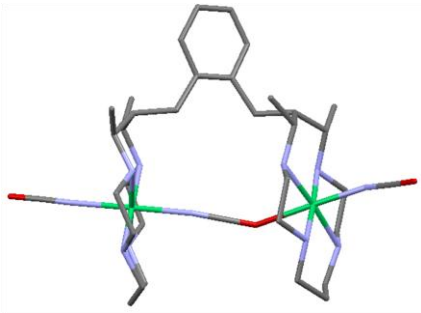
[a] Centro Grandi Strumenti, Università degli Studi di Pavia, I-27100 Pavia (PV)
[b] Dipartimento di Chimica, Università degli Studi di Pavia, I-27100 Pavia (PV);
presenting author e-mail: nadia.fusco01@unipv.it

Bicyclams and their metal complexes are promising systems in a variety of fields, from pharmacology to anion recognition.[1] The careful choice of a spacer able to arrange the two macrocyclic moieties face-to-face can define a cavity to stabilize host-guest complex formation with anionic species; the best option in this sense seems to be *o*-xylylene moiety.[2]



1

The dinickel(II) complex **1** has been synthesized and its ability to act as an anion receptor has been studied through spectrophotometric and electrochemical titration experiments in solution and diffractometric measurements in the solid state. Absorption spectra taken in various solvents point out the co-presence in solution of both diamagnetic and paramagnetic nickel, though no temperature dependent equilibrium is observed. Unlike previously reported structures with halides,[2-4] in the pseudohalide complexes (e.g $[Ni^{II}_2(\mathbf{1})(\mu\text{-NCO})(NCO)_2]^+$, see Figure) both nickel(II) ions present a high-spin configuration; this is probably due to the different shapes of these anions: rod-like pseudohalides fit the cavity better than spheric halogens and act as a real brigding ligand.



References:

[1] De Clercq, E., Inhibition of HIV Infection by Bicyclams, Highly Potent and Specific CXCR4 Antagonists. *Mol. Pharmacol.*, **2000**, 57 (5), 833-839.

[2] Kajiwara, T.; Yamaguchi, T.; Kido, H.; Kawabata, S.; Kuroda, R.; Ito, T., A Dinucleating Bis(dimethylcyclam) Ligand and Its Dinickel(II) and Dizinc(II) Complexes with the Face-to-Face Ring Arrangement. *Inorg. Chem.*, **1993**, 32 (23), 4990-4991.

[3] Kajiwara, T.; Yamaguchi, T.; Oshio, H.; Ito, T., Synthesis, Structure, and Magnetic Property of Linear Chloro-Bridged Nickel(II) Tetramer with Dinucleating Bis-dimethylcyclam Ligand. *Bull. Chem. Soc. Jpn.*, **1994**, 67 (8), 2130-2135.

[4] Szacilowski, K. T.; Xie, P.; Malkhasian, A. Y. S.; Heeg, M. J.; Udugala-Ganehenege, M. Y.; Wenger, L. E.; Endicott, J. F., Solid-State Structures and Magnetic Properties of Halide-Bridged, Face-to-Face Bis-Nickel(II)-Macrocyclic Ligand Complexes: Ligand-Mediated Interchanges of Electronic Configuration. *Inorg. Chem.*, **2005**, 44 (17), 6019-6033.

Binding studies of a dicopper(II) cryptate with dicarboxylate anions

Catarina V. ESTEVES,[a] Pedro MATEUS,[a] Rita DELGADO,[a]

[a] *Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Av. da República, 2780-157 Oeiras, Portugal; cvesteves@itqb.unl.pt*

Selective recognition of anions by artificial receptors has proved to be difficult to achieve, nevertheless the potential biomedical and environmental applications that might arise continues to interest many researchers in this field.[1] Metal complexes as receptors exhibit several advantages when compared to exclusively organic ones. The metal–anion interactions are strong enough to compensate anion dehydration energy, allowing recognition studies in water, and transition metal ions of different electronic configurations exhibit diverse geometries, introducing a further element of selectivity.[2] Macrobicycles or cryptands derived from tren (tris(2-aminoethyl)amine) subunits act as ligands for coordination of two copper(II) centers, each one with a position directed to the three-dimensional cavity, occupied in general, by the solvent. These positions can then be taken by a desired anion, given that the intermetallic distance and the shape of the formed pocket are appropriate for the formation of a cascade complex, as depicted in Figure 1.[1]

In the present work the stability constants of the dicopper(II) complex with the tren derived cryptand (t_2pN_8), shown in Figure 1, and the association constants of the dicopper(II) cryptate with dicarboxylate substrates were determined by potentiometry in aqueous solution at 298.2 K and ionic strength 0.10 M in KNO_3. The results showed that the receptor ($Cu_2t_2pN_8$) displays a larger affinity for oxalate (oxa^{2-}).

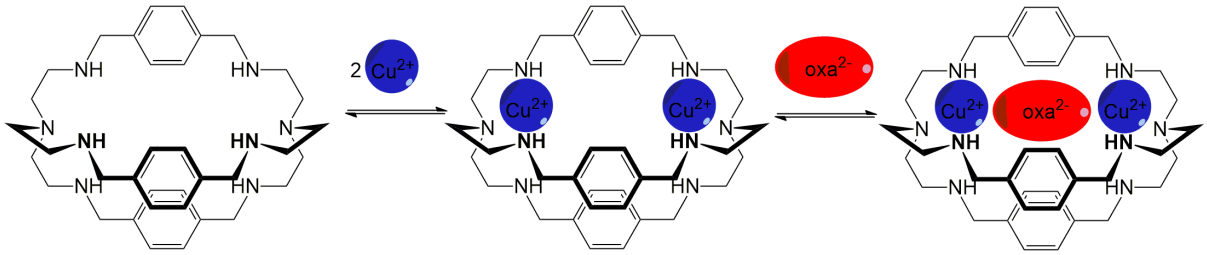


Figure 1: Representation of the cascade complex formation for a dicopper(II) cryptate in presence of oxa^{2-}.

References:

[1] Mateus, P.; Lima, L. M. P.; Delgado, R. *Polyhedron* **2013**, *52*, 25-42.
[2] Fabbrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **2013**, *42*, 1681-99.

The structural role of the fluorinated group in copper(II) complexes of the p-(trifluoromethyl)iminodiacetate chelating ligand (p3F): A co-crystal with mononuclear and dinuclear complex units.

Marina SERRANO-BRACERAS, [a] Duane CHOQUESILLO-LAZARTE, [b] Alicia DOMÍNGUEZ-MARTÍN, [a,c] Hanan EL BAKKALI, [a] Alfonso CASTIÑEIRAS, [d] Josefa María GONZÁLEZ-PÉREZ, [a] 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 Chemistry, Winterthurerstrasse 190, CH-8057 Zurich , Switzerland [d] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain; jniclos@ugr.es

In recent years a promising field of work is defined by the interest in studying intra- and inter-molecular interactions involving F-rich groups [1,2] In this connection, our research group has designed a research program to study 1RT-metal(II) chelates of o-, m- and p-(trifluoromethyl-benzyl)iminodiacetate(2-) chelators. This work deals with the synthesis of the p-(F_3C-benzyl)iminodiacetic acid (H_2p3F) and its copper(II) derivatives {[Cu(p3F)(H_2O)] ·3H_2O}$_n$ (**1**), [Cu(p3F)(Him)(H_2O)] (**2**), [Cu(p3F)(2apyr)(H_2O)] (**3**) and [Cu(μ_2-p3F)(2,2'-bpy)]$_2$·2[Cu(p3F)(2,2'-bpy)(H_2O)]·8H_2O (**4**), where Him, 2apy and 2,2'-bpy are the N-heterocyclic co-ligands imidazole, 2-aminopyridine and 2,2'-bipyridine, respectively. The Cu(II) compounds have been studied by single crystal XRD, FT-IR and electronic spectroscopies as well as coupled thermogravimetry + time-spaced FT-IR spectroscopy (in order to identify the evolved gases).

Compound **1** is an hydrated polymer where the Cu(II) centre exhibits square-based pyramidal coordination, type 4+1. The chelator p3F adopts a fac-NO+O(apical) conformation. The aqua ligand is in cis-coordination respect to the Cu-N(p3F)bond, whereas the corresponding trans-position is occupied by the O'-carboxylate donor form an adjacent complex unit. The polymer is built by an anti,syn-carboxylate bridging group of each p3F, as zig-zag chains extending parallel to the b axis of the crystal. Aqua ligands, water solvent and O-carboxylate (p3F) acceptors build an H-bonded 3D-network.

Compound **2** is molecular and the Cu(II) exhibits an elongated square-based pyramidal coordination (with the Addison-Reedijk parameter τ as low as 0.006). As expected, p3F is in mer-NO_2 conformation and the Him ligand is linked to the metal in trans- to the Cu-N(p3F) bond giving the shortest bond distance (1.951(2) Å). Hence the aqua ligand is in the apical/distal site (Cu-OW 2.344(2) Å). In the crystal, (Him)N-H···O(p3F) interactions build H-bonded chains along the b axis. Additional (aqua)O-H···O(p3F) interactions connect these chains in 2D frameworks parallel to the ab plane, in such a way that the p-(F_3C-benzyl)- arms of p3F ligands result oriented to both external faces. These layers interact via Van der Walls forces.

Compound **3** is also molecular and builds crystals closely related to those of compound **2** (both in orthorhombic system, space group *Pbca*). Compound **3** also takes part of a broad program to discern the rare formation of the Cu-N1(adenine) bond in copper(II) complexes. Note that 2-aminopyridine is the six-membered ring moiety of 3-deaza-adenine. In this case the Cu-N22(2apyr) bond cooperates with the intra-molecular interligand interaction (2apyr)N21-H···O4(p3F) 2.807(3), 153.3º).
Compound **4** (triclinic system, $P\bar{1}$ space group) is an unintended hydrated co-crystal of a dinuclear unit $[Cu(\mu_2\text{-p3F})(2,2'\text{-bpy})]_2$ and mononuclear units $[Cu(p3F)(2,2'\text{-bpy})(H_2O)]$ (see figure) and non-coordinated solvent molecules. This compound also differs to complexes **2** and **3** in the conformation of the p3F chelating group. In **4**, p3F adopts a fac-O_2+N(apical) conformation in both the mononuclear and the dinuclear complex molecules (see Figure). The driving interactions of this framework are under discussion. Interestingly, dinuclear molecules build sheets parallel to the *ab* plane, stabilized by symmetry related pairs of $(C\text{-}H)_{bpy}\cdots F$ interactions and weak intermolecular π,π-stacking between bpy ligands. Such interactions are missing between mononuclear molecules.

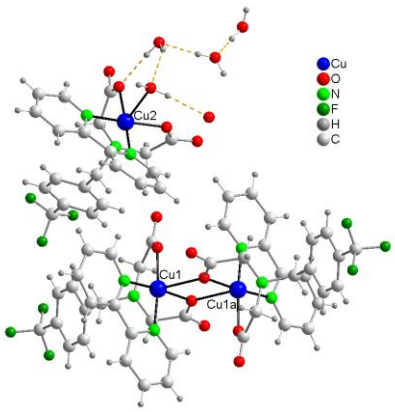


Figure. Mononuclear and dinuclear complex molecules in the co-crystal **4**.

Financial support from the Research Group FQM-283 (Junta de Andalucía) and MICINN-Spain (Project MAT2010-15594) is acknowledged. The project 'Factoría de Cristalización, CONSOLIDER INGENIO-2010' provided X-ray structural facilities. ERDF Funds and Junta de Andalucía support to acquire the FT-IR spectrophotometer Jasco 6300 is acknowledged. ADM thanks Ramón Areces Foundation for a Pot-doctoral grant.

References:

[1] Burger, K.; Henning, L.; Tsouker, P.; Spengler, J.; Albericio, F.; Koksch, B., Synthesis of α-trifluoromethyl α-amino acids with aromatic, heteroaromatic and ferrocenyl subunits in the side chain. *Amino Acids* **2006,** 31 (1), 55-62.
[2] Panini, P.; Chopra, D., Quantitative insights into energy contributions of intermolecular interactions in fluorine and trifluoromethyl substituted isomeric N-phenylacetamides and N-methylbenzamides. *CrystEngComm.* **2013** 15 (18), 3711-3733.

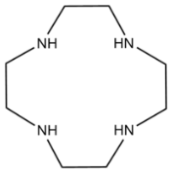
Cation-anion interactions in the crystals of the cyclam-copper(II) macrochelate and some inorganic oxoanions.

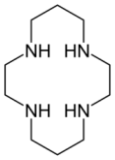
Josefa María GONZÁLEZ-PÉREZ, [a] Inmaculada PÉREZ-TORO, [a] Alicia DOMÍNGUEZ-MARTÍN, [a,b] Duane CHOQUESILLO-LAZARTE, [c] Hanan EL BAKKALI, [a] Alfonso CASTIÑEIRAS, [d] Juan NICLÓS-GUTIÉRREZ [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071-Granada, Spain [b] Department of Chemistry, Winterthurerstrasse 190, CH-8057 Zurich , Switzerland [c] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain [d] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain; jmgp@ugr.es

In past decades a great effort has been carried out to better understand the metal binding patterns of nucleobases or closely related N-heterocyclic ligands in mixed-ligand metal complexes [1, 2]. Attention is paid to the cooperation between coordination bonds and weak intramolecular interligand interactions, among which H-bonds play a relevant role. These studies have revealed that the Cu(cyclen) complex is able to bind an N-heterocyclic donor of some purine ligands in their anionic form (adenine, hypoxanthine, xanthine or theophylline) to the apical/distal coordination site of the copper(II) center, provided that this metal ion is chelated out of the plane of cyclen since imposes a 4+1 coordination in such complexes.

In a series of experiments concerning the ternary systems Cu(II):polyamine:acyclovir, we have used the N_4-tetradentate macrocyles cyclen and cyclam which have result in crystals without acyclovir. That offers us the opportunity to report for the first time the molecular and/or crystal structure of the compounds trans-[Cu(cyclam)$(ClO_4)_2$] (**1**), {[Cu(cyclam)$(\mu_2$-$NO_3]NO_3\}_n$ (**2**) and {[Cu(cyclam)$(\mu_2$-$SO_4]\}_n$ (**3**). A comparison between their structures reveals different patterns of anion-cation interactions.

cyclen 

cyclam 

The crystal of compound **1** (triclinic system, space group $P\bar{1}$) consists of centro-symmetric molecules where Cu(II) is in the plane defined by four N-cyclam donors (Fig.1-A). Perchlorate anions give the trans-apical Cu1-O11 bonds (2.547(1) Å). Each of these bonds cooperates with two weak intramolecular H-bonds (N1-H1···O13 (2.209(2) Å, 146.5º) and N4-H4···O14 (2.236(2) Å, 142.6º)). The framework is built by van der Waals forces.

Compound **2** is a salt with 1D-polymeric cations and nitrate counter-anions. The polymer extend parallel to the *b* axis and is built by μ_2-O11,O12-nitrate ligands bridging between Cu(cyclam) macrochelates. The Cu1-O11 (2.510(2) Å) and Cu1-O12 (2.603(2) Å)

bonds formed by the bridging nitrate ligands cooperates with intra-chain H-bonds (N1-H1···O13 (2.968(3) Å, 149.8º) and N8-H8···O13 (2.887(3) Å, 162.7º) respectively) (Fig 1-B)

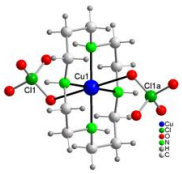


Fig. 1-A

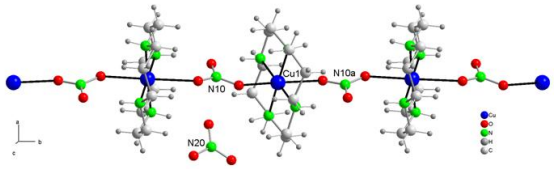


Fig. 1-B

Compound **3** (monoclinic, $P2_1/c$) is a methanol-solvated 1-D polymer, $\{[Cu(cyclam)(\mu_2\text{-}O,O'\text{-}SO_4)]MeOH\}_n$, with chains extending parallel to the a axis. There are two non-equivalent Cu(II) centers alternating with two non-equivalent bridging sulfate ligands in the chain, having 4+1+1 (Cu1) or ~ 4+2 (Cu2) coordination. Both sulfate ligands play a similar bridging role, consisting in two Cu-O coordination bonds, each of them cooperating with two (cyclam)N-H···O(sulfate) interactions. That is, each non-coordinated O-sulfate atom acts twice as H-acceptor for two adjacent Cu(cyclam) units (Fig. 2):

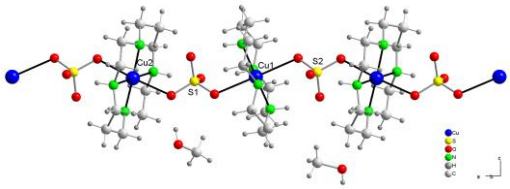


Fig. 2.

Financial support from the Research Group FQM-283 (Junta de Andalucía) and MICINN-Spain (Project MAT2010-15594) is acknowledged. The project 'Factoría de Cristalización, CONSOLIDER INGENIO-2010' provided X-ray structural facilities. ERDF Funds and Junta de Andalucía support to acquire the FT-IR spectrophotometer Jasco 6300 is acknowledged. ADM thanks Ramón Areces Foundation for a Post-doctoral grant.

References:

[1] Aoki, K.; Fujisawa, I.; Murayama, K.; Hu, N.-H., Stereospecific intra-molecular interligand interactions affecting base-specific metal bonding to purine nucleobases in solid state. *Coord. Chem. Rev.* **2013**, 257 (19-20), 2798-2813.

[2] Domínguez-Martín, A.; Brandi-Blanco, M.P.; Matilla-Hernández, A.; El Bakkali, H.; Nurchi, V.M.; González-Pérez, J.M.; Castiñeiras; A.; Niclós-Gutiérrez, J. Unraveling the versatile metal binding modes of adenine: Looking at the molecular recognition patterns of deaza- and aza-adenines in mixed-ligand metal complexes. *Coord. Chem. Rev.* **2013**, 257 (19-20), 2814-2838.

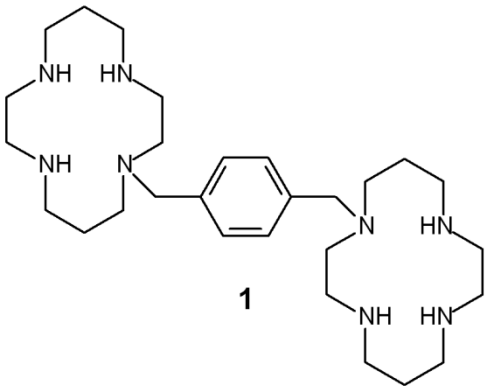
[2] Rahman, Md.S.; Yuan, H.Q.; Kikuchi,; T. Fujisawa, I.; Aoki, K. *J. Mol. Struct.* **2010**, 966 (1-3) 92-101.

The interaction of Mozobil™ with dicarboxylates

Valeria AMENDOLA, [a] Greta BERGAMASCHI, [a] Luigi FABBRIZZI, [a] Maurizio LICCHELLI, [a] Carlo MANGANO [a]

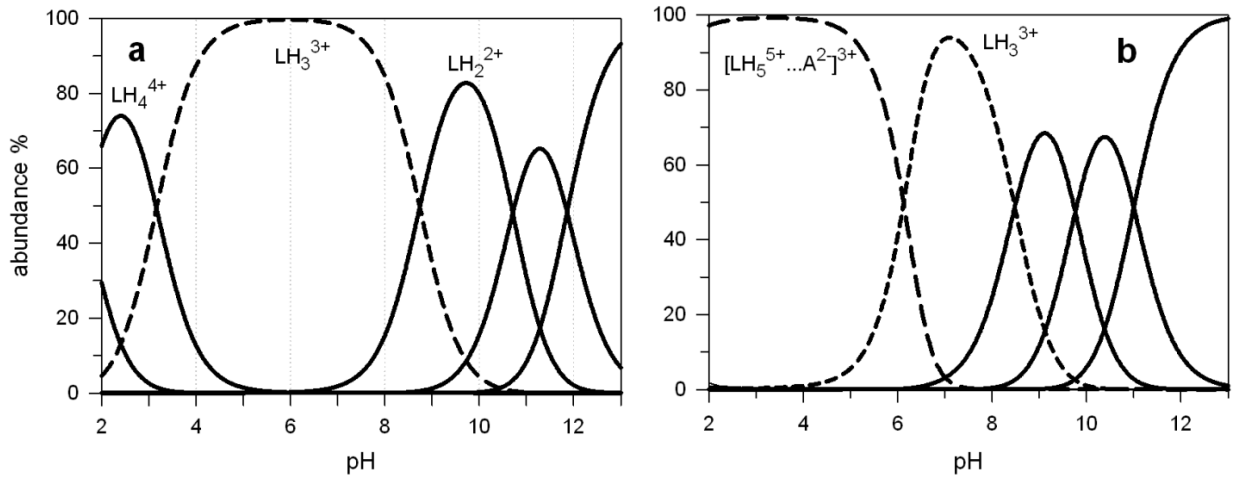
[a] *Dipartimento di Chimica, Università di Pavia, 27100 Pavia, Italy; mngcrllf@unipv.it*

Mozobil™ (1,1′-[1,4-phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane], **1**) is an immuno-stimulant used to mobilize hematopoietic stem cells in cancer patients.[1] Recent studies have consolidated the role of Mozobil in mobilizing hematopoietic stem cells and hematopoietic progenitor cells from the bone marrow into the blood circulation, a practice which eliminates any invasive surgical intervention.



1

Quite interestingly, Mozobil was first synthesised in our laboratory in 1987 to carry out basic studies on the redox chemistry of dimetallic coordination compounds [2]. Then, it was serendipitously discovered by De Clercq that such a molecule could have a potential use in the treatment of HIV [3]. Activity of Mozobil seems related to its ability, in its protonated form, to establish hydrogen bond interactions with two aspartate fragments of the co-receptor CXCR4 [3]. These considerations prompted us to investigate the interaction of Mozobil with carboxylate groups in an aqueous solution buffered at pH 7, namely linear dicarboxylates of rigid nature and varying length were considered, in order to assess the existence of a structural relationship between the Mozobil polyammonium ion and the dicarboxylate. This could provide useful information on the position of the two aspartate fragments of CXCR4 involved in the hydrogen bonding interaction. Investigations were carried out by pH-metric titrations of an acidic solution of Mozobil in 0.1 M $NaNO_3$ at 25°C with standard NaOH, with and without dicarboxylates.



Preliminary experiments have shown that diphenyl-4,4'-dilcarboxylate forms an especially stable 1:1 hydrogen bond complex, as can be seen by comparing Figure 1a (concentration profiles over the pH interval 2-13 in the absence of diphenyl-4,4'-dicarboxylate) and Figure 2a (concentration of the species over the same pH range in the presence of 1 equiv. of diphenyl-4,4'-dilcarboxylate (A^{2-})) where the formation of the stable H-bond complex $[LH_5^{5+}\cdots A^{2-}]^{3+}$, involving the pentaprotonated form of Mozobil it is observed. Further studies involving a variety of anions, including polyphosphates, are being currently carried out in our laboratory.

References:

[1] Eric De Clerq, Recent advances on the use of the CXCR4 antagonist plerixafor (AMD3100, Mozobil™) and potential of other CXCR4 antagonists as stem cell mobilizers, Pharmacology & Therapeutics 128 (2010) 509–518

[2] Ciampolini, M.; Fabbrizzi, L.; Perotti, A.; Poggi, A.; Seghi, B.; Zanobini, F. (1987). "Dinickel and dicopper complexes with *N*,*N*-linked bis(cyclam) ligands. An ideal system for the investigation of electrostatic effects on the redox behavior of pairs of metal ions". *Inorganic Chemistry***26** (21): 3527

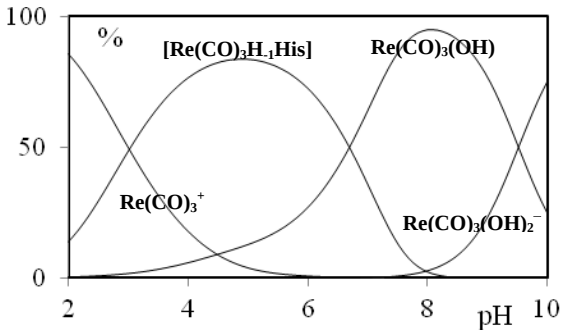
[3] De Clercq E, Yamamoto N, Pauwels R, Balzarini J, Witvrouw M, De Vreese K, Debyser Z, Rosenwirth B, Peichl P, Datema R, et al. (1994) Highly potent and selective inhibition of human immunodeficiency virus by the bicyclam derivative JM3100. *Antimicrob Agents Chemother* **38:**668–674.

Interaction between *fac*-$[Re(H_2O)_3(CO)_3]^+$ ion and histidine in aqueous solution

[a] Gaetano DE TOMMASO, [a] Mauro IULIANO, [b] Veronica CELENTANO, [b] Luca Domenico D'ANDREA, [c] Carla ISERNIA, [c] Gaetano MALGIERI

[a] Università di Napoli "Federico II" Via Cinthia, 4 – 80126 Napoli (ITALIA)
[b] Istituto Biostrutture e Bioimmagini CNR Via Mezzocannone,16 – 80134 Napoli (ITALIA)
[c] DiSTABiF SUN Via Vivaldi,43 – 81110 Caserta (ITALIA)
gaetano.detommaso@unina.it

The chemistry of Rhenium(I) has assumed recently an important role for the synthesis of $^{186,188}Re$ radiopharmaceuticals. Furthermore, the spectral properties of Rhenium(I) tricarbonyl complexes have been demonstrated to have applications as fluorochromes in fluorescence microscopy. The organometallic complex *fac*-$[Re(H_2O)_3(CO)_3]^+$ is taken into account due to its simple synthesis and its complexing properties towards biological molecules. Although numerous studies have been carried out on complexes with organic ligands in the solid state, there is little information on the speciation of Rhenium(I) in aqueous solution. By the presence of histidine residues in many biological systems, this work concerns the complexation of the $Re(CO)_3^+$ core with histidine in solutions 0.1 M $NaClO_4$, at 25°C by potentiometric measurements by a glass electrode in the range of pH 2-10. Order to do this is necessary to establish hydrolytic equilibria of tricabonyl Rhenium(I). Data processing suggests the formation of the two hydrolytic species: $Re(OH)(CO)_3$ and $Re(OH)_2(CO)_3^-$.



For pH values above 10, equilibria are very slow. The complexing properties of $Re(CO)_3^+$ toward the histidine (His) can be explained assuming the specie $[Re(CO)_3H_{-1}His]$ as is evident in the distribution diagram obtained for a total concentration of rhenium(I) of 2×10^{-3} M and a concentration of histidine 2×10^{-3} M.

In order to obtain information about the binding sites of histidine, similar studies have been performed with the imidazole (Im). Potentiometric and fluorimetric measurements have shown the formation of 1:1 complexes of the type $[Re(CO)_3H_{-1}Im]$.

References:

[1] A. T. Taylor, M. Lipowska, L. G. Marzilli, *J. Nucl. Med.* **2010**, 51, 391–396.
[2] N. Lazarova, J. Babich, J. Valliant, P. Schaffer, S. James, and J. Zubieta, *Inorg. Chem.* **2005**, 44, 6763-6770.

The formation of Xx(II)/Cu(II) dinuclear complexes by cyclopeptides.

Justyna BRASUŃ, [a] **Aleksandra KOTYNIA,** [a] **Żaneta CZYŻNIKOWSKA,** [a]

[a] *Department of Inorganic Chemistry, Wrocław Medical University, Borowska 211a ,50-556 Wrocław, Poland; justyna.brasun@umed.wroc.pl*

Cyclopeptides are the special group of peptides having the cyclic motif in their structure. This characteristic feature of the structure leads to a more restricted mobility of the peptide chain what influences metal ion binding [1]. The efficiency and the coordination manner strongly depends on the structural modification *e.g.* the optical izomeration of the histidyl moiety, size of peptide cycle or acid/base properties of side chains (Table 1) [2-4].

The interesting group of cyclopeptides are ligands with two Pro amino acid residues in their sequence. The consequence of the insertion of these two residues in the peptide cycle is creation of two potential metal binding sites.

The studies performed for the system with two equivalents of Cu(II) ions and c(HKHPHKHP) have shown that in acidic conditions it prefers formation of the mononuclear species with the $\{4N_{Im}\}$ binding mode. The formation of binuclear complexes was observed above pH 6.5. The final species was the Cu(II)-complex with two different binding manners: $\{2N_{Im}, 2N^-_{amide}\}$ and $\{N_{Im}, 3N^-_{amide}\}$ (Fig.1) [5] .

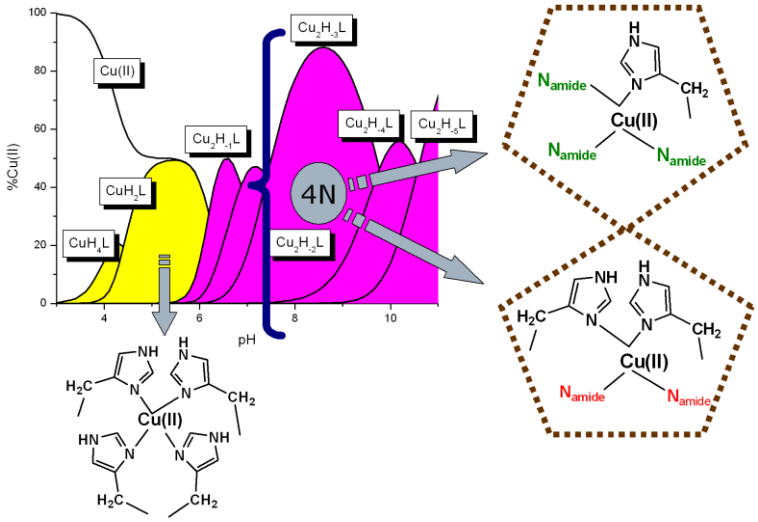


Figure 1. The scheme of coordination abilities c(HKHPHKHP) toward Cu(II) ions in the system with the molar ratio $n_{Cu(II)}:n_l$ =2:1 [5].

In presented work we focused on the formation of heteronuclear complexes Cu(II)/ligand/Zn(II) and Cu(II)/ligand/Ni(II) by c(HKHPHKHP). The analysis of results obtained from the theoretical calculations allow to detailed analysis of the structural abilities of formed complexes. We analyzed the influence of Zn(II) or Ni(II) ions on the Cu(II) binding by investigated peptide and the structural properties of formed complex.

Acknowledgements: This work has been supported by Wroclaw Medical University (ST-705). Authors gratefully acknowledge the allotment of the CPU time in Wroclaw Center of Networking and Supercomputing (WCSS).

References:

[1] Brasuń, J.; Gabbiani, Ch.; Ginanneschi, M.; Messori, L.; Orfei, M.; Świątek-Kozłowska, J.;.'The copper(II) binding properties of the cyclic peptide c(HGHK)' *J.Inorg.Biochem.* **2004,** 98, 2016-2021

[2] Brasuń, J.; Matera, A.; Ołdziej, S.; Świątek-Kozłowska, J.; Messori, L.; Gabbiani, Ch.; Orfei, M.; Ginanneschi, M.; 'The copper(II) coordination abilities of three novel cyclic tetrapeptides with -His-Xaa-His- motif' *J. Inorg. Biochem.* **2007,** 101, 452-460

[3] Brasuń, J.; Matera, A.; Ołdziej, S.; Pratesi, A.; Ginnaneschi, M.; Messori, L.; 'Impact of ring size on the copper(II) coordination abilities of cyclic tetrapeptides' *J. Inorg. Biochem.* **2009** 103, 813-817

[4] Czapor, H.; Bielińska, S.; Kamysz, W.; Szyrwiel, L.; Brasuń, J.; 'The cyclopeptides with the multi-His motif as ligands for copper(II)' *J.Inorg.Biochem.*, **2011**, 105, 297-302

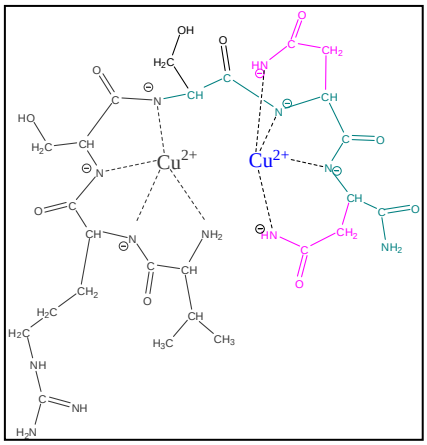
[5] Kotynia, A.; Bielińska, S.; Kamysz, W.; Brasuń, J.; 'The coordination abilities of the multiHis-cyclopeptide with two metal-binding centers - potentiometric and spectroscopic investigation' *Dalton Trans.*, 2012, 41, 12114-12120

Binding sites of rat amylin fragments

Ágnes DÁVID [a], Katalin VÁRNAGY [a], Csilla KÁLLAY [b], Daniele SANNA [c] and Imre SÓVÁGÓ [a]

[a] *Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1., Debrecen H-4032, Hungary*
[b] *MTA –DE Homogeneous Catalysis and Reaction Mechanism Research Group, University of Debrecen, Egyetem tér 1., Debrecen H-4032, Hungary*
[c] *Istituto CNR di Chimica Biomolecolare, trav. La Crucca 3, I-07040 Li Punti, Sassari, Italy*
e-mail: david.agnes@science.unideb.hu

Amylin is a 37-residue peptide hormone cosecreted with insulin by pancreatic β-cells. It is the principal constituent of the amyloid deposits that form in the islets of Lagerhans in patients with type-2 diabetes mellitus. However rat amylin does not form amyloid-like fibrils. The main difference is in the two sequences that histidine is not present in rat amylin. Despite the lack of any common strongly coordinating donor functions this peptide is able to bind metal ions. According to our earlier results the hexapeptide domain –VRSSNN– can be the main metal binding sequence[1].



For getting more information about metal binding of rat amylin, this fragment and its mutants (NH_2-VRSSNN-NH_2, NH_2-VRAANN-NH_2, NH_2-VRSSAA-NH_2) have been synthesized and their metal complexes studied by pH-potentiometric, UV-Vis, CD and EPR spectroscopic methods. These peptides can be effective metal binding ligands even in the absence of the common anchoring groups (Cys, His), if more polar side chains (mainly asparagine) are present in a specific sequence. Furthermore, the presence of dimeric complexes with contribution of amide nitrogens in side chains is established by MS and EPR (Figure I.).

Acknowledgement: The research was supported by the EU and co-financed by the European Social Fund under the project ENVIKUT (TÁMOP-4.2.2.A-11/1/KONV-2012-0043) and TÁMOP 4.2.4A/2-11-1-2012-000. The work was also supported by the Campus Hungary Scholarship Program (TÁMOP 4.2.4. B/2-11/1-2012-0001).

References:

[1] Kállay, Cs.; Dávid, Á.; Timári, S.; Nagy, E. M.; Sanna, D.; Garribba, E.; Micera, G.; De Bona, P.; Pappalardo, G.; Rizzarelli, E.; Sóvágó, I., Copper(II) complexes of rat amylin fragments. *Dalton Trans.* **2011,** 40 (38), 9711 – 9721.

Phytate in aqueous solution: unveiling its microprotonation equilibria and coordination ability under physiological conditions

Nicolás VEIGA,[a] Julia TORRES,[a] Israel MACHO,[b] Kerman GÓMEZ,[b] Gabriel GONZÁLEZ,[b] Carlos KREMER[a]

[a] Cátedra de Química Inorgánica, Departamento Estrella Campos, Facultad de Química, Universidad de la República, CC 1157, Montevideo, Uruguay. [b] Institut Català d'Investigació Química, Av. Països Catalans 16, 43007 Tarragona, Spain; nveiga@fq.edu.uy

Within all the eukaryotic cells there is an important group of biomolecules that has been potentially related to signalling functions: the *myo*-inositol phosphates (Ins*P*s) [1]. The research of their cellular roles has been held back so far, mainly because of the enormous number of intertwined chemical processes that they undergo. In nature, the most abundant Ins*P* is InsP_6 (phytate, L^{12-}, Figure 1), for which our group has strived in the past to elucidate its intricate chemical behaviour [2]. In this work we expand on our earlier findings, shedding light on the inframolecular details of its protonation and complexation processes, in a non-interacting medium and under simulated physiological conditions (0.15 M NMe_4Cl, 37.0 °C).

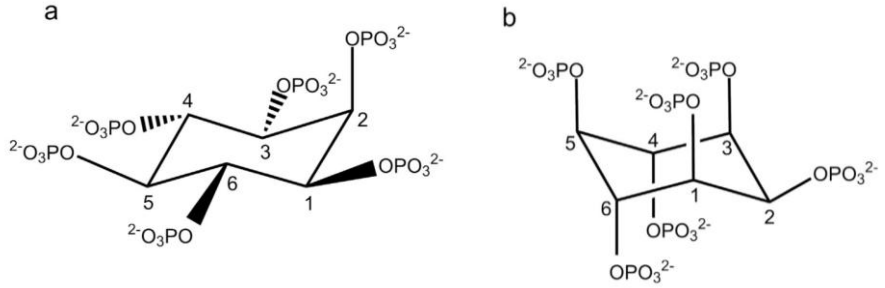


Figure 1. Structure of InsP_6 for both conformations: (a) 1 axial-5 equatorial (1a5e) and (b) 5 axial-1 equatorial (5a1e).

For the metal-free system, the ^{31}P NMR results indicate that the predominant species at physiological pH are H_4L^{8-} and H_5L^{7-}, being H_4L^{8-}(1234/1236), H_4L^{8-}(1346), H_5L^{7-}(12345/12356) and H_5L^{7-}(12346) the predominant microspecies. Under acidic conditions found in some vesicular compartments the most abundant microspecies are H_6L^{6-}, H_5L^{7-}(12345/12356) and H_5L^{7-}(12346). Experimental and computational data support a pH-dependant conformational change operative for InsP_6, being triggered by the process involving HL^{11-} and H_2L^{10-} species.

In the presence of physiological concentrations of Na^+ or K^+, the adjustment of the NMR spectra as a function of pH allowed us to detect polynuclear complexes of general formula $[M_i(H_jL)]^{(12-i-j)-}$ with *i:j* = (3:4), (4:3), (5:2) and (6:0). Among them, those predominant under conditions close to the cytosol and nucleus are $[Na_3(H_4L)]^{5-}$ and $[Na_4(H_3L)]^{5-}$ for Na^+ and $[K_3(H_4L)]^{5-}$ for K^+. Besides, in the presence of Mg^{2+} or Ca^{2+} species of general stoichiometry $[M(H_xL)]^{(10-x)-}$, with x = 1-6 for Mg and x = 0-6 for Ca were detected. Through the information provided by the ^{31}P NMR spectra and some molecular modelling tools, we have characterised these metal complexes from a structural and energetic

point of view, unravelling the metal complexation sequence and its influence on the phytate conformational change.

Specifically under the cytosolic-nuclear environment, the InsP_6 is predicted to be completely in the form of the [Mg_5H_2L] complex, a polymetallic species that coexists at a cellular level with the protein-bound phytate and the solid magnesium phytate [3]. So as to have a better view of the soluble forms of cellular InsP_6, B3LYP/6-31+G* geometries for both conformers of this neutral complex were calculated (Figure 2). All the magnesium cations are strongly anchored to more than one phosphate group, in a bidentate way, as though they were negatively charged clamps. This protonation and complexation scheme strongly stabilizes the structure, by setting up a metal-proton-phosphate bond network with a small distortion of the inositol ring.

All the obtained data are essential in the process of gaining reliable knowledge about the stability and structure of the most important InsP_6 species in the *in vitro* and *in vivo* experiments, and how these features modulate their probable biological functions.

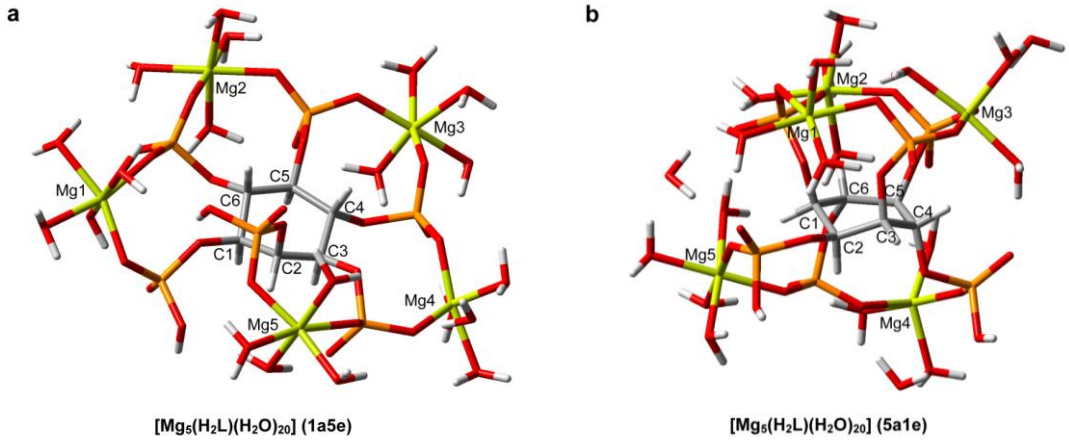


Figure 2. RB3LYP/6-31+G* geometries for both conformations of the InsP_6 species predominant under intracellular conditions. Color code: C (grey), H (white), O (red), P (orange), Mg (yellow).

References:

[1] Raboy, V.; Bowen, D., Genetics of inositol polyphosphates. *Sub-cellular biochemistry* **2006**, 39, 71-101.

[2] Torres, J.; Veiga, N.; Gancheff, J. S.; Domínguez, S.; Mederos, A.; Sundberg, M.; Sánchez, A.; Castiglioni, J.; Díaz, A.; Kremer, C., Interaction of myo-inositol hexakisphosphate with alkali and alkaline earth metal ions: Spectroscopic, potentiometric and theoretical studies. *Journal of Molecular Structure* **2008**, 874 (1-3), 77-88.

[3] Veiga, N.; Torres, J.; Domínguez, S.; Mederos, A.; Irvine, R. F.; Díaz, A.; Kremer, C., The behaviour of myo-inositol hexakisphosphate in the presence of magnesium(II) and calcium(II): Protein-free soluble InsP6 is limited to 49 μM under cytosolic/nuclear conditions. *Journal of Inorganic Biochemistry* **2006**, 100, 1800-1810.

On Formation, Thermal and Mechanical (In)Stability and Structure of Vanilin Nickel(II) Complex

Tomáš WEIDLICH,[a] Zdeňka PADĚLKOVÁ,[b] Zdeněk ČERNOŠEK,[b] Aleš RŮŽIČKA,[b]

[a] Institute of Environmental and Chemical Engineering, Faculty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic, E-mail:tomas.weidlich@upce.cz

[b] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic, Fax: +420-466037068

The vanilin approach for complexation of compounds, modelling lignin fragments, as a cheap agent, used by Buschkova et al. [1] has been suggested by us for removing of nickel ions from aqueous methanol solution. The vaniline-nickel complexes are known for almost forty years [2-3], the IR spectra were used for these first trials of the structure description showing distorted octahedral geometry. The same geometry of Ni(II) and several phenolates including vanilin has been validated by the electronic spectra and magnetic moments measurements [4].

The title complex ({Ni[2-OMe-4-(C(H)=O)C_6H_3O](OCH_3)(CH_3OH)}$_4$) is formed from the vanilin and nickel(II) chloride in aqueous methanol solution with the presence of NaOH. The structure of the complex is tetranuclear cubane-like with nickel atoms in alternative positions of the cubane core. The remaining corners of distorted cube are occupied by OMe ligands. Three OMe, the chelating vanilinate and coordinated methanol are present in the coordination sphere of each nickel atom with distorted octahedron geometry. The complex reveals high thermal stability of up to 210°C when the vanilin is liberated and nickel methoxide formed.

References:

[1] Bushkova, E. S.; Yusman, T. A.; Dorokhova, N. I.; Zaletov, V. G.; Kuznetsova, S. A.; Kuznetsov, B. N.; Garnovskii, A. D. *Koordinatsionnaya Khimiya* **1994**, 20(8-9), 630-2.

[2] Biedermann, H. G.; Schwarzhans, K. E. *Zeitschrift fuer Naturforschung, Teil B* **1971**, 26(6), 531-4. b)

[3] Bullock, J. I.; Jones, S. L. *J.Chem. Soc. A* **1970**, (15), 2472-5.

[4] Bullock, J. I.; Hobson, R. J. *Inorg. Chim. Acta* **1976**, 19(1), 79-85.

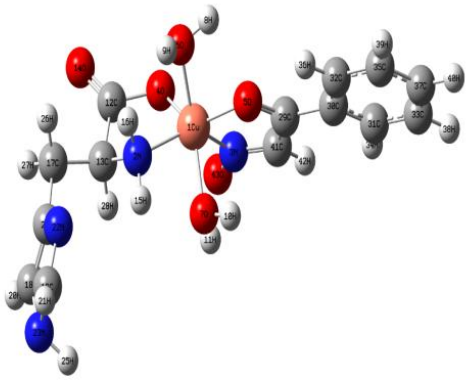
Synthesis, characterization, electrochemical studies and DFT calculations of amino acids ternary complexes of copper(II) with isonitrosoacetophenone. Biological activities.

Nabila TIDJANI-RAHMOUNI, [a] Nour El Houda BENSIRADJ, [b] Safia DJEBBAR, [a] Ouassini BENALI-BAITICH [a]

[a] *Laboratoire d'hydrométallurgie et chimie inorganique moléculaire, Faculté de Chimie, USTHB, BP 32, El-Alia, Bab Ezzouar, Alger.*
[b] *Laboratoire de Chimie Théorique Computationnelle et Photonique, Faculté de Chimie, USTHB, BP 32, El Alia, Bab Ezzouar, Alger*
benali.baitich@gmail.com

Three mixed complexes having formula $[Cu(INAP)L(H_2O)_2]$ where INAP= deprotonated isonitrosoacetophenone and L= deprotonated amino acid such as Phenylalanine, Tryptophane and Histidine have been synthesized.

They have been characterized using elemental analyses, molar conductance, UV-Vis, IR and ESR spectra. The spectral studies support the binding of the ligands with two N and two O donor sites to the copper(II) ion, giving a pseudo-octahedral arrangement with two coordinated water molecules. The geometry optimization was carried out by the density functional theory (DFT) and shows that the *trans*-form is the most stable (see figure) .



The optimized structure of $[Cu(INAP)(Hist)(H_2O)_2]$

The ESR data indicates that the covalent character of the metal-ligand bonding in the copper(II) complexes increases on going from histidine to phenylalanine to tryptophan.

The electrochemical behavior of the copper(II) complexes was determined by cyclic voltammetry which shows that the chelate structure and electron donating effects of the ligands substituents are among the factors influencing the redox potentials of the complexes.

The antimicrobial activities of the complexes were evaluated against several pathogenic microorganisms to assess their antimicrobial potentials. The copper complexes were found to be more active against Gram-positive than Gram-negative bacteria.

Pt(II) complexes of oxime-containing acetylcholinesterase reactivators

Ahmed NEDZHIB, [a] Ivayla PANTCHEVA, [a] Liudmil ANTONOV,[b]

[a] Laboratory of Biocoordination and Bioanalytical Chemistry, Faculty of Chemistry and Pharmacy, "St. Kl. Ohridski" University of Sofia, 1, J. Bourchier blvd., Sofia, Bulgaria;
[b] Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria;
Ahmed.Nedzhib@chem.uni-sofia.bg

Organophosphorous compounds (OPC) are used in the agriculture as insecticides (Chlorpyrifos, Methyl parathion, Dimethoate, Azinphos-methyl etc.) and can present serious health risks in case of improper handling or production/transportation accidents. Chemical warfare nerve agents (sarin, soman, tabun, VX etc.), also belonging to OPC, are classified as weapons of mass destruction according to UN Resolution 687. Both groups are irreversible inhibitors of acetylcholinesterase (AChE), responsible for the breakdown of acetylcholine in the synapse.

The chemical antidotes used for treatment of OPC intoxications are known as cholinesterase reactivators (ChR). The most effective ChR represent mono- or bis-quaternary pyridinium aldoximes containing variety of substituents in the pyridinium rings and/or different bridges (as type/length) between rings. There are some difficulties in application of ChR due to their fast elimination and to the non-complete recovery of enzymatic activity. On the other hand, the antidotal activity of reactivators is different against various OPC and universal antidotes are still not developed.

From chemical point of view the oxime-containing compounds represent potential ligands able to bind metal ions. Their coordination could be used as a strategy to increase the efficacy (or bioavailability) of active oxime species in the organism since many metal complexes improve the biological properties of starting ligands.

In the present study we report the results on ability of BT-07, BT-08 and BT-07-4M (H_2LBr_2) to bind platinum(II) ions. The complexation was followed spectrophotometrically in aqueous solutions (Britton-Robinson buffer, pH 7.4) at metal-to-ligand molar ratio from 1:10 to 10:1 and was monitored within one week after mixing the reagents.

The main problem in the investigated systems (Fig. 1) is that the equilibrium is never shifted to the pure complex. For this reason its individual absorption spectrum is experimentally unknown and the quantitative analysis by means of UV-Vis spectroscopy is impossible using classical methods for data processing. One possibility is to apply the FiNAl procedure, which is based on resolution of overlapping bands technique, specially developed for quantitative analysis of such systems [1, 2]. By using this approach we were able to obtain the molar parts of unreacted and complexed oxime species in each solution taking into account the initial pH-dependent conversion of oxime to oximate, and further - to calculate conditional stability constants (β') of complex species observed.

The experimental data revealed that addition of platinum(II) ions leads to formation of oximate species but the spectral changes differ from those observed in the presence of

inorganic base Na_2CO_3. The data obtained suggest that deprotonated oximes are engaged in coordination with platinum(II) ions. It was also found that complexation reaction is time-dependent and the equilibrium is affected by secondary reaction which occurs in the presence of metal(II) ions excess (data are not shown).

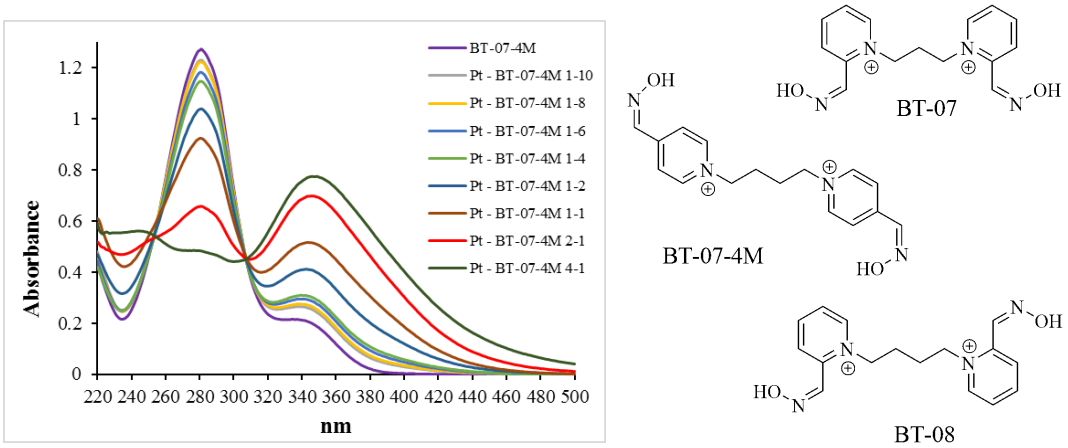


Figure 1. Representative spectra of Pt(II) – BT-07-4M system (pH 7.4, 24 h)

From the results obtained it can be concluded that complex species of composition $[PtL]^{2+}$ appear up to 24th h after mixing the reagents. The conditional stability constants determined are as follows: Pt-BT-07 – lgβ' = 5.91; Pt-BT-07-4M – lgβ' = 6.30; Pt-BT-08 – lgβ' = 6.61. Due to the high solubility of complex species observed we were not able up to now to isolate new compounds in solid state for their precise structure characterization. Further studies in this respect are in progress.

Acknowledgement: This work was supported by the Bulgarian National Science Fund (DDVU-02-78/2010). AN acknowledges the Grant BG051PO001-3.3.06-0040 of the European Social Fund Operative Program "Human Resources Development".

References:

[1] Antonov, L.; Nedeltcheva, D., Resolution of overlapping UV-Vis absorption bands and quantitative analysis. *Chem. Soc. Rev.* **2000**, 29, 217-227.

[2] Antonov, L., Absorption UV-Vis spectroscopy and chemometrics: from qualitative conclusions to quantitative analysis. In *Tautomerism: Methods and Theories*, Antonov, L., Ed. Wiley-VCH, **2013**, pp. 25-49.

Complexation of acetylcholinesterase reactivator Pralidoxime

Ahmed NEDZHIB, [a] Ivayla PANTCHEVA, [a] Liudmil ANTONOV,[b]

[a] Laboratory of Biocoordination and Bioanalytical Chemistry, Faculty of Chemistry and Pharmacy, "St. Kl. Ohridski" University of Sofia, 1, J. Bourchier blvd., Sofia, Bulgaria;
[b] Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria;
IPancheva@chem.uni-sofia.bg

Pralidoxime (N-methyl-pyridinium-2-aldoxime iodide, 2-PAM) belongs to oxime family that binds organophosphate-inactivated acetylcholinesterase. It is a chemical antidote applied in therapy of organophosphorous poisoning occuring in case of terrorist attack (chemical warfare agents) or in agriculture accidents (insecticides). It is known that the presence of some metal ions as Mn(II), Mg(II), Co(II), Zn(II), Ni(II) potentiate reactivation ability of 2-PAM [1] although until now no detailed study on possible complex formation was performed. Later coordination with pentacyanoferrate(II) and Pd(II) ions was monitored with respect to drug determination in dosage forms and biological materials [2, 3].

Recently we evaluated the ability of some oxime-containing compounds to bind Pd(II) or Pt(II) ions and found that the equilibrium never shifts to the pure complex. Obviously, the individual spectrum of the complex species formed is experimentally unknown and the classical methods for data processing cannot be used for quantitative purposes. We applied the FiNAl procedure, which is based on resolution of overlapping bands technique, specially developed for quantitative analysis of such systems [4].

In the present study we demonstrate this approach studying Pt(II)- and Pd(II)-Pralidoxime systems. The complexation reactions were evaluated spectrophotometrically (220-500 nm) for a week at metal-to-ligand molar ratio from 1:10 to 10:1 at pH 7.4 (Britton-Robinson buffer). Using FiNAl we obtained the molar parts of unreacted and complexed ligand species taking into account the initial pH-dependent conversion of oxime to oximate ions. Next, we calculated conditional stability constants (β') of complex species observed.

The experimental results showed that at pH 7.4 *c.a.* 20% 2-PAM exist in the form of corresponding oximate and the ratio oxime/oximate does not change within 48 h after mixing the reagents. The addition of metal(II) ions undergoes formation of oximate species immediately (Pd(II)) or slower (24 h) in case of Pt(II) ions. In both reaction mixtures the metal(II) ions excess leads to time-dependent side reactions which limited calculations of molar parts and stability constants, respectively, using spectra recorded at metal-to-ligand molar ratio from 1:10 to 1:1 (Fig. 1, Pt(II), 24 h).

The molar parts were derived from the total concentration of the free ligand according to $C^0_{H_2L^{2+}} = C_{H_2L^{2+}} + C^*; C^* = C_L + C_{complex}$ (Eq. 1); $1 = x_{H_2L^{2+}} + x^*; x^* = x_L + x_{complex}$ (Eq. 2)

($C^0_{H_2L^{2+}}$ is the total concentration of obidoxime, $C_{H_2L^{2+}}$, C_L, and $C_{complex}$ are the equilibrium concentrations of the free unreacted ligand, initially formed oximate and the complex,

respectively, at given experimental conditions). The molar part of the complex was calculated from the total molar part of oximate anions (x^*): $x_{complex} = x^* - x_L$ (Eq. 3).

Next, the conditional stability constants (β') of complexes formed were calculated based on complexation reaction n Pd^{2+} + H_2L^{2+} → complex ($\beta' = \frac{C_{complex}}{C_{Pd^{2+}}^n . C_{H_2L^{2+}}}$). Using Eq. 3 and under logarithmic conditions the number of coordinated Pd(II) ions (n) and the stability constant (β') are calculated from the plot $\lg \frac{x_{complex}}{x_{H_2L^{2+}}}$ *vs.* $\lg C_{Pd^{2+}}$.

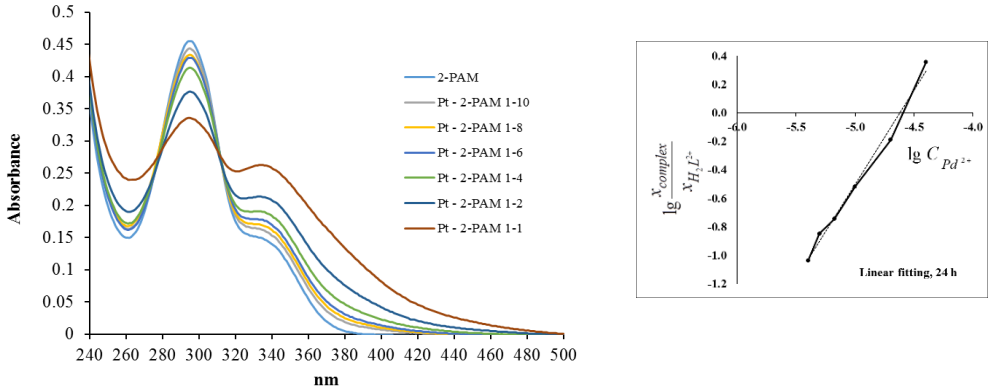


Figure 1. Spectral changes in system Pt(II)-2-PAM, 24 h

The coordination of Pralidoxime to Pd(II) or Pt(II) ions undergoes formation of 1:1 complex species at pH 7.4 (Britton-Robinson buffer). Using FiNAl procedure we were able to determine the conditional stability constants as follows: Pd(II)-2-PAM – $\lg\beta_1$ = 5.61; Pt(II)-2-PAM – $\lg\beta_1$ = 6.12.

Acknowledgement: This work was supported by the Bulgarian National Science Fund (DDVU-02-78/2010).

References:

[1] Cier, A.; Cuisinaud, G.; Solal, M.; Rossi, C., Reactivation of cholinesterase inhibited by organophosphates. Activity of oximes and metal ions alone and in combination. *Bull. Soc. Chim. Biol. (Paris)* **1969**, 51, 753-62.

[2] Burger, N.; Karas-Gasparec, V., The reactions of pentacyanoferrate(II) ions - spectrophotometric study, detection and determination of Toxogonine. *Talanta* **1977**, 24, 704-707.

[3] Karljiković-Rajic, K.; Stanković, B.; Granov, A.; Binenfeld, Z., Use of palladium(II) chloride as colour-forming reagent in determination of pralidoxime chloride in water and tablets. *J. Pharm. Biomed. Anal.* **1988**, 6, 773-780.

[4] Antonov, L., Absorption UV-Vis spectroscopy and chemometrics: from qualitative conclusions to quantitative analysis. In *Tautomerism: Methods and Theories*, Antonov, L., Ed. Wiley-VCH, **2013**, pp. 25-49.

Metal Complexes Containing Various Chiral Aminobenzothiazole Ligands

Vladimir PEJCHAL,[a] Zdenka PADELKOVA,[b] Ales RUZICKA[b] Marcela PEJCHALOVA [c], Marketa JANOTOVA[c]

[b] Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic. e-mail: vladimir.pejchal@upce.cz

[b] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic.

[c] Department of Biological and Biochemical Sciences, Faculty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic.

Benzothiazole derivatives showed a number of uses in medicinal and pharmaceutical areas[1] with special focus to anticandidous activity[2], Parkinson's disease and antihistaminic and antiflammatory activity,[3] while some of them have been screened for antitumor activity[4].

The Schiff base palladium complexes of the same core structure, reported by the same authors during the ISMEC 2013, revealed the square planar geometries and are currently under vigorous investigation as homogenous C-C coupling catalysts.

New complexes based on the reduced Schiff base ones, depicted in Fig. 1, with various platinum metals were prepared and its properties as structure, catalytic activity and interaction with living organisms will be discussed during the ISMEC 2014.

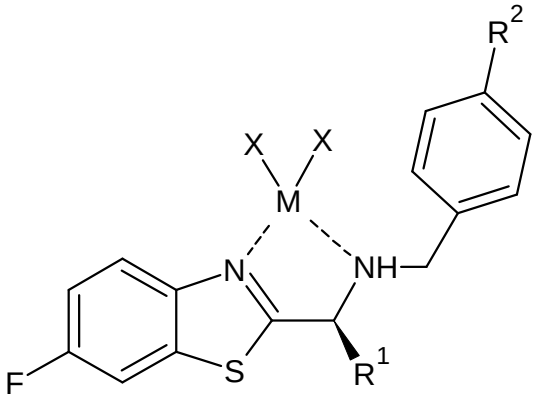


Figure 1: Structure of the compounds studied; M=Ni, Pd, Pt; R^1=*i*Pr, Bz, *iB*u; X=halide; R^2=OMe, NMe_2, F

Acknowledgement: The financial support of the Czech Science Foundation (Project no. P207/12/0223) is gratefully acknowledged.

References:

[1] Karia, F. D.;.Parsania P. H.,: Biologically active Co(II) and Ni(II) complexes of N-(2-thienylmethylene)-2-aminothiadiazole. *Asian J. Chem.*, **1999**, 11, 991-995.

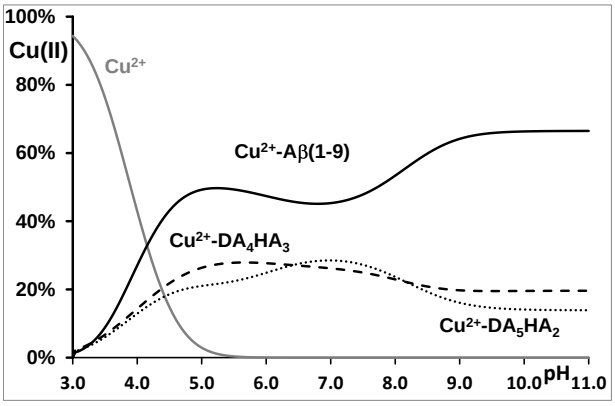
[2] Sidoova, E.; Loos, D.; Bujdakova, H., New anti candid us 2-alky/thio-6-amino benzoyhiazole; *Molecules*, **1997**, 2, 36-42.
[3] Abignente, E.; De-Capariis, P.; Sacchi, A.; Marmole, E.,(1983): Synthesis and Antibacterial Activity of Some New Phenothiazine Derivatives, *Pharmaco-Ed. Sci.*, **1983**, 38, 533-545.
[4] Bradshaw, T. D.; Bibby, M.C.; Double, J.A.; Fichtner, I.; Cooper, P.A.; Alley, M.C.; Donohue, S.; Stinson, S.F.; Tomaszewjski, J.E.; Sausville, E.A.; Stevens, M.F.G., Preclinical Evaluation of Amino Acid Prodrugs of Novel Antitumor 2-(4-Amino-3-Methylphenyl) Benzothiazoles, *Mol. Cancer Therapeutics*, **2002**, 1, 239-246.

Copper(II), nickel(II) and zinc(II) binding ability of the N-terminal fragments of amyloid-β peptide

Ágnes GRENÁCS, Imre SÓVÁGÓ

Department of Inorganic and Analytical Chemistry, University of Debrecen, H-4010 Debrecen, Hungary; grenacs.agnes@science.unideb.hu

Amyloid-β is a 40-43 residue peptide responsible for the development of Alzheimer's disease. The N-terminus of the peptide is reach in histidyl residues and contains some other polar side chains which enhance the metal binding ability of the peptide. Speciation and characterization of the copper(II), nickel(II) and zinc(II) complexes of the N-terminal hexadecapeptide fragment, Aβ(1-16)-PEG, have already been reported in our previous publications [1] but the elucidation of the metal binding sites requires further studies. In this work we report the synthesis of two nonapeptide domains of the native peptide: Aβ(1-9) and Aβ(8-16) and their mutants. The sequences of the six peptides studied are NH_2-DAEFRHDSG-NH_2, NH_2-DAAAAHAAA-NH_2 and NH_2-DAAAAAHAA-NH_2 for Aβ(1-9) and Ac-SGAEGHHQK-NH_2, Ac-SGAEGHAQK-NH_2 and Ac-SGAEGAHQK-NH_2 for Aβ(8-16). The results obtained from combined potentiometric and spectroscopic (UV-Vis, CD, ESR, NMR and ESI-MS) studies will be presented here. Both thermodynamic and structural data support the primary role of the amino termini of peptides in copper(II) and nickel(II) binding. Moreover, it can be unambiguously stated that the amino acid sequence of the N-terminal domains of amyloid peptides is especially well suited for the complexation with copper(II) ions as it is represented by the Figure showing the distribution of copper ions among the native and two mutant peptides. The enhanced stability of the copper(II) complexes was attributed to the secondary interactions of the polar side chains of Asp, Glu, Ser and Arg residues present in the native peptides.



The research was supported by EU and co-financed by the European Social Fund under the project ENVIKUT (TAMOP-4.2.2.A-11/1/KONV-2012-0043). The work was also supported by the Campus Hungary Scholarship Program (TÁMOP 4.2.4. B/2-11/1-2012-0001).

Reference

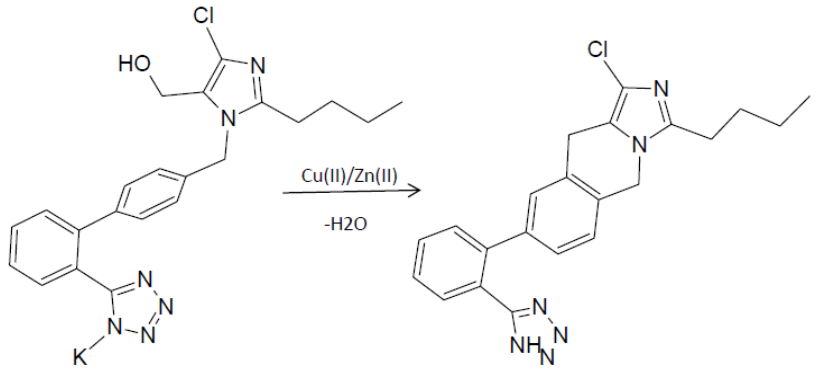
[1] Arena G, Pappalardo G, Sóvágó I, Rizzarelli E (2012) Coord Chem Rev 256:3-12.

Losartan: a low water soluble oral drug with Cu(II) and Zn(II) coordination properties.

Guadalupe JARAQUEMADA PELAEZ, Valeria M. NURCHI, Joanna I. LACHOWICZ, Miriam CRESPO-ALONSO

Dipartimento di Scienze Chimiche e Geologiche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy lupe_jaraquemada@hotmail.co

(2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazol-5-yl) methanol (Fig. 1) commercially known as Losartan is a drug mainly used in the treatment of high blood pressure. It was the first angiotensin II antagonist drug to be marketed. Losartan may delay progression of diabetic nephropathy and in this regard is associated with a positive clinical outcome. It is a suitable pharmacological agent for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours) [1].



Losartan **D1**

Figure 1: Hypothesis of losartan derivative (D1) formation induced by the presence of metal ions.

Losartan's bioavailability is about 32%. It is well absorbed following oral administration and undergoes significant first-pass metabolism to produce 5-carboxylic acid metabolite (EXP3174). About 14% of an oral dosage is converted to EXP3174, which is a long-acting (6 to 8 hr) non-competitive antagonist at the AT1 receptor. EXP3174 is 10-40 times more potent in blocking AT1 receptors than Losartan. Peak plasma concentrations of losartan and E-3174 occur about one hour and three to four hours, respectively, after oral administration. Both Losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the feces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine, and about 6% is excreted in urine as the active metabolite. The terminal elimination half lives of Losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively [2].

We present here a study of Cu(II) and Zn(II) coordination by Losartan carried out by potentiometric, NMR and ESI-MS techniques. Losartan-Cu(II) and Losartan-Zn(II) complexes have been thoroughly characterized. It has been furthermore revealed that the presence of these two metal ions induces the formation of the derivative D1 shown in Figure 1.

References:

[1] Boersma, C.; Atthobari, J.; Gansevoort, R.T.; de Jong, P.E.; de Zeeuw, D.; Annemans, L.J.; Postma, M.J., Pharmacoeconomics of angiotensin ii antagonists in type 2 diabetic patients with nephropathy. *Pharmacoeconomics* **2006**, *24*, 523-535.

[2] Sica, D.A.; Gehr, T.W.; Ghosh, S., Clinical pharmacokinetics of losartan. *Clinical pharmacokinetics* **2005**, *44*, 797-814.

Iron-Sandwich Complexes - Additive Character of Interligand Substituent Effects

Jan TUREK,[a] Roman OLEJNIK,[a] Bohumil STIBR,[b] Zdenka PADELKOVA[a]

[a] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentska 573, CZ-532 10, Pardubice, Czech Republic.
b) Institute of Inorganic Chemistry, Academy of Sciences of the Czech Republic, CZ-250 68 Rez, Czech Republic
e-mail: zdenka.padelkova@upce.cz

The straightforward linear correlation of the number of methyl substituents on the arene ring (*n*) with ^{1}H and ^{11}B NMR chemical shifts of the dicarbollide cage atoms was revealed in the contiguous series of the [1-(η^6-$Me_nC_6H_{6-n}$ Fe) (η^5-2,3-$C_2B_9H_{11}$)] arene-dicarbollide complexes (where n = 1 - 6). This is in line with additive character of electron donation by the arene methyl substituents and its transfer onto the second sandwiching ring via the Fe^{II} center.[1] Similar linear relationships were also observed in the ^{1}H and ^{13}C NMR spectra of the cyclohexadienyl and cyclopentadienyl ring atoms in the contiguous series of the isoelectronic cations [(η^5-C_6H_7)Fe(η^6-$Me_nC_6H_{6-n}$)]$^+$ and [(η^5-C_5H_5)Fe(η^6-$Me_nC_6H_{6-n}$)]$^+$.[2] Surprisingly, the trend of this interesting interligand NMR effect was found rather different for ^{13}C nuclei. It has become also obvious that the sensitivities to this effect differ, which might be taken as a quantitative measure for electron donating/withdrawing efficiency of various substituents attached to the arene ring.

Moreover, structures of some these compounds were determined by XRD techniques.

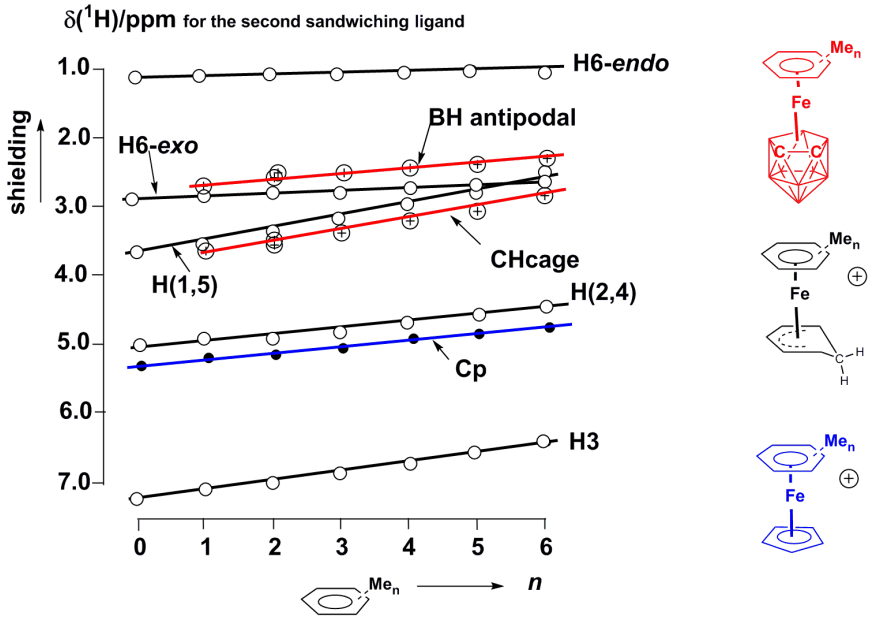


Figure 1 – Linear correlation between the number of arene methyls (n) and δ(1H) chemical shifts.

Acknowledgement: The financial support of the Czech Science Foundation (Project no. P207/11/0705) is gratefully acknowledged.

References:

[1] Stibr, B.; Bakardjiev, M.; Holub, J.; Ruzicka, A.; Padelkova, Z. Stepnicka, P. *Inorg. Chem.*, **2011**, *50*, 3097–3102.

[2] Turek, J.; Olejník, R.; Štíbr, B. *Organometallics*, **2014**, in press (DOI: 10.1021/om500165w)

Solvent- and wavelength-dependent fluorescent properties of chromone derivatives complexes with Cu(II), Zn(II) and Ru(II)

Bogumiła KUPCEWICZ, [a] **Paulina MUCHA,** [b] **Łukasz OSTROWSKI,**[a] **Mateusz KŁOBUKOWSKI,** [a] **Elzbieta BUDZISZ** [b]

[a] *Department of Inorganic and Analytical Chemistry, Faculty of Pharmacy, Nicolaus Copernicus University, Jurasza 2, 85-089 Bydgoszcz (Poland)* [b] *Department of Cosmetic Raw Materials Chemistry, Medical University of Lodz, Muszynskiego 1, (Poland); kupcewicz@cm.umk.pl*

Over the past decades, synthesis of metal complexes with chromone derivatives has attracted great attention due to their various biological activities and development of new materials based on metal-organic coordination compounds. The aim of this study is to conduct a comprehensive fluorescent characterization of two compounds: 7-aminoflavone and 7-amino-2-methylchromone and their complexes with copper(II), zinc(II) and organoruthenium(II) ions. Both compounds are bifunctional molecules because they contain both electron donor group $–NH_2$ and electron withdrawing group C=O. These compounds may act as monodentate N-donor or O-donor ligands, thus two different coordination mode with metal ions can be obtained.

Fig. 1 Ligands, 7-aminoflavone **L1** (left) and 7-amino-2-methylchromone **L2** (right)

These ligands act as monodentate neutral O donor and coordinates Zn(II) ion through O-atom of carbonyl group [1], whereas organorutenium(II) is coordinated through N-atom of amino group [2].

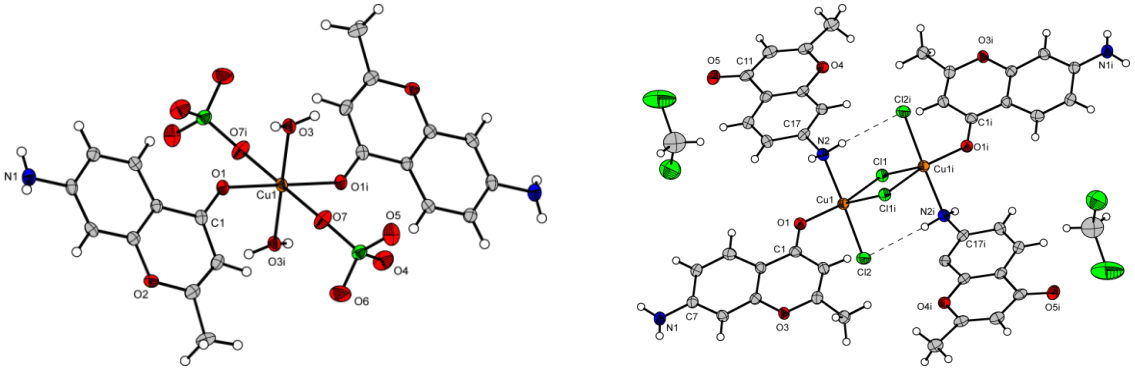


Fig. 2 View of the molecular structure of $Cu(L1)_2(ClO_4)_2(H2O)_2$ and dinuclear unit of $[Cu(L)_2Cl_2]_2$ (right). Hydrogen bonds are shown as dashed lines. Displacement ellipsoids are drawn at the 50% probability level. [Symmetry codes: i = 1−x, 1−y, 1−z]

In case of Cu(II) two different complexes were obtained. The first molecular structure show, that the copper is coordinate by two ClO_4 groups and two O-bonded 7-amino-2-methylchromone ligands (Fig. 2), in the second complex the ligand **L2** acts once as monodendate neutral O-donor and once as monodentade neutral N-donor.

The fluorescent properties of ligands and their complexes were examined in series of solvents: nonpolar (chloroform), polar aprotic (acetonitrile, DMSO, DMF) and polar protic (ethanol, methanol and water). Both ligands are well soluble in common polar organic solvents as well as in water and slightly soluble in nonpolar solvents. Coordination of various metal ions cause differences of solubility of the obtained complexes. The fluorescence excitation-emission matrix spectra (EEM) demonstrate significant solvent dependent shifts in emission maxima. The position of the peaks are related to nature of the metal and ligand as well as polarity of solvent. For some complexes excitation-wavelength dependent emission was observed. To describe the effect of polarity of solvents the Lippert-Mataga plot (Stokes' shift vs. polarizability of the solvent) was used. Moreover the fluorescence quantum yield was measured.

Acknowledgements
This work is financially supported by Nicolaus Copernicus University (PDS No 411) and Medical University of Lodz (grant No 503/3-066-02/503-1).

References:

[1] Kupcewicz, B.; Kaczmarek-Kedziera, A.; Lux, K.; Budzisz, B., Novel bright-blue luminescent complex of Zn(II) with 7-amino-methylchromen-4-one: Synthesis, photophysical properties and DFT calculations. *Polyhedron* **2013,** 55, 259-269.

[2] Pastuszko, A.; Niewinna, K., Czyz, M.; Jóźwiak, A., Małecka, M.; Budzisz, E., Synthesis, X-ray structure, electrochemical properties and cytotoxic effects of new arene ruthenium(II) complexes. *Journal of Organometallic Chemistry* **2013,** 745-746, 64-70.

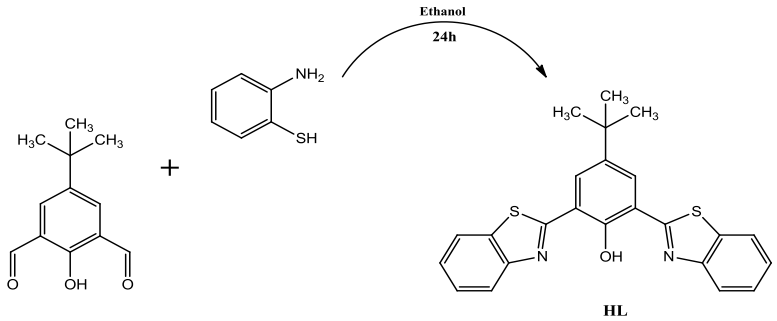
Transition metal(II) complexes of a novel symmetrical benzothiazole-based ligand: Synthesis, spectral/structural characterization and fluorescence properties

Mehmet GÜLCAN, [a] Yaşar KARATAŞ, [a] Esvet AKBAŞ,[a] Gülsiye ÖZTÜRK,[b] Ertan ŞAHİN [c]

[a]Department of Chemistry, Faculty of Science, Yüzüncü Yıl University, 65080, Van, Turkey
[b]Department of Chemistry, Faculty of Science, Dokuz Eylül University, 35160, İzmir, Turkey
[c]Department of Chemistry, Faculty of Science, Atatürk University, 25000, Erzurum, Turkey
mehmetgulcan@yyu.edu.tr

The thiazole units are found in many naturally occurring compounds. Thiazole ring is also a part of vitamin B_1, penicillin and coenzymes. Thiazole derivatives are used in inorganic chemistry for building polydentate ligands [1]. Benzothiazole are bicyclic ring system with multiple applications. İt is an aromatic heterocyclic compound with the chemical formula C_7H_5NS. Benzothiazoles consist of a 5-membered 1,3-thiazole ring fused to a benzene ring. The nine atoms of the bicycle and the attached substituents are coplanar. Benzothiazoles constitute an important class of compounds with profound interest to medicinal/industrial chemists as compounds bearing the benzothiazolyl moiety. They exhibit diverse biological properties such as antitumour, antimicrobial, antiglutamate/antiparkinson, broad spectrum Ca^{2+} channel antagonist, inhibition of enzymes such as aldose reductase , monoamine oxidase, lipoxygenase, cyclooxygenase, acetylcholine esterase, thrombine, proteases, H^+–K^+ ATpase, carbonic anhydrase, HCV helicase, plant growth regulation and have industrial applications such as antioxidants [2]. In addition they have been studied because of their fluorescent and luminescent properties and the possibility to give rise to supramolecular arrangements [3].

In this work the benzothiazole-based ligand, HL, (***Scheme 1***) and its Cu(II), Ni(II) and Co(II) transition metal complexes were synthesized, characterized and their fluorescence features were determined in different solvents. The compounds were characterized by elemental analysis, FT-IR, ^1H and ^{13}C NMR techniques. In addition, the structure of the ligand has been determined by X-ray crystallographic analysis.



Scheme 1. Synthesis protocol of the ligand

References:

[1] Karmaka, T.; Kuang, Y.; Neamati, N.; Baruah, J.B., Cadmium complexes and cocrystals of indium complexes of benzothiazole derivatives and anticancer activities of the cadmium complexes. *Polyhedron* **2013**, 54, 285–293.

[2] Arjunana, V.; Sakiladevib, S.; Ranic, T.; Mythilid, C.V.; Mohane, S., FTIR, FT-Raman, FT-NMR, UV–visible and quantum chemical investigations of 2-amino-4-methylbenzothiazole. *Spectrochimica Acta Part A* **2012**, 88, 220– 231.

[3] Freinbichlera, W.; Solimanb, A.; Jamesonc, R.F.; Jamesond, G.N.L.; Linerta, W., Kinetic study of the complex reaction between copper(II) and 2-(2-hydroxy-3-methoxyphenyl)benzothiazole. *Spectrochimica Acta Part A* **2009**, 74, 30–35.

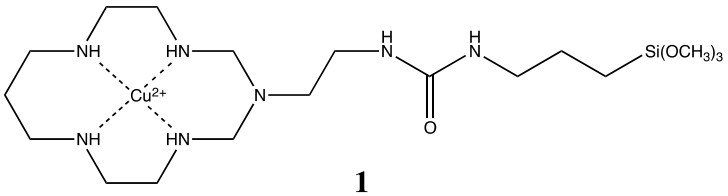
Fluorogenic detection of HS^- in water by MCM41-based hybrid material functionalized with macrocyclic complex subunits

Sameh EL SAYED,[a] Michele MILANI,[b] Maurizio LICCHELLI,[b] Ramón Martínez-Máñez,[a] and Félix Sancenón[a]

[a] Universidad Politecnica de Valencia [b] Università di Pavia; michele.milani@unipv.it

Organic-inorganic hybrid materials based on functionalised mesoporous silica nanoparticles (e.g. MCM-41) have been recently applied in the optical detection of different substrates. [1] These materials are obtained by combining the inorganic nanometric scaffold with organic fragments that are properly anchored on its surface. The new sensing strategy is based on a gate-like behaviour of the hybrid materials, which are able to modulate the mass transport at the nanometric level depending on the presence of certain chemical species.

In this work MCM41 was loaded with $[Ru(Bipy)_3]^{2+}$ dye and the external surface functionalised by the macrocyclic copper(II) complex **1**.



1

Complex **1** was obtained by a 3-step synthesis involving a template reaction (synthesis of the macrocyclic framework) and a further functionalization.

The resulting hybrid material allows a free release of the entrapped dye from the pores to the solution ("open gate" behaviour), as showed by the increasing of fluorescence intensity with time when it is suspended in water. Copper(II) macrocyclic subunits efficiently interact with multiply charged anionic species (e.g ATP at neutral pH), which, as a consequence block the pores and inhibit the dye release ("closed gate" behaviour).

Material obtained by combination of loaded functionalised MCM41 and ATP was studied in the presence of different anionic species. In particular, it was suspended in neutral water and dye release was monitored by measuring the emission intensity of $[Ru(Bipy)_3]^{2+}$ (608 nm) at different time intervals. The relative fluorescence intensity values determined after 5 h in the presence of various anionic species are reported in Figure1.

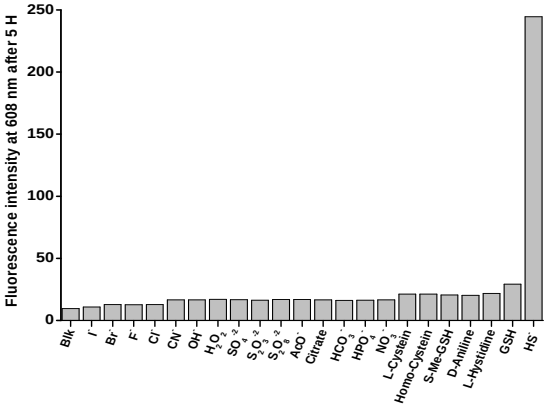


Figure 1. Dye release in the presence of different anion species

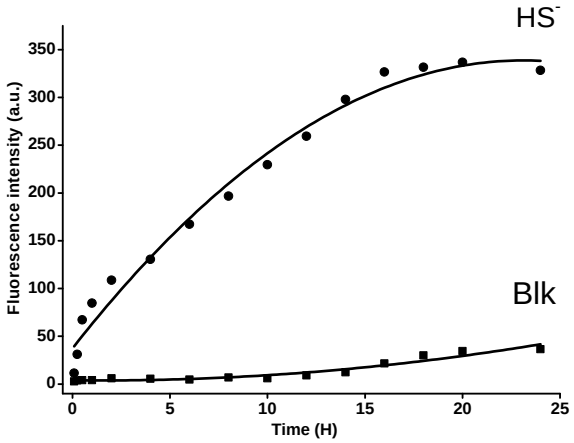


Figure 2. Kinetic of dye release in the presence of hydrogensulfide (20 mg of solid in 35 ml of H_20, pH 7.5, 30 mM HEPES, 1mM of Na_2S). Release curve obtained for hybrid material (closed gate) is reported for comparison

The studied system allow a fast dye release only in the presence of sulphide (HS^- at the experimental pH value, see Figure 2) and is not responsive towards other common anions, aminoacids and bio-thiols that may interfere in the detection of sulfide (e.g. GSH, Cys, Homo-cys). This highly selective response can be ascribed to the interaction of sulphide with copper ion which is removed from the macrocyclic complex owing to the formation of strongly insoluble CuS. [2] As a consequence, ATP is no longer held close to the pores and dye release is allowed again.

Further investigations will assess the sensing ability of the hybrid material in living cells.

References:

[1] Oroval,M.; Climent,E.; Coll,C.; Eritja,R.; Avino,A.; Marcos,M.D.; Sancenon,F.; Martınez-Manez,R.; and Amoros,P., An aptamer-gated silica mesoporous material for thrombin detection. *Chem. Commun.*, **2013,** 49, 5480-5482

[2] Santos-Figueroa, L.; De la Torre, M.; El Sayed, S.; Sancenon,F.; Martınez-Manez,R.; Costero, A.M.; Gil, S.; Parra, M., Highly Selective Fluorescence Detection of Hydrogen Sulfide by Using an Anthracene-Functionalized Cyclam–Cu^{II} Complex, *Eur. J. Inorg. Chem.* **2014**, 41–45

Synthesis and characterization of a rhodamine B derivative as a chemosensor for the determination of Hg^{2+} in water in environmental samples.

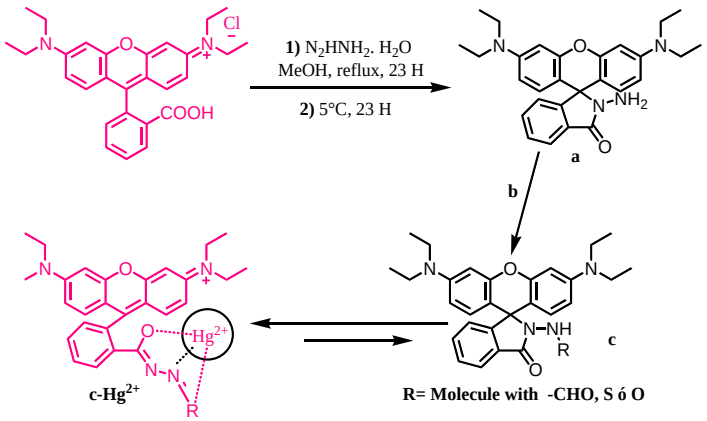
Sergio David MOSQUERA GONZÁLEZ, [a] **Rubén A. SANCHÉZ ANDICA,** [a] **Walter TORRES HERNÁNDEZ,** [b]

[a] *Environmental pollution by heavy metals and pesticides research group (GICAMP), Departament of Chemistry, Faculty of Natural and Exact Sciences, Universidad del Valle, A.A.25360, Cali, Colombia, sergio.mosquera@correounivalle.edu.co* [b] *Electrochemical Group (GELEC) Departament of Chemistry, Faculty of Natural and Exact Sciences, Universidad del Valle, A.A.25360, Cali, Colombia.*

keywords: *Mercury, rhodamine B hidrazide, sensor, fluorescence.*

Introduction

There is a great interest in the development of good sensors for detection of heavy metal ions because, although some have vital and beneficial effects, the toxicity of others is of particular concern. Specifically Hg^{2+} is considered as one of the most hazardous environmental contaminants. It is widely distributed in air, water, and soil through different processes such as volcanic emissions, mining, solid waste incineration, and combustion of fossil fuels, and the ability of some anaerobic organisms to transform the elemental and inorganic forms of mercury into methylmercury, in the food chain through bioaccumulation in edible animals [1]. Usually, rhodamine system based sensors are formed by the rhodamine fluorophore linked to a mercury receptor with different structures in the sensor. In the absence of the analyte, the sensor fluorophore has the spirolactamic structure (nonfluorescent), with a carbon atom with sp^3 hybridization that prevents planarity and electronic delocalization between aromatic rings. After Hg^{2+} complexation, a strong structural change in the receptor is produced, which implies C-N spiranic bond rupture and formation of dideoxidiaminofluorone rings of rhodamine.(fluorescent) [1-2]



Scheme 1. Synthesis of **c**, reference compounds and formation complex **c-Hg^{2+}.**

Materials and methods

The procedure for the synthesis of the precursor compounds needed for the sensor flourophore are based on the previous work of Culzoni [1], and it will be synthesized in two steps: the first step involves the reaction between the rhodamine and hydrazine (scheme 1a) under conditions of scheme 1a. The second step implicate the reaction of the compound 1a and other that must have sulfur or oxygen atoms or formile group in order to facilitate the complexation with mercury ion (scheme 1c-Hg^{2+}). The reaction between the fluorophore (1c) and mercury ion is intented to get a complex (scheme 1) that emits fluorescence, in order to, standardize and validate an analytical method, which may be applicable to environmental analysis of water with more sensitivity and selectivity than others. The fluorimetrics measures will be carried out with a JASCO FP-8500 spectrofluorimeter. It will be evaluated factors that may affect the complexation between the fluorophore with Hg^{+2}, such as pH, temperature, solvents, etc. The obtaining of the fluorophore will be optimized with a experimental design of answer surface statistical technique. The polarity of the solvent must be taken into account due to the binding to the rhodamine derivatives depends on the type and spatial distribution of the donors attached and are frequently influenced by the nature of solvents used.

Results and Discussion

A rhodamine-hydrazide derivative (scheme 1a) is obtained in the first step by a modification of the procedure of Guo *et al* [2]. The rhodamine derivative is obtained with an excess of hydrated hydrazine in methanol at 0° C for 23 hours. This compound has been characterized by RMN-^{1}H and RMN-^{13}C spectroscopy which matches with the desired compound cited in the literature [ ]. In the second step, it has been tested vainillin (aldehyde compound) as a reactant, in which a Schiff base (imine derivative) was obtained; nevertheless, this compound not exhibited fluorescence in the presence with mercury ion.

Based on this methodology, it will be evaluated others compounds that reacts with **1a** to get the desired sensor, taking into account the chemical characteristics of these kind of chemosensors and that are reported in the literature, especially for Hg^{+2} [1].

Importance

Our goal is to propose an analytical methodology that achieves detection limits and selectivity as good as other analytical techniques, which can be more economic and may have analytical procedures easier to apply, especially for the governmental entities of the environment. This work also contributes to the application of the organometallic chemistry to the chemosensor development useful in modern analytical chemistry.

Acknowledgements

The authors gratefully acknowledge to Laboratorio de Análisis Industriales (Industrial Chemical Analysis) of the Universidad del Valle (University of Valley) for the support of this work.

References

[1] Culzoni, M.; Muñoz de la Peña, A.; Machuca, A.; Goicoechea, H.; Babiano, R., Rhodamine and BODIPY chemodosimeters and chemosensors for the detection of Hg2+, based on fluorescence enhancement effects. Anal. Methods, 2013, 5, 30-49.

[2] Guo, X.; Yang, X.; Zhao, Y., Development of a novel rhodamine-type fluorescent probe to determine peroxynitrite. Talanta, 2002, 57, 883-890.
[3] Liu, W.; Dou, W.; Tang, X.; Qin, W.; Wang, L., Development and Applications of fluorescent Indicators for Mg2+ and Zn2+. J. Phys. Chem. A, 2011, 115, 1609-1616.

Analysis of the selective sensing ability of a bifunctional crown ether-perylene fluoroionophore

Tarita BIVER,[a,b] Andrea PUCCI,[a,b] Giacomo RUGGERI,[a,b] Fernando SECCO,[a] Camila TELLES DE BESSA,[a] Marcella VENTURINI [a]

[a] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy. Tel: +39 0502219270; fax: +39 0502219320; [b] INSTM, Unità di Ricerca di Pisa, Via Risorgimento 35, 56126 Pisa, Italy; tarita.biver@unipi-it

The design of chemosensors able to selectively recognize and sense specific analytes has attracted considerable interests due to their importance in biological and environmental scenarios and stimulated the development of chromoionophores sensors for the detection of metal cations.[1,2] Chromoionophores and fluoroionophores are chemical species based on the principle that a selective complexation of a cation by means of a crown ether compound can be rendered detectable by a colour effect initiated within the same molecule. This requires a chromophore attached close to the ligand moiety and an electronic coupling between the two parts of the molecule.

As far as fluorogenic units are concerned, considerable attention has been recently devoted in literature to perylene based dyes,[3] due to the effective combination of properties ranging from electro-optical and redox characteristics to thermal and migration stability which allow applications as fluorescence standards, thin film transistors, liquid crystals, light emitting diodes, and devices for photovoltaics.[4-7]

Intrigued by these preliminary considerations, we have carried out detailed studies aimed at exploring the cation fluorescence sensing properties of crown ethers covalently linked to a perylene chromophore (Pery-Crown5, Figure 1).

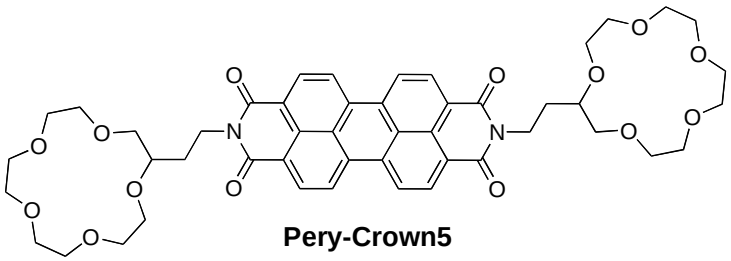


Figure 1. Fluoroionophore compound used in this study

For this purpose Pery-Crown5 was prepared and the sensing properties for various metal cations were investigated by means of absorption and emission spectroscopies.

References:

[1] Fan, L.-J.; Zhang, Y.; Murphy, C. B.; Angell, S. E.; Parker, M. F. L.; Flynn, B. R.; Jones W. E., Fluorescent conjugated polymer molecular wire chemosensors for transition metal ion recognition and signaling. *Coordination Chemistry Reviews*, **2009**, 253, 410-422.

[2] Guo, Z.; Shin, I.; Yoon, J., Recognition and sensing of various species using boronic acid derivatives. *Chemical Communications*, **2012**, 48, 5956-5967.

[3] Wuerthner, F., Bay-substituted perylene bisimides: twisted fluorophores for supramolecular chemistry. *Pure and Applied Chemistry*, **2006**, 78, 2341-2349.

[4] Schmidt-Mende, L.; Fechtenkotter, A.; Mullen, K.; Moons, E.; Friend, R. H.; J. D. MacKenzie, J. D., Self-organized discotic liquid crystals for high-efficiency organic photovoltaics. *Science*, **2001**, 293, 1119-1122.

[5] Woehrle, D.; Meissner, D., *Advanced Materials*, **1991**, 3, 129-138.

[6] Donati, F.; Pucci, A.; Ruggeri, G., *Physical Chemistry Chemical Physics*, **2009**, 11, 6276-6282.

[7] Donati, F.; Pucci, A.; Cappelli, C.; Mennucci, B.; Ruggeri, G., *Journal of Physical Chemistry B* **2008**, 112, 3668-3679.

A Small Size and Low Cost Deferoxamine Self Assembled Monolayer Sensor Based on Surface Plasmon Resonance for detection of Fe(III)

Federico QUATTRINI,[b] Nunzio CENNAMO,[a] Giancarla ALBERTI,[b] Maria PESAVENTO,[b] Raffaela BIESUZ,[b] Luigi ZENI,[a]

[a] Department of Industrial and Information Engineering, Second University of Naples, Via Roma 29, Aversa 81031, Italy; [b]Department of Chemistry, University of Pavia, Via Taramelli 12, Pavia 27100, Italy; federico.quattrini01@ateneopv.it

Iron(III) concentration in biological and environmental systems is of crucial relevance; new methods for iron analysis are widely required, in particular for *in situ* applications. A simple, small size, and low cost sensor based on a Deferoxamine Self Assembled Monolayer (DFO-SAM) and Surface Plasmon Resonance (SPR) transduction, in connection with a Plastic Optical Fiber (POF), has been developed for the selective detection of Fe(III).

Although a DFO-SAM sensor based on appropriate electrochemical techniques has been already presented in the scientific literature [1], this is the first effort to develop a DFO-SAM sensors based on SPR in an optical fiber. This experimental set-up offers several advantages over the classical Kretschmann configuration, due to the characteristics of the plastic optical fiber, including excellent flexibility, easy manipulation, large diameter, and the fact that plastic is able to withstand smaller bend radii than glass.

The SPR sensing platform was realized by removing the cladding of a plastic optical fiber along half the circumference, spin coating (using an original, low-cost technique) a buffer of Microposit S1813 photoresist on the exposed core, and finally sputtering a thin gold film. The hydroxamate siderophore deferoxamine (DFO) is then immobilized as a self-assembled monolayer on the gold layer, following a previously developed procedure [2]. DFO is one of the most employed drugs used in chelation therapy to remove excess iron from blood due to its high affinity for Fe(III). For this reason it is here selected as the receptor in the sensor.

The results showed that the DFO-SAM-POF sensor was able to detect Fe(III) in the range of concentrations between 1 μm and 50 μm with a linearity range from 0 to 30 μm.

The interaction of iron(III) with the immobilized DFO was investigated by the SPR technique, assuming that the instrumental response, i.e. the shift of the resonance wavelength due to variation of the refraction index after combination of Fe(III) with DFO, is directly proportional to the concentration of Fe(III) in the monolayer.

The value of the conditional stability constant in the solid phase, K_C, seems to be similar and just slightly higher than that in aqueous solution, assuming the 1:1 complex formation in both phases.

The selectivity of the sensor towards ions that are likely to be found in real life samples (*e*.g. natural water) as Na^+ and Ca^{2+} was also proved by interference tests; the effects of pH variation on the sensor's behavior have been similarly investigated.

References:

[1] Shervedani, R.K.; Akrami, Z.; Gold–deferrioxamine nanometric interface for selective recognition of Fe(III) using square wave voltammetry and electrochemical impedance spectroscopy methods. *Biosensors and Bioelectronics* **2013**, 39, 31–36

[2] Shervedani, R.K.; Akrami, Z.; Sabzyan, H. Nanostructure Molecular Assemblies Constructed Based on *Ex-Situ* and *In-Situ* Layer-by-Layer Ferrioxamation Characterized by Electrochemical and Scanning Tunneling Microscopy Methods. *J. Phys. Chem. C* **2011**, *115*, 8042–8055

Development of a sensor for trivalent metals: AHP fixed on mesoporous silica

Roberta COLLEONI, [a] Luisa ALLEGRI, [a] Maite URRUTIA ANTIA, [b] Giancarla ALBERTI, [a] Raffaela BIESUZ, [a] Greta BERGAMASCHI, [a] Valeria AMENDOLA, [a] Maria Amelia SANTOS, [c]

[a] Department of Chemistry, Università degli Studi di Pavia, via Taramelli 12 – 27100 Pavia (Italy);
[b] Department of Chemistry; Universidad del Pais Vasco, Paseo Manuel de Lardizábal 3 – 20018 San Sebastián (Spain);
[c] Centro de Quimica Estrutural - Istituto Superior Técnico, Universitade de Lisboa, Av. Rovisco Pais 1 – 1049-001 Lisboa (Portugal).
e-mail: roberta.colleoni01@universitadipavia.it

A class of O,O donor ligands, **hydroxypyridinones,** known for high affinity for trivalent metal ions, are particularly interesting since their complexes are stable at physiological pH and have low toxicity [1]. For iron this kind of ligands is already exploited: *deferiprone* is one of the most used drugs [2] for chelation therapy. For lanthanum this ligands were recently explored as possible carriers in orally active therapy for hyperohosphatemia and bone disorder diseases [3,4].

We present the prosecution of a former study in which we used as a solid-phase, mesoporous silica MCM-41, functionalized with a hydroxypyridinone, **N(3'-aminopropyl)-3-hydroxy-2-methyl-4-pyridinone (AHP)** (figure 1), for sensing those two trivalent metals.

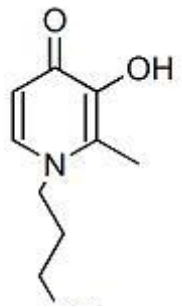


Figure 1: AHP structure

The kinetics of Fe(III) and La(III) sorption have been more accurately verified in several conditions, being similar to that found for other silica based solid materials [5]. It is rapid: in two hours the metals are completely sorbed, it means that this material is not so different from commercially available synthetic resins [6].

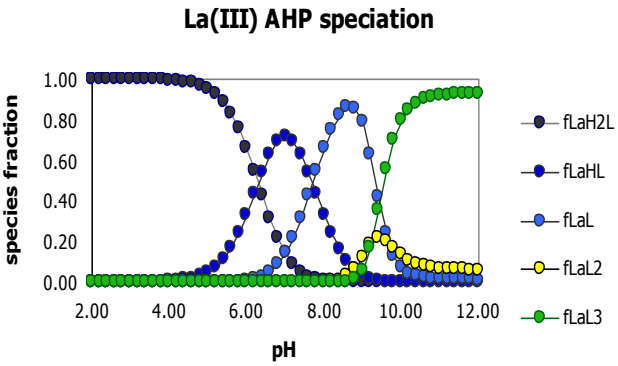


Figure 2: La(III)-AHP complexes distribution diagram

There is a large variety of complexes that can be formed in solution between the metal ion and AHP, of different stoichiometry and different degree of protonation, MH_pL_n with p=0, 1, 2, 3 and n=1, 2, 3. For iron(III) the speciation was already known in literature [8] while for lanthanum(III) suitable experiments had to be performed (figure 2). Our interest was to determine whether the stoichiometry in solution was retained in the solid phase since no complex with metal/ligand stoichiometry ratio of 1:3 has ever been reported in literature before.

Physical measurements (solid state NMR, EPR) proved to be unsuccessful for various reasons for this determination. For what concerns iron(III) the complexes formed are colored both in solution and in the solid phase. We took advantage of this particular property and determined the stoichiometry of the complexes via solid vis-spectrophotometry.

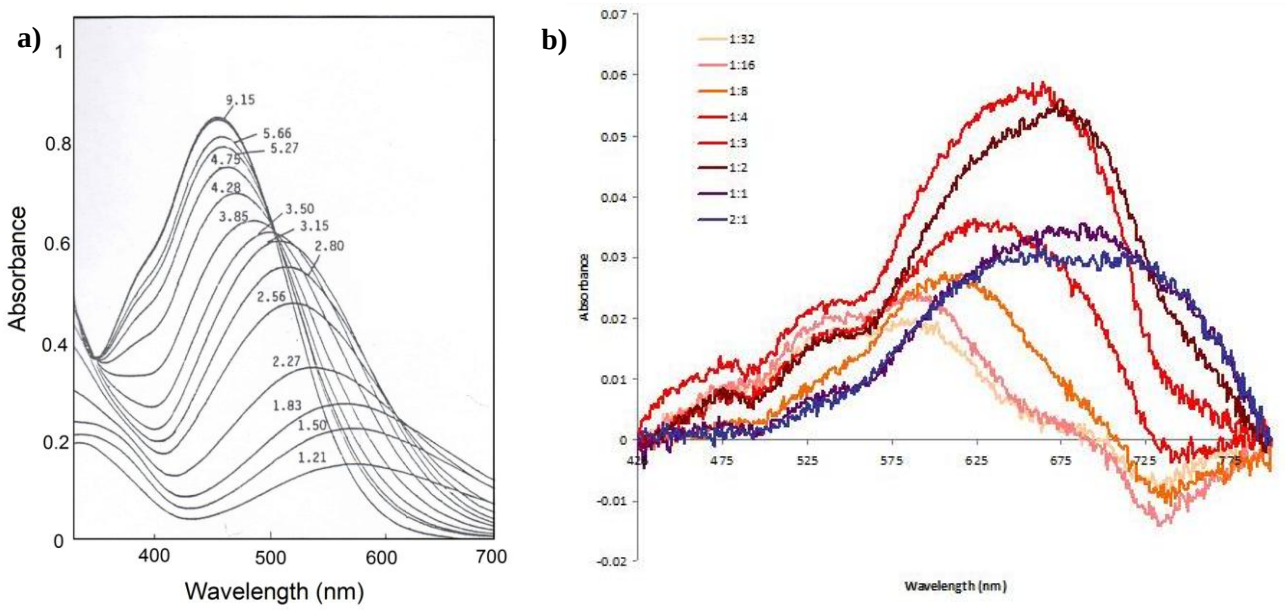


Figure 3: a) UV spectra of iron(III)-deferiprone complexes in solution at various pHs. **b)** UV spectra of differently loaded solid phases.

We observed a good match between the colorations in solution [9] (figure 3a) and those in solid phase (figure 3b): a further evidence that the complex stoichiometries are retained in solid phase, producing an orange complex with metal/ligand ratio of 1:3, as previously detected from sorption equilibria of iron(III) on the silica-base material in function of pH.

References:

[1] Numes, A.; Marques, S. M.; Quintanova, C.; Silva, D. F.; Cardoso, S.; Chaves, S.; Santos, M. A., Multifunctional iron-chelators with protective roles against neurodegenerative diseases. *Dalton transactions* **2013,** 42(17), 6058-6073.

[2] Jamuar, S. S.; Lai, A. H. M., Safety and efficacy of iron chelation therapy with deferiprone in patients with transfusion-dependent thalassemia. *Therapeutic advances in Hematology* **2012,** 3(5), 299-307.

[3] Zhang, C.; Wen, J.; Li, Z.; Fan, J., Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. *BMC Nephrology* **2013,** 14, 226/1-226/14.

[4] Mawani, Y.; Cawthray, J. F.; Chang, S.; Sachs-Barrable, K.; Weekes, D. M.; Wasan, K. M.; Orvig, C., In vitro studies of lanthanide complexes for the treatment of osteoporosis. *Dalton transactions* **2013,** 42(17), 5999-6011.

[5] Biesuz, R.; Emma, G.; Milanese, C.; Dacarro, G.; Taglietti, A.; Nurchi, V. M.; Alberti, G., Novel DFO SAM on mesoporous silica for iron sensing. Part I. Synthesis optimization and characterization of the material. *Analyst. In press*

[6] Alberti, G.; Biesuz, R., Empore™ membrane vs. Chelex100: Thermodynamic and kinetic studies on metal sorption. *Reactive & Functional Polymers* **2011**, 71(5), 588-598.

[7] Santos, M. A.; Gil, M.; Gano, L.; Chaves, S., Bifunctional 3-hydroxy-4pyridinone derivatives as potential pharmaceuticals: syntesis, complexation with Fe(III), Al(III) and Ga(III) and in vivo evaluation with ^{67}Ga. *J. Biol. Inorg. Chem* **2005,** 10, 564-580.

[8] Montekaitis, R. J.; Martell, A. E., Stabities of the iron(III) chelates of 1,2-dimethyl-3-hydroxy-4-pyridinone and related ligands. *Inorganica Chimica Acta* **1991,** 183, 71-80.

Novel Kojic acid-based polymeric membrane for iron sensing

Roberta COLLEONI, [a] **Luisa ALLEGRI,** [a] **Maite URRUTIA ANTIA,** [b] **Giancarla ALBERTI,** [a] **Raffaela BIESUZ,** [a] **Saúl VALLEJOS** [c], **Félix C. GARCÍA** [c], **José Miguel GARCÍA,** [c]

[a] *Department of Chemistry, Università degli Studi di Pavia, via Taramelli 12 – 27100 Pavia (Italy);*
[b] *Department of Chemistry; Universidad del Pais Vasco, Paseo Manuel de Lardizábal 3 – 20018 San Sebastián (Spain);*
[c] *Faculty of Science; Universidad de Burgos, Plaza de Misael Bañuelos s/n – 09001 Burgos (Spain);*

e-mail: roberta.colleoni01@universitadipavia.it

We present a novel polymeric material for iron(III) sensing that features kojic acid as receptor moiety.

The membrane copolymer is composed by N-vinyl-2-pyrrolidinone and 2-hydroxyethylacrylate with ethylene glycol dimethacrylate as a crosslinker. In order to include kojic acid, this ligand was previously functionalized with a polymerizable moiety.

The whole preparation of the material was performed by Prof. García and collaborators with a procedure already reported in literature [1].

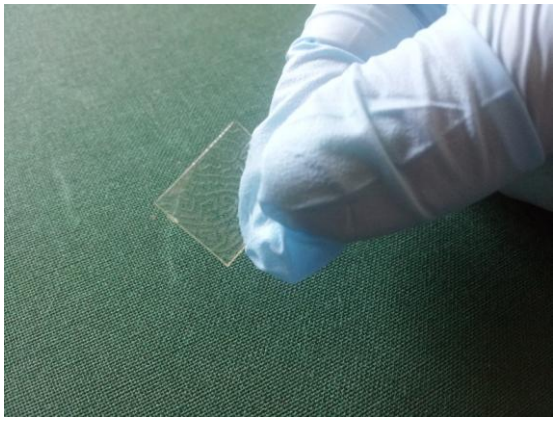


Figure 1: sensory membrane appearance

The final material (figure 1) is transparent with good mechanical properties and is being characterized with various experiments. In García's laboratory chromatic properties of the support are now being studied via spectrophotometric measurements. In our laboratory we have undertaken the characterization of the material performing kinetics, isotherms and sorption profiles in function of the pH.

Kinetics profiles showed that the iron(III) uptake requires about one hour and a half (figure 2), the behaviour makes this material not so different from other silica based solids for iron(III) sorption [2]. Preliminary sorption isotherms confirmed the expected amount of ligand copolymerized in the membrane. The sorption profiles in function of pH, also in

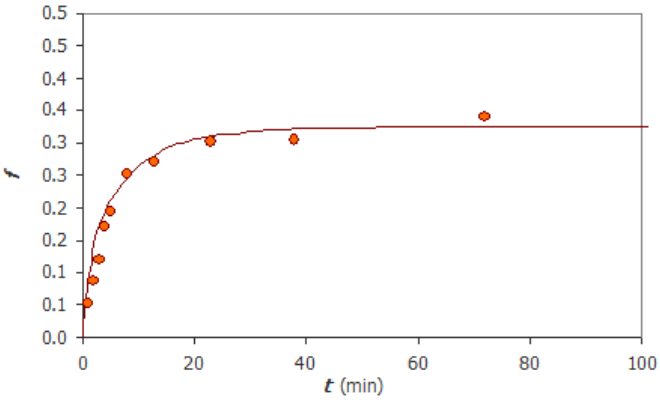


Figure 2: Kinetics profile for iron (III) sorption

presence of different competitors have been produced. The sorption exchange coefficient of iron(III) seems, so long, in pretty good agreement with the ones reported in literature for the complex in solution. [3,4]

Further investigations are in progress, but we are confident that such material could be employed for several feasible purposes.

References:

[1] El Kaoutit, H.; Estévez, P.; García, F. C.; Serna, F.; García, J. M., Sub-ppm quantification of Hg(II) in aqueous media using both the naked eye and digital information from pictures of a colorimetric sensory polymer membrane take with the digital camera of a conventional mobile phone. *Analytical Methods* **2013,** 5, 54-58.

[2] Alberti, G.; Emma, G.; Colleoni, R.; Pesavento, M.; Nurchi, V. M.; Biesuz, R., Novel DFO SAM on mesoporous silica for iron sensing. Part 2 Experimental detection of free iron concentration (pFe) in urine samples. *Analyst, in press.*

[3] Okac, A.; Kolarik, Z., Potentiometrische untersuchung von komplexsalzen der kojisäure in wässrigen lösungen. *Collec. Czech Chem. Commun.* **1959,** 24(1), 266.

[4] Nurchi, V. M.; Crisponi, G.; Lachowicz, J. I.; Murgia, S.; Pivetta, T.; Remelli, M; Rescigno, A.; Niclós-Gutíerrez, J.; Gonzáles-Pérez, J.; Domínguez-Martín, A.; Castiñeiras, A; Szewczuk, Z., Iron(III) and Aluminum(III) complexes with hydroxypyrone ligands aimed to design kojic acid derivatives with new perspectives. *Journal of Inorganic Biochemistry* **2010,** 104, 560-569.

Selective Cu(II) naked-eye sensors based on water soluble NDIs

Filippo DORIA, [a] Valeria AMENDOLA, [a] Vincenzo GRANDE, [b] Greta BERGAMASCHI, [a] Mauro FRECCERO, [a]

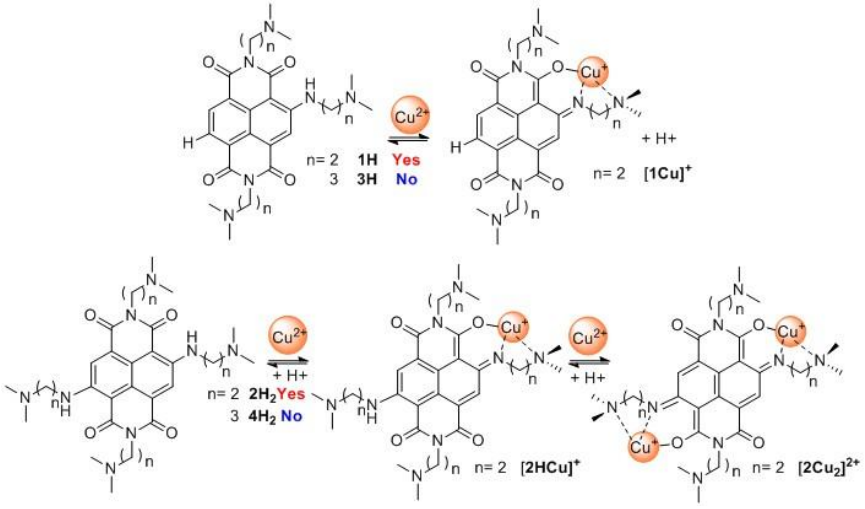
[a] Department of Chemistry, Università degli Studi di Pavia, via Taramelli 12 – 27100 Pavia (Italy);

e-mail: vincenzo.grande01@universitadipavia.it

Development of selective, sensible, low cost, rapid tracking Cu^{2+} sensors have attracted considerable attention since the widespread presence of Cu^{2+} as pollutant and its key role in many mononuclear copper-active monooxygenases.[1]

Furthermore, in recent works, we and other have shown that naphthalene diimides (NDIs) may act as a potent G-quadruplex (G4) DNA and RNA ligand. Moreover, the interesting photophysical and photochemical behaviour of these NDIs, suggest multimodal theragnostic applications against cancer progression.[2]

With the aim of combining the optoelectronic properties of NDIs with Cu^{2+} sensing and its catalytic activity we have synthesized and investigated the Cu^{2+} coordination of water soluble NDIs **1H**, **$2H_2$**, **3H** and **$4H_2$** (**Scheme 1**). Unexpectedly, only **1H** and **$2H_2$** form detectable complexes exhibiting a considerable blue-shift of the CT band, so that Cu^{2+} sensing is possible with the naked-eye (**Figure 1**). Interestingly, the binding is highly specific for Cu^{2+} ion with respect to other interfering metal ions such as Fe^{2+}, Co^{2+}, Ni^{2+} and Zn^{2+}.



Scheme 1. Cu^{2+} complexation reaction scheme with NDIs **1H**, **$2H_2$**, **3H** and **$4H_2$**.

The complexation was fully investigated with UV-Vis and fluorescence titrations at different pH conditions. Moreover, **$2H_2$** revealed the formation of two different coordinated species with a pH dependant behaviour: beside the mononuclear complex **$[2HCu]^+$**, the formation of the binuclear complex **$[2Cu_2]^{2+}$** was confirmed by mass analysis.

A complete computational study was performed to rationalize the different behaviour of ligand **1H** and **3H** toward the complexation. Firstly, the energy minimum geometries for increasing number of water molecules were optimized both in gas phase and in water as a solvent revealing square planar and pyramidal square as possible coordination geometries.

Subsequently, a direct comparison of the series of **1H** and **3H** Cu^{2+}-complexes was made from an energetic and geometric point of view. In all cases the terminal dimethylamino moiety tethered to the imide was involved in a strong H-bonding with a water molecule. Such interaction, together with solvation effects theoretically rationalise the computed differences in the binding properties between **1H** and **3H** Cu^{2+}-complexes in favour of the former. The addition of a second water molecule results in Cu^{2+} complexation only in the case of $\mathbf{[1Cu(H_2O)_2]^+}$, which is fully consistent with the EPR spectrum. A similar trend is maintained for $\mathbf{2H_2}$ and $\mathbf{4H_2}$ Cu^{2+}-complexes.

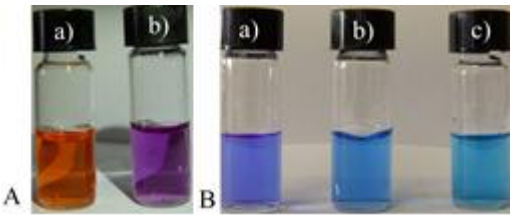


Figure 3. Change in colour of a solution of A) **1H** and B) $\mathbf{2H_2}$ a) before and b) after Cu^{2+} addition at pH=7 and c) after Cu^{2+} addition at pH=8.

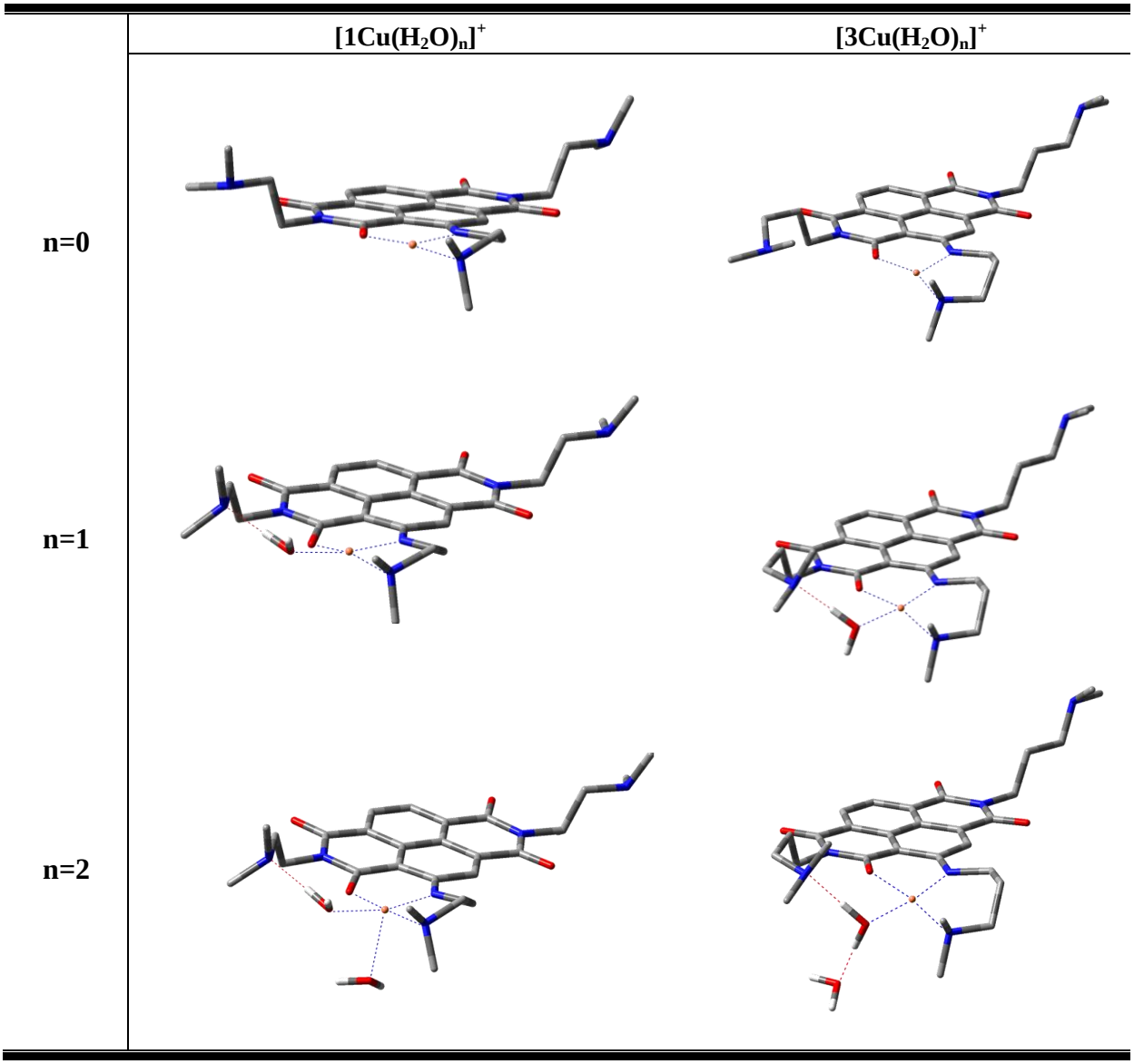


Figure 4. Geometry optimizations of the series of **1H** and **3H** Cu^{2+}-complexes by computational studies at B3LYP level of theory, in water as a solvent.

References:

[1] Klinman, J.P.; Mechanisms Whereby Mononuclear Copper Proteins Functionalize Organic Substrates. *Chem. Rev.* **1996, 96**, 2541-2561.
[2] Doria, F.; Manet, I.; Grande, V.; Monti, S.; Freccero, M.; Water-Soluble Naphthalene Diimides as Singlet Oxygen Sensitizers. *J. Org. Chem* **2013, 78**, 8065-8073.

Powerful Trident Scavengers for Some Alkali and Alkaline Earth Metal Cations

Ines DESPOTOVIĆ

Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Zagreb, 10000, Croatia

Ines.Despotovic@irb.hr

It is a common wisdom that macrocyclic ligands have the ability to selectively bind the metal ions [1] which has proved to be very useful in ion transporting phenomena, chemosensing, metaloenzyme mimics, catalysis, and nuclear waste treatments [2]. Among a large variety of macrocycles synthesized to serve as scavengers of metal ions, calixarenes play a notable role.

This presentation reports on the results of the complexation of Li^+, Na^+ and Be^{2+} metal cations with several derivatives of the parent *N*-(phenyl)-substituted azacalix[3](2,6)pyridine (Figure 1), both in gas phase and in acetonitrile solution. The gas phase molecular structures

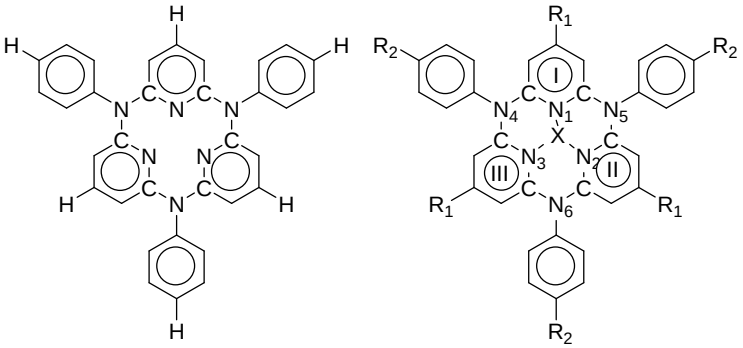


Figure 1 *N*-(phenyl)-substituted azacalix[3](2,6)pyridine scafold **1** and its derivatives **1a**, **1b** and **1c** serving as scavengers of cations X = Li^+, Na^+ and Be^{2+}.

and complexation energies were calculated by the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) method including basis set superposition error (BSSE) calculated by counterpoise (CP) correction scheme at the same level of theory. The solvent effects were assessed using the polarized continuum method (PCM).

The results have shown that supramolecular structures **1a**, **1b** and **1c** offer useful ligands capable of efficient and selective sequestration of Li^+, Na^+ and Be^{2+} cations, being the most suitable for the Be^{2+} cation. The binding affinity for Be^{2+} is extremely high, both in the gas

phase and in the acetonitrile [3], which might be very useful in prevention of berylliosis desease.

References:

[1] Lehn, J. M., *Supramolecular Chemistry*; VCH: Weinheim, **1995**.
[2] Izatt, R. M.; Bradshaw, J. S.; Nielson, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D., *Chem. Rev*. **1985**, *85*, 271-339.
[3] Despotović, I.; Maksić, Z. B., *Tetrahedron Lett*. **2011**, *52*, 6263-6266.

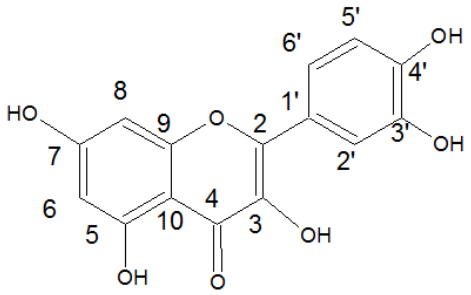
Quantum chemical study of the mechanism of quercetin oxidation by DMSO in the presence of Au(I) complexes

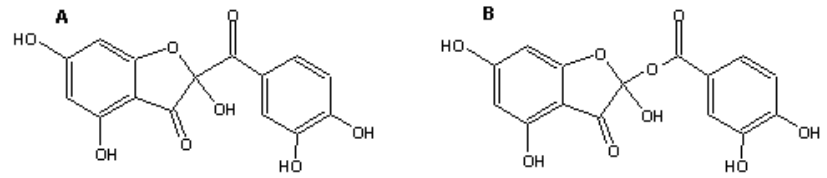
Alexander SHESTAKOV

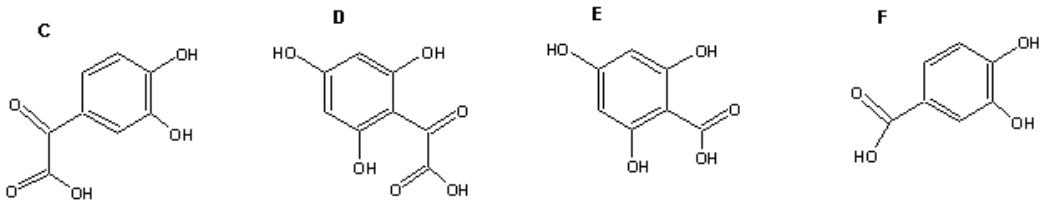
Institute of Problems of Chemical Physics of RAS, Ac. Semenov ave. 1, Chernogolovka, Moscow region, 142432, RUSSIA, e-mail a.s@icp.ac.rul

Previously, we examined the mechanism of activation of C - H bonds in light alkanes in an interesting process of the selective oxidation of methane and its homologues in biomimetic Au-bioflavonoid system under mild conditions [1] by quantum chemistry methods [2,3]. To find the proposed catalytically active Au complex, ^{1}H and ^{13}C NMR spectroscopy was used for investigation of the interaction of quercetin and $HAuCl_4$ in the d^6-ДМСО-D_2O (4:1) mixture, which allows achieving high concentrations of the reactants. In addition to the stoichiometric oxidation of quercetin to a cyclic semiketal **A** with simultaneous reduction of Au(III) to Au(I) it was discovered the presence of HD exchange with the solvent in the 2' position, which occurs only in the presence of gold complexes [4].

Furthermore, in these conditions in the absence of air it was observed over time the formation of a known complex Me_2SAuCl, indicating the oxidation function of DMSO. The presence of hydrolysis products **C-F** by data of NMR spectroscopy pointed out that the product **B** is formed as a result of **A** oxidation by DMSO







To study the mechanism of these processes quantum-chemical calculations of the energy profiles of possible reactions were carried out. PBE density functional method was applied using an extended basis set for SBK pseudopotential.

It was found that the obvious mechanism of H-D exchange via keto-enol tautomerism can be realized only in the positions 6 and 8, and for the 2' position it requires significant activation energy. Activation of aromatic C-H bond in the position 2' in the presence of an

Au(I) complex occurs by a mechanism of electrophilic substitution accompanied by the proton transfer to an O atom of a ligand. The same mechanism was found for activation of aliphatic C-H bonds [2-3]. The only difference is that the π-complex with the C-C bond of the substrate is intermediately formed instead of σ sigma-complex with a C-H bond.

Strictly the same value of H-D exchange in the primary oxidation product **A** at the 6 and 8 positions [4] indicates a fast equilibrium between the semiketal **A** and its isomer with an opened five-membered ring ($\mathbf{A_{izo}}$). Our calculations show that for this particular form of **A** the smallest activation barrier is realized for the insertion of the O atom in the C- C bond (see Fig.)

$$\mathbf{A_{izo}} + Me_2SOAuCl = Me_2SAuCl + \mathbf{B_{izo}}$$

The oxidation of **A** to **B** by means of the $Me_2SOAuCl$ complex is very favorable reaction with an energy release of 42.3 kcal/mol.

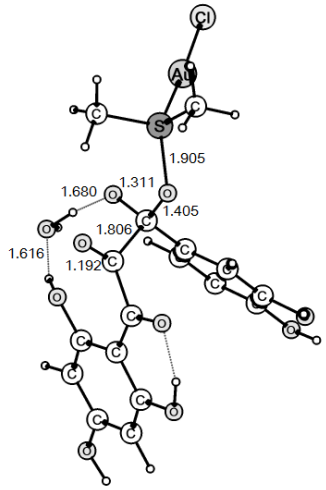


Fig. The structure of the transition state for the O atom insertion into the C- C bond.

The presence of conjugated π-electron system in quercetin greatly increase energy costs for the distortion of its structure in the transition state for the O atom insertion into the C(2)-C(1') bond from DMSO and therefore this reaction is unlikely.

For the calculations, the facilities of the Joint Supercomputer Center of the Russian Academy of Sciences were used.

References:

[1] Levchenko, L. A., Lobanova, N. G., Martynenko, V. M., Sadkov, A. P., Shestakov, A. F., Shilova, A. K., Shilov, A. E., Selective Oxidation of Methane and Its Homologues to Alcohols Catalyzed by Gold Compounds and a Proposed Reaction Mechanism. *Dokl. Chem.*, **2010**, 430 (2), 50–53.

[2] Nikitenko, N. G., Shestakov, A. F., Quantum Chemical Modeling of the Activation and Oxidation of Light Alkanes under Mild Conditions by Au(I) Complexes with Bioflavonoids. *Kinet. Catal.*, **2013**, 54 (2), 168–178.

[3] Nikitenko, N. G., Shestakov, A. F., Quantum Chemical Study of C-H Bond Activation in Methane and Methanol by Au(I) Quercetin Complexes under Mild Conditions *Dokl. Chem.*, **2013**, 450 (2), 127-130.

[4] Shestakov, A. F., Chernyak, A.V. Lariontseva, N.V., Golovanova, S.A., Sadkov A.P., Levchenko, L. A., Stoichiometric oxidation of quercetin by $HAuCl_4$ accompanied by H-D exchange with the solvent *Mendeleev Comm.*, **2013**, 23 (2), 98-100.

X-ray structure of a new bis-3-hydroxy-4-pyrone and of related Fe^{III} and Zn^{II} complexes

Delara MANSOORI,[a,b] Guido CRISPONI,[a] Juan NICLÓS-GUTIÉRREZ,[b] Josefa María GONZÁLEZ-PÉREZ,[b] Alicia DOMÍNGUEZ-MARTÍN,[b,c] Duane CHOQUESILLO-LAZARTE [d]

[a] *Dipartimento di Scienze Chimiche e Geologiche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy; dely88@hotmail.it*
[b] *Deparment of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain*
[c] *Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland*
[d] *Laboratorio de Estudios Cristalográficos, IACT, CSIC-UGR, Avda. de las Palmeras 4, 18100 Armilla, Granada, Spain.*

The interest in research on iron chelators in medicine has become continuously increasing in the last two decades. In the framework of our research on kojic acid derivatives as chelating agents for iron and aluminum [1-2], we have designed, synthesized and characterized a new ligand 6,6'-(((2-(diethylamino)ethyl)azanediyl)bis(methylene))bis(5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one), L9. In particular the structure of the ligand and of the related metal complexes has been thoroughly studied. L9 exists in the lattice as a zwitterion, crystallized in the dihydrate form (Figure 1).

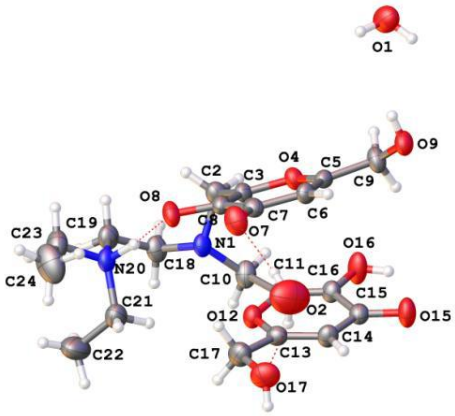


Figure 1: Asymmetric unit in the crystal of L9•2H_2O ligand. Intramolecular H-bonding interaction in the zwitterion L9 and the stabilizing role of the O2-water molecule are plotted in dashed lines.

In this communication we will present the X-ray structures of ligand L9 and that of the corresponding 1:1 complex with Zn^{II}. In this last complex, with stoichiometry [ZnL(H_2O)]·2.6H_2O, the Zn^{II} atom exhibits a trigonal bipyramidal coordination where the

equatorial plane is defined by two O-phenolate (kojic) and the tail/terminal-N20 (ethylenediamine) atoms from dianionic form of the L9 ligand.

In the absence of crystal structure of the iron complex with L9, we present here the structure of the corresponding complex with L4 as its surrogate, which gives useful insights on the coordination geometry of this kind of tetradentate chelator. In fact L4 differs from L9 just for a methyl group, instead of the diethylaminoethyl moiety, on the linker nitrogen atom. Fe_2L4_3 crystallizes as an hydrated complex salt according to a formula $[Fe_2(\mu_2\text{-}HL)_3]Cl_3{\cdot}nH_2O$. In the crystal structure only four water molecules have been localized, meanwhile the remaining highly disordered solvent molecules have been removed during the structure refinement (Figure 2). [3]

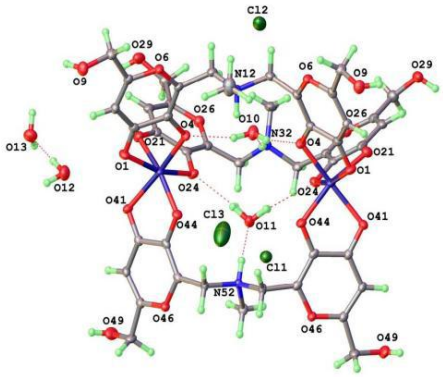


Figure 2: Asymmetric unit in the crystal of $[Fe_2(\mu_2\text{-}HL)_3]Cl_3{\cdot}nH_2O$ complex of iron withL4 ligand. The stabilization of the complex conformation by H-bonding interactions is plotted.

References:

[1] Toso L.; Crisponi G.; Nurchi V.M.; Crespo-Alonso M.; Lachowicz J.I.; Santos M.A.; Marques S.M.; Niclós-Gutiérrez J.; González-Pérez J.M.; Domínguez-Martín A.; Choquesillo-Lazarte D.; Szewczuk Z., A family of hydroxypyrone ligands designed and synthesized as iron chelators. *J. Inorganic Biochemistry*, **2013,** 127, 220-231

[2] Toso L.; Crisponi G.; Nurchi V.M.; Crespo-Alonso M.; Lachowicz J.I.; Mansoori D.; Arca M.; Santos M.A.; Marques S.M.; Gano L.; Niclós-Gutiérrez J.; González-Pérez J.M.; Domínguez-Martín A.; Choquesillo-Lazarte D.; Szewczuk Z., Searching for new aluminium chelating agents: A family of hydroxypyrone ligands, *J. Inorganic Biochemistry*, **2014** 130, 112-121

[3] Crisponi G.; Nurchi V.M.; Arca M.; Crespo-Alonso M.; Lachowicz J.I.; Mansoori D.; Toso L.; Pichiri G.; Santos M.A.; Marques S.M.; Niclós-Gutiérrez J.; González-Pérez J.M.; Domínguez-Martín A.; Choquesillo-Lazarte D.; Szewczuk Z.; Zoroddu M.A.; Peana M., A bis-3-hydroxy-4-pyrone as a potential therapeutic iron chelating agent. Effect of connecting and side chains on the complex structures and metal ion selectivity, *Dalton.Trans*. (**2014**, *Submitted*).

Chiral copper complexes for biomimetic oxidation

Eliana LO PRESTI, [a] Maria Lucia PERRONE, [a] Luigi CASELLA, [a] Enrico MONZANI, [a] Simone DELL'ACQUA [a]

[a] Università degli Studi di Pavia, Dipartimento di chimica, Viale Taramelli,12, 27100- Pavia.
email: eliana.lopresti01@gmail.com

Many enzymatic systems have been developed by natural organisms that perform their activities exploiting the peculiar characteristics of mono- or multi-nuclear metal centers, especially for redox reactions. Enzyme catalyzed oxidation reactions, in particular, often occur with considerable specificity and stereo-selectivity, in mild conditions, and exploiting molecular oxygen as oxidizing agent.

For these reasons, the challenge of mimicking enzymatic processes with biomimetic catalysts, building up low molecular weight compounds with similar structures as those present in the enzyme active sites, is worthwhile.

This project is based on building up synthetic biomimetic systems, taking advantage of nature's design of the active site of peculiar enzymes, like those of copper oxidases, to catalyze stereoselective oxidations. The main aim is to transfer enzymatic efficiency typical of natural systems to low molecular weight compounds, which are more easily manageable.

It is basically founded on synthesis, characterization, and reactivity of metal complexes with multidentate chiral ligands, able to host two or more metal ions, to generate oxygen-activating systems capable to promote asymmetric oxidations in mild conditions. It is important to emphasize that ligands will be selected trying to duplicate the features of enzymatic active sites, in terms of donor atoms and coordination environment. All studies are on the possibility of using these systems as catalysts in many types of oxidative reactions, both using natural substrates of the enzymes and substrates of synthetic interest**.**

The interest is focused on develop a structurally simpler dinuclear copper complex with a chiral hexadentate nitrogen ligand, changing the structure of a previously studied tyrosinase biomimetic model, labelled as L55 [1-3]. This ligand is built by the connection of two amino-bis-benzimidazolic units with a *meta*-xylyl bridge. In order to make this ligand intrinsically chiral, the N-methyl groups, originally present on the four benzimidazole rings of L55, are substituted by 2-methyl-butane chains (Figure 1).

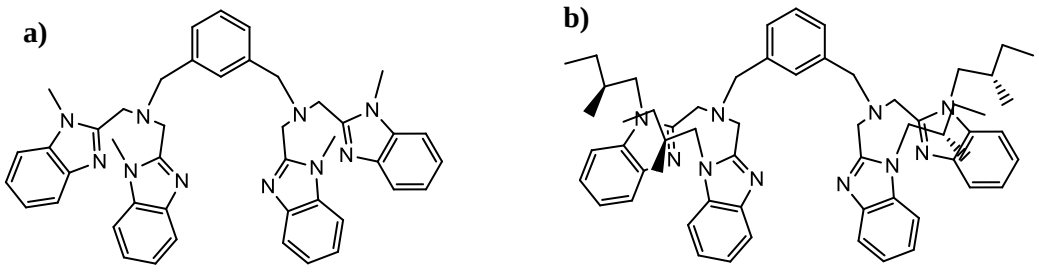


Figure 1- a) L55-ligand, **b)** L55($MeBu_4$)*, obtained by **a)** modification.

The catecholase activity, promoted by the dinuclear copper complex of L55($MeBu_4$)*, has been investigated on a set of chiral cathecols, in order to evaluate its enantio-differentiating capability.

References:

[1] L. Casella, O. Carugo, M. Gullotti, S. Gullotti, P. Zanello, *Inorg. Chem.* 1993, 32, 2056-2067.

[2] G. Battaini, L. Casella, M. Gullotti, E. Monzani, G. Nardin, A. Perotti, L. Randaccio, L. Santagostini, F. W. Heinemann, S. Schindler, *Eur. J. Inorg. Chem.* 2003, 1197-1205.

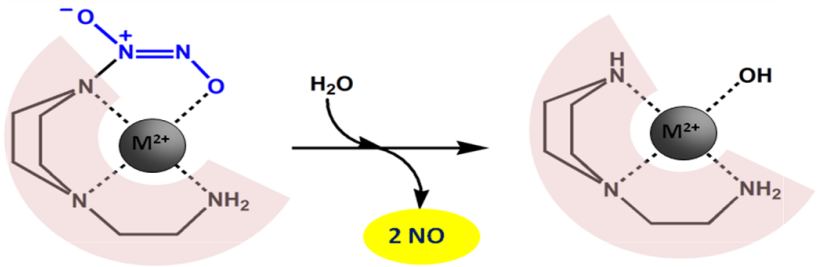
[3] (a) A. Granata, E. Monzani, L. Casella, *J. Biol. Inorg. Chem.* 2004, 9, 903-913; (b) S. Palavicini, A. Granata, E. Monzani, L. Casella, *J. Am. Chem. Soc.* 2005, 127, 18031-18036; (c) I. Garcia-Bosch, A. Company, J. R. Frisch, M. Torrent-Sucarrat, M. Cardellach, I. Gamba, M. Güell, L. Casella, L. Que Jr., X. Ribas, J. M. Luis, M. Costas, *Angew. Chem. Int. Ed.* 2010, 49, 2406-2409.

Metal complexes based on N-aminoethylpiperazine-N-diazeniumdiolate as NO donors

Aurora PACINI, [a), b)] Luca PASOTTI, [a), b)] Silvia PIZZOCARO, [a)] Enrico MONZANI, [a), b)] and Luigi CASELLA. [a), b)]

[a)] Dipartimento di Chimica, Università di Pavia, Viale Taramelli 12, 27100 Pavia; [b)] Noxamet Srl, Sede Operativa di Pavia, Viale Taramelli 12, 27100 Pavia; aurora.pacini01@ateneopv.it

We report on a series of metal complexes characterized by the property of controlled NO release, in which the chemical structure and composition are based on N-aminoethylpiperazine-N-diazeniumdiolate residue and are termed "metal-nonoates".[1]



Simple metal-nonoate complexes have already demonstrated their potential in pharmacology as powerful vasodilators even at very low doses.[1] Here we report on the preparation and spectroscopic characterization of second-generation metal-nonoates, in which the primary amino group of N-aminoethylpiperazine-N-diazeniumdiolate is conjugated with an amino acid, a short peptide or other residues. We will also show how the introduction of new chelating groups can modulate the NO release by the resulting complexes. An important objective of the extended ligand modification is the thermodynamic and kinetic stabilization of the metal-nonoates, through the increase of denticity of the polydentate ligands. The metal ion itself has an important role in the control of the kinetics of NO release, as it has been shown in our previous studies.[1] In the present context, we will consider metal-nonoates containing Ni(II), Cu(II) and Zn(II).

Another motivation for introducing peptide residues into the "nonoate" ligand of these complexes is linked to different reasons: (i) using peptides as biomimetic portions, (ii) taking advantage of receptors for penetration through biological membranes, (iii) having useful building-blocks to synthesize molecules with different chemical and physical characteristics, and (iv) introducing new metal controlled redox reactivity into the cell through the released NO.

References:

[1] Ziche, M.; Donnini, S.; Morbidelli, L.; Monzani, E.; Roncone, R.; Gabbini, R.; Casella, L., *Chem Med Chem.* **2008**, *3*, 1039-47.

Heme interaction and reactivity with neuronal Tau protein fragment

Valentina PIROTA, Enrico MONZANI, Simone DELL'ACQUA, Luigi CASELLA

Dipartimento di Chimica, Università degli Studi di Pavia, viale Taramelli 12, 27100 Pavia, Italy; valentina.pirota01@ateneopv.it

Alzheimer's disease (AD) is a fatal neurodegenerative disorder with still unknown cause and no cure, characterized by two abnormal protein deposits in the brain: senile plaques and neurofibrillary tangles (NFTs) [1,2]. The senile plaques are made by insoluble aggregates of amyloid-β (Aβ) peptide and NFTs are mainly composed by aggregates of microtubule-associated protein Tau441; their distribution in the AD patient brains is closely correlated with cognitive deficits [3]. Furthermore, several observations suggest a link between heme and AD [4]. In order to assess the possible oxidative damage associated with the neuronal peptides, here was study their binding and reactivity properties toward ferric heme.

In particular, we studied the interaction of hemin with Tau peptide R1 (R1τ), the first of four highly conserved 18-amino acid repeats (residues 256-273: ^{256}VKSKIGSTENLKHQPGGG^{273}) [5] that presents a binding affinity for Fe^{3+}-hemin similar to that of Aβ16 peptide [6], with a histidine as axial ligand for the iron.

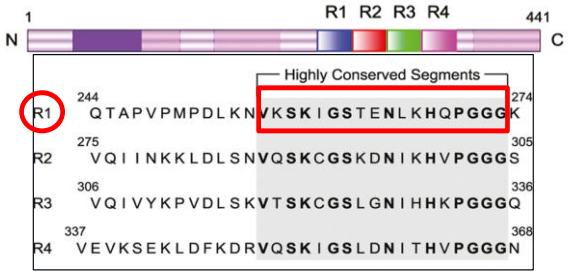


Figure 1 *- Tau441 protein's four highly conserved 18-amino acid repeats*

In a previous study, [6] our group found that hemin can coordinate two Aβ16 fragments to form the low-spin, six-coordinated complex [hemin(Aβ16)$_2$]. In contrast, R1τ is able to coordinate the Fe^{3+} center of hemin only in 1:1 ratio, giving rise to the complex [hemin-R1τ], with a K_1 binding constant two times larger than that of complex [hemin(Aβ16)].

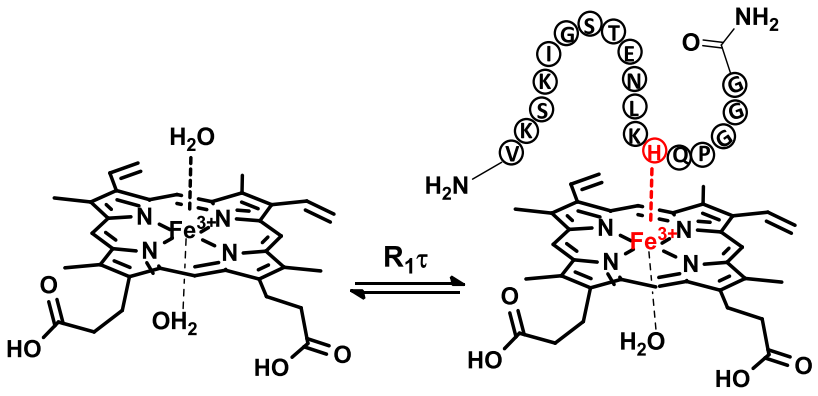
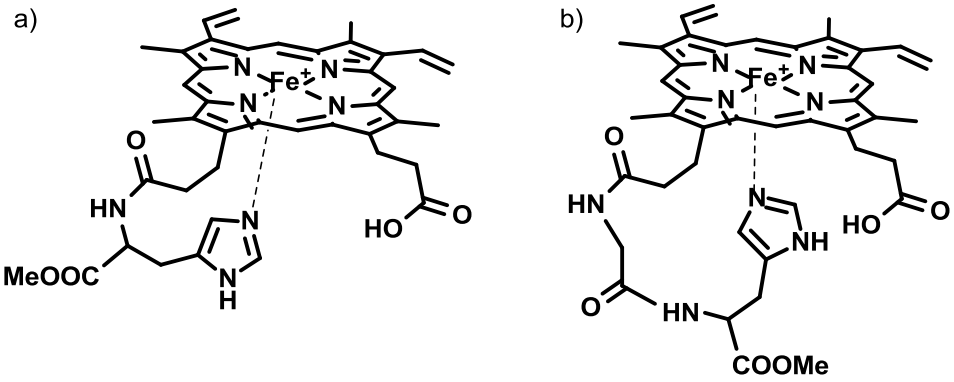


Figure 2 *– Binding of R1τ fragment with Fe^{3+}-hemin*

To gain an appreciation of the catalytic potential of the hemin-R1τ complex, we performed a detailed comparative study of its pseudo-peroxidase activity towards ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)]. The kinetic parameters confirmed that the peroxidase activity of hemin-R1τ is comparable with those of hemin derivatives containing a L-histidine methyl ester (hemin-H) or a glycyl-L-histidine methyl ester (hemin-GH) residue connected to one of the propionate side chains of protoporphyrin IX (Scheme 1). However, as for [hemin(Aβ16)], [6] this activity is much

lower than that of peroxidases, indicating that the association between heme and neuronal peptides does not, per se, involve a gain of any significant, potentially toxic, pseudo-enzymatic activity.



Scheme 1 *– a) Hemin L-histidine methyl ester, b) Hemin glycyl-L-histidine methyl ester*

References:

[1] Hardy, J.; Selkoe, D.J.; *Science* **2002**, 297, 353-356
[2] Mendelkow, E.; *Nature* **1999**, 402, 588-589
[3] Arriagada, P.V.; Marzloff, K.; Hyman, B.T.; *Neurology* **1992**, 42, 1681-1688
[4] Cottrell, D.A.; Blakely, E.L.; Johnson, M.A.; Ince, P.G.; Turnbull, D.M.; *Neurology* **2001**, 57, 260
[5] Shin, B.; Saxena, S.J.; *Phys. Chem.B* **2011**, 115, 15067-15078
[6] Thiabaud, G.; Pizzocaro, S.; Garcia-Serres, R.; Latour, J.M.; Monzani, E.; Casella, L.; *Angewandte* **2013**, 52, 8041-8044

Metal ion interaction with hemopressin

Maurizio REMELLI,[a] Carlo CECILIATO,[a] Remo GUERRINI,[a] Karolina KRZYWOSZYŃSKA,[b] Henryk KOZŁOWSKI,[b] Severo SALVADORI,[b]

[a] Department of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17, I-44121 Ferrara, Italy. e-mail: maurizio.remelli@unife.it
[b] Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50-383 Wroclaw, Poland

Hemopressin is a peptidic cannabinoid receptor ligand that is able to block cannabinoid CB1 receptor activity, *in vitro* and *in vivo*. It derives from the alpha(1)-chain of hemoglobin and was originally isolated from rat brain homogenates, under acidic conditions; it consists of a nonapetide with the sequence PVNFKFLSH [1].

Hemopressin proved to exert an antinociceptive action [2] and it was reported to cause dose-dependent hypotension in rats, rabbits, and mice [3]; in addition, hemopressin was shown to inhibit food intake in normal and obese animal models without causing obvious adverse side effects [4].

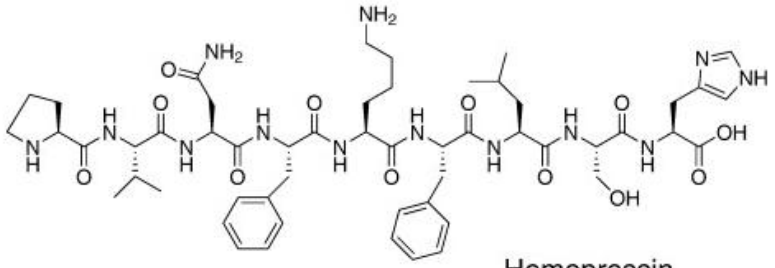
With a deep inspection of available HPLC-MS data of mouse brain extracts, Gomes and coworkers identified some N-terminally extended peptides containing 11- or 12-aa residues, i.e. VD-PVNFKLLSH and RVD-PVNFKLLSH, respectively [5]. Interestingly, while hemopressin acts as a CB1 cannabinoid receptor antagonist, both VD-PVNFKLLSH and RVD-PVNFKLLSH work as agonists [5].

In addition to RVD-PVNFKLLSH, other N-terminally extended peptides were identified in rodent brain extracts and human and mouse plasma, by immunoaffinity MS experiments [6]. This new peptides were designated Pepcans (peptide endocannabinoids); Pepcan-12 (RVD-PVNFKLLSH), -14, -15, -17, and -20 were found to be the most relevant endogenous Pepcans occurring in mouse brain and mouse/human plasma samples. The study showed that Pepcans act as negative allosteric modulators at CB1 receptors and this effect occurs at nanomolar concentrations, in agreement with the concentrations detected in mouse brain and human plasma samples.

A recent NMR investigation on rat hemopressin reported a random coil conformation in water and a series of turn-like structures in mixed micelles [7]. Transmission electron microscopy (TEM) of hemopressin in solution revealed that the peptide self-assembles into fibrils at physiological pH, while the sequence-related peptide RVD-PVNFKFLSH did not exhibit any evidence of self-assembly or fibril formation [8].

The presence of a His residue at the C-terminus of hemopressin sequence (in addition to the terminal amino-group) makes this peptide able to bind endogenous transition metal ions, like Cu^{2+} and Zn^{2+}. The possible role of these metals on both the biological or pharmacological activity of hemopressin and other sequence-related peptides has never been investigated. In the present paper, a preliminary study is presented, concerning the complex-formation equilibria, in aqueous solution, of hemopressin and related peptides with Cu^{2+}, Zn^{2+} and, for the sake of comparison, Ni^{2+} ions. The investigated peptides, synthesized using solid-phase Fmoc chemistry, are the following: rat hemopressin (rHpα, **PVNFKFLSH**); human and

mouse hemopressin (hHpα, **PVNFKLLSH**); N-terminally extended human and mouse hemopressin (RVD-hHpα, **RVD-PVNFKLLSH**). The study has been carried out in aqueous solution and in a wide pH range, at I = 0.1 M and T = 25 °C. Protonation and complex-formation constants were potentiometrically determined and species stoichiometries were



checked by ESI-MS; structural hypotheses on the main complex species are suggested, on the basis of UV-Vis absorption, CD and EPR spectra.

References:

[1] Heimann, A.S.; Gomes, L.; Dale, C.S.; Pagano, R.L.; Gupta, A.; de Souza, L.L.; Luchessi, A.D.; Castro, L.M.; Giorgi, R.; Rioli, V.; Ferro, E.S.; Devi, L.A., Hemopressin is an inverse agonist of CB1 cannabinoid receptors. *Proc. Nat. Acad. Sci. U.S.A.*, **2007**, *104*, (51), 20588-20593.

[2] Dale, C.S.; Pagano, R.D.L.; Rioli, V.; Hyslop, S.; Giorgi, R.; Ferro, E.S., Antinociceptive action of hemopressin in experimental hyperalgesia. *Peptides*, **2005**, *26*, (3), 431-436.

[3] Blais, P.A.; Cote, J.; Morin, J.; Larouche, A.; Gendron, G.; Fortier, A.; Regoli, D.; Neugebauer, W.; Gobeil, F., Hypotensive effects of hemopressin and bradykinin in rabbits, rats and mice - A comparative study. *Peptides*, **2005**, *26*, (8), 1317-1322.

[4] Dodd, G.T.; Mancini, G.; Lutz, B.; Luckman, S.M., The Peptide Hemopressin Acts through CB1 Cannabinoid Receptors to Reduce Food Intake in Rats and Mice. *J. Neurosci.*, **2010**, *30*, (21), 7369-7376.

[5] Gomes, I.; Grushko, J.S.; Golebiewska, U.; Hoogendoorn, S.; Gupta, A.; Heimann, A.S.; Ferro, E.S.; Scarlata, S.; Fricker, L.D.; Devi, L.A., Novel endogenous peptide agonists of cannabinoid receptors. *Faseb J.*, **2009**, *23*, (9), 3020-3029.

[6] Bauer, M.; Chicca, A.; Tamborrini, M.; Eisen, D.; Lerner, R.; Lutz, B.; Poetz, O.; Pluschke, G.; Gertsch, J., Identification and Quantification of a New Family of Peptide Endocannabinoids (Pepcans) Showing Negative Allosteric Modulation at CB1 Receptors. *J. Biol. Chem.*, **2012**, *287*, (44), 36944-36967.

[7] Scrima, M.; Di Marino, S.; Grimaldi, M.; Mastrogiacomo, A.; Novellino, E.; Bifulco, M.; D'Ursi, A.M., Binding of the Hemopressin Peptide to the Cannabinoid CB1 Receptor: Structural Insights. *Biochemistry*, **2010**, *49*, (49), 10449-10457.

[8] Bomar, M.G.; Samuelsson, S.J.; Kibler, P.; Kodukula, K.; Galande, A.K., Hemopressin Forms Self-Assembled Fibrillar Nanostructures under Physiologically Relevant Conditions. *Biomacromol.*, **2012**, *13*, (3), 579-583.

DNA binding assays of novel high-valent ruthenium complexes. Crystal structure, spectral and electrochemical studies

Agnieszka JABŁOŃSKA – WAWRZYCKA, [a] Patrycja ROGALA, [a] Grzegorz CZERWONKA, [b] Maciej HODOROWICZ, [c] Barbara BARSZCZ [a]

[a] *Institute of Chemistry, Jan Kochanowski University, 15G Świętokrzyska Str., 25-406 Kielce, Poland, e-mail: patrycja.rogala@gmail.com*

[b] *Department of Microbiology, Institute of Biology, Jan Kochanowski University, 15G Świętokrzyska Str., 25-406 Kielce, Poland,*

[c] *Faculty of Chemistry, Jagiellonian University, 3 Ingardena Str., 30-060 Kraków, Poland*

High-valent ruthenium complexes have not been well studied so far. It is noticed that are only connections to oxygen atom in types of ruthenium–oxo or –dioxo complexes are well-known [1-2]. High-valent ruthenium complexes as it is excepted are very reactive towards living forms due to their strong oxidizing properties. It is known that the oxidation state of ruthenium determines its applications. Thus ruthenium complexes (II), (III) have the ability to binding to DNA wherefore could be use in medicine [4-5].

Our aim was to study how the ruthenium complexes inhibit *Pseudomonas aeruginosa* PAO1biofilm formation. Moreover, Ru(IV) and Ru(VI) complexes interacts with DNA were also determined. We also studied an influence of coordination environment on DNA binding possibility. Therefore, we focused our studies on correlation between structure of ruthenium compounds in higher oxidation states and their biological properties.

Herein, we report the synthesis as well as spectroscopic, electrochemical and structural studies of two novel ruthenium complexes in +IV and +VI oxidation states. Type of oxidation states is caused by the fact that they strongly depends on synthesis conditions, such as: ligands type, solvents type, molar and volumetric ratios, temperature, and time of reaction. We received complexes by reaction of a mother solution of $RuCl_3$ with 2-hydroxymethylbenzimidazole (2-CH_2OHBIm, L^1): $(HL^1)_4[Ru^{IV}Cl_6]\cdot 2Cl\cdot 4H_2O$ (**1**) [5] and $(HL^1)_2[Ru^{VI}Cl_6]\cdot 2Cl\cdot 2C_2H_5OH\cdot 2H_2O$ (**2**). We used 2-CH_2OHBIm as ligand because it contain two potential donor sites, *viz.* to pyridine nitrogen and hydroxymethyl oxygen atoms. This ligand has also biological activity: antibacterial, antifungal, and antiviral activities.

Tetravalent and hexavalent ruthenium is coordinated by six chloride anions. In both the spaces we observe the existence of protonated ligands 2-CH_2OHBIm, chloride ions, water molecules. In addition complex **2** contains two molecules of ethanol. These compounds have a very interesting coordination networks and a remarkable supramolecular architectures generated by hydrogen bonds of O–H···O, N–H···O, N–H···Cl, C–H···Cl and C–H···π types and intermolecular π···π, Cl^-···π interactions.

The obtained complexes have been characterized also using biological assays. Compounds **1** and **2** revealed anti-biofilm properties against *Pseudomonas aeruginosa* PAO1 (Figure 1). The study of microorganisms growing as a biofilm is justified because the bacteria prefer this form of growth both in the environment as well as in during tissue infections. In

concentration from 200 µg/ml **1** decreased total amount of *Pseudomonas aeruginosa* PAO1 biofilm by 54% whereas **2** decreased by 23%. Concentration 500 µg/ml revealed fully eradication of biofilm. PCR reaction proved that ruthenium complexes binds to DNA, where specify of reaction is altered in concentration 1-2 µg/ml. Concentration 5.5 µg/ml of tested complexes stopped reaction, while influence of free ligand on reaction was not observed.

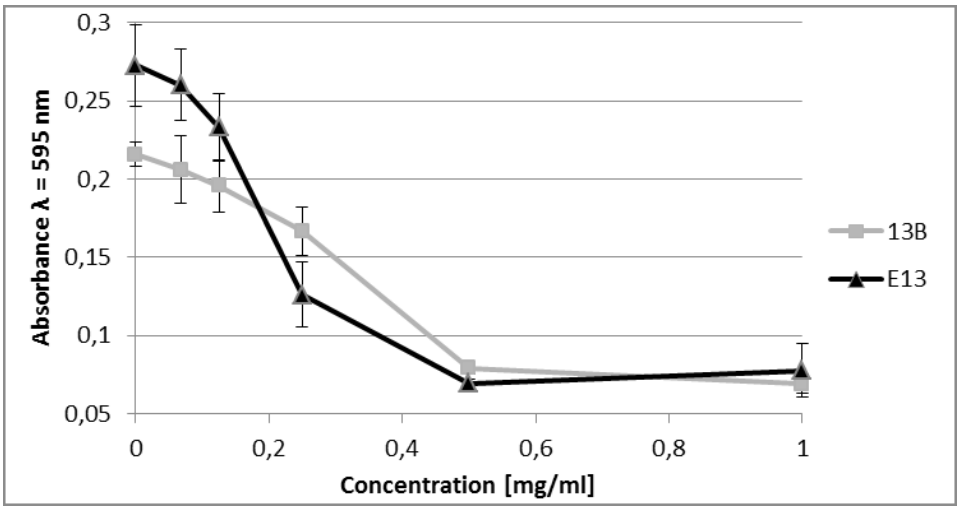


Fig. 1. *Pseudomonas aeruginosa* biofilm eradication by ruthenium complexes assay.

References:

[1] Man, W.-L.; Lam, W. W. Y.; Ng, S.-M.; Tsang, W. Y. K.; Lau, T-C.; Oxygen Atom Transfer from a trans-Dioxoruthenium(VI) Complex to Nitric Oxide. *Chem. Eur. J.* **2012**, 18, 138-144.

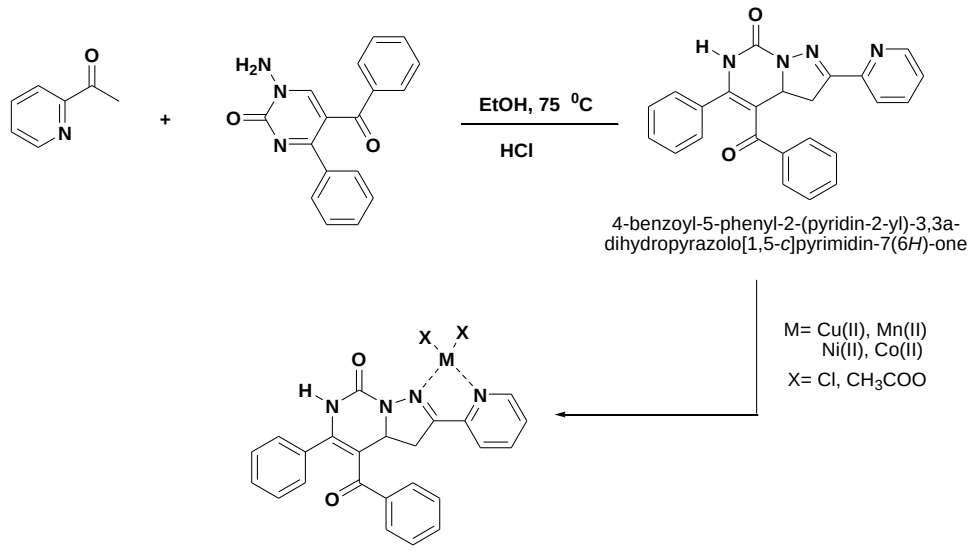
[2] Ohzu, S.; Ishizuka, T.; Hirai, Y.; Jiang, H.; Sakaguchi, M.; Ogura, T.; Fukuzumi, S.; Kojima, T.; Mechanistic insights into catalytic oxidations of organic compounds by ruthenium(IV)-oxo complexes with pyridylamine ligands. *Chem. Sci.* **2012**, 3 (12), 3421-3431.

Synthesis, Antioxidant Assays of Novel Heterocyclic Ligand and Metal Complexes

Mecit ÖZDEMİR [a)], Mehmet SÖNMEZ [b)]

[a]Department of Chemistry, Faculty of Art & Science, University of Kilis 7 Aralik, Kilis, Turkey, TR 79000
[b]Department of Chemistry, Faculty of Science and Art, University of Gaziantep, TR 27310 Gaziantep, Turkey. E-mail: msonmez@gantep.edu.tr

Superoxide anion($O_2^{-\cdot}$) and hydroxyl radıcal($OH^{\cdot}$) generated in normal metabolic processes can result in various diseases such as cancer development, drug-induced toxicity, inflammation, atherogenesis and aging in aerobic organisms [1]. Pyridine and its derivatives are widely distributed in nature and are well known to exhibit broad spectrum of biological activities such as antimicrobial, anti-HIV, anti-inflammatory, analgesic and anticonvulsant [2]. In addition, these compounds are an important class of organic complexes in medicinal chemistry due to their great potential for antibacterial and chemotherapeutic application [3]. Pyrimidine and pyrazole derived metal ions complexes are also being extensively investigated in current years due to the their important antioxidant activity [4]. Herein, we've described the synthesis, characterization carried out by using ^{1}H NMR, ^{13}C NMR, Elemental analysis, FT-IR, UV-Vis spectroscopy and X-ray crystallographic methods and antioxidant properties of titled compound and its four metal complexes against some reactive oxidative species such as DPPH, Hydroxyl and rhodamine tempo. Consequently, there were observed that all synthesized compounds have the antioxidant potential. Thus, copper complex has more antioxidant activity than others.



Scheme 1. Representation of the synthesis of titled compound and its four metal complexes

References

[1] Liu, Y.C.; Yang, Z.Y., *Journal of Inorganic Biochemistry* **2009**, 103, 1014-1022.
[2] Patel, N.B.; Shaikh, F.M., *Saudi Pharmaceutical Journal* **2010**, 18, 129–136.
[3] Ma, Z.Y.; Qiao, X.; Xie, C.Z.; Shao, J.; Xu, J.Y.; Qiang, Z.Y.; Lou, J.S., *Journal of Inorganic Biochemistry* **2012**,117, 1–9.
[4] Fadda, A.A.; Berghot, M.A.; Amer F.A.; Badawy, D.S. and Bayoumy, N.M., *Archiv der Pharmazie* **2012**, 345 (5), 378-385.

Indole derivatives of Diketoacids as dual chelating inhibitors of HIV-1 integration process

Mauro CARCELLI, Dominga ROGOLINO, Anna GATTI, Gabriele RISPOLI

Dipartimento di Chimica, Università degli Studi di Parma, Parco Area delle Scienze17/A, I-43124 Parma, Italy; anna.gatti3@studenti.unipr.it

The integrase (IN) is one of the three viral enzymes involved in HIV replication. Based on a mechanism with two subsequent steps, 3'-processing and stand transfer (ST), it is responsible for the insertion of proviral DNA into the host cell genome. Essential for the process are two divalent Mg^{2+} cofactors present in the catalytic core domain of IN, that is why ions chelation has emerged as successful strategy in the drug design of integrase repressors. [1]

Considering this, α,ß-diketoacids are a class of compounds that emerged as potent inhibitors (DKAs): consisting of an aromatic unit, a beta diketo moiety and a carboxylic function, they are able to coordinate the two ions, blocking the interaction of the enzyme with the substrate.

This communication aims at introducing three different indole derivatives of DKAs that exhibited a good IN inhibition activity and low toxicity. [2]

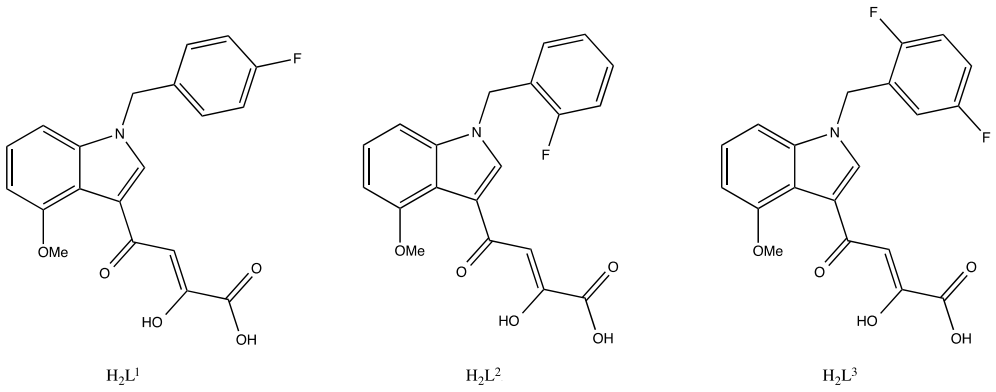
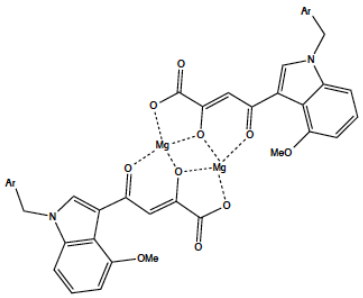


Fig. 1. Stucture of three different indole derivatives of DKAs (reference D. Rogoloino et al., *European Journal of Medicinal Chemistry* **2014,** 78, 425-430).

Both ligands and the related metal complexes were isolated in order to study their chemical structure and biological activity. Ligands were synthesized according to a literature procedure: once isolated, they are reacted with magnesium hydroxide to obtain the relative complexes.



OBJ

Fig. 2. Structure of metal complex $Mg_2Lç_2$ (reference D. Rogoloino et al., *European Journal of Medicinal Chemistry* **2014,** 78, 425-430).

All products were characterized with typical spectrometric and spectroscopic analysis. The chemical studies made on the final structure of these compounds have demonstrated that α,ß-diketoacids are able to chelate divalent metals in two different ways: the hydroxy-carboxylate or the acetyl-acetonate coordination mode; when these two modes are adopted in a conjoined way, dimer Mg_2L_2 is obtained, and this means that the ligands are completely deprotonated.

Biological studies *in vitro* performed on these compounds have demonstrated that both ligands and complexes showed inhibition power in low nanomolar/micromolar concentration for ST process, even if the metal compounds are less selective for stand transfer. Moreover they both can inhibit the IN interaction with LEDGF/p75, an integrase cofactor involved in the viral integration, at low µM ratio: in this case, the activity is directly dependent on the position of fluorine atom in the aromatic ring.

The proved ability of these compounds to block both ST and IN-LEDGF interactions shows that they have an encouraging antiviral activity due to a dual inhibition mechanism, and this is confirmed by tests made on infected cells: both ligands and metal complexes have good value of EC_{50} even if metal complexes are more cytotoxic than the relative ligands.

References:

[1] Beare, K.D.; Coster, M.J.; Rutledge, P.J., Diketoacid inhibitors of HIV-1 integrase: from L-708,906 to raltegravir and beyond. *Current Medical Chemistry* **2012**, 19 (8), 1177-92.

[2] Rogolino, D. et al., Diketoacid chelating ligands as dual inhibitors of HIV-1 integration process. *European Journal of Medicinal Chemistry* **2014,** 78, 425-430.

Structure, Cytotoxicity, DNA Interactions and Enzimes Inhibition of Cationic Palladium(II) Complexes

Fillipe V. ROCHA, [a] Carolina V. BARRA, [a] Antonio E. MAURO, [a] Saulo S. GARRIDO, [b] Iracilda Z. CARLOS, [c] Javier A. ELLENA, [d] Flávio H. da SILVA, [e] Arnaud GAUTIER, [f], Laurent MOREL, [g], Adelino V. G. NETTO. [a]

[a] Depto de Química Geral e Inorgânica, Instituto de Química de Araraquara, UNESP , Araraquara, SP, Brazil. [b] Depto de Bioquímica e Tecnologia Química, Instituto de Química de Araraquara, UNESP , Araraquara, SP, Brazil. [c] Depto de Análises Clínicas, Faculdade de Ciências Farmacêuticas de Araraquara, UNESP, Araraquara, SP, Brazil. [d] Instituto de Física de São Carlos, USP, São Carlos, SP, Brazil. [e] Depto de Genética e Evolução da Universidade Federal de São Carlos, UFSCAR, São Carlos, SP, Brazil. [f] Clermont–Université, Université Blaise Pascal, ICCF, Aubière, France. [g] Clermont–Université, Université Blaise Pascal, GreD UMR 6247 CNRS, Aubière, France.
author emal: passaras47@yahoo.com.br

Palladium(II) complexes are interesting alternative candidates for metal antitumor drugs due to their structural similarities to Pt(II) complexes[1]. It has been demonstrated that Pd(II) complexes with N,S-chelating ligands posses good antitumor activity[2,3]. Besides that, the presence of phosphine ligands is supposed to provide better cytotoxicity by enhancing lipophilicity – and consequently permeability through the cell membrane. Motivated by the potential uses of these complexes as anticancer agents, we present the synthesis and cytotoxicity of two cationic complexes of the type $[PdX(MeT)(PPh_3)]X$ {X = Br^- (**1**); I^- (**2**); MeT = 4–methyl–3–thiosemicarbazide; PPh_3 = triphenylphosphine} and their ability to interact with DNA, topoisomerases I and II and cathepsin B.

The precursor complex $[PdCl(MeT)(PPh_3)]Cl$ was obtained from reaction of PPh_3 and thiosemicarbazide with $[PdCl_2(CH_3CN)_2$. In a second step, the Cl atoms were replaced by Br and I ions by the addition of two equivalents of the appropriate potassium salt to afford **1** (Br) and **2** (I).

Spectroscopic data strongly support the formation of the *N,S*-chelated products. IR spectra show an important variation of 30 cm^{-1} for the νC=S after coordination. Variation of ~ 4 ppm downfield of the chemical shift (^{1}H NMR) was observed for the two N2 protons after complexation. Ultimately, the structure was proved by X–ray diffraction of a crystal of complex **2** (ORTEP view in figure 1).

The new complexes and cisplatin were assayed against two murine cell lines, LM3 (mammary adenocarcinoma) and LP07 (lung adenocarcinoma). Compounds **1** and **2** revealed to be more cytotoxic than cisplatin towards LM3. Guanosine was used as a model system to study the ability of complexes to interact with a purine base. The coordination of guanosine occurred through N7 and was highlighted by ^{1}H NMR and mass spectrometry. ^{1}H NMR spectra exhibit a 0.4 ppm downfield shift for the guanosine's H8, typical of the transition metal coordination through N7. Mass spectrometry shows a molecular peak corresponding to a monocharged adduct. The influence of the complexes on the structure of a supercoils DNA was determined by a gel electrophoresis assay. It demonstrated that **1** and **2** unwind the DNA

plasmid only at high concentrations, suggesting that the cytotoxicity mechanisms of **1**-**2** may not necessarily involve interaction with DNA.

Therefore, the capacity of the complexes to inhibit topoisomerases enzymes was evaluated by electrophoresis, and the data showed that the compounds inhibit the topoismerase IIα enzyme at a concentration rage of 5-25 µM, but they fail to inhibit the action of topoisomerase I. Moreover, the compound [(PdI(4-MeT)(PPh3)]I (**2**), had its ability to inhibit cathepsin b investigated, with a IC_{50} value of 5.83 µM. These system showed high potentiality in obtaining topo II and cathepsin B inhibitors with antitumor activity.

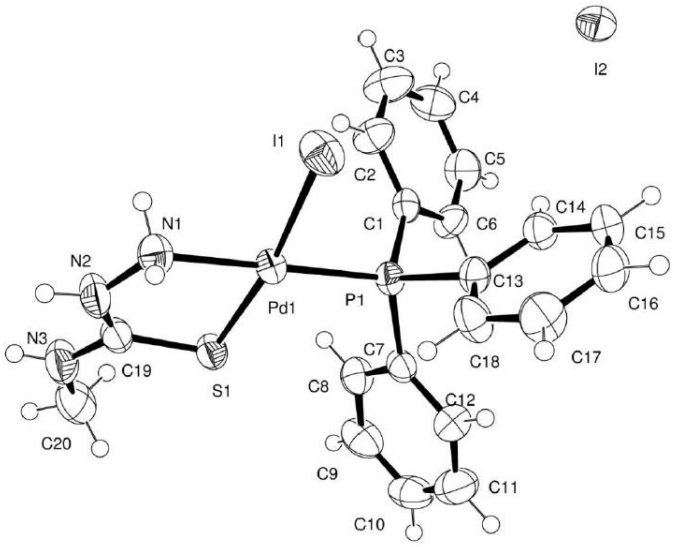


Figure 1. ORTEP view of [PdI(PPh_3)(4-MeT)]I (**2**) structure

References:

[1] Carreira M.; Calvo-Sanjuán R.; Sanaú, M.; Marzo, I.; Contel, M., Organometallic Palladium Complexes with a Water-Soluble Iminophosphorane Ligand As Potential Anticancer Agents. *Organometallics* **2012**, 31, 5772-5781

[2] Matesanz, A. I.; Hernandez, C.; Rodriguez, A.; Souza, P., 3,5-Diacetyl-1,2,4-triazol bis(^{4}N-substituted thiosemicarbazone) palladium(II) complexes: Synthesis, structure, antiproliferative activity and low toxicity on normal kidney cells. *J. Inorg. Biochem.* **2011**, 105, 1613-1622

[3] Garoufis, A.; Hadjikakou, S. K.; Hadjiliadis, N., Palladium coordination compounds as anti-viral, anti-fungal, anti-microbial and anti-tumor agents. *Coord. Chem. Rev.* **2009**, 253, 1384-1397.

Novel neural "piano-stool" ruthenium(II) complexes: structural and *in vitro* cytotoxic studies

Iwona ŁAKOMSKA,[a)] Krystian STEFAŃCZAK,[a)] Andrzej WOJTCZAK,[b)] Jerzy SITKOWSKI,[c)]

[a)] Bioinorganic Chemistry Research Group, Faculty of Chemistry, Nicolaus Copernicus University, Gagarina 7, 87-100 Toruń, Poland; iwolak@chem.umk.pl
[b)] Faculty of Chemistry, Nicolaus Copernicus University, Gagarina 7, 87-100 Toruń, Poland;
[c)] National Institute of Medicine, Chełmska 30/34, 00-725 Warsaw, Poland

Recent years have witnessed a surge of interest in the application of organometallic compounds to treat various type of cancer and other disease[1]. Indeed, the unique properties of organometallic compounds, intermediate between those of classical inorganic and organic materials provide new opportunities in medicinal chemistry. Additionally, organometallic chemistry offers a potentially rich fields for development of new medicinal agents with novel mechanism of actions.

On the other hand, ruthenium-based compounds are now a proven effective alternative to Pt-based complexes in cancer therapy, affording different mechanisms of action, a different spectrum of activity and the potential to overcome platinum-resistance, as well as lower toxicity. Therefore organoruthenium(II) mononuclear "piano-stool" complexes are the subject of interest in the design of metal-based complexes as anticancer agents [2]. Following this research line, we decided to study the ruthenium(II)-arene complexes of general formulae [η^6-p-cymene)Ru(L)Cl_2], where L- 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dmtp), 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dptp), 5,7-ditertbutyl-1,2,4-triazolo [1,5-*a*]pyrimidine (dbtp), 7-isobutyl-5methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (ibmtp) (Figure 1). All novel ruthenium(II) complexes have been obtained in direct reaction between the dinuclear complex [η^6-p-cymene)$_2$Ru(μ-Cl_2)Cl_2] and different triazolopyrimidine (L) in molar ratio 1:2.

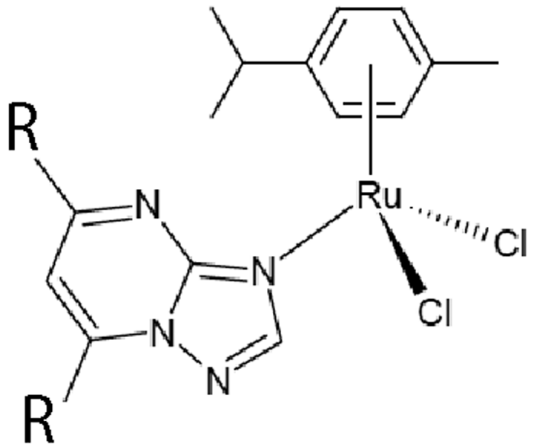


Figure 1. Chemical structure of [η^6-p-cymene)Ru(L)Cl_2].

We decided to involve different types of triazolopyrimidine, because our previous studies on platinum(II) [3] and ruthenium(III) [4] compounds with triazolopyrimidine demonstrated that the cytotoxicity *in vitro* of both types of coordination compounds depend on the nature of the alkyl group substituent in heterocyclic ligands and the composition of coordination sphere influence directly on cytotoxicity.

All the ruthenium(II) complexes have been fully characterized by IR, NMR (^{1}H, ^{13}C, ^{15}N). The successful complexation of triazolopyrimidine ligand to Ru(II) can be followed using NMR studies. The coordination of N-donor ligand to the Ru(II) ion results in the deshielding of both H(2) and H(6) signals. However, the largest coordination shift was observed for H(2) ($\Delta_{coord.}$ ~ 0.40 ppm). However, those changes do not indicate clear which of the heterocyclic nitrogen atoms is engaged in formation of the platinum-nitrogen bond. This problem was solved by means of ^{15}N-^{1}H HMBC spectra analysis. The biggest coordination shift (Δ_{coord} = ~63 ppm) was calculated only for the N(3) signal. Such a significant shielding of N(3) resonances signal clearly indicates the monodentate coordination to Ru(II) in solution, what is very important for *in vitro* test and their application as antitumor prodrugs. Furthermore, the octahedral structure of our complexes has been confirmed by X-ray study for [η^6-p-cymene)Ru(dmtp)Cl_2].

The antiproliferative activity *in vitro* of four ruthenium(II) complexes have been tested against the cisplatin−resistant human ductal breast epithelial tumour (T47D) cell line and the human lung adenocarcinoma epithelial cell line (A549). The results indicate a moderate antiproliferative activity and direct influence of the type of stable N-donor ligand on creation the *in vitro* cytotoxicity of our ruthenium(II) complexes.

Acknowledgements

This work was financed by the CHEMO-KOP (grant no. 46/2013) *"Development of modern second degree chemical studies at the Nicolaus Copernicus University in order to increase the number of graduates of special importance for the economy";* project co-funded by the European Union under the European Social Fund.

References:

[1] Peacock A.F.A.; Sadler P. J., *Chem. Asian. J.*, **2008**, 3, 1890-1899.
[2] Gupta R. K; Pandey R.; Sharma G; Prasad R.; Koch B.; Srikrishna S.; Li p-Z.; Xu Q.; Pandey D.S, *Inorg. Chem.*, **2013**, 52, 3687-3698.
[3] Łakomska I., *Inorg. Chim. Acta*, **2009**, 362, 669-681.
[4] Łakomska I.; Fandzloch M.; Muzioł T.; Lis T.; Jezierska J., *Dalton Trans.*, **2013**, 42, 6219-6226.

Antibacterial supra-nanomaterials: a "silver and gold" approach

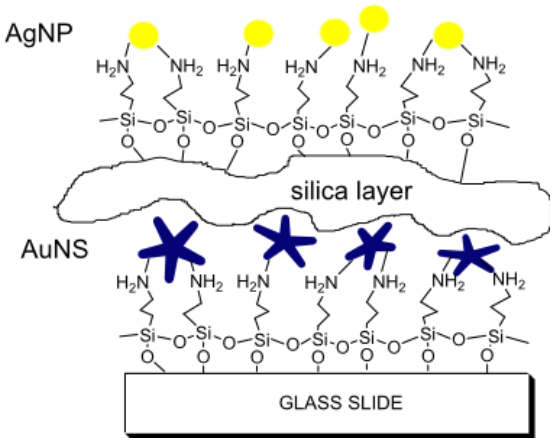
Angelo TAGLIETTI, [a] Barbara BASSI, [a] Elisa CABRINI, [a] Lucia CUCCA, [a] Giacomo DACARRO, [a] Emiliano FRATINI, [b] Pietro GRISOLI, [c] Chiara MILANESE, [a] Piersandro PALLAVICINI [a]

[a] Department of Chemistry, University of Pavia, viale Taramelli 12, 27100 Pavia, Italy
[b] Department of Chemistry "Ugo Schiff" and CSGI, University of Florence, Italy
[c] Department of Drug Sciences, University of Pavia, Italy;
barbara.bassi02@universitadipavia.it

Under laser excitation close to the proper near-infrared Localized Surface Plasmon Resonance (LSPR) absorption wavelength, gold nanostars (AuNS) display an intense photo-thermal response, causing a sensible temperature increase, as a function of irradiance, in their surroundings. When AuNS are grafted on glass slides preventively coated with a Self-assembled monolayer (SAM) of a given alcoxysilane, the photo-thermal effect can be exploited in principle to exert antibacterial actions on the surface, [1] in order to fight biofilm formation killing bacteria and obtaining the biofilm eradication which is growing on it.

These materials, anyway, may suffer of a possible drawback, as prolonged contact with water and physiological environment may lead to objects detachment or degradation, affecting the surface long term usability.

We here describe an easy method to prepare a SAM with (3-aminopropyl)triethoxysilane (APTES), with subsequent grafting of a controlled amount of AuNS, followed by the deposition of a thin layer of silica, obtaining a material which is inherently protected, but, as we demonstrate, with unchanged photo-thermal response.



Moreover, a further SAM of APTES can be deposed on the silica layer, allowing the grafting of a further monolayer of silver nanoparticles (AgNP), to exploit their well-known antibacterial and antibiofilm properties, based on silver ion release, when grafted on glass. [2,3] Once again, photo-thermal properties are not affected by this new coating process. A step by step characterization with several techniques has been performed. Preliminary results

of antibacterial and antibiofilm actions produced by the presence of the two kind of noble metal nano-objects brought on glass surfaces will be presented, with special attention to possible synergic behaviour.

References:

[1] Pallavicini P.; Donà A.; Taglietti A.; Minzioni P.; Patrini M., Dacarro G.; Chirico G.; Sironi L.; Bloise N.; Visai L.; Scarabelli L., Self-assembled monolayers of gold nanostars: a convenient tool for near-IR photothermal biofilm eradication. *Chem Commun.* **2014**, 50, 1969-1971.

[2] Taglietti A.; Diaz-Fernandez Y.; Amato E.; Cucca L.; Dacarro G.; Grisoli P.; Necchi V.; Pallavicini P.; Pasotti L.; Patrini M., Antibacterial Activity of Glutathione Coated Silver Nanoparticles against Gram positive and Gram negative bacteria. *Langmuir.* **2012**, 28, 8140-8148.

[3] Taglietti A.; Arciola C.R.; D'Agostino A.; Dacarro G.; Montanaro L.; Campoccia D.; Cucca L.; Vercellino M.; Poggi A.; Pallavicini P.; Visai L., Antibiofilm activity of a monolayer of silver nanoparticles anchored to an amino-silanized glass surface. *Biomaterials.* **2014**, 35 (6), 1779-1788.

Iron oxide nanoparticles: synthesis, coating and interaction with nanoparticles of noble metals.

Piersandro PALLAVICINI, [a] Elisa CABRINI, [a] Francesco VITA [b]

[a] Department of Chemistry, Università di Pavia, v.le Taramelli, 12-27100 Pavia, Italy
[b] Department of Chemistry, Università degli studi di Parma, Parco Area delle Scienze, 17/A 43124 Parma, Italy; e-mail: elisa.cabrini01@ateneopv.it

The objective of this work is the synthesis and coating of iron oxides nanoparticles (FeOx NP) in order to make them stable and capable of adhering to other nano-objects, in particular with gold nanostars and branched nanoparticles[1] .

Iron oxides are compounds that widely occur in nature, and the most common forms are hematite, magnetite and maghemite. In nanometric form these oxides gain magnetic

properties different from bulk material: they show the phenomenon of superparamagnetism, that is a magnetization of the material when exposed to an external magnetic field [2] . Another peculiar property of iron oxides nanoparticles is the so-called magneto-thermal effect, that consists on the emission of heat due to magnetic hysteresis loss when an external magnetic field is applied. Thanks to these special properties, iron oxides nanoparticles can have many biological applications, such as cellular labeling, magnetic resonance imaging, hyperthermia, for example in treatment of tumors, and drug delivery[3,4].

A simple, green and reproducible method to prepare such particles has been developed by us, modifying published procedures,[5] obtaining small FeOx NP (d=5-10nm, see Figure 1, left). We have then developed methods for coating the iron oxide nanoparticles, in order to make them capable of further interactions with surfaces and gold nanostars. First, through a silanization with MPTS (i.e. a molecule with a terminal –SH group), regulating the number of free –SH on each particle between 5 and 60, depending on the reaction conditions. Second, exploiting the positive Z potential of the iron oxide NP to coat them electrostatically with the negatively charged polymer PSS (Polystyrene sulfonate). In both cases stabilization of the FeOx NP is obtained, and possibility of further growth of the coating layers is demonstrated (eg by reacting –SH groups with maleimide-terminated functions)

Finally, interactions between coated FeOx NP, bearing external free –SH groups, and gold Nanostars or silver nanoparticles have been studied by UV-Visible spectrophotometry and TEM imaging, finding out how to advantageously prepare eg gold-FeOx nanohybrids (see Figure 1, right).

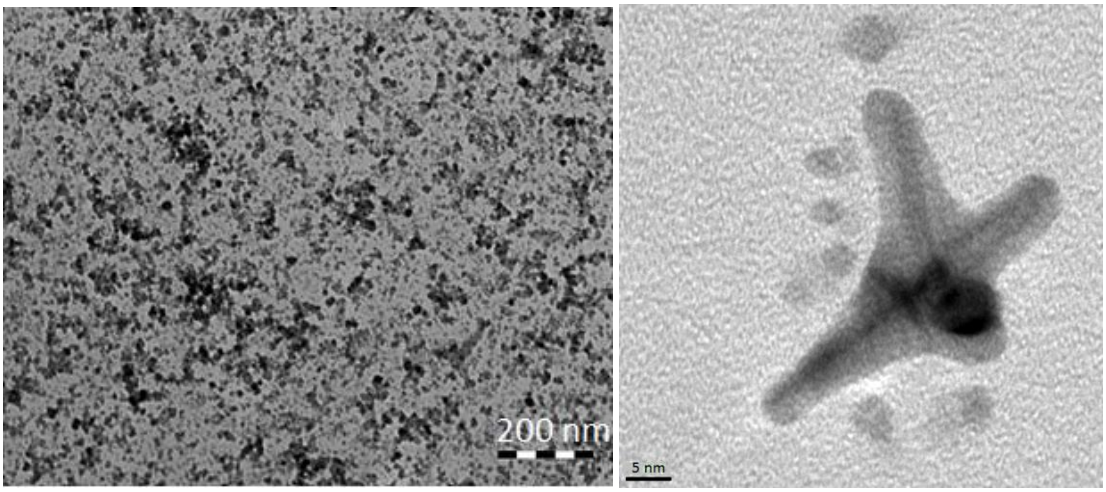


Figure 1: TEM images of iron nanoparticle and their interaction with gold nanostar

References:

[1] P. Pallavicini, G. Chirico, M. Collini, G. Dacarro, A. Donà , L. DAlfonso, A. Falqui, Y. Diaz-Fernandez, S.Freddi, B. Garofalo, A. Genovese, L. Sironi and A. Taglietti, Chem. Commun., 2011, 47, 1315–1317

[2] R.M. Cornell, U. Schwertmann, The Iron Oxides: Structure, Properties, Reactions, Occurrences and Uses, second ed. Wiley-VCH, Weinheim, 2003

[3] O.S. Nielsen, M. Horsman, J. Overgaard, Eur J Cancer 2001;37:1587–9

[4] O. Olsvik, T. Popovic, E. Skjerve, K.S. Cudjoe , E. Hornes, J. Ugelstad, M. Uhlen, Clin Microbiol Rev 1994;7:43–54

[5] G.W. Reimer, S.E. Khalafalla, US Bureau Mines Tech Rep 1972;59

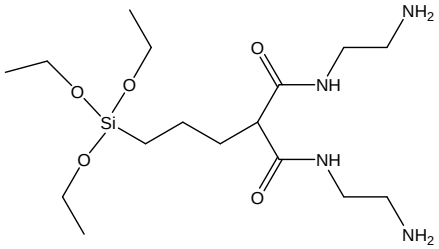
Antibacterial Surfaces based on a dioxotetramino Cu (II) complex

Angelo TAGLIETTI, [a] Agnese D'AGOSTINO, [a] Lucia CUCCA, [a] Giacomo DACARRO, [a] Arianna GATTESCO, [a] Pietro GRISOLI, [b] Carlo MANGANO, [a] Piersandro PALLAVICINI [a]

[a] Department of Chemistry, University of Pavia, viale Taramelli 12, 27100 Pavia, Italy
[b] Department of Drug Sciences, University of Pavia, Italy;
agnese.dagostino01@universitadipavia.it

In this work we have prepared antibacterial glass samples based on a coordination compound, [1] using a silane-derivatized dioxotetramino-Cu^{2+} complex covalently bound to glass or quartz surfaces, and capable to release the cation in the surface proximity when immersed in water solution.

The ligand used for this purpose is the N^1,N^3-bis(2-aminoethyl)-2-(3-(triethoxysilyl)propyl)malonamide, (TEP-dioxo-2,3,2-tet, see scheme), which possess a dioxo-2,3,2-tet fragment ready to bind Cu(II), and which can give condensation reactions between the alkoxysilane moiety and the hydroxyl groups of the activated glass or quartz surfaces and/or with the alkoxysilane moieties of adjacent ligand molecules. Copper can bind inside the dioxo-2,3,2-tet cavities in a square planar geometry, after the deprotonation of the amido groups. It has been demonstrated [2] that in aqueous solution this process is complete at a pH value of 7. At lower pH, in the range between 5 and 7, Cu(II) is coordinated to the terminal amino groups, while under pH 4 the binding moiety is unable to bind the cation.



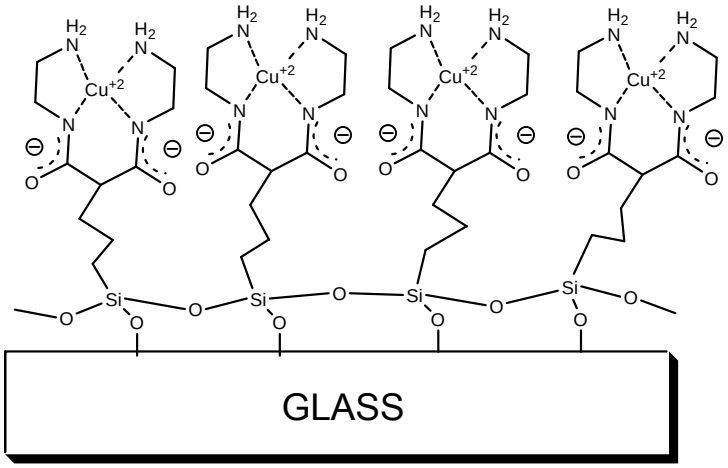
TEP-dioxo-2,3,2-tet

Two synthetic strategies were adopted to prepare the surfaces: i) using the free ligand; ii) using the copper complex (which was prepared in three different concentrations). In both cases ethanolic solution were used, and binding to the glass surfaces was performed by simple immersion of activated glass slides in the solutions.

Spectrophotometric characterizations have been carried on to study the behaviour of the complex in solution (acid-base titrations in ethanol) or the behavior of an analogous ligand in aqueous solution. The surfaces were examined with Uv-visible spectroscopy, contact angle measurements, Atomic Force Microscopy and ICP measurements of copper released after immersion in water in different conditions.

It has been found that the first synthetic strategy apparently does not work, with a small quantity of ligand found on the glass surface, as seen by the poorly reproducible contact angle

values measured, and by a specific colorimetric assay with fluorescein isothiocyanate which quantifies the free amino groups present on the surface.



With the second strategy, a good correlation was found between the complex concentration used in the surface coating and the quantity of copper brought on the surface, which ranges between 0.3 and 1.5 nanomoles of Cu^{2+} ion per cm^2. Finally, the microbicidal effect (ME) of functionalized surfaces was calculated for Gram positive (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*), demonstrating that such a low surface concentration of copper ions is able to exert a sensible antibacterial action, and finding a preliminary correlation between the quantity of complex brought on the surface used and the ME obtained.

References:

[1] Pallavicini P.; Dacarro G.; Grisoli P.; Mangano C.; Patrini M.; Rigoni F.; Sangaletti L.; Taglietti A., Coordination chemistry for antibacterial materials: a monolayer of a Cu^{2+} 2,2 '-bipyridine complex grafted on a glass surface. *Dalton Trans.* **2013**, 42 (13), 4552-60.

[2] Fabbrizzi L.; Licchelli M.; Pallavicini P.; Perotti A.; Taglietti A.; Sacchi D., Fluorescent Sensors for Transition Metals Based on the Electron Transfer and Energy Transfer Mechanisms. *Chem. Eur. J.* **1996**, 2, 167.

Controlling the dimension of star-shaped gold nanoparticles

Annalisa DO, [a] Alice DONA', [a] Piersandro PALLAVICINI [a]

[a] *Università degli Studi di Pavia, alice.dona@gmail.com*

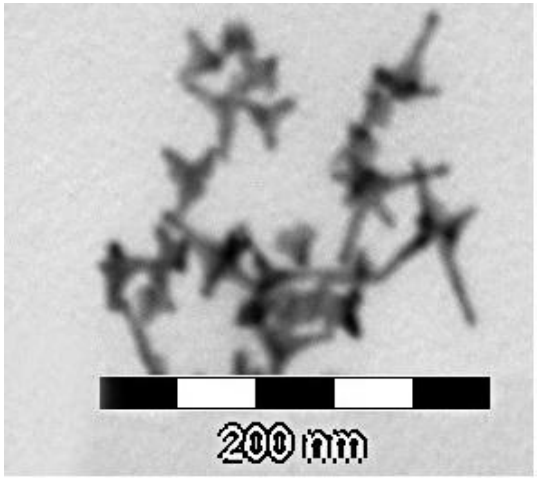
Anisotropic gold nanoparticles have received a lot of attention in the last years, because of their optical and photothermal properties. They are characterized by intense LSPR (Localized Surface Plasmon Resonance) bands in the region of the near infrared, where tissues, blood and water are transparent to the electromagnetic radiation. It has been demonstrated that, when irradiated on their LSPR, these objects are able to return the absorbed light into heat[1] which can be used to destroy for example tumor cells. Moreover, gold nanostars can be tracked in vitro and in vivo taking advantage of their Two Photon Luminescence (TPL) properties[2]. Previously, we have established a synthetic protocol to produce photothermally active gold nanostars[3]. These nanoparticles can be obtained by using a seed growth method in which the zwitterionic surfactant LSB (*N*-Dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate) is used to direct the anisotropic growth of the nanostars. In particular, a seed is firstly prepared reducing tetrachloroauric acid with sodium borohydride in the precence of the stabilizing agent LSB. Then, a growth solution is prepared: it contains all the reactants necessary to the asymmetric growth of gold nanostars, (LSB, silver nitrate, tetrachloroauric acid, ascorbic acid). When a specific amount of the seed is added to the growth solution (12μL), the solution changes from colourless to pink, violet and finally blue, corresponding to the formation of gold nanostars. The process is complete in about one hour. The threshold of 30-50 nm is often indicated as that allowing the penetration of nanoparticles in the cell nucleus, a process that would enormously increase the efficiency of their photothermal effect in antitumoral therapies, or their ability to act as vectors of antitumoral drugs. As in our published procedures we obtain gold nanostars in the 60nm dimensional range, we have now concentrated on their dimensions, modifying the seed growth procedure to produce smaller nanoparticles of the same morphology.

We made use of two strategies:

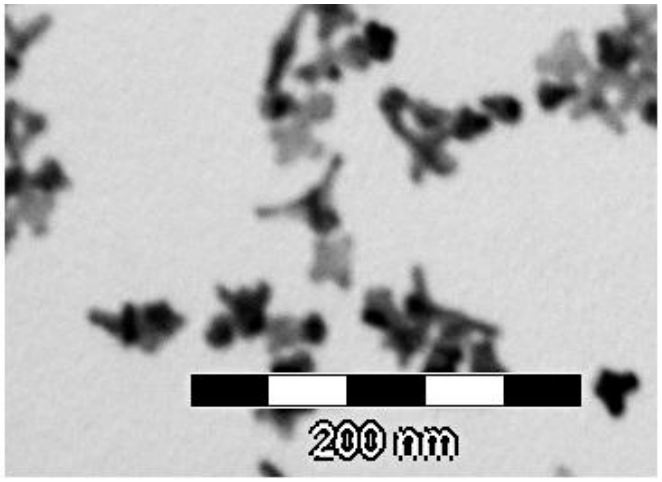
i) stopping the growth by the addition of a thiol at controlled times from the addition of the seed. The thiol can be of a different type (we used the biocompatible polyethylene glycols, PEG_{2000}-SH, PEG_{5000}-SH, HS-PEG_{3000}-COOH, HS-PEG_{3000}-NH_2). The thiol reacts with the gold surface of the growing nanoparticles preventing the deposition of more amount of gold from the solution and thus stopping the growth of the nanostars.

ii) adding a larger volume of the seed to the growth solution (keeping constant the total amount of tetrachloroauric acid in the growth solution). In this way, more nucleation sites are at disposition, but the total gold is the same, so the dimensions of the nanoparticles remains little.

Both strategies were successful in controlling the dimensions of gold nanostars, allowing to obtain nanostars with overall dimensions < 50 nm.



a) gold nanostars obtained with previously established method



b) gold nanostars obtained with the stopped the growth

References:

[1] Freddi, S.; Sironi, L.; D'Antuono, R.; Morone, D.; Donà, A.; Cabrini, E.; D'Alfonso, L.; Collini, M.; Pallavicini, P.; Baldi, G.; Maggioni, D.; Chirico, G.; A Molecular Thermometer for Nanoparticles for Optical Hyperthermia; *Nano Lett.* **2013**, 13, 2004−2010

[2] Sironi, L.; Freddi, S.; Caccia, M.; Pozzi, P.; Rossetti, L.; Pallavicni, P.; Donà, A.; Cabrini, E.; Gualtieri, M.; Rivolta, I.; Panariti, A.; D'Alfonso, L.; Collini, M.; Chirico, G.; Gold Branched Nanoparticles for Cellular Treatments; *J. Phys. Chem. C* **2012**, 116, 18407−18418

[3] Casu, A.; Cabrini, E.; Donà, A.; Falqui, A.; Diaz-Fernandez, Y.; Milanese, C.; Taglietti, A.; Pallavicini, P.; Controlled Synthesis of Gold Nanostars by Using a Zwitterionic Surfactant; *Chem. Eur. J.* **2012**, 18, 9381–9390

Interaction of Silver Salts, Nanoparticles and Complexes with Bacterial and Yeast Cell Components

Iryna GONCHAROVA[a], **Oleksiy LYUTAKOV**[b], **Marie URBANOVÁ**[c]

[a] *Department of Analytical Chemistry Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic, gonchari@vscht.cz*
[b] *Department of Solid State Engineering, Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic*
[c] *Department of Physics and Measurement, Institute of Chemical Technology, Technická 5, Prague 166 28, Czech Republic*

The origin of the bioactivity of Ag(I) compounds is currently unknown. The fact that silver compounds do not destroy mammalian cells makes them prospective agents in drug design.

The antibacterial effects and mechanism of action of silver were investigated for *Escherichia coli* and *Saccharomyces cerevisiae* by analysing the morphology and ultrastructure of the cells that were grown on PMMA matrix contained various silver compounds (Ag(I) complexes of amino- and hydroxyacids, Ag(I) salts and Ag nanoparticles). Release of the Ag^+ ions and Ag(0) nanoparticles and their interactions with the cells and their components were studied by combination of circular dichroism, absorption and fluorescence spectroscopies. Transmission electron microscopy showed considerable changes in both the cell membranes and intracellular structures and two ways of the antimicrobial activity of the studied Ag compounds were tested.

In the first case, interactions with the bacterial cell wall components (peptidoglycans, polysaccharides and proteins) were studied. In the second case, a systematic chiroptical study on Ag(I) complexes interactions with nucleotides, RNA, and DNA was made. In the case of DNA, strong coordination of Ag(I) to G-C pair was observed. It was also found, that even in the case of nucleotides, the formation of the Ag(I)-mediated base pairs and their self-assembles were observed in wide pH range. Based on the obtained data, in the first time, the formation of the Ag(I)-mediated self-assembled species of cytidine and its derivatives with a structure similar to the i-motif structure in DNA was proposed.

Acknowledgements
The work was supported by the Grant agency of the Czech Republic (P205/12/P584)

Indium and gallium maltolate as antineoplastic agents: in vitro efficacy and mitoxantrone potentiation

Daniele MERLI, [a] **Giulia RISI,** [b] **Stefano MOMENTE',** [a] **Fabrizio PIVI,** [a] **Antonella PROFUMO** [a], **Livia VISAI** [b]

[a] *Dipartimento di Chimica, Università degli Studi di Pavia, Via Taramelli 12, 27100 Pavia*
[b] *Dipartimento di Medicina Molecolare e Centro per l'Ingegneria Tissutale (C.I.T), Università degli Studi di Pavia, Via Taramelli 3/B, 27100 Pavia;*
daniele.merli@unipv.it

Gallium, a metallic element of group 13 (IIIa) of the periodic table, has shown efficacy in the treatment of several apparently different disorders [1]. In particular, it acts as an antineoplastic both *in vitro* and *in vivo*. Gallium is particularly effective against some lymphatic and urothelial cancers, due to its ability to reach high concentration in these sites [1]. Moreover, it can inhibit DNA synthesis through substitution of Ga^{3+} for Fe^{3+} in the M_2 subunit of ribonucleotide reductase, thus blocking its action; furthermore, it seems to interfere with iron absorption and metabolism of proliferating cells. Indium as well was studied for its *in vitro* antitumor activity, but its properties and these of its complexes are so far unexplored [2].

In recent years, gallium maltolate has gained same popularity as antineoplastic for the treatment of scarcely responding tumors (e.g. hepatocellular carcinoma and lymphomas) [3]. Starting from these consideration and from the chemical properties of group IIIa elements, we have decided to synthesize the analogous compound of indium, that is to say In(III) maltolate, and tested its *in vitro* ability of killing cancerous cell.

First results seems very promising, as these two compound showed similar cell grow inhibition properties against the neoplastic cell line MDA-231.

From apoptosis tests (annexin V), it seem that a cytostatic rather than a cytotoxic effect characterize these two molecules.

The synergic effect of these two metal complexes and of a well-known cytotoxic compound (mitoxantrone, MTO) were tested as well; it appears that the co-administration of the two drugs causes a deeper cell death with respect to each compound alone.

The effect of the substances on the non-neoplastic murine cell line NIH3T3 was tested as well.

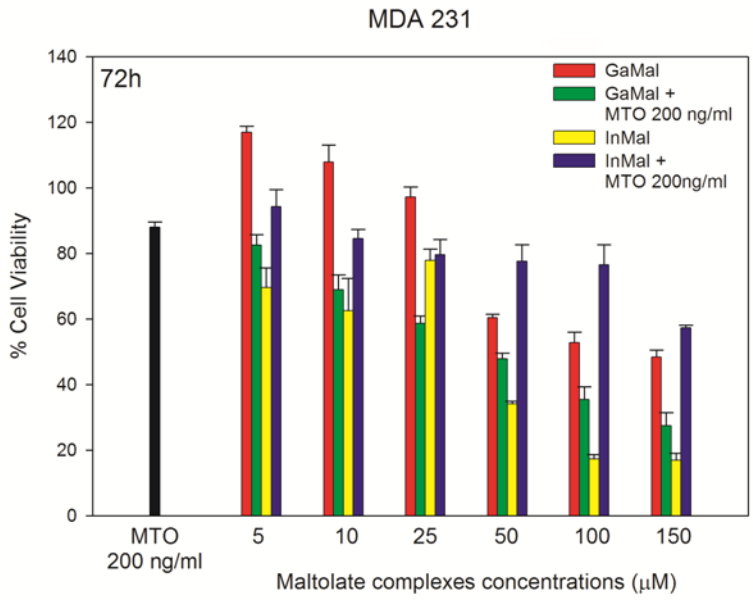


Figure 1: The effect of MTO (200 ng/ml, black bar), different concentration of gallium maltolate (red bar) and indium maltolate (yellow bar), gallium plus MTO 200 ng/ml (green bar) and indium maltolate plus MTO 200 ng/ml (blue bar) on MDA-231 viability at 72 h incubation time.

References:

[1] Bernstein L.R., Mechanisms of Therapeutic Activity for Gallium. *Pharmacological reviews* **1998**, 50 (4), 665-682.

[2] Head J.F.; Wang F.; Elliott R.L., Antineoplastic Drugs that Interfere with Iron Metabolism in Cancer Cells. Advances in Enzyme Regulation 1997, 37, 147-169.

[3] Chitambar, C.R.; Purpi, D.P.; Woodliff, J.; Yang, M.; Wereley, J. P., Development of Gallium Compounds for Treatment of Lymphoma: Gallium Maltolate, a Novel Hydroxypyrone Gallium Compound, Induces Apoptosis and Circumvents Lymphoma Cell Resistance to Gallium Nitrate. *The Journal of Pharmacology and Experimental Therapeutics* **2007,** 322 (3), 1228-1236.

Biological activity and physicochemical properties of *fac* and *mer* Ru(III) triphenylphosphine complexes with benzothiazole derivatives as co-ligand

Monika RICHERT [a], Mariusz WALCZYK [b], Stanisław BINIAK [b], Tadeusz MUZIOŁ [c], Marcin Janusz CIEŚLAK [d], Julia KAŹMIERCZAK-BARAŃSKA [d], Karolina KRÓLEWSKA [d]

[a] Department of Inorganic and Analytical Chemistry, Faculty of Pharmacy, Collegium Medicum Nicolaus Copernicus University; Jurasza St. 2; 85-094 Bydgoszcz, Poland; monika.richert@cm.umk.pl; [b] Faculty of Chemistry, Nicolaus Copernicus University; Gagarina St. 7, 87-100 Toruń, Poland; [c] Department of Inorganic Chemistry, Faculty of Chemistry, Nicolaus Copernicus University; Gagarina St. 7, 87-100 Toruń, Poland; [d] The Centre of Molecular and Macromolecular Studies in Łódź,, Polish Academy of Sciences Institutes; H. Sienkiewicza 112, 90-363 Łódź, Poland

Chemotherapy, besides radiotherapy and surgery is still an important method of cancer treatment, and is often a complementary therapy after surgery. For many years one of the most important chemotherapeutic agents was cisplatin, discovered by Rosenberg in 1969 [1], and its analogues [2]. However, its serious side effects, such as neuro-, nephro- or ototoxicity, stimulated intensive research into new compounds with greater selectivity of action, fewer toxic side-effects and lack of resistance against primary and secondary tumours. The most promising non-platinum-based compounds with potential anticancer properties are those containing ruthenium. A basic advantage of ruthenium complexes is their ability to mimic the properties linking iron with biomolecules such as transferrin, which enable their transport throughout the body; they are less toxic than cisplatin with respect to healthy cells. The reductive microenvironment of hypoxic tumours favours interaction between ruthenium ions and biomolecules such as glutathione, which can activate an inert prodrug to become a highly reactive and cytotoxic compound. The activation induced by the reduction of the metal centre is of great interest to researchers and is used by Pt(IV) and Ru(III) compounds. The ions of these metals are reduced to an active form of M(II). The octahedral environment of the Ru(II) ion, as opposed to the square planar geometry of Pt(II) compounds, suggests a different mechanism of reactivity, which offers new opportunities for anticancer therapy [3].

In our works we have focused on study of *fac* and *mer* isomers of $RuCl_3(PPh_3)L$, where L = benzothiazole derivatives. It is known that the biological activity of every potential metal-based pharmaceutical is a function of the oxidation state of the metal centre and the properties of the coordinated ligands. Also we have determined physicochemical properties and tried found correlation between the structure, biological and chemical activity. Redox properties of isomers have been identified by cyclic voltammetry. However biological activity have characterized by interactions with DNA and the cytotoxicity using a standard MTT assay against human cell lines, in order to test their capacity for antitumor applications.

Acknowledgments

The authors wish to acknowledge the Polish National Science Centre for financial support grants no. 2011/03/D/NZ7/02283

References:

[1] Reedijk J., Improved understanding in platinium antitumour chemistry, *Chem. Commun*., **1996**, 801-806

[2] M.A. Jakupec, M. Galanski, B.K. Keppler, Tumour-inhibiting platinum complexes - state of the art and future perspectives, *Rev. Physiol. Biochem. Pharmacol*., 2003, 146, 1-54

[3] C.S. Allardyce, P.J. Dyson, Ruthenium in Medicine: Current Clinical Uses and Future Prospects, *Platinum Metals Rev*., **2001**, 45, (2), 62-69

Investigation on charge transfer complexes of DDQ with pharmaceuticals

Valentina RIBOTTA, Enrico CHIAVAZZA, [a] Silvia BERTO, [a] Pier Giuseppe DANIELE, [a] Mery MALANDRINO, [a]

[a] Dipartimento di Chimica, Università di Torino, Via Pietro Giuria 7 , 10125, Torino, Italy
silvia.berto@unito.it

The properties of charge-transfer (CT) complexes formed in the reaction of electron acceptors with donors containing nitrogen, sulphur or oxygen, have growing importance in recent years. In particular they can play a role in the quantitative estimations of drugs [1-6]. The CT complexes formed between the drugs and the acceptors absorb radiations in the visible range and the absorbance values at the maxima absorption wavelengths are used for the quantification of the drugs. The linear range of the response and the sensitivity of the detection system are linked to the stoichiometry and to the stability of complexes formed. The acceptors more used with this aim are the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), tetracyanoethylene (TCNE), 2,3,5,6-tetrabromo-1,4-benzoquinone (bromanil), 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil).

The interaction of the electron acceptor DDQ with molecules containing nitrogen atoms was studied in acetonitrile and ethanol by molecular absorption spectrophotometry and NMR spectroscopy. We evaluated that the DDQ preferentially interact with alkyl amine, therefore the attention was focused on the study of the interaction of DDQ with two molecules containing this functional group: a β-adrenergic blocking drug, the atenolol, and a synthetic local anaesthetic drug, procaine. In order to obtain stable and coherent results we evaluated preliminarily the stability of DDQ in the two polar solvents and the time necessary to obtain a stable and high response with the drugs. The stability of DDQ is not excellent and the deteriorated solution absorb in the same range of CT complexes. Under inert atmosphere the absorbance at 460 nm increase of 0.001 unit *per* minute. In order to avoid an excessive degradation of free DDQ, but to allow the complex formation, all signals were recorded after 15 minutes from the solutions preparation. All the experiments were conducted at 25 ± 0.1°C. For both the systems, the stoichiometry of the complexes were defined with Job's plot method and the stability constants were calculated from spectrophotometric batch titration data using the software Hyspec [7]. The NMR spectra recorded at room and at low temperature allowed us to define the portion of the donor molecule involved in the complex formation and to confirm the values of formation constants.

In accordance with the cited works the CT complexes formed show spectra with 6-7 bands in the range 350-600 nm and the stoichiometry of the complexes are in all cases 1:1. The absorbance values at the λ_{max} increase with the concentration of the drugs in solution and the linearity range is linked to the stoichiometry of the complexes, the signals increase linearly with the concentration of the drugs until the concentration of DDQ is in excess.

References:

[1] Pandeeswaran, M.; Elango, K.P., Spectroscopic studies on the interaction of cimetidine drug with biologically significant σ- and π-acceptors. *Spectrochimica Acta Part A* **2010**, 75, 1462-1469.

[2] Pandeeswaran, M.; Elango, K.P., Solvent effect on the charge transfer complex of oxatomide with 2,3-dichloro-5,6 dicyanobenzoquinone. *Spectrochimica Acta Part A* **2006**, 65, 1148-1153.

[3] Salem, H. H., Spectrophotometric determination of β-adrenergic blocking agents in pharmaceutical formulations. *Journal of Pharmaceutical and Biomedical Analysis* **2002**, 29, 527-538.

[4] Fathima, A.; Rao, S.; Venkateshwarlu, G., Spectrophotometric determination of drugs using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone as analytical reagent. *International Journal of Chem Tech Research* **2011**, 3**,** 1769-1780.

[5] Refata, M. S.; El-Didamony, A. M., Spectrophotometric and electrical studies of charge-transfer complexes of sodium flucloxacillin with π-acceptors. *Spectrochimica Acta Part A* **2006**, 65, 732-741.

[6] Veeraiah, T.; Anjaiah, G.; Kista Reddy, P., Charge transfer complexes of chloranil with drugs. *Journal of Scientific & Industrial Research* **2005,** 64, 504-508.

[7] Gans, P.; Sabatini, A.; Vacca, A., Investigation on equilibria in solutions. Determination of equilibrium constants with the HYPERQUAD suite of programs. *Talanta* **43** (1996) 1739-1753.

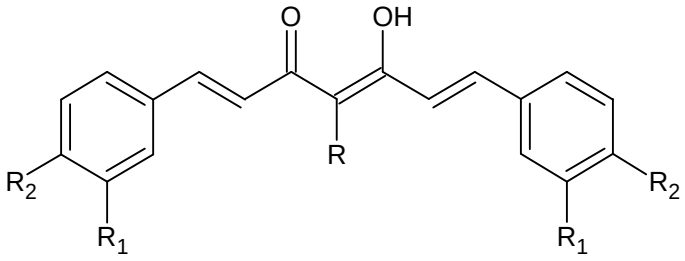
^{68}Ga-labelled curcuminoids complexes: potential radiotracers for imaging of cancer and Alzheimer's disease

Erika FERRARI,[a] Mattia ASTI,[b] Stefania CROCI,[c] Giulia ATTI,[b] Sara RUBAGOTTI [b], Monica SALADINI[a]

[a] Department of Chemical and Geological Sciences, University of Modena, via Campi, 183, 41125 Modena, Italy; [b] Nuclear Medicine Unit, Oncology and Advanced Technologies Department, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; [c] Clinical Immunology, Allergy, and Advanced Biotechnologies Unit, Diagnostic Imaging and Laboratory Medicine Department, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

erika.ferrari@unimore.it

Curcumin is a phyto-compound and dietary spice extracted from the rhizome of the herb *Curcuma longa* L., commonly known as turmeric. It is used in traditional medicines of eastern world countries thanks to its properties such as antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. In recent years, curcumin and curcuminoids complexes with metals, have been subjected to a large number of studies due to their interesting potential as therapeutics in varying diseases. Iron complexes of curcumin seem to have high potential in the treatment of cancer [1], while gallium complexes have remarkable antiviral effects on HSV-1 in cell culture [2]. Curcumin structure includes a heptadiene with two 3-methoxy, 4-hydroxy phenyl groups, and an α,β-diketone which is subjected to a keto-enol tautomerism, pH and solvent dependent, that also influences its metal-chelation capability [3]. The keto-enolic moiety of curcumin have also been exploited in the complexation of radioactive metals for synthesizing ^{99m}Tc-labelled radiopharmaceuticals where curcumin acts as OO bidentate ligand on a ^{99m}Tc-tricarbonyl core with the aim of projecting a target specific probes for potential diagnosis of Alzheimer's disease (AD) or cancer [4].



Compound	R	R_1	R_2
Curcumin	H	OCH_3	OH
DAC	H	OCH_3	OAc
bDHC	H	OCH_3	H
K2A21	CH_2COOH	OCH_3	OH
K2A23	CH_2COOH	OCH_3	H
K2T21	$CH_2COOC(CH_3)_3$	OCH_3	OH
K2T23	$CH_2COOC(CH_3)_3$	OCH_3	H

Figure 1

The aim of the present study is to investigate the feasibility of the labelling of curcuminoids with gallium-68 in order to obtain potential diagnostic tools for cancer and Alzheimer's disease.

For this purpose, different classes of curcuminoids (**Figure 1**) were selected and a complete characterization of the equivalent ^{nat}Ga-complexes structures and properties was performed by means of experimental and theoretical approach. Stoichiometry and formation of the curcuminoids complexes were investigated by MALDI-TOF-MS, NMR, UV-Vis, and Fluorescence spectroscopy on the ^{nat}Ga-

Curcuminoids complexes and their structure was computed by theoretical DFT calculations. The corresponding ^{68}Ga-labelled complexes with the most promising curcuminoids were then synthesized and characterized. The radiotracers were prepared by reacting $^{68}Ga^{3+}$ obtained from a ^{68}Ge/^{68}Ga generator with curcuminoids solutions. Reaction parameters (precursor amount, reaction temperature, and pH) were optimized in order to obtain high and reproducible radiochemical yield and purity. The complexes showed high stability in saline, human serum or when challenged with DTPA or with Fe^{3+}, Zn^{2+}, and Cu^{2+} for transchelation or transmetallation studies, respectively. In order to test the possibility to use ^{68}Ga-curcuminoids complexes as radiotracers for AD, a first evaluation of their affinity for Aβ(1-40) amyloid synthetic fibrils was here investigated *in vitro*. Finally study *in vitro* on lung cancer cells showed quite high level of cellular uptake of ^{nat}Ga-complexes (**Figure 2**), confirmed by ICP-MS spectrometry.

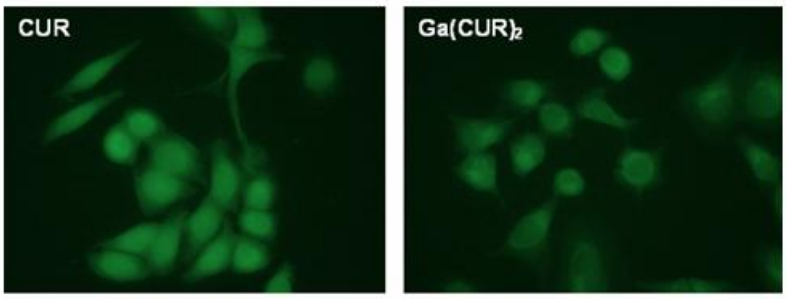


Figure 2

The obtained results are encouraging and shed new light on the potential use of curcuminoids as radiotracers for PET (positron emission tomography), in addition the intrinsic fluorescent emission of the Ga-curcuminoids complexes paves the way to the possibility of synthesizing a mixed radioactive/fluorescent pharmacophore that could be exploited as a dual-mode imaging tool.

References:

[5] Kovacevic, Z.; Kalinowski, S.D.; Lovejoy, B.D.; Yu, Y; Rahmanto, S. Y.; Sharpe, C.P.; Bernhardt, V. P.; Richardson, R. *Curr. Top. Med. Chem*. **2011**, 11, 483-499.

[6] Zandi, K.; Ramedani, E.; Mohammadi, K.; Tajbakhsh, S. ; Deilami, I.; Rastian, Z.; Fouladvand, M.; Yousefi, F.; Farshadpour, F. *Nat. Prod. Commun*. **2010**, 5, 1935-1938.

[7] Ferrari, E.; Asti, M.; Benassi, R.; Pignedoli, F.; Saladini, M. *Dalton Trans*. **2013**, *42*, 5304-5313.

[8] Sagnou, M.; Benaki, D.; Triantis, C.; Tsotakos, T. ; Psycharis, V.; Raptopoulou, C.P.; Pirmettis, I.; Papadopoulos, M.; Pelecanou. M. *Inorg. Chem.* **2011**, *50*, 1295–1303.

Comparison of different aromatic Pt(IV) complexes as antitumor prodrugs

Sabrina BIANCO, [a] Mauro RAVERA, [a] Elisabetta GABANO, [a] Giulia CARON, [b] Giuseppe ERMONDI, [b] Domenico OSELLA [a]

[a] Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale "Amedeo Avogadro", Viale Michel 11, 15121 Alessandria (Italy)
[b] CASSMedChem, Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università di Torino, Torino (Italy)
sabrina.bianco@mfn.unipmn.it

In the recent years octahedral Pt(IV) complexes have emerged as an alternative to the traditional square planar cisplatin-like Pt(II) compounds as anticancer drugs. The presence of two additional ligands in axial position can be used to tune the lipophilicity, the reactivity and then the overall pharmacokinetic profile of the Pt(IV) complexes.

Axial carboxylato ligands having long hydrocarbon chains are known to offer the best results in terms of potency of the resulting Pt(IV) complexes in vitro [1]. Moreover, Pt(IV) compounds bearing aromatic carboxylato ligands have proved to enormously improve their uptake with resulting high potency in vitro [2].

The aim of this work was the synthesis, characterization and the evaluation of the antiproliferative activity of two small series of Pt(IV) complexes having the "$[Pt(Am)_2Cl_2]$" (Am = $2\times NH_3$ series **1**, or cyclohexane-1,2-diamine, dach, series **2**, Figure 1) moiety as equatorial arrangement and bearing axial aromatic carboxylato ligands with different length of the $-(CH_2)_n-$ spacer between the phenyl and the carboxylic groups.

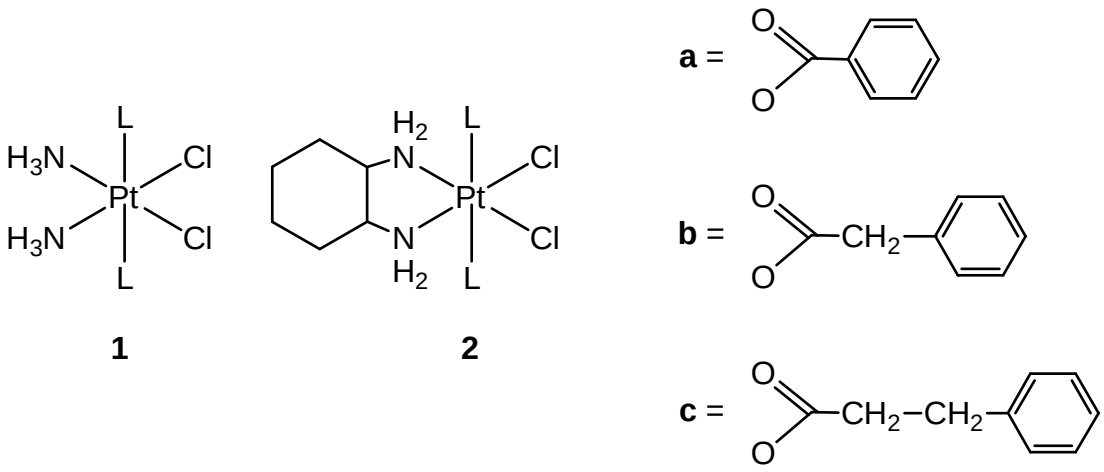


Figure 1 Sketch of the Pt(IV) complexes under investigation

To investigate the pharmacokinetic behavior of these Pt(IV) complexes, their propensity to form Intramolecular Hydrogen Bonding (IMHB) was also examined. The presence of IMHB has been shown to significantly alter molecular properties due to the formation of

various conformers that in turn influences the solubility, permeability, pharmacodynamic process and protein binding of the complexes [3].

The formation of IMHB was experimentally proven for **1a**, **1b** and **2a** through X-ray crystallography. To evaluate if the same pattern is maintained in the remaining structures, a mixed approach obtained with the combination of conformational analysis and lipophilicity data was applied.

References:

[1] Gramatica, P.; Papa, E.; Luini, M.; Monti, E.; Gariboldi, M. B.; Ravera, M.; Gabano, E.; Gaviglio, L.; Osella, D., *J. Biol. Inorg. Chem*. **2010**, 15, 1157–1169.

[2] Ang, W.; Pilet, S.; Scopelliti, R.; Bussy, F.; Juillerat-Jeanneret, L.; Dyson, P. J., *J. Med. Chem.* **2005**, 48, 8060-8069.

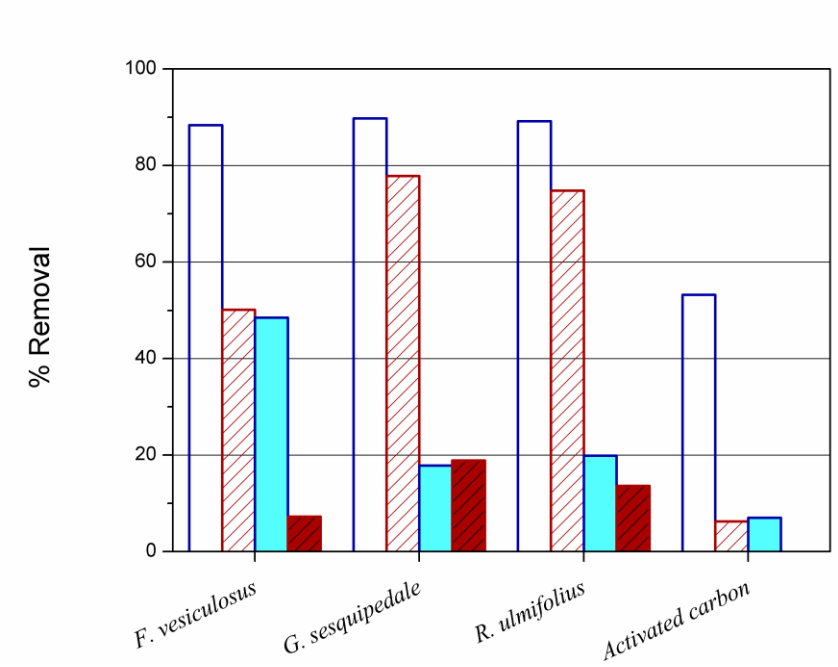
[3] Shalaeva, M.; Caron, G.; Abramov, Y. A.; O'Connell, T.N.; Plummer, M. S.; Yalamanchi, G.; Farley, K. A.; Goetz, G. H.; Philippe, L.; Shapiro, M. J., *J Med Chem*. **2013**, 56(12), 4870-9.

Considering dead leaves of blackberry (Rubus ulmifolius) as organic amendment: non-metabolic (passive) uptake of Al^{+3} versus metabolic bioaccumulation data

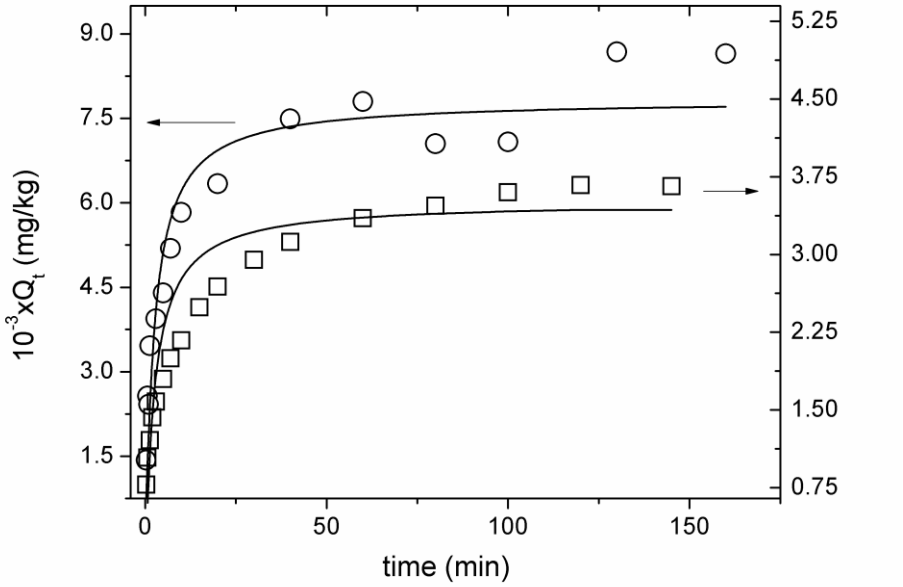
Pablo LODEIRO[a),b)], Marta LÓPEZ-GARCÍA[a)], Luz HERRERO[c)], José L. BARRIADA[a)], Roberto HERRERO[a)], Leticia CARRO[a)], Teresa VILARIÑO[a)], Pilar RODRÍGUEZ BARRO[a)] and Manuel E. SASTRE DE VICENTE[a)]

[a)]Departamento de Química Física e Enxeñería Química I, Universidade de A Coruña, Rúa da Fraga 10, 15008 A Coruña (Spain) [b)]Ocean and Earth Science, National Oceanography Center Southampton, University of Southampton, Waterfront Campus, European Way, SO14 3ZH Southampton (UK) [c)]Centro Tecnológico AIMEN. Relva, 27 A, 36410, Torneiros, Porriño, Pontevedra (Spain); pilar.rbarro@udc.es

This comunication reports a physicochemical study (thermodynamic and kinetic data) describing the ability of *Rubus ulmifolius* biomass (dead leaves) for metal uptake. Aluminium, which toxicity is a major problem for crops in acid soils, has been the selected metal [1]. The obtained results indicate that dead *R. ulmifolius* leaves, uptake up to 10000 mg/kg on its surface in less than 60 minutes. This suggests that aluminium can be an excellent component with adsorbent properties for amendments to be used in acid soils in order to control aluminium levels, thus its toxicity. Results have been critically analysed and compared with previous work on aluminium bioaccumulation. Kinetic equations, not previously used in toxicity studies, are discussed.



Percentage of aluminium removal by different biomaterials.



Aluminium uptake from solution, as function of time, for *R. ulmifolius* leaves.

References:

[1] Lodeiro, P.; Gudiña, A.; Herrero, L.; Herrero, R.; Sastre de Vicente, M.E., Aluminium removal from wastewater by refused beach cast seaweed. Equilibrium and dynamic studies. *Journal of Hazardous Materials* **2010,** 178**,** 861-866.

Authors wish to thank Ministerio de Economía y Competividad for the financial support through the research project CTM2012-37272, co-funded by the FEDER program.

In situ synthesis of Cd(II) complexes obtained using 1-hydroxymethyl-3,5-dimethylpyrazole as a starting ligand. Crystal structures, spectroscopic and biological properties

Barbara BARSZCZ,[a] Joanna MASTERNAK,[a] Wanda SAWKA–DOBROWOLSKA,[b] Joanna WIETRZYK,[c] Magdalena MILCZAREK[c]

[a] *Institute of Chemistry, Jan Kochanowski University, 15 G Świętokrzyska Str., 25-406 Kielce, Poland. E-mail: Barbara.Barszcz@ujk.edu.pl*

[b] *Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie Str., 50-383 Wrocław, Poland*

[c] *Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, 12 Weigla Str., Wrocław 53-114, Poland*

Cadmium plays an unusual role as a significant toxic species because of its obvious accumulation in the human body, which can lead to serious cadmium intoxication [1, 2]. It causes cancer of the lungs, kidney and prostate, and possibly female breast and endometrial cancer. Resent publications [3, 4] point out the molecular mechanisms of carcinogenicity. Metal is not directly mutagenic but it is a strong co-mutagen. Persistent DNA damage is due to indirect processes, such as increased ROS formation. Additionally, ROS signaling may also induce proliferation and/or redox-sensitive transcription factors that promote carcinogenicity. Therefore, we try to find effective, chelating agents for treating cadmium intoxication. So, in this work we have demonstrated a simple process that involves one-pot reaction leading to efficient preparation of new cadmium complexes with N4-donating ligands $[CdX_2L^1]$ (X = I^- (**1**), Br^- (**2**), SCN^- (**4**), L^1 = tris(1-(3,5-dimethylpyrazolyl)methyl)amine), $[Cd_2(L^2)_2(SCN)_4(MeOH)_2]_n$ (X = SCN^- (**3**), L^2 = 3, 3, 5, 7 – tetraazadamantane) (**Fig. 1**).

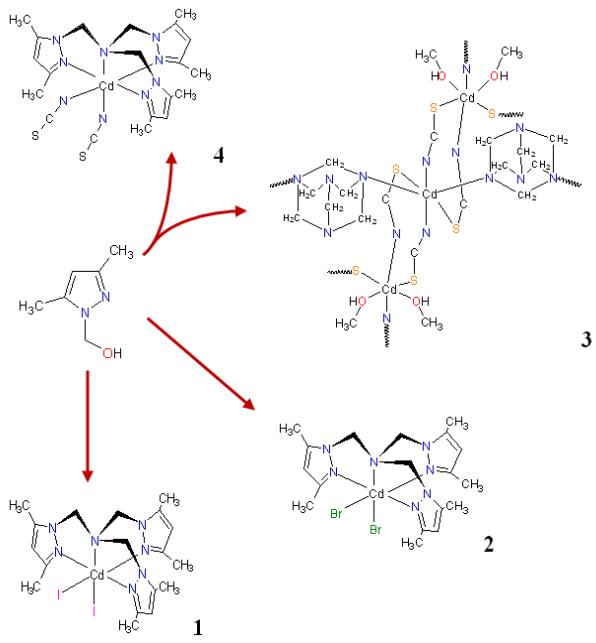


Figure 1. The diversity of cadmium(II) complexes obtained *in situ*.

The most prominent feature of the synthesis is *in situ* formation of new organic tripodal ligands (L^1) or urotropine (L^2) in condensation reaction between a starting ligand (1hydroxymethyl-3,5-dimethylpyrazole) and ammonia. A single-crystal X-ray analysis confirmed that the complexes obtained are monomers (**1**, **2**, **4**) or polymer (**3**) with octahedral geometry of cadmium centres. IR, ^1H and ^{13}C NMR, as well as simultaneous TG/DTG were carried out to characterise the products. Moreover, biological studies demonstrated that Cd(II) complexes with N-scorpionate ligand (**1**, **2**, **4**) have similar cytotoxicity, which points

to a structure-cytotoxicity relationship. Thus, all the complexes (except **3**) exhibited a lower cytotoxic activity compared to a cadmium ion in salts (**Fig. 2**). This may be a pointer to a good chelating ability of the scorpionate ligand (L^1).

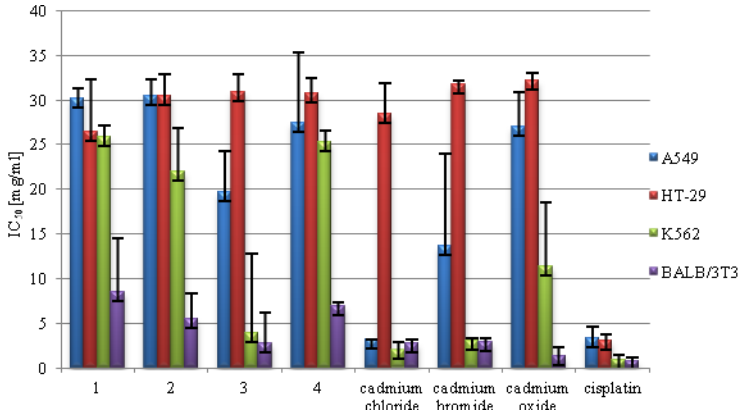


Figure 2. Assessment of cadmium-induced inhibition of cells growth.

References:

[1] Moulis, J.-M., Thévenod, F., New perspectives in cadmium toxicity: an introduction, *Biometals* 2010, 23, 763–768.

[2] Nawrot, T. S., Staessen, J. A, H., Roels, A., Munters, E., Cuypers, A., Richart, T., Ruttens, A., Smeets, K., Clijsters, H., Vangronsveld, J., Cadmium exposure in the population: from health risks to strategies of prevention, *Biometals* 2010, 23, 769–782.

[3] Waisberg, M.; Joseph, P.; Hale, B.; Beyrsmann, D.; Molecular and cellular mechanisms of cadmium carcinogenesis. *Toxicology* 2003, 192 (2-3), 95-117.

[4] Waalkes, M. P., Cadmium carcinogenesis in review. *J. Inorg. Biochem.*, 2000, 79, 241-244.

Biomonitoring of toxic element exposure by ICP-AES and ICP-MS analysis

Miriam CRESPO-ALONSO,[a] Valeria M. NURCHI,[a] Joanna I. LACHOWICZ,[a] M. Guadalupe JARAQUEMADA-PELÁEZ,[a] Gavino SANNA[b]

[a] Dipartimento di Scienze Chimiche e Geologiche, University of Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy, [b] Dipartimento di Chimica e Farmacia, University of Sassari, Via Vienna 2, 07100, Sassari, Italy; m.crespo@unica.it

The spread of toxic elements in the environment is a consequence of global pollution. Toxic elements can be absorbed through air, water and food, becoming so available for bioaccumulation in food chain. Estimated exposure to metals was assessed with respect to safe/tolerable exposure levels, and described by various national and public health organizations.[1] In order to develop risk assessment, accurate determination of toxic elements is needed.

Due to their morphology, high accumulation rate, intensive annual growth and wide availability of historical samples, cervid antlers are suited for detecting accumulation of metals. In particular this accumulation acts in a more persistent way in antlers than in soft tissues and can thus be used as long term or life-span biomonitors of exposure. [2-3]

Thank to the collaboration with the local WWF, we have been able to collect deer antlers in the Monte Arcosu Park, located in south west Sardinia, where more than one thousand deers are living. This forest is largely extended (3600 h), without any human settlements except some folds, and completely wild. Nevertheless it can enter in contact, mainly through winds, with the pollutants deriving from a refinery on the south coast, and from minerary plants and metallurgical industries on the west border.

Therefore the study area should be exposed to high ambient level of pollutants due to its closeness to industrial areas. The chemical analysis of toxic elements such as As, Cd, Co, Cr, Hg, Ni, Pb and Se, has been carried out by inductively coupled plasma atomic emission spectroscopy (ICP-AES) and by inductively coupled plasma-mass spectrometry (ICP-MS) that are the most sensitive techniques for trace elements in solution. In this communication the analytical techniques will be discussed and some preliminary results will be presented.

Acknowledgments
MCA is grateful to RAS for the program Master and Back – Percorsi di rientro, PRR-MAB-A2011-19107. MCA also acknowledges CRF for his great contribution to this work.

References:

[1] World Health Organization (WHO): Health risks of heavy metals from long-range transboundary air pollution (**2007**). http://www.euro.who.int/__data/assets/pdf_file/0007/78649/E91044.pdf

[2] Pokorny, B., Roe deer (*Capreolus capreolus L.*) antlers as an accumulative and reactive bioindicator of lead pollution near the largest Slovene thermal power plant. *Vet. Arhiv*. **2006**, 76 (suppl.), S131-S142.

[3] Dobrowolska, A., Chemical composition of the red deer *(Cervus elaphus)* antlers, with a particular reference to the toxic metal contents, *Z. Jagdwiss* **2002**, 48 (suppl.), 148-155.

Technology based on grape stalks for chromium plating industry wastewater treatment

David PUJOL[a], Chang Liu[a], Núria FIOL[a], Florencio de la TORRE[a], Jordi POCH[b], Isabel VILLAESCUSA[a]

[a)] Chemical Engineering Department, Escola Politècnica Superior, Universitat de Girona, Campus Montilivi, 17071 Girona (Spain); nuria.fiol@udg.edu
[b)] Applied Mathematics Department, Escola Politècnica Superior, Universitat de Girona, Campus Montilivi, 17071 Girona (Spain);

During the last two decades our research group has been investigating the potential application of grape stalks wastes for water treatment to remove metals and organic compounds from aqueous solutions [1-4]. Results of these studies demonstrated that grape stalk is a good sorbent for the elimination of hexavalent chromium and divalent metal ions in aqueous solutions. In view to use this sorbent for wastewater metal treatment, sorption studies by using industrial wastewater were needed to confirm the effectiveness of this material for wastewater metal decontamination.

In this work, results of chromium plating industry wastewater treated by using a technology based on grape stalk sorption are presented. To do this, a wastewater sample from a chromium plating industry were collected, characterized and used as influent on sorption experiments.

Wastewater treatment experiments were carried out in a pilot plant operating in batch mode. In a first step, grape stalks were put into contact with the wastewater in a stirred batch reactor where metal elimination and hexavalent chromium reduction took place. After that, the residual water was introduced into a clarifier to eliminate the remaining metal ions in solution by coagulation-floculation reaction.

For metal sorption process and Cr(VI) reduction, 6.6 g of grape stalks per litre of contaminated water were put into a 10L stirred batch reactor. Two operational conditions were tested: experiments at not controlled pH and experiments at fixed pH 3.0, controlled automatically using a programmable logic control (PLC). After reach the equilibrium, the solution was filtered and introduced to a 10L clarifier.

For coagulation-floculation process, the solution was adjusted at pH 9 by adding a 0.1M NaOH solution. Three different coagulant-floculant reagents were tested: $FeCl_3$, $Al_2(SO_4)_3$ and a commercial aluminium polyelectrolyte (PAC) to determine the most appropriated. As coagulant-floculant dose is critical to ensure effective separation process, the optimum coagulant-flocculant dose was determined by jart-testing.

Results demonstrate that the most efficient conditions for water treatment was the sorption-reduction process at controlled pH 3, followed by the clarification process by using $Al_2(SO_4)_3$ as coagulant-floculant reagent. After this complete water treatment process, metal ions concentrations were below the regulated discharge limits.

References:

[1] Fiol, N.; Villaescusa, I.; Martínez, M.; Miralles, N.; Poch, J.; Serarols, J., Biosorption of Cr(VI) using low cost sorbents. Environmental Chemistry Letters 2003, 1 (2), 135-139.
[2] Miralles, N.; Martínez, M.; Florido, A.; Casas, I.; Fiol, N.; Villaescusa, I. Grape Stalks Waste as Low Cost Biosorbents: An Alternative for Metal Removal from Aqueous Solutions, Solvent Extraction and Ion Exchange 2008, 26 (3): 261 — 270
[3] Escudero, C.; Fiol, N.; Poch, J.; Villaescusa, I. Modeling of kinetics of Cr(VI) sorption onto grape stalk waste in a stirred batch reactor, Journal of Hazardous Materials, 2009, 170: 286–291
[4] Escudero, C.; Poch, J.; Villaescusa, I. Modelling of breakthrough curves of single and binary mixtures of Cu(II), Cd(II), Ni(II) and Pb(II) sorption onto grape stalks waste. Chemical Engineering Journal,2013, 217:129-138

Acknowledgements:
This work has been financially supported by the Spanish Ministry of Economy and Competitiveness, Spain, Project CTM2012-37215-C02-01.

Exhausted coffee encapsulated in calcium alginate for Cr(VI) sorption from binary mixtures Cr(VI)-Cu(II)

Lucia GUSMAROLI [a], Chang LIU [b], Nuria FIOL[b], Giancarla ALBERTI [a], Isabel VILLAESCUSA [b]

[a] Dipartimento di Chimica, Università di Pavia, Via Taramelli, 12, 27100 Pavia (Italy); lucia.gusmaroli01@universitadipavia.it
[b] Chemical Engineering Department, EPS, Universitat de Girona, Avda. Lluis Santaló, s/n, 17071, Girona (Spain)

Exhausted coffee (EC) proved to be an efficient sorbent for Cr(VI) removal from aqueous solution from both single metal solution [1] and binary mixtures with Cu(II) and Ni(II) [2] at acidic pH values. In these conditions copper and nickel are fairly sorbed onto EC. In order to enhance sorption efficiency and sorbent consistency, exhausted coffee has been encapsulated in calcium alginate (CA) beads. Calcium alginate beads have the ability to remove divalent metal via ion exchange between metal and calcium ions [3 - 5]. Therefore, exhausted coffee encapsulated in calcium alginate beads is expected to be efficient for the removal of Cr(VI) and other divalent metal cations from aqueous solutions.

Firstly, the beads were synthetized by adding 2% of EC to 1% sodium alginate and dropping the mixture into a 0.1 M $CaCl_2$ solution. After 24 hours curing in this solution, calcium alginate beads (EC-CA) were formed. Before their use for sorption purposes the beads were characterized by analysing different parameters (water content, diameter, density, porosity, morphology). Once characterized the beads were used for Cr(VI) removal from binary mixtures of these two metal ions.

A preliminary work was carried out to study the effect of pH on metals sorption. pH 3 was found to be the most favourable for both chromium and copper removal.

Kinetics studies were performed at pH 3 in stoppered glass tubes containing 40 EC-CA beads and 15 mL of single metal or binary mixtures in different concentration ranging from 0.2 mM and 0.8 mM . The tubes were removed from the stirrer at different intervals of time; the pH of the filtered solution was measured, metals concentration was analysed by Flame Atomic Absorption Spectroscopy and calcium released from the beads by Flame Emission Spectroscopy.

Results showed that EC encapsulated in CA is an efficient reducing material for Cr(VI) and a good sorbent for copper. Absence of Cr(III) in the filtered solution and pH increase indicate that when Cr (VI) enters the beads and gets into contact with coffee, reduction takes place and Cr(III) is retained in the bead via cation exchange with calcium. Ion exchange is also the main mechanism responsible for Cu removal. The presence of Cu(II) has a synergistic effect on Cr (VI) sorption, as it increases the percentage of chromium uptake; Cu (II) removal was found not to be influenced by Cr (VI) concentration.

References:

[1] Fiol, N.; Escudero, C.; Villaescusa, I., Sep. Sci. & Technol. **2008**, 43 (3), 582-596.
[2] Pujol, D.; Bartrolí, M.; Fiol, N.; de la Torre, F.; Villaescusa, I.; Poch, J., Chemical Engineering Journal **2013**, 230, 396–405
[3] Escudero, C.; Fiol, N.; Villaescusa, I.; Bollinger, J.-C.; Arabian Journal of Chemistry **2013**, in press.
[4] Cataldo, S.; Cavallaro, G.; Gianguzza, A.; Lazzara, G.; Pettignano, A.; Piazzese, D.; Villaescusa, I., Journal of Environmental Chemical Engineering **2013**, 1 (4), 1252–1260
[5] Cataldo, S.; Gianguzza, A.; Pettignano, A.; Villaescusa, I., Reactive & Functional Polymers **2013**, 73, 207-217.

Determination of vanadium(V) in tea infusions and wines after pre-concentration on immobilized nanometer titanium dioxide

Elisa RIVAGLI[a)], Federica MARASCHI[a)], Michela STURINI[a)], Andrea SPELTINI[a)], Lucia CUCCA[a)], Antonella PROFUMO[a)], Valentina CARATTO[b)], Maurizio FERRETTI[b)]

[a)]Department of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy
[b)]Department of Chemistry and Industrial Chemistry, University of Genoa, via Dodecaneso 31, 16146 Genova, Italy; elisa.rivagli@unipv.it

Vanadium is a trace metal widely distributed in the environment. It may exist in different oxidation states, the most common being V(IV) and V(V). This last is the most stable and toxic form of the element [1]. Although vanadium is generally present at low concentrations in foods, they represent the primary route of exposure to vanadium for the general population [2, 3]. Vanadium can be found in different drinks at concentration levels ranging from 1-5 μg Kg^{-1} and up to 90 μg L^{-1} in wines [4]. Its determination/monitoring in beverages appears, therefore, essential. A pre-concentration step is generally required, due to both the low analyte concentration and the need to remove the matrix interferences.
In this study, V(V) determination in untreated drinks was performed by solid-phase extraction (SPE) on nanosized titanium dioxide immobilized on silica gel, followed by inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis. Three different sorbents were prepared by sol-gel method and characterized by X-ray powder diffraction (XRPD), scanning electron microscopy (SEM) and BET analysis. V(V) was selectively sorbed in the pH range 2.3-7.0 and quantitatively eluted by 0.1 M HCl. The effectiveness of the procedure was first assessed on tap water enriched with 1 μg L^{-1} of V(V) with satisfactory recoveries (92% *n*=4). The pre-concentration step was subsequently optimized for more complex matrices such as tea infusions, red and white wines after spike. Quantitative recoveries (82-95%, *n*=4) were obtained with no any further pre-treatment. The developed method was finally applied to the determination of V(V) in commercial tea infusions and wines samples.

References:

[1] WHO (World Health Organization), Geneva, **2001**.
[2] ATSDR (Agency for Toxic Substances and Disease Registry), Draft toxicological profile for vanadium, Atlanta, **2009**, 378.
[3] Barceloux, D.G., Vanadium. *Journal of Toxicology - Clinical Toxicology* **1999,** 37 (2), 265-278.
[4] Teissèdre, P.L.; Krosniak, M.; Portet, K.; Gasc, F.; Waterhouse, A.L.; Serrano, J.J.; Cabanis, J.C.; Cros, G., Vanadium levels in French and Californian wines: Influence on vanadium dietary intake. *Food Additives & Contaminants* **1998,** 15 (5), 585-591.

Polynuclear, dinuclear and mononuclear manganese(II) complexes with pyridine alcohols as an effective catalysts for H_2O_2 disproportionation in water

Małgorzata ZIENKIEWICZ,[a] Agnieszka JABŁOŃSKA-WAWRZYCKA,[a] Katarzyna STADNICKA,[b] Maciej HODOROWICZ,[b] Wanda SAWKA-DOBROWOLSKA,[c] Jacinto SÁ,[d] Jakub SZLACHETKO,[d] Barbara BARSZCZ,[a]

*[a]Institute of Chemistry, Jan Kochanowski University in Kielce, 15G Świętokrzyska Str., 25-406 Kielce, Poland, *e-mail: zienkiewicz.malgorzata@gmail.com*
[b]Faculty of Chemistry, Jagiellonian University, 3 Ingardena Str., 30-060 Kraków, Poland
[c]Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie Str., 50-383 Wrocław, Poland
[d]Paul Scherrer Institute (PSI), 5232 Villigen, Switzerland

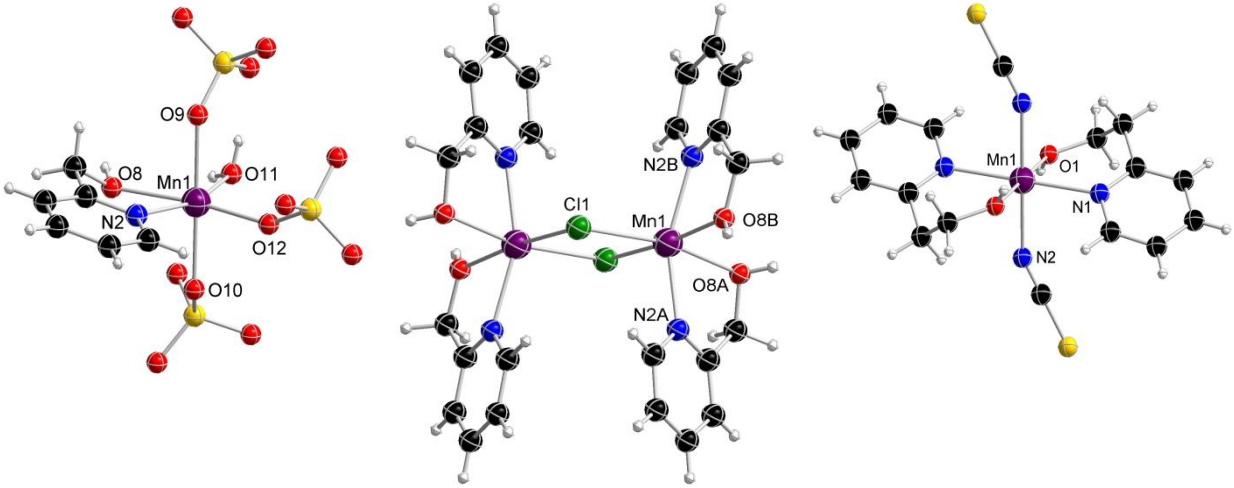
The coordination chemistry of manganese complexes with N,O-donor ligands has attracted great interest because of their structural diversity and the importance as mimetics of Mn-dependent biomolecules [1, 2]. Hence, our efforts have been focused on the preparation and characterisation of low-molecular inorganic analogues that would mimic physicochemical properties and catalytic activity of manganese-containing enzymes.

Herein, we report the structural characterisation of three new structurally different manganese(II) complexes with two homologous pyridine alcohols: 2-hydroxymethylpyridine (2-CH_2OHpy) and 2-hydroxyethylpyridine (2-$(CH_2)_2OH$py), elucidated by spectroscopic (IR, Raman, EPR), X-ray crystallographic methods and magnetic studies.

In all isolated complexes the N,O-donor heteroaromatic ligands are bound to Mn(II) centres in a bidentate fashion. Obtained complex $[Mn(2\text{-}CH_2OHpy)(SO_4)(H_2O)]_n$ (**1**) has a polymeric structure (Fig. 1) with the asymmetric unit consisting of two bivalent manganese metal centres, two water moieties, two chelating molecules of 2-CH_2OHpy and two sulphate(VI) anions bridging Mn(II) ions. The Mn(1) cation is six-coordinated and the coordination sphere (a chromophore of $\{MnO_5N\}$ type) is distorted octahedral with basal plane formed by N(2), O(8), O(11) and O(12) atoms [3]. In dinuclear complex $[Mn_2(\mu_2\text{-}Cl)(2\text{-}CH_2OHpy)_4]Cl_2\cdot 2H_2O$ (**2**), each Mn(II) ion (CN=6) assumes distorted octahedral geometry in which it is surrounded by two N,O-chelating 2-CH_2OHpy ligands and two bridging chloride anions forming a $\{MnN_2O_2Cl_2\}$ chromophore (Fig. 1). Two Mn(II) ions are doubly-bridged by two chloride anions, with a Mn···Mn distance of 3.65 Å and Mn-Cl-Mn bridging angle of 92.81°. Molecular structure of symmetric monomeric complex (**3**) is best represented by the formula $[Mn(2\text{-}(CH_2)_2OHpy)_2(NCS)_2]$ and the Mn centre is surrounded by two nitrogen from the SCN^- anions and two nitrogen and two oxygen from the chelating 2-$(CH_2)_2OH$py ligands (a chromophore of $\{MnO_2N_4\}$ type) that form an almost perfect octahedron with angular deviations smaller than 5° (Fig. 1).

Isolated Mn(II) complexes were found to be stable (HR-XAS) and show promising catalase-like properties. RIXS measurements revealed that the manganese redox chemistry is a key for the process, and the complexes are not stoichiometric catalysts but truly catalytic

system. Additionally, the reported complexes are active in neutral aqueous conditions (physiological conditions), uncommon for catalase-mimics, making these low-molecular systems a promising class of materials.



(1) **(2)** **(3)**

Fig. 1. Molecular structures of obtained Mn(II) complexes.

References:

[1] Wu, A. J.; Penner-Hahn, J. E.; Pecoraro, V. L., Structural, Spectroscopic, and Reactivity Models for the Manganese Catalase. *Chemical Reviews* **2004**, 104, 903-958.

[2] Signorella, S.; Hureau, Ch., Bioinspired Functional Mimics of the Manganese Catalase. *Coordination Chemistry Reviews* **2012**, 256, 1129-1245.

[3] Zienkiewicz M.; Szlachetko J.; Lothschütz Ch.; Hodorowicz M.; Jabłońska-Wawrzycka A.; Sá J.; Barszcz B., A Novel Single-site Manganese(II) Complex of a Pyridine Derivative as a Mimetic for Disproportionation of H_2O_2 in Water. *Dalton Transactions* **2013**, 42, 7761-7767.

The contribution of contaminant metals in beachrock formation

Nikole ARRIETA, Ane ITURREGUI, Marian OLAZABAL, Irantzu MARTÍNEZ-ARKARAZO, Juan Manuel MADARIAGA

Department of Analytical Chemistry, University of the Basque Country UPV/EHU, P.O. Box 644, E-48080 Bilbao, Spain, marian.olazabal@ehu.es

Beachrocks are sedimentary structures formed in the intertidal zone as a consequence of a relatively rapid cementation of beach grains by the precipitation of mainly calcium carbonates [1]. The beachrocks object of this study, in contrast to the most documented ones [1], are located in a temperate latitude, more exactly around the Nerbioi-Ibaizabal estuary (North of Spain, Bay of Biscay). From the geochemical point of view, it is necessary that waters reach saturation in calcium carbonate at sometime previous to the formation of the beachrock. As those saturation conditions can hardly be reached in the typical conditions of sea water at these latitudes, in the endeavor to elucidate the mechanism of beachrock formation in our coasts, the influence of the estuary as well as waste waters spills in the vicinity of the beaches should be taken into account. In this particular case, it is also necessary to consider other inputs such as the slag spilled from iron and steel companies in the past as well as other anthropic materials probably coming from the river. Moreover, recent evidences raise awareness about the possibility of biological mechanisms being involved in the early stages of the cementation, followed by abiotic processes.

Concretely in Azkorri beach, the amalgamated outcrops are characterised by marked stratigraphic sequences composed of coarse and fine-grained sand layers [2]. These layers display wide porous spaces where early diagenesis could afford less resistant cementation if the cements are not completely covering the entire pore spaces [3]. Samples were taken from a 1.8 m high stratigraphic column (including cemented sand and partially cemented sand at the top of the selected column) with the aim of understanding the phenomena involved in its formation and analysing the composition of the materials trapped into the outcrops during the cementation process. For that purpose, apart from total carbonate quantification, ICP-MS quantitative analyses were reinforced with chemometric analyses which allowed estimating the provenance of the elements.

Indeed, the high metallic concentrations found in the sedimentary sequences revealed that the area of study presents a clear anthropogenic influence since many of the metals found are characteristic of mining industrial activities and suggest that there has been a clear affection from the materials derived from the slag submarine disposal zone and the Nerbioi-Ibaizabal estuary plume. In fact, most of the quantitative analyses performed over the metallic compounds, such as the vertical distribution of the metal contents in the different stratigraphic sequences supported by the correlation analysis or the principal component analysis indicated a common origin of the majority of the heavy metals (as for example Fe, Ni, Zn, Cu, Sn, As, Mo, Cr, Mn, V, Ba, Pb and Co) which corroborates the influence of the two sources of pollution, but does not prevent to rule out other possible sources of contamination. What is more, the organic material coming from the different anthropogenic influences present in the

area, apart from augmenting the volume of the cemented structures, could have stimulated a microbial growth probably favoring the initial cementation. In fact, the organic matter could act as a ligand fixing the metallic elements and their further enclosing within the beachrock outcrops, through precipitation processes.

Finally, according to the quantitative results, except for the layer on the top, no significant differences were found between the different strata in terms of the concentration of total carbonates, nor as to the metal concentration. On one side, the layer showing the lower concentration of carbonates and of elements related to the cement forms such as Ca and Mg (the top layer), is the only one presenting non-cemented sand. On the other side, the high metallic concentration found in top layer suggests that those values are derived from the percolation of water rich in metal concentration after the disintegration of upper stratigraphic layers possibly eroded by diverse weathering processes and resulting on the accumulation of the trace metal compounds in that top layer. Consequently, it could be mentioned that the phenomenon might be in a regression process and that the magnitude of the beachrock sedimentary units was probably greater in the past.

References:

[1] Vousdoukas, M.I.; Velegrakis, A.F.; Plomaritisn, T.A., Beachrock Occurrence, characteristics, formation mechanisms and impacts. *Earth-Science Reviews* **2007**, 85, 23-46.

[2] Arrieta, N.; Goienaga, N.; Martinez-Arkarazo, I.; Murelaga, X.; Baceta, J.I.; Sarmiento, A.; Madariaga, J.M., Beachrock formation in temperate coastlines: Examples in sand-gravel beaches adjacent to the Bilbao River Estuary (Bay of Biscay, North Spain), *Spectrochim. Acta Part A*, **2011**, 80, 55-65

[3] Bernier, P.; Guidi, J.B.; Bottcher, M.E., Coastal progradation and very early diagenesis of ultramafic sands as a result of rubble discharge from asbestos excavations (northern Corsica, western Mediterranean). *Marine Geology* **1997**, 144, 163-175.

Acknowledgments:

This work has been financially supported by the project PRIACE (Ref: CTM2012-36612) from the Spanish Ministry of Economy and Competitiveness (MINECO). Ane Iturregui and Nikole Arrieta are grateful to the Basque Government and the University of the Basque Country (UPV/EHU), respectively, for their predoctoral fellowships.

Coordination compounds of lead(II) with O-, N-donor ligands: syntheses, structures and DFT calculation

Joanna MASTERNAK,[a] Barbara BARSZCZ,[a] Maciej HODOROWICZ,[b] Oleksiy V. KHAVRYUCHENKO,[c] Alina MAJKA[d]

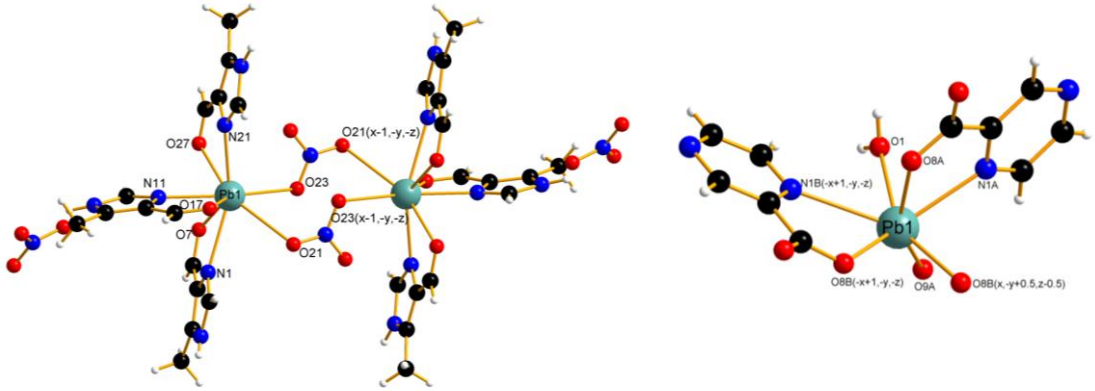
[a] Institute of Chemistry, Jan Kochanowski University in Kielce, 15G Świętokrzyska Str., 25-406 Kielce, Poland, e-mail: masternak.joanna@gmail.com
[b] Faculty of Chemistry, Jagiellonian University, 3 Ingardena Str., 30-060 Kraków, Poland
[c] Chemistry Department, Taras Shevchenko National University of Kyiv, 64 Volodymyrska Str., Kyiv UA-01601, Ukraine
[d] Institute of Physical Chemistry, Polish Academy of Sciences, 44/52 Kasprzaka Str., 01-224 Warsaw, Poland

The interest of coordination chemistry of Pb(II) is motivated by the toxicity of lead and its widespread occurrence in the environment due to its numerous industrial applications [1-3]. The coordination properties of lead over other essential metal ions is crucial to understand the toxicological properties of this metal, the design of selective chelation therapy agents, and the development of efficient chelating agents for the remediation of polluted water and soil. Lead(II) has a particular fascination for coordination chemists as it can adopt many different geometries in its complex. The literature data mainly pointed on:

(i) the effect of so-called "inert electron-pair", which means the size and extent of the lone-pair in the coordination sphere,
(ii) the broad range of coordination numbers from 2 to 12,
(iii) the kind of donating ligands and their flexibility.

To counteract the effects of lead poisoning it is necessary to establish the preferred ligands of Pb(II) and their stereochemistry. Ours interest has emerged in synthesis and study of the properties of Pb(II) model complexes with N,O- chelating ligands (5-methylimidazole-4-carbaldehyde, pyrazine-2-carboxylic acid) to express the effect of a stereochemically active lone pair in Pb(II) on the stereochemistry and properties of lead(II) complexes.

A dinuclear $[Pb_2(4\text{-CHO-5-MeIm})_6(NO_3)_2](NO_3)_2$ (**1**) and a polynuclear $[Pb(2\text{-pzc})_2(H_2O)]_n$ (**2**) complexes (where 5(4)-carbaldehyde-4(5)-methylimidazole (5(4)-CHO-4(5)-MeIm) and pyrazine-2-carboxylic acid (2-pzcH)) have been synthesized and characterized by elemental analysis, IR spectroscopy and X-ray crystallography. Structural determination for complex **1** reveals a cationic species $[Pb(4\text{-CHO-5-MeIm})_3]^{2+}$ connected through bridging nitrate(V) ions (**Fig. 1a**). There are also an uncoordinated nitrate ions as counterions. Complex **2** is a three-dimensional architecture consisting of Pb_6O_{12} building units. The pyrazine-2-carboxylato ligand behaves as a chelating agent and a bi-connective bridge (**Fig. 1b**). The coordination polyhedra around lead(II) ion could be described as a distorted docecahedron (**1**) or monocapped trigonal prism (**2**).



a **b**

Figure 1. Molecular structures of $[Pb(4\text{-}CHO\text{-}5\text{-}MeIm)_3(NO_3)_2](NO_3)_2$ (**a**) and asymmetric unit of polymeric complex $[Pb(2\text{-}pzc)_2(H_2O)]_n$ (**b**).

The luminescent properties of **1** and **2** investigated in the solid state at room temperature indicate structure-dependent photoluminescent properties. Additionally, a possible stereochemical activity of the lone pair in the complexes obtained has been discussed by us based on the molecular structure of the complexes provided by DFT calculations. According to the literature data, holo- and hemidirected geometry are two general structural types of lead(II) complexes [4, 5]. The DFT calculations and the X-ray structural data point on rather hemidirected type of coordination around Pb(II) ions of **1** and **2**.

References:

[1] Ahmadzadi, H., Marandi, F., Morsali, A., Structural and X-ray powder diffraction studies of nano-structured lead(II) coordination polymer with η2 Pb···C interactions. *J. Organomet. Chem.* 2009, 694, 3565-69.

[2] Katz, M.J., Kaluarachchi, H., Batchelor, R.J., Bokov, A.A., Ye, A.-G., Leznoff, D.B., Highly birefringent materials designed using coordination polymer. Synthetic methodology. *Angew. Chem.* 2007, 119, 8960-63.

[3] Murray, C.B., Sun, S., Gaschler, W., Doyle, H., Betley, T.A., Kagan, C.R., Colloidal synthesis of nanocrystals and nanocrystal superlattices *IBM J. Res. Dev.* 2001, 45, 47-55.

[4] Davidovich, R.L., Stavila, V., Marinin, D.V., Voit, E.I., Whitmire, K.H., Stereochemistry of lead(II) complexes with oxygen donor ligands *Coord Chem Rev* 2009, 253,1316-52.

[5] Harrowfield, J.M., Maghaminia, S., Soudi, A.A., Polyhapto-Aromatic Interactions in Lead(II) Coordination *Inorg. Chem.* 2004, 43, 1810.

Potentiometric and calorimetric study of fluoride adsorption onto mesoporous alumina nanoparticles.

Sara GRACIA[a)], Andrea MELCHIOR[a)], Manuel VALIENTE[b)], Marilena TOLAZZI[a)]

[a)]Dipartimento di Chimica Fisica e Ambiente, Università di Udine, Via del Cotonificio 108, 33100 Udine, Italy; [b)]Departamento de Quimica, Centre GTS, Universitat Autònoma de Barcelona, Campus Bellaterra Edificio CN, Barcelona, Spain; marilena.tolazzi@uniud.it

Fluoride contamination in groundwater has been recognized as one of the serious problems for water quality worldwide, and it is classified as one of the contaminants of water for human consumption by the World Health Organization (WHO). Besides the natural geological sources of fluoride enrichment in groundwater, fluoride-containing minerals are used in several industries which contribute to fluoride pollution. The effluents of these industries have fluoride concentrations extending from ten to thousands of $mg \cdot L^{-1}$ [1,2].

The WHO has established that acceptable F^- concentration in water should be < 1.5 $mg \cdot L^{-1}$. Depending on the concentration and the consumption lasted of water with fluoride excess the effects can be very harmful for health [1].

Nowadays many methods exist to remove fluoride from wastewater, such as adsorption [3-5], precipitation [6], electrocuagulation [7] or ion-exchange [8]. Adsorption shows considerable potential for fluoride removal from contaminated water [1-5], offering strategic advantages when compared to other techniques. Improvement of well-designed adsorbents is therefore of a great importance to the effective application of adsorption in water remediation. A wide variety of materials has been developed and used for fluoride removal from wastewater. However, the lowest limit achieved for fluoride removal with most adsorbents is greater than 2 $mg \cdot L^{-1}$.

Nanomaterials can offer several advantages in waste water treatments over traditional methods, such as high surface area and a short diffusion route. The high surface in relation to their volume offers the opportunity to treat contaminated water using nanoparticles instead of using large scale solid: therefore nanomaterials are expected to give better results than traditional sorbents (higher loading, lower residual concentration) with the advantage of cost and materials savings. Preliminary studies have shown that alumina has high affinity for fluoride [1,9] and that mesoporous alumina has high adsorption efficiency [3].

The scope of this work is to perform a thermodynamic study to characterize fluoride adsorption process on nano-alumina and screen the synthesized materials to obtain an optimal candidate for applications. We synthesized and characterized mesoporous alumina nanoparticles by transmission electron microscopy (TEM) and scanning electron microscopy (SEM) and then carried out adsorption studies. Fluoride adsorption has been investigated using a combined experimental approach which includes potentiometry (using a F^- selective electrode) and, for the first time in this field, isothermal titration calorimetry (Fig.1).

In our method, potentiometric data have been fitted with a Langmuir isotherm to obtain the value of K_{ads}. Then, the K_{ads} has been used to calculate the free F^- concentration for each titrant addition in the calorimetric titrations in order to fit the experimental heat and ultimately obtain the ΔH_{ads} value for the fluoride adsorption.

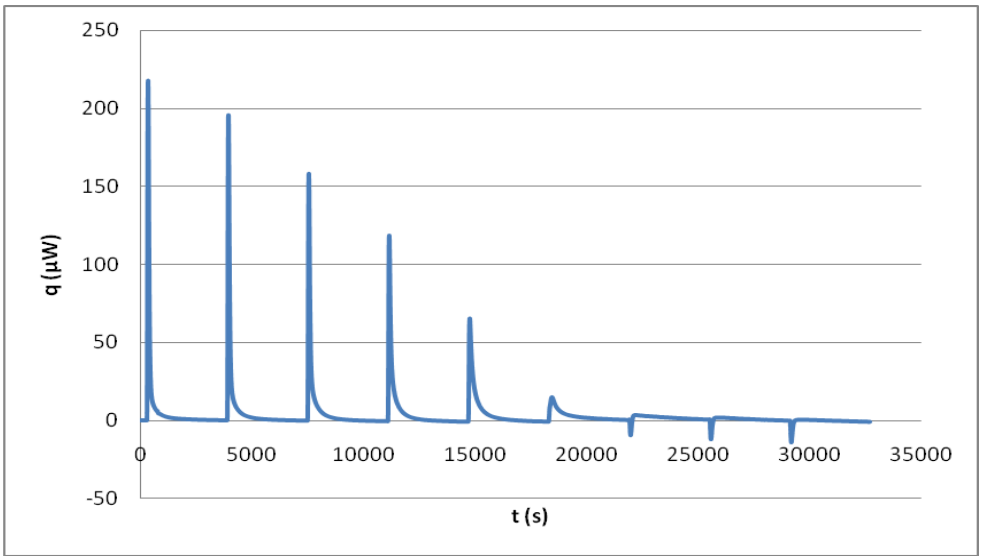


Fig.1. A representative Isothermal titration calorimetry measurement of fluoride adsorption into mesoporous alumina adsorbent at pH 5.5. Each peak represents an injection of 17,5µl of 80mM fluoride solution to 0.7mL of 0.5g·L^{-1} alumina nanoparticles suspension.

References:

[1] Bhatnagar A.; Kumar E.; Sillanpa A., Fluoride removal from water by adsorption - A review. *Chem. Eng. J.* **2011**, 171(3), 811-840.

[2] Fawell, J.; Bailey, K.; Chilton, J.; Dahi, E.; Fewtrell, L.; Magara, Y., Fluoride in Drinking-water. *World Health Organization (WHO)* **2006**.

[3] Li W.; Cao C. Y.; Wu L. Y.; Ge M. F.; Song W. G., Superb fluoride and arsenic removal performance of highly ordered mesoporous aluminas. *J. Hazard. Mater.* **2011**, *198*, 143-150.

[4] Zhao X. L.; Wang J. M.; Wu F. C.; Wang T.; Cai Y. Q.; Shi Y. L.; Jiang, G. B., Removal of fluoride from aqueous media by Fe_3O_4@$Al(OH)_3$ magnetic nanoparticles. *J. Hazard. Mater.* **2010**, *173*(1-3), 102-109.

[5] Gong, W. X.; Qu, J. H.; Liu, R. P.; Lan, H. C.; Adsorption of fluoride onto different types of aluminas. *Chem. Eng. J.* **2012**, *189*, 126-133.

[6] Reardon, E. J.; Wang, Y. X., A limestone reactor for fluoride removal from wastewaters. *Environmental Science & Technology* **2000**, *34*(15), 3247-3253.

[7] Bennajah M.; Gourich, B.; Essadki, A. H.; Vial, C.; Delmas, H., Defluoridation of Morocco drinking water by electrocoagulation/electroflottation in an electrochemical external-loop airlift reactor. *Chem. Eng. J.* **2009**, *148*(1), 122-131.

[8] Castel, C.; Schweizer, M.; Simonnot, M. O.; Sardin, M., Selective removal of fluoride ions by a two-way ion-exchange cyclic process. *Chem. Eng. Sci.* **2000**, *55*(17), 3341-3352.

[9] Kumar, E.; Bhatnagar, A.; Kumar, U.; Sillanpaa, M., Defluoridation from aqueous solutions by nano-alumina: Characterization and sorption studies. *J. Hazard. Mater.* **2011**, *186*(2-3), 1042-1049.

Structural characterisation, spectral and redox studies of novel ruthenium(IV) complex. Potential biological activity.

Agnieszka JABŁOŃSKA-WAWRZYCKA,[a] Patrycja ROGALA,[a] Grzegorz CZERWONKA[b]

[a] Institute of Chemistry, Jan Kochanowski University in Kielce, 15 G Świętokrzyska Str., 25-406 Kielce, Poland, agajw@yahoo.com, agnieszka.jablonska-wawrzycka@ujk.edu.pl
[b] Department of Microbiology, Institute of Biology, Jan Kochanowski University in Kielce, 15G Świetokrzyska Str., 25-406 Kielce, Poland

Ruthenium-based molecules have been studied as promising compounds from both chemical and biological perspectives. Further, an oxidation state of ruthenium is often essential for applicability of these complexes. Thus, Ru(II) and Ru(III) compounds can be used as alternatives to platinum because they are predicted to show antitumor activity and clinical toxicity [1-4]. Ruthenium complexes posses different geometry in comparison to platinum compounds, different oxidation states and can bind to DNA or biological target other than DNA [5]. These biochemical features combine to design improved antitumor drugs with increased potency and reduce side effects.

It should be noticed that less attention have been paid to Ru(IV) complexes and their potential application in medicine [6]. Our studies aim to present the synthesis and characterisation of ruthenium(IV) complexes of pyridine derivatives in order to explore its biological activities such as DNA-binding assay and anti-biofilm activity. We used 2,3-pydcH_2 as ligand because of its versatility as well as its potential antimicrobial and antiviral activity. The complex was formed by reacting mother solution of ruthenium(III) chloride with N,O-donor ligand in experimental conditions. Ruthenium(IV) complex crystallizes in the triclinic space group $P\ \bar{1}$. Tetravalent ruthenium is surrounded by two molecules of monodeprotonated ligand acting as bidentate. The ruthenium ion also coordinates with two chloride anions in *cis* position to give $RuN_2O_2Cl_2$ chromophore. Coordination sphere is distorted octahedral and the form of distortion in the complex involves not only bond-lengths but also apparent bond-angles distortion. The neutral complexes are held together by donor and acceptor bifurcated H-bonds of O-H···O and C-H···Cl type. There are also some π···π contacts which complete the supramolecular architecture. The free ligand and its Ru(IV) complex were screened *in vitro* for their anti-biofilm activity against *Pseudomonas aeruginosa* PAO1. The study of microorganisms growing as a biofilm is justified because the bacteria prefer this form of growth both in the environment as well as during tissue infections. The obtained results indicate that complex is more toxic than 2,3-pydcH_2 under identical experimental conditions. *Pseudomonas aeruginosa* PAO1 biofilm formation assay revealed inhibition of biofilm formation in concentrations above 100 µg/ml (Figure 1). Fully eradication of biofilm was observed in concentration 400 µg/ml. Hypothesis that explains its anti-biofilm activity is that ruthenium complex oxidizes pyocyanin, which was observed by alterations in pyocyanin spectrum after incubation with Ru(IV) complex. Interactions with siderophores of

Pseudomonas aeruginosa PAO1 could be also considered as potential mechanisms anti-bacterial activity *via* iron starvation process. Ruthenium complex revealed DNA binding properties and in high concentrations it acts as DNase. DNA binding assay showed that examined complex binds to DNA. Migration through agarose gel proved that complex do not intercalate double strand DNA where ethidium bromide used as positive control slowed migration of supercoiled and open circle forms of pDsRed2 plasmid.

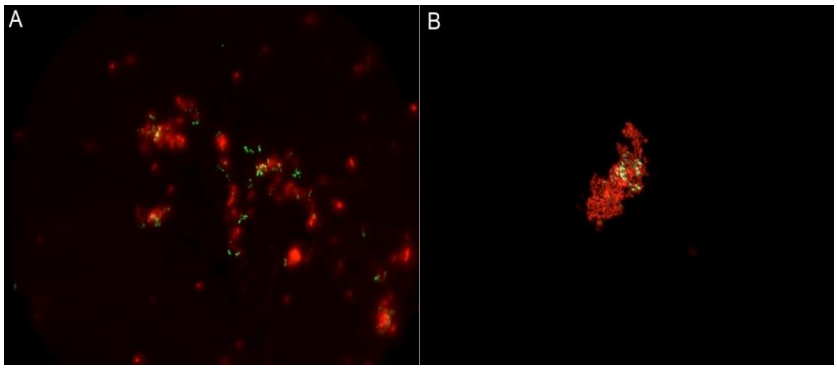


Fig. 1. Representative views of *Pseudomonas aeruginosa* PAO1 biofilm. A) negative control, B) biofilm treated with Ru(IV) complex in concentration 100 µg/ml. Biofilms stained with Live/Dead staining with FilmTracer kit (Invitrogen).

References:

[1] Clarke, M. J., Ruthenium metallopharmaceuticals. *Coord Chem Rev.* **2003,** 236, 209-233.

[2] Antonarakis, E. S.; Emadi, A., Ruthenium-based chemotherapeutics:are they ready for prime time? *Cancer Chemother Pharmacol.* **2010,** 66, 1-9.

[3] Griffith, D.; Cecco, S.; Zangrando, E.; Bergamo, A.; Sava, G.; Marmion, C. J, Ruthenium (III) dimethyl sulfoxide pyridinehydroxamic acid complexes as potential antimetastatic agents: synthesis, characterization and in vitro pharmacological evaluation. *J Bil Inorg Chem.* **2008,** 13, 511-520.

[4] Brabec, V.; Novakova, O., DNA binding mode of ruthenium complexes and relationship to tumor cell toxicity. *Drug Resistance Updates.* **2006,** 9, 111-122.

[5] Allardyce, C. S.; Dyson, P. J., Ruthenium in medicine: current clinical uses and future prospects. *Platinum Metals Rev.* **2001,** 45 (2), 62-69.

[6] Vilaplana, R. A.; Castineiras, A.; Gonzalez-Vichez, F., Synthesis, structure and biological behavior of the complex $[Ru(H_2L)Cl_2]\cdot H_2O$. *Bioinorg Chem Appl* **2004**, 2(3-4), 275-292.

Novel complexes of dissymmetric amidinates

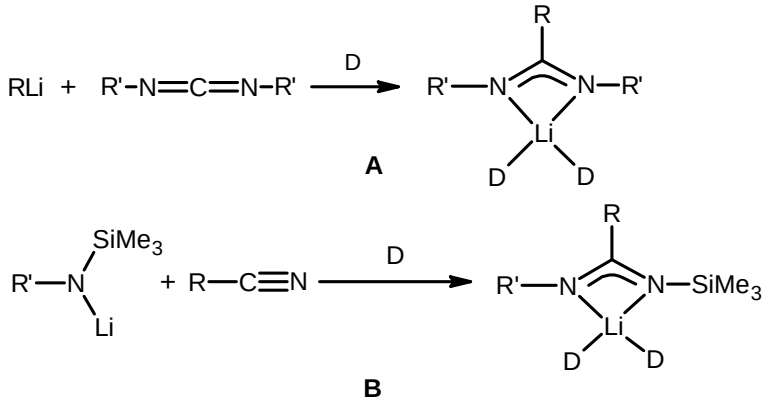
Martin NOVONÝ, Aleš RŮŽIČKA, Zdeňka PADĚLKOVÁ

Department of General and Inorganic Chemistry, Facuty of Chemical Technology, University of Pardubice, Studentská 573, CZ-532 10, Pardubice, Czech Republic;
martin.novotny1@student.upce.cz

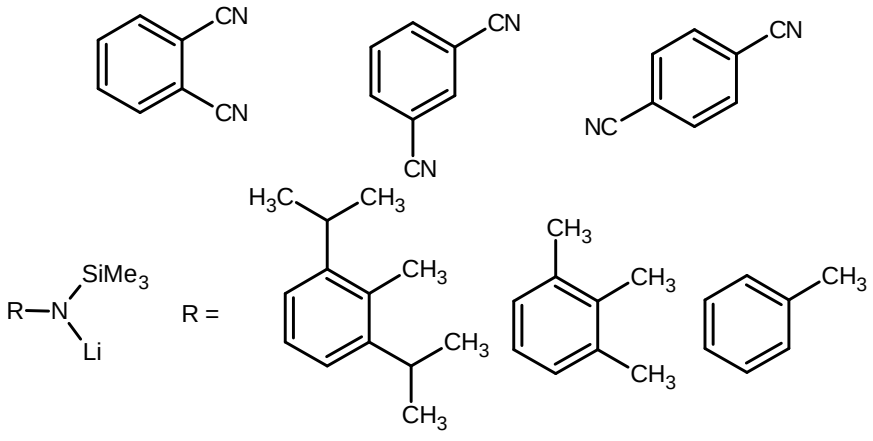
Amidinate complexes, of general formula shown in Scheme 1, are due to their catalytic activity and importance in material science frequently studied compounds. [1][2] Almost all metal complexes of amidinates are prepared from their lithium precursors, therefore study and preparation of lithium amidinates is crucial in this field of chemistry. [3]

Most amidinate complexes are prepared by the reaction shown in Scheme 1A, but due to the lack of bis(carbodiimides), we decided to prepare suggested amidinates by an addition reaction of *N,N'*-disubstitued lithium amide to highly polarized C-N triple bond of carbonitrile moiety with subsequent migration of substituents among the nitrogen atoms.[4]

So far there is no report on prepared dissymetric bis-amidinates connected by amidinate carbon atom via ring or chain. Main idea was to prepare series of amidinates formed by reaction *N*-trimethylsilyl amide with carbodinitriles shown in Scheme 2.



Scheme 1



Scheme 2

Authors would like to thank Czech Science Foundation for financial support.
(Grant No. P207/12/0223)

References:

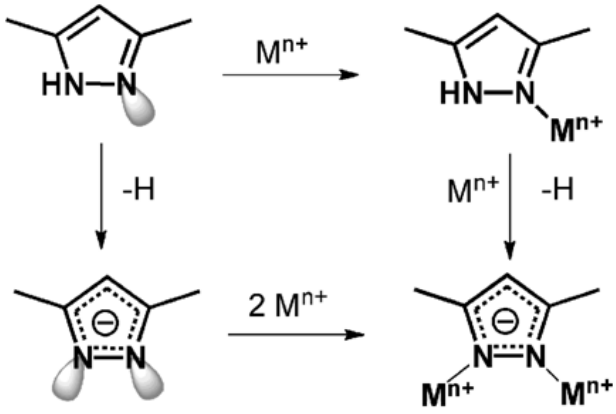
[1] Hagadorn, J. R.; Arnold, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1729.
[2] Brunner, H.; Agrifoglio, G.; Bernal, I.; Creswick, M. W. *Angew. Chem. Int. Ed.* **1980**, *19*, 641.
[3] Edelmann, F. T. In *Adv. in Organom. Chem.*; Anthony, F. H., Mark, J. F., Eds.; Academic Press: **2008**; *57*, 183.
[4] Zhou, M.; Tong, H.; Wei, X.; Liu, D. *J. Organomet. Chem.* **2007**, *692*, 5195.

Binding Modes in 1*H*-pyrazole Coordination Chemistry

Alberto LOPERA,[a] Raquel BELDA,[a] Javier PITARCH-JARQUE,[a] Enrique GARCÍA-ESPAÑA,[a]

[a] *Instituto de Ciencia Molecular, Universidad de Valencia, C/ Catedrático José Beltrán, no.2, 46980 Paterna, Valencia. España; alberto.lopera@uv.es*

1*H*-pyrazole in its neutral form can behave both as a hydrogen bond acceptor and donor, while in its pyrazolate anionic form it can accept two hydrogen bonds from donor groups. When pyrazole coordinates with metals, neutral 1*H*-pyrazole typically acts as a monodentate ligand while as a pyrazolate anion it behaves typically as a bridging bis(monodentate) or exobidentate ligand [1-3].



Herein, we present a series of crystal structures of metallocomplexes obtained depending on the nature of the polyamine ligand, the pH value and the M(II):L molar ratio. Potentiometric titration, EPR measurements and HR-ESI mass spectroscopy support the formation of the same complexes in aqueous solution.

References:

[1] Katrizky, A. R., Rees, C. V., Scriven, E. F. V., *Pyrazoles in Comprehensive Heterocyclic Chemistry II, A Review of the Literature 1982−1995*, Eds.; Pergamon: New York, **1997**; Vol. 3, pp 1−75.

[2] Mukheerjee, R., Coordination chemistry with pyrazole-based chelating ligands: molecular structural aspects. *Coord. Chem. Rev.* **2000**; Vol. 203, pp. 151−258.

[3] Belda R., Pitarch-Jarque J., Soriano C., Llinares José M., Blasco S., Ferrando-Soria J., García-España E., Intermolecular Binding Modes in a Novel [1 + 1] Condensation 1*H*-Pyrazole Azamacrocycle: A Solution and Solid State Study with Evidence for CO2 Fixation. *Inorg. Chem.* **2013**; Vol. 52, pp. 10795-10803.

AUTHORS INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Y

Z