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ISMEC2012

International Symposium on Metal Complexes

Lisbon 18-22 June

* Acta of the International Symposia on Metal Complexes

INSTITUTO SUPERIOR TÉCNICO
Universidade Técnica de Lisboa

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Maria Amélia Santos, Editor

Instituto Superior Técnico, UTL, Lisbon, Portugal

President of the Scientific Committee of ISMEC2012

Guido Crisponi, Editor

University of Cagliari, Italy

President of the ISMEC group

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Foreword

The **International Symposium on Metal Complexes** (**ISMEC2012**) is also the **XXIII Italian-Spanish Congress on Thermodynamics of Metal Complexes**, but over the years there has been an increased number of contributions from all over the world, which rendered in its actual internationalization. The ISMEC2012, held in Lisboa, came up as the first symposium edition out of Spain or Italy. It appeared as a step forward in the ISMEC internationalization, namely based on the 100% increased participation and contributions from 27 countries of 5 continents. This strategic option on the ISMEC symposia will facilitate the creation of many collaborative projects and allow the opening to new cutting edge areas, namely related with the most recent advances on metal complexes in view of a wide range of applications, from environmental to biomedical purposes.
In particular, several topics are presented and discussed under the scope of this meeting, focused on the chemistry and applications of metal complexes.

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

The present edition of ISMEC (ISMEC2012), held from 18th to 22nd June 2012 at Lisboa (Portugal) was organized by Instituto Superior Técnico from Technical University of Lisboa, under the coordination of Prof Maria Amélia Santos (Chair-Person) and the co-coordination of Prof. Sílvia Chaves and Dr. Sérgio Marques.

Thank to the Chairman of previous conference ISMEC2011, Prof. Silvio Sammartano from the University of Messina, a book series has started with the publication of *Acta of ISMEC Symposia (Vol 1)*. The aim of this series is a quick disclosure of the most recent advances of scientific research in the field of the thermodynamics of complexes, by publishing timely comprehensive books developed from our symposia. Every book of the series will be edited both by the President of the Scientific Committee of each ISMEC edition, in collaboration with all other members, and by the President of the ISMEC Group.

Occasionally, other books of the series will be published, but always with the aim of providing readily accessible but accurate information both on the basic aspects and the new findings of chemical research in the same field.

M. Amélia Santos

and

Guido Crisponi

June 2012

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Guido Crisponi	(University of Cagliari, Italy)
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Acta website: http://mat520.unime.it/ismecacta

CONFERENCE PROGRAM

Monday, June 18th

14.00 - 16.25 *Registration of participants*

16.25 – 16.55 *Coffee break*

Auditorium 3

Chairman**: Margarida C. dos Santos**

16.55 – 17.30 *Welcome words*

KN1 - The chemistry behind the use of bioassays to assess metal toxicity: pH influence, complexation equilibria

Isabel Villaescusa

17.30 – 17.50 **OC1 -** Metal leaching capacity of rainwater in an abandoned lead-zinc mine

Ainhoa Tirapu, Leire Kortazar, Naiara Goienaga, Maitane Olivares, Jose Antonio Carrero, Juan Manuel Madariaga, Luis Ángel Fernández

17.50 – 18.10 **OC2 -** Characterization of the interactions between proteinaceous binders and inorganic pigments in paint reconstructions

Ilaria Bonaduce, Emilia Bramanti, Maria Perla Colombini, Celia Duce, Lisa Ghezzi, Alessio Spepi, Maria Rosaria Tinè

18.10 – 18.30 **OC3 -** Insights on the U(VI) speciation with bacterial isolates from Äspö and Mont Terri

Laura Lütke, Henry Moll, Velina Bachvarova, Sonja Selenska-Pobell, Gert Bernhard

19.00 – 20.00 *Welcome reception*

Tuesday, June 19th

8.00 – 9.00 *Registration of participants*

Auditorium 3

9.00 – 9.15 *Opening ceremony*

Chairman: **Guido Crisponi**

9.15 – 10.10 **PL1 -** Redox metals in neurodegenerative diseases, and therapeutic perspectives

Robert R. Crichton, Roberta J.Ward, David T. Dexter

Chairman: **Chris Exley**

10.10 – 10.30 **OC4 -** Histidine-rich branched peptides as copper and zinc chelators with potential therapeutic application in Alzheimer's disease

Andrea Lakatos, Béla Gyurcsik, Nóra V. Nagy, Zita Csendes, Edit Wéber, Lívia Fülöp, Tamás Kiss

10.30 – 10.50 **OC5 -** Biomimetic analogues of siderophores as structural probes for microbial iron uptake processes

Agnieszka Szebesczyk, Jenny Kolsenik, Evgenia Olshvang, Abraham Shanzer, Elzbieta Gumienna-Kontecka

10.50 – 11.20 *Coffee break*

Chairman: **Roberta Ward**

11.20 – 11.50 **KN2 -** Structural and thermodynamic aspects of thiol binding to metal ions in excentric proteins

Henryk Kozlowski, Karolina Krzywoszynska, Slawomir Potocki, Magdalena Rowinska-Zyrek, Danuta Witkowska

Chairman: **Manuel Valiente**

11.50 – 12.10 **OC6 -** A peptidic turn with high affinity for heavy metal ions

Sara Pires, Murat Sezer, Cláudio M. Soares, Lars Hemmingsen, Olga Iranzo

12.10 – 12.30 **OC7 -** Microprotonation and Na(I)/Mg(II)-interaction of inositol 1,3,4,5,6-pentakis phosphate: ^{31}P NMR and computational insights

Nicolás Veiga, Julia Torres, Israel Macho, Kerman Gómez, Gabriel González, Carlos Kremer

12.30 – 14.30 *Lunch break, exhibition and poster viewing*

Chairman: **Chris Orvig**

14.30 – 15.30 **PL2 -** Metal ion selective sequestering agents, with selective properties

Kenneth N. Raymond

Chairman: **Etelka Farkas**

15.30 – 16.00 **KN3 -** Metal complexes defining aluminium's exposome

Chris Exley

16.00 – 16.20 **OC8** - Siderophores - transport properties and environmental stability

Günther Winkelmann

16.20 – 16.40 **OC9** - Actinide complexes incorporating environmentally relevant chelators: a structural, thermodynamic, and kinetic prospect

Michel Meyer

16.40 – 17.10 *Coffee break*

Chairman: **Alexander Shestakov**

17.10 – 17.40 **KN4** - Modeling of molecular properties. Fundamental principles and case studies with transition metal compounds

Peter Comba

17.40 – 18.00 **OC10** - Computational studies of cesium-137 recognition by cucurbituril

Fabio Pichierri

18.00 – 18.20 **OC11** - Protonation sequence of zoledronic acid: a DFT and QTAIM study

Ignacy Cukrowski, Anindita Sarkar, Anton van Aswegen, David Liles

18.20 – 19.30 *Poster session 1*

19.30 – 20.30 *GTC Meeting*

Room 2

Chairman: **Elia Grueso**

10.10 – 10.30 **OC31** - The mechanism of the reaction of gold(III) ion with pyridine-2-azo-p-dimethylaniline in water and SDS

Sabriye Aydinoğlu, Tarita Biver, Fernando Secco, Marcella Venturini

10.30 – 10.50 **OC32** - New synthesis of dinuclear metal complexes which include gold(III), ruthenium(II) and platinum(II), induce apoptosis in cancer cells via activation of mitochondrial pathway

R. Beklem Bostancioglu, A. Tansu Koparal, Kadriye Benkli

10.50 – 11.20 *Coffee break*

Chairman: **Alessandro de Robertis**

11.50 – 12.10 **OC33 -** Tuning the hydrolytic properties of half-sandwich type organometallic cations in aqueous solution

Péter Buglyó, Linda Bíró, Eugenio Garribba, Zsolt Bihari

12.10 – 12.30 **OC34 -** The leaving group of ruthenium arene complexes plays an essential role in biological activity

Natalia Busto, Begoña García, José M. Leal, Héctor J. Lozano, Jesús Valladolid, Gustavo A. Espino, Tarita Biver

12.30 – 14.30 *Lunch break, exhibition and poster viewing*

Chairman: **Igor Nikolayenko**

16.00 – 16.20 **OC35 -** Synergistic effects of copper(II) complexes and cisplatin: an application of artificial neural networks and experimental design

Tiziana Pivetta, Francesco Isaia, Federica Trudu, Alessandra Pani, Matteo Manca, Daniela Perra, Filippo Amato, Josef Havel

16.20 – 16.40 **OC36 -** Reliability of protonation constants and chemical model of drugs using SQUAD(84) and SPECFIT/32 regression analysis of pH-UV/VIS spectra

Milan Meloun

Chairman: **Marian Olazabal**

17.40 – 18.00 **OC37 -** Aqueous complexation and interactions of Nd(III) and Am(III) with citrate in perchlorate media

M. Alex Brown, Alena Paulenova, Artem V. Gelis

18.00 – 18.20 **OC38 -** Neurotoxic effect of nano-alumina on SD rats *in vivo*

Qinli Zhang, Meiqin Li, Li Xu, Xia Jiao, Qiao Niu

Wednesday, June 20th

Auditorium 3

Chairman: **Maria Rangel**

9.10 – 10.10 **PL3 -** Therapeutic and diagnostic metal complexes in medicinal inorganic chemistry

Chris Orvig

Chairman: **Enrique García-España**

10.10 – 10.30 **OC12 -** (Thio)pyrone–derived organometallics: an approach for new metal–based anticancer drugs

Wolfgang Kandioller, Samuel M. Meier, Michael A. Jakupec, Bernhard K. Keppler, Christian G. Hartinger

10.30 – 10.50 **OC13 -** Solution and biological behaviour of fluoroquinolones metalloantibiotics: a route to counteract bacterial resistance?

Maria J. Feio, Paula Gameiro

10.50 – 11.20 *Coffee break*

Chairman: **Juan Niclós-Gutiérrez**

11.20 – 11.50 **KN5 -** Cation, anion and ion-pair binding with branched polyamines

Carla Bazzicalupi, Antonio Bianchi, Claudia Giorgi, Barbara Valtancoli

11.50 – 12.10 **OC14 -** Supramolecular chirogenesis with schiff base complexes: a gateway for determination of absolute configurations

Martha V. Escárcega-Bobadilla, Giovanni Salassa, Sander J. Wezenberg, Arjan W. Kleij

12.10 – 12.30 **OC15 -** Complex formation equilibria of copper(II) with triethylentetramine and its human acetyl metabolites

Guido Crisponi, Valeria M. Nurchi, Miriam Crespo-Alonso, Garth J. S. Cooper

12.30 – 12.50 **OC16 -** Metal complexes of the antitumor drug Triapine and related thiosemicarbazones

Éva A. Enyedy, Christian R. Kowol, Nóra V. Nagy, Éva Zsigó, Tamás Jakusch, Vladimir B. Arion, Bernhard K. Keppler, Tamás Kiss

12.50 – 14.45 *Lunch break*

15.00 –20.00 *Excursion*

Room2

Chairman: **Plinio di Bernardo**

10.10 – 10.30 **OC39 -** Speciation of vanadyl complexes with simple organic ligands in aqueous solutions

Nadira Batool, Danielle Meyrick, Peter May

10.30 – 10.50 **OC40 -** Thermodynamic studies on new copper(I) and silver(I) phosphine complexes with potential antitumor activity

Francesco Endrizzi, Plinio DI Bernardo, Pierluigi Zanonato, Francesco Tisato, Marina Porchia

10.50 – 11.20 *Coffee break*

Chairman: **Rita Delgado**

11.50 – 12.10 **OC41 -** Molecular recognition patterns in ternary copper(II) complexes with deaza-adenine and amino-polycarboxylate ligands

Alicia Domínguez-Martín, Duane Choquesillo-Lazarte, Jose A. Dobado, Isaac Vidal, Josefa M. González-Pérez, Alfonso Castiñeiras, Juan Niclós-Gutiérrez

12.10 – 12.30 **OC42 -** MALDI and SALDI TOF mass spectrometry - fast and efficient way to search for supramolecular complex formation and new drug carriers

Filippo Amato, Eladia Maria Peña-Méndez, Tiziana Pivetta, Reddy Nagender Panyala, Josef Havel

12.30 – 12.50 **OC43 -** Supramolecular systems connecting flavylium moities with metal complexes

Ana M. Diniz, Fernando Pina, A. Jorge Parola

Thursday, June 21st

Auditorium 3

Chairman: **Marilena Tolazzi**

9.10 – 10.10 **PL4** - Metal-based chelates and nanosystems for multimodal molecular imaging applications

Carlos F.G.C. Geraldes

Chairman: **João P. André**

10.10 – 10.30 **OC17** - Equilibrium, kinetic, relaxation and structural properties of H_3DO3A-sulfonamide ligand and its Ca^{2+}, Zn^{2+}, Cu^{2+} and Ln^{3+}-complexes

Zsolt Baranyai, Anett Takács, Balázs Podolyák, Mihály Purgel, Roberta Napolitano, Silvio Aime, Ernő Brücher, Imre Tóth

10.30 – 10.50 **OC18** - Monopicolinate cyclen and cyclam derivatives for stable copper(II) complexation

Luís M. P. Lima, David Esteban-Gómez, Rita Delgado, Carlos Platas-Iglesias, Raphaël Tripier

10.50 – 11.20 *Coffee break*

Chairman: **Antonio Bianchi**

11.20 – 11.50 **KN6** - Macrobicyclic architectures for recognition of anions

Rita Delgado, Pedro Mateus

11.50 – 12.10 **OC19** - Mn(II) chelates with potential interest for MRI

Arsénio de Sá, Célia S. Bonnet, Carlos F. G. C. Geraldes, Eva Tóth, Paula M.T. Ferreira, João P. André

12.10 – 12.30 **OC20** - Binding properties of *p-tert*-butylcalix[4]arene derivatives and their application in ion selective electrodes

Véronique Hubscher-Bruder, Joanna Kulesza, Françoise Arnaud-Neu, Maria Bochenska

12.30 – 14.30 *Lunch break, exhibition and poster viewing*

Chairman: **Fernando Pina**

14.30 – 15.30 **PL5** - Luminescent silica nanoparticles: extending the frontiers of brightness

Sara Bonacchi, Damiano Genovese, Riccardo Juris, Marco Montalti, Enrico Rampazzo, Nelsi Zaccheroni, Luca Prodi

Chairman: **Carlos Geraldes**

15.30 – 16.00 **KN7** - Cation and anion coordination and self-assembling capabilities of 1H-pyrazole containing ligands. Surface modification of nanoparticles

Enrique García-España, Javier Pitarch, Felipe Reviriego, Salvador Blasco, M. Paz Clares, Raquel Belda, José M. Llinares, Javier Alarcón, Estefanía Delgado-Pinar, Pilar Navarro

16.00 – 16.20 **OC21** - BODIPY-phosphane as a versatile tool for an easy access to new metal-based theranostics

Semra Tasan, Olivier Zava, Julien PIerron, Benoît Bertrand, Claire Bernhard, Christine Goze, Michel Picquet, Pierre Le Gendre, Franck Denat, Angela Casini, Ewen Bodio

16.20 – 16.40 **OC22** - Effect of ethanol on gold nanoparticles-induced DNA compaction: thermodynamic, kinetic and conformational aspects of the interaction

Consuelo Cerrillos, Pilar Pérez-Tejeda, Rafael Prado-Gotor, Elia Grueso

16.40 – 17.10 Coffee break

Chairman: **Maurizio Remelli**

17.10 – 17.40 **KN8** - Interaction of hydroxamic acids with metals: from simple complexes to metallacrowns

Maria Rosa Beccia, Tarita Biver, Begoña García, José Maria Leal, Fernando Secco, Matteo Tegoni, Marcella Venturini

17.40 – 18.00 **OC23** - Factors affecting the thermodynamic and redox stability of manganese(II) – and cobalt(II) – hydroxamate complexes

Etelka Farkas, Orsolya Szabó

18.00 – 18.20 **OC24** - Kinetic study of metal complexes with tetraazamacrocyclic ligands with carboxylate/phosphonate pendant arms

Přemysl Lubal, Petr Hermann, Jan Kotek, M. Paula C. Campello, Isabel Santos

18.20 – 19.30 Poster session 2

20.30 Social dinner

Room2

Chairman: **Katalin Várnagy**

10.10 – 10.30 **OC44** - Interaction of vanadate, niobate, molybdate and tungstate oxometalates with calcium pump from sarcoplasmic reticulum: Ca^{2+}-ATPase conformational changes

Manuel Aureliano, Gil Fraqueza, C. André Ohlin, William H. Casey, M. Paula M. Marques, Luís A.E. Carvalho

10.30 – 10.50 **OC45** - Magnesium and nickel metal ions can induce poly(rU)poly(rA)poly(rU) triplexes formation or quadruplexes stabilization

Maria Rosa Beccia, Tarita Biver, Natalia Busto, Begoña García, José Maria Leal, Luisa Menichetti, Fernando Secco, Marcella Venturini

10.50 – 11.20 Coffee break

Chairman: **Jose Maria Leal**

11.50 – 12.10 **OC46 -** Multinuclear cytotoxic metallodrugs: synthesis and biological properties of novel bimetallic ruthenium-titanium and gold-titanium complexes

Margot Wenzel, Benoît Bertrand, Philippe Richard, Michael Groessl, Olivier Zava, Pierre Le Gendre, Michel Picquet, Angela casini

12.10 – 12.30 **OC47**- New polydentate Ru(III)-Salan complexes: synthesis, characterization, anti-tumour activity and interaction with human serum proteins

Cristina P. Matos, Andreia Valente, Fernanda Marques, Pedro Adão, Rodrigo F. M. Almeida, João Costa Pessoa, M. Helena Garcia, Ana Isabel Tomaz

12.30 – 14.30 Lunch break, exhibition and poster viewing

Chairman: **Barbara Barszcz**

16.00 – 16.20 **OC48 -** Tuning structure and properties of Pd and Pt camphorimine complexes

M. Fernanda N. N. Carvalho, Ana S.D. Ferreira, Adelino M. Galvão

16.20 – 16.40 **OC49 -** How CO releasing molecules CO-RMs interact with proteins

Teresa Santos-Silva, Abhik Mukhopadhyay, Marino F. A. Santos, João D. Seixas, Ana C. Coelho, Patrícia M. Reis, Maria J. Romão, Carlos C. Romão

Chairman: **Andrea Gómez-Zavaglia**

17.40 – 18.00 **OC50 -** Mechanism of sulfide ion incorporation into the metal cluster of metallothioneins

Tamara Huber, Eva Freisinger

18.00 – 18.20 **OC51 -** Orange proteins in sulphate reducing bacteria: Mo-Cu heterometallic clusters in proteins involved in cell division

Marta. S.P. Carepo, Raquel Grazina, Cíntia.C.S. Carreira, Corrine Aubert, Allan Dolla, José J.G. Moura, Isabel Moura

Friday, June 22nd

Auditorium 3

Chairman: **Begoña García**

9.10 – 9.40 **KN9 -** Mechanistic modelling of An and Ln extraction by ILs: a first step towards a general model

Isabelle Billard

9.40 – 10.00 **OC25 -** Novel functional materials as Ionic Liquids based on metal complexes

Luis C. Branco, Fernando Pina

10.00 – 10.20 **OC26 -** Grafted squaramide nanoparticle systems for sulfate recognition in pure water

Estefanía Delgado-Pinar, Esther Carbonell, Carmen Rotger, Antoni Costa, M. Neus Piña, Hermas R. Jiménez, Javier Alarcón, Enrique García-España

10.20 – 10.40 **OC27 -** Thermodynamics of protonation and metallation of the TPTZ ligand with a variety of cations

Igor V. Nikolayenko, Robert D. Hancock, Galen C. Littman

10.40 – 11.10 *Coffee break*

Chairman: **Raffaela Biesuz**

11.10 – 11.40 **KN10 -** Chemical speciation in environment and biomedicine: examples to technological development

Manuel Valiente

11.40 – 12.00 **OC28 -** Modeling of Sn^{2+} speciation in aqueous solution, with particular reference to natural fluids

Clemente Bretti, Rosalia Maria Cigala, Francesco Crea, Concetta De Stefano, Gabriele Lando, Demetrio Milea, Silvio Sammartano

12.00 – 12.20 **OC29 -** DMT and AGNES: determination of free Zn(II) concentrations in synthetic systems, in river water and in soils

Diana Chito, Encarna Companys, Josep Galceran, Mireia Lao, Jaume Puy, Liping Weng, Willem H. van Riemsdijk, Herman P. van Leeuwen

Chairman: **Maurizio Remelli**

12.20 – 12.45 **OC30 (Pulidori award) -** Molecular reorganisations in polytopic receptors

Jorge González, Raquel Gavara, Carmen E. Castillo, J. M. Llinares, H. Jimenez, M. A. Mañez, Fernando Pina, M. G. Basallote, Enrique García-España

12.45 – 13.15 *Closing remarks and presentation of ISMEC2013*

LIST OF COMMUNICATIONS

Plenary Lectures

PL1 - Redox metals in neurodegenerative diseases, and therapeutic perspectives
Robert R. Crichton, Roberta J.Ward, David T. Dexter

PL2 - Metal ion selective sequestering agents, with selective properties
Kenneth N. Raymond

PL3 - Therapeutic and diagnostic metal complexes in medicinal inorganic chemistry
Chris Orvig

PL4 - Metal-based chelates and nanosystems for multimodal molecular imaging applications
Carlos F.G.C. Geraldes

PL5 - Luminescent silica nanoparticles: extending the frontiers of brightness
Sara Bonacchi, Damiano Genovese, Riccardo Juris, Marco Montalti, Enrico Rampazzo, Nelsi Zaccheroni, Luca Prodi

Keynote Lectures

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Isabel Villaescusa

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Christopher Exley

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Isabelle Billard

KN10 - Chemical speciation in environment and biomedicine: examples to technological development
Manuel Valiente

Oral Communications

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Ainhoa Tirapu, Leire Kortazar, Naiara Goienaga, Maitane Olivares, Jose Antonio Carrero, Juan Manuel Madariaga, Luis Ángel Fernández

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OC3 - Insights on the U(VI) speciation with bacterial isolates from Äspö and Mont Terri
Laura Lütke, Henry Moll, Velina Bachvarova, Sonja Selenska-Pobell, Gert Bernhard

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Andrea Lakatos, Béla Gyurcsik, Nóra V. Nagy, Zita Csendes, Edit Wéber, Lívia Fülöp, Tamás Kiss

OC5 - Biomimetic analogues of siderophores as structural probes for microbial iron uptake processes
Agnieszka Szebesczyk, Jenny Kolsenik, Evgenia Olshvang, Abraham Shanzer, Elzbieta Gumienna-Kontecka

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Sara Pires, Murat Sezer, Cláudio M. Soares, Lars Hemmingsen, Olga Iranzo

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OC9 - Actinide complexes incorporating environmentally relevant chelators: a structural, thermodynamic, and kinetic prospect
Michel Meyer

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Fabio Pichierri

OC11 - Protonation sequence of zoledronic acid: A DFT and QTAIM Study
Ignacy Cukrowski, Anindita Sarkar, Anton van Aswegen, David Liles

OC12 - (Thio)pyrone–derived organometallics: an approach for new metal–based anticancer drugs
Wolfgang Kandioller, Samuel M. Meier, Michael A. Jakupec, Bernhard K. Keppler, Christian G. Hartinger

OC13 - Solution and biological behaviour of fluoroquinolones metalloantibiotics: a route to counteract bacterial resistance?
Maria J. Feio, Paula Gameiro

OC14 - Supramolecular chirogenesis with schiff base complexes: a gateway for determination of absolute configurations
Martha V. Escárcega-Bobadilla, Giovanni Salassa, Sander J. Wezenberg, Arjan W. Kleij

OC15 - Complex formation equilibria of copper(II) with triethylentetramine and its human acetyl metabolites
Guido Crisponi, Valeria M. Nurchi, Miriam Crespo-Alonso, Garth J. S. Cooper

OC16 - Metal complexes of the antitumor drug Triapine and related thiosemicarbazones
Éva A. Enyedy, Christian R. Kowol, Nóra V. Nagy, Éva Zsigó, Tamás Jakusch, Vladimir B. Arion, Bernhard K. Keppler, Tamás Kiss

OC17 - Equilibrium, kinetic, relaxation and structural properties of H_3DO3A-sulfonamide ligand and its Ca^{2+}, Zn^{2+}, Cu^{2+} and Ln^{3+}-complexes
Zsolt Baranyai, Anett Takács, Balázs Podolyák, Mihály Purgel, Roberta Napolitano, Silvio Aime, Ernő Brücher, Imre Tóth

OC18 - Monopicolinate cyclen and cyclam derivatives for stable copper(II) complexation
Luís M. P. Lima, David Esteban-Gómez, Rita Delgado, Carlos Platas-Iglesias, Raphaël Tripier

OC19 - Mn(II) chelates with potential interest for MRI
Arsénio de Sá, Célia S. Bonnet, Carlos F. G. C. Geraldes, Eva Tóth, Paula M.T. Ferreira, João P. André

OC20 - Binding properties of *p-tert*-butylcalix[4]arene derivatives and their application in ion selective electrodes
Véronique Hubscher-Bruder, Joanna Kulesza, Françoise Arnaud-Neu, Maria Bochenska

OC21 - BODIPY-phosphane as a versatile tool for an easy access to new metal-based theranostics
Semra Tasan, Olivier Zava, Julien PIerron, Benoît Bertrand, Claire Bernhard, Christine Goze, Michel Picquet, Pierre Le Gendre, Franck Denat, Angela Casini, Ewen Bodio

OC22 - Effect of ethanol on gold nanoparticles-induced DNA compaction: thermodynamic, kinetic and conformational aspects of the interaction
Consuelo Cerrillos, Pilar Pérez-Tejeda, Rafael Prado-Gotor, Elia Grueso

OC23 - Factors affecting the thermodynamic and redox stability of manganese(II) – and cobalt(II) – hydroxamate complexes
Etelka Farkas, Orsolya Szabó

OC24 - Kinetic study of metal complexes with tetraazamacrocyclic ligands with carboxylate/phosphonate pendant arms
Přemysl Lubal, Petr Hermann, Jan Kotek, M. Paula C. Campello, Isabel Santos

OC25 - Novel functional materials as Ionic Liquids based on metal complexes
Luis C. Branco, Fernando Pina

OC26 - Grafted squaramide nanoparticles systems for sulfate recognition in pure water
Estefanía Delgado-Pinar, Esther Carbonell, Carmen Rotger, Antoni Costa, M. Neus Piña, Hermas R. Jiménez, Javier Alarcón, Enrique García-España

OC27 - Thermodynamics of protonation and metallation of the TPTZ ligand with a variety of cations
Igor V. Nikolayenko, Robert D. Hancock, Galen C. Littman

OC28 - Modeling of Sn^{2+} speciation in aqueous solution, with particular reference to natural fluids
Clemente Bretti, Rosalia Maria Cigala, Francesco Crea, Concetta De Stefano, Gabriele Lando, Demetrio Milea, Silvio Sammartano

OC29 - DMT and AGNES: determination of free Zn(II) concentrations in synthetic systems, in river water and in soils
Diana Chito, Encarna Companys, Josep Galceran, Mireia Lao, Jaume Puy, Liping Weng, Willem H. van Riemsdijk, Herman P. van Leeuwen

OC30 - Molecular reorganisations in polytopic receptors
Jorge González, Raquel Gavara, Carmen E. Castillo, J. M. Llinares, H. Jimenez, M. A. Mañez, Fernando Pina, M. G. Basallote, Enrique García-España

OC31 - The mechanism of the reaction of gold(III) ion with pyridine-2-azo-p-dimethylaniline in water and SDS
Sabriye Aydinoğlu, Tarita Biver, Fernando Secco, Marcella Venturini

OC32 - New synthesis dinuclear metal complexes which including gold(III), ruthenium(II) and platinum(II), induce apoptosis in cancer cells via activation of mitochondrial pathway
R. Beklem Bostancioglu, A. Tansu Koparal, Kadriye Benkli

OC33 - Tuning the hydrolytic properties of half-sandwich type organometallic cations in aqueous solution
Péter Buglyó, Linda Bíró, Eugenio Garribba, Zsolt Bihari

OC34 - The leaving group of ruthenium arene complexes plays an essential role in biological activity
Natalia Busto, Begoña García, José M. Leal, Héctor J. Lozano, Jesús Valladolid, Gustavo A. Espino, Tarita Biver

OC35 - Synergistic effects of copper(II) complexes and cisplatin: an application of artificial neural networks and experimental design
Tiziana Pivetta, Francesco Isaia, Federica Trudu, Alessandra Pani, Matteo Manca, Daniela Perra, Filippo Amato, Josef Havel

OC36 - Reliability of protonation constants and chemical model of drugs using SQUAD(84) and SPECFIT/32 regression analysis of pH-UV/VIS spectra
Milan Meloun

OC37 - Aqueous complexation and interactions of Nd(III) and Am(III) with Citrate in perchlorate media
M. Alex Brown, Alena Paulenova, Artem V. Gelis

OC38 - Neurotoxic effect of nano-alumina on SD rats *in vivo*
Qinli Zhang, Meiqin Li, Li Xu, Xia Jiao, Qiao Niu

OC39 - Speciation of vanadyl complexes with simple organic ligands in aqueous solutions
Nadira Batool, Danielle Meyrick, Peter May

OC40 - Thermodynamic studies on new copper(I) and silver(I) phosphine complexes with potential antitumor activity
Francesco Endrizzi, Plinio DI Bernardo, Pierluigi Zanonato, Francesco Tisato, Marina Porchia

OC41 - Molecular recognition patterns in ternary copper(II) complexes with deaza-adenine and amino-polycarboxylate ligands
Alicia Domínguez-Martín, Duane Choquesillo-Lazarte, Jose A. Dobado, Isaac Vidal, Josefa M. González-Pérez, Alfonso Castiñeiras, Juan Niclós-Gutiérrez

OC42 - MALDI and SALDI TOF mass spectrometry - fast and efficient way to search for supramolecular complex formation and new drug carriers

Filippo Amato, Eladia Maria Peña-Méndez, Tiziana Pivetta, Reddy Nagender Panyala, Josef Havel

OC43 - Supramolecular systems connecting flavylium moities with metal complexes
Ana M. Diniz, Fernando Pina, A. Jorge Parola

OC44 - Interaction of vanadate, niobate, molybdate and tungstate oxometalates with calcium pump from sarcoplasmic reticulum: Ca^{2+}-ATPase conformational changes
Manuel Aureliano, Gil Fraqueza, C. André Ohlin, William H. Casey, M. Paula M. Marques, Luís A.E. Carvalho

OC45 - Magnesium and nickel metal ions can induce poly(rU)poly(rA)poly(rU) triplexes formation or quadruplexes stabilization
Maria Rosa Beccia, Tarita Biver, Natalia Busto, Begoña García, José Maria Leal, Luisa Menichetti, Fernando Secco, Marcella Venturini

OC46 - Multinuclear cytotoxic metallodrugs: synthesis and biological properties of novel bimetallic ruthenium-titanium and gold-titanium complexes
Margot Wenzel, Benoît Bertrand, Philippe Richard, Michael Groessl, Olivier Zava, Pierre Le Gendre, Michel Picquet, Angela casini

OC47- New polydentate Ru(III)-Salan complexes: synthesis, characterization, anti-tumour activity and interaction with human serum proteins
Cristina P. Matos, Andreia Valente, Fernanda Marques, Pedro Adão, Rodrigo F. M. Almeida, João Costa Pessoa, M. Helena Garcia, Ana Isabel Tomaz

OC48 - Tuning structure and properties of Pd and Pt camphorimine complexes
M. Fernanda N. N. Carvalho, Ana S.D. Ferreira, Adelino M. Galvão

OC49 - How CO Releasing Molecules CO-RMs interact with proteins
Teresa Santos-Silva, Abhik Mukhopadhyay, Marino F. A. Santos, João D. Seixas, Ana C. Coelho, Patrícia M. Reis, Maria J. Romão, Carlos C. Romão

OC50 - Mechanism of sulfide ion incorporation into the metal cluster of metallothioneins
Tamara Huber, Eva Freisinger

OC51 - Orange proteins in sulphate reducing bacteria: Mo-Cu heterometallic clusters in proteins involved in cell division
Marta. S.P. Carepo, Raquel Grazina, Cíntia.C.S. Carreira, Corrine Aubert, Allan Dolla, José J.G. Moura, Isabel Moura

Poster Communications

P1 - Equilibrium and kinetic studies on copper(II) complexes of scorpiand-like ligands
Carmen E. Castillo, M. Angeles Máñez, Manuel G. Basallote, M. Paz Clares, Salvador Blasco, Enrique García-España

P2 - Full characterization of synthetic *pheomelanins*, and its complexation by Cu(II) ion
Thiago G. Costa, Bruno Szpoganicz, Mateus Feldhaus, Maria M. Humanes, Olinda Monteiro, Gustavo Micke, David Fonseca, Giovanni Caramori

P3 - Mixed transition metal complexes of model peptides related to the metal binding site of prion protein
Ildikó Turi, Imre Sóvágó

P4 - Solution studies on antitumor gallium(III) complexes and their interactions with human serum proteins
Orsolya Dömötör, Erika Varga, Krisztina Bali, Christian G. Hartinger, Bernhard B. Keppler, Tamás Kiss, Éva A. Enyedy

P5 - Coordination ability of small multihistidine peptides
Katalin Várnagy, Sarolta Timári, Dóra Serfőző, József Asztalos, Mariann Kiss

P6 - Potentiometric studies and stability constants of manganese(II), cobalt(II), nickel(II) and copper(II) complexes with a ligand derived from 1,2,4 triazole
Nawel Lechani, Maamar Hamdi, Fahima Aklil, Samia Khabouche, Ouassini Benali Baitich

P7 - Mixed thiophene-phenanthroline Cu(II) complexes: synthesis, equilibria and cytotoxicity
Federica Trudu, Tiziana Pivetta, Francesco Isaia, Eva Antoniotti, M. Grazia Cabiddu, Matteo Manca, Daniela Perra, Alessandra Pani

P8 - Redox reactions of the peroxomonosulfate ion in the ferroin/ferriin system
Gábor Bellér, Gábor Lente, István Fábián

P9 - Cross-bridged cyclen derivative: synthesis, acid-base and metal complexation studies
Catarina V. Esteves, Luís M. P. Lima, Rita Delgado

P10 - Substituent effect on the stability of iron(III)-salicylate complexes. Structure of *trans*-$[Fe(H5Nsal)_2(H_2O)_2]Cl{\cdot}2H_2O$
Valeria M. Nurchi, Guido Crisponi, Miriam Crespo-Alonso, Alicia Domínguez-Martín, Josefa M. González-Pérez, Juan Niclos-Gutierrez, Alfonso Castineiras

P11 - Control of copper(II) complexes speciation and properties by harnessing the flexible nature of peptidic ligands
Ana Fragoso, Pedro Lamosa, Rita Delgado, Olga Iranzo

P12 - The mutual separation of rare earth elements etilizing the reaction of corresponding complexes coordinated by Tris(2-aminoethyl)amine with 2-hydroxy-3-methoxybenzaldehyde
Masatoshi Kanesato, Yuuta Fujimoto, Ayumi Kashiwada, Kiyomi Matsuda, Yoshihiro Kikkawa, Yoriko Sonoda, Midori Goto

P13 - Systematic studies of dimeric gold(I)-NHC-complexes
Stefanie Kobialka, Christina Mueller, Marianne Engeser

P14 - Use of amino–polycarboxylic chelating agents for the sequestration of $(CH_3)Hg^+$ ion in aqueous solution
Salvatore Cataldo, Concetta De Stefano, Antonio Gianguzza, Alberto Pettignano

P15 - Some solution thermodynamic properties of penicillin derivatives. The effect of ionic strength and temperature on the solubility and acid-base properties of the amoxycillin, ampicillin and 6-aminopenicillanic acid
Francesco Crea, Daniela Cucinotta, Demetrio Milea, Silvio Sammartano and Giuseppina Vianelli

P16 - The evaluation of the water infiltration chemical attack in building materials by spectroscopic techniques: raman and DRIFT
Olivia Gómez-Laserna, Iker Arrizabalaga, Nagore Prieto-Taboada, Marian Olazabal, Gorka Arana, Juan Manuel Madariaga

P17 - Coordination chemistry of copper(II) complexes with heteroaromatic alcohols. Synthesis, spectroscopic characterization and antioxidant activity studies
Barbara Barszcz, Maciej Hodorowicz, Joanna Masternak, Katarzyna Michalska, Kinga Dumin

P18 - Factors controlling the structures of Cu(II) and Cd(II) complexes obtained *in situ* using 1-hydroxymethyl-3,5-dimethylpyrazole as a starting ligand
Barbara Barszcz, Joanna Masternak, Wanda Sawka-Dobrowolska, Angelika Kamizela

P19 - Interaction of divalent cations with Park9 protein fragments
Maurizio Remelli, Massimiliano Peana, Serenella Medici, Roberto Anedda, Maria Antonietta Zoroddu

P20 - Preparation and characterization of the polydentate Schiff base derived from 2,6-diformyl-4-methylphenol and N-aminopyrimidine-2-thione and its metal complexes
Mehmet Gülcan, Metin Çelebi, Mehmet Sönmez

P21 - Kinetics and mechanism of the reaction between a Mn(III) porphyrin and *N*-hydroxyurea in aqueous solution
József Kalmár, Bernadett BIRI, Gábor Lente, István Bányai, István Fábián, Ana Budimir, Mladen Biruš, Ines Batinić-Haberle

P22 - Kinetic studies on the light-induced water splitting catalyzed by the Ce(III)/Ce(IV) redox system

Éva Józsa, Ádám Péter Pap, Judit Michnyóczki, Katalin Ősz

P23 - Oxidative dehydrogenation of an Fe(II) complex with a scopiand-type ligand
Laura Acosta-Rueda, Manuel G. Basallote, M. Paz Clares, Conxa Soriano, Salvador Blasco, Enrique García-España

P24 - Coordination abilities of mono and multi-histidinic and glutamate peptide fragments towards manganese(II) and cobalt(II)
Maria Antonietta Zoroddu, Massimiliano Peana, Serenella Medici, Costantino Solinas, Claudia Juliano, Roberto Anedda, Valeria M. Nurchi, Guido Crisponi

P25 - Synthesis, structural characterization, catalytic and thermal investigations of multidentate Schiff base ligand derived from pyrimidine compound and its metal complexes
Mehmet Gülcan, Esin İspir, Mehmet Sönmez

P26 - Structural studies on the interaction of group 12 metal ions with the water soluble 8-hydroxy-sulfo-quinoline
M. Luísa Ramos, Licínia L.G. Justino, Adriana Branco, Sofia M. Fonseca, Hugh D. Burrows

P27 - Liquid chromatography combined with elemental and molecular mass spectrometry for analysis of phytosiderophores and metal-phytosiderophore complexes in the context of strategy II iron acquisition by plants
Yvonne Schindlegger, Anna Regelsberger, Madeleine Dell'mour, Gunda Koellensperger, Walter D. C. Schenkeveld, Stephan M. Kraemer, Eva Oburger, Barbara Gruber, Markus Puschenreiter, Stephan Hann

P28 - Kojic derivatives: a promising class of iron(III) chelators
Leonardo Toso, Sérgio M. Marques, Valeria M. Nurchi, M. Amélia Santos, Guido Crisponi

P29 - Alkylamine-bearing N-heterocyclic chelators for hard metal ions
Anabela Capelo, Laurinda Areias, M. Alexandra Esteves, Lurdes Gano, Sílvia Chaves, M. Amélia Santos

P30 – Bifunctional iron-chelators with protective roles against neurodegenerative diseases
Andreia Nunes, Ranganath Keri, Sérgio M. Marques, Sílvia Chaves, M. Amélia Santos

P31 - A tripodal hydroxypyrimidinone-Gd chelate for potential diagnostic use
Sílvia Chaves, Anabela Capelo, Laurinda Areias, Sérgio M. Marques, M. Alexandra Esteves, M. Amélia Santos

P32 - The effect of N-methylimidazole on the reactivity of a model complex for compound II. A combined experimental and theoretical study
Maria Oszajca, Agnieszka Drzewiecka-Matuszek, Alicja Franke, Małgorzata Brindell, Dorota Rutkowska-Zbik, Małgorzata Witko, Grażyna Stochel, Rudi Van Eldik

P33 - Synthesis, photophysical properties and DFT calculation of bright-blue luminescent of Zn(II) complex with 7-amino-2-methylchromone
Bogumiła Kupcewicz, Anna Kaczmarek-Kędziera, Karin Lux, Elżbieta Budzisz

P34 - NMR and density functional theory characterization of the structures of oxoperoxo vanadium(V) complexes of L-malic and L-tartaric acids
Licínia L.G. Justino, M. Luísa Ramos, Hugh D. Burrows

P35 - Determination of the number of complex in equilibrium mixture
Zuzana Ferenčíková, Milan Meloun

P36 - DFT study of the interaction of heavy metal ions with thioethers.
Andrea Melchior, Elena Peralta, Marilena Tolazzi, Manuel Valiente

P37 - Using the MS-Excel™ spreadsheet in potentiometric studies ofcomplex formation equilibria: PKPOT_L1 functions
José Luis Beltrán

P38 - Protonation sequence of risedronic acid: experimental and theoretical studies
Clemente Bretti, Concetta De Stefano, Gabriele Lando, Ignacy Cukrowski

P39 - Novel N,O-chelated rare earth metal complexes with luminescent activity: DFT analysis of structure luminescent properties relationship
Alexander F. Shestakov

P40 - Ruthenium complexes in different oxidation states. Synthesis, crystal structure, spectra and magnetic characterization
Agnieszka Jabłońska-Wawrzycka, Patrycja Rogala, Maciej Hodorowicz, Barbara Barszcz

P41 - Solid-state studies of manganese(II) complexes with chelating alcohol and aldehyde. Crystal structure, spectroscopic, magnetic and thermal behaviors
Agnieszka Jabłońska-Wawrzycka, Małgorzata Zienkiewicz, Katarzyna Stadnicka, Maciej Hodorowicz, Julia Jezierska, Andrzej Ożarowski, Barbara Barszcz, Dagmara Galas

P42 - Comparison of crystal structure of Ca(II) complexes with heterocyclic alcohol, aldehyde and carboxylate ligands and their cadmium analogues
Joanna Masternak, Barbara Barszcz, Maciej Hodorowicz, Ewa Matczak-Jon, Agnieszka Jabłońska-Wawrzycka, Agnieszka Borek, Anna Fulara

P43 - Nickel speciation in xylem sap of endemic and facultative species of serpentine soils
Sheila Alves, Cristina Nabais, Maria de Lurdes S. Gonçalves, Margarida M. Correia dos Santos

P44 - The use of chemometrics for classification and calibration of seawater using the H^+ affinity spectrum
Elisa Astigarraga, Luis Ángel Fernández, Naiara Goienaga, Leire Kortazar, Janire Sáez, Ainhoa Tirapu

P45 - The interaction mechanism of gold(III) with the metal extractant PADA in DTAC micellar medium and applications to gold(III) extraction
Sabriye Aydinoğlu, Tarita Biver, Fernando Secco, Marcella Venturini

P46 - Speciation and bioavailability of Cd in freshwater bivalves – effect of the TiO_2 nanoparticles
Gonçalo Vale, Margarida M. Correia dos Santos, Rute F. Domingos

P47 - Dissolution and aggregation of various ZnO nanoparticles – effects of pH, ionic strength and concentration
Carlos E. Monteiro, Kevin J. Wilkinson , Rute F. Domingos

P48 - Stability of CdTe/CdS quantum dots – role of pH and small organic ligands
Cristiana Franco, José P. Pinheiro, Rute F. Domingos

P49 - Thermodynamics and kinetics of the dissolution of ZnO nanoparticles followed by AGNES
Calin David, Sara Cruz-González, José Salvador, Josep Monné, José Luís Garcés, Joan Cecilia, Sandrine Mongin, Encarna Companys, Jaume Puy, Carlos Rey-Castro, Josep Galceran

P50 - Boron removal from aqueous solutions using alginate gel beads in fixed-bed systems
Hary Demey-Cedeño, Montserrat Ruiz Planas, Lourdes Roset, Carlos Tobalina, Sergio Castro, Jesús Alberto Barron-Zambrano, Ana M. Sastre

P51 - Role of surface biomolecules in the heavy metals sequestrant capacity of lactic acid bacteria. A Vibrational Spectroscopy study
Esteban Gerbino, Pablo Mobili, E. Elizabeth Tymczyszyn, Cuauhtémoc Araujo-Andrade, Claudio Frausto Reyes, Rui Fausto, Andrea Gómez-Zavaglia

P52 - Metal-sorption based on hydroxypyrimidinone functionalized solid supports
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P53 - Application of cork as sorbent of azo-dyes in coloured effluents
Valeria M. Nurchi, Miriam Crespo-Alonso, Delara Mansoori, Valentina De Maria, Elena Cau

P54 - Arsenic sorption onto natural, modified and synthetic sorbents
Linda Ansone, Maris Klavins, Linda Eglite

P55 - Effect of pH on Cu(II) and Cr(VI) removal by using exhausted coffee in a batch reactor
Chang Liu, Jordi Poch, Núria Fiol, Florencio De La Torre, Tianhu Chen, Isabel Villaescusa

P56 - Chromium (VI) sorption onto granulated cork from *Quercus suber* and *Quercus cerris*
Ali Şen, M. Àngels Olivella, Núria Fiol, Isabel Miranda, Isabel Villaescusa, Helena Pereira

P57 - Supramolecular receptors in solid phase: developing sensors for anionic radionuclides
Valeria Amendola, Giancarla Alberti, Greta Bergamaschi, Roberta Colleoni, Raffaela Biesuz

P58 - Synthesis of a water soluble naphthalimide modified 3-hydroxy-4-pyridinone metal ion sensor
Tânia Moniz, Carla Queirós, Rita Ferreira, Andreia Leite, Ana M.G. Silva, Maria Rangel

P59 - Kinetic gas-phase studies on the reaction of ferracyclobutadienes with alkynes
Yvonne Lorenz, Marianne Engeser, Ujjal Das, Alexander C. Filippou

P60 - Optimization of the spectrometric determination of Cr(III) with a SIA system combined with a dilutor-autosampler
Florencio De La Torre, Lindy Reunes, Núria Fiol, Isabel Villaescusa

P61 - Ferrocene-glutatione conjugates as electrochemical sensors for human Glutathione S-transferase P1-1
Indalecio Quesada-Soriano, Manuel C. Martos-Maldonado, Inmaculada Feria-Fernández, Federico García-Maroto, Antonio Vargas-Berenguel, Luís García-Fuentes

P62 - Development of catechol-based fluorescent chemosensors. Synthesis and evaluation of metal ion sensing behaviour
C. Queirós, A. M. G. Silva, M. Rangel

P63 - "Turn-on" sensor based on the opening of the spirocyclic form of rhodamine B
A. Leite, A. M. G. Silva, L. C. Silva, P. Gameiro, M. Rangel

P64 - Microwave-assisted synthesis of catechol-based rosamines for metal sensing
A. L. Amorim, A. Leite, A. M. G. Silva, B. de Castro, M. Rangel

P65 - Zigzag 1D-copper(II) polymer with alternating bridging units of two different ligands: Synthesis, crystal structure and properties of $\{[Cu_2(\mu_2\text{-trans-1,4-CDTA})(\mu_2\text{-4,4'-bipy})(H_2O)_2]\cdot 4H_2O\}_n$
Hanan El Bakkali, Duane Choquesillo-Lazarte, Elena Bugella-Altamirano, Josefa María González-Pérez, Alfonso Castiñeiras, Juan Niclós-Gutiérrez

P66 - Recognition properties of polyazapolyoxa heteroditopic macrobicyclic compounds
Pedro Mateus, Rita Delgado, Patrick Groves, Paula Brandão, Vítor Félix

P67 - Lanthanide cation binding properties of homooxacalixarenes bearing pyridyl pendant groups at the lower rim
Paula M. Marcos, Filipa A. Teixeira, Manuel A. P. Segurado, José R. Ascenso, Véronique Hubscher-Bruder

P68 - Transition and heavy metal ions complexation by *p-tert*-butylhexahomotrioxacalix[3]arene tri(2-pyridylmethoxy) derivatives
Filipa A. Teixeira, Paula M. Marcos, Véronique Hubscher-Bruder, Françoise Arnaud-Neu, José R. Ascenso, Raul J. Bernardino

P69 - A new polycentred heptacopper(II)/adenine complex: synthesis and characterization of $[Cu_7(\mu_2\text{-}O)_6(\mu_3\text{-}O)_6(adenine)_6](NO_3)_y.xH_2O$
Paula Brandão, Bárbara Ferreira, Teresa M. Santos, Vítor M. Félix

P70 - Different crystallization modes of dinuclear copper(II) complexes of an azacryptand containing *1H*-pyrazole units, depending copper salts, solvents and pH
Javier Pitarch, Raquel Belda, Salvador Blasco, Jesús Ferrando-Soria, Francisco Lloret, Pilar Navarro, Enrique García-España

P71 - Design of Co(II) metal - organic frameworks
Alessandro De Robertis, Giuseppe Bruno, Viviana Mollica Nardo, Francesco Nicolò

P72 - Study of metal cyano "supercomplexes" with a new macrocyclic bipyridinophane
Sandra Gago, Jorge González, Salvador Blasco, A. Jorge Parola, Enrique García-España, Fernando Pina

P73 - Rotaxanes and catenanes containing units of azamacrocyclic complexes of Cu(II) and Ni(II)
Mateusz Woźny, Iwona Mames, Bohdan Korybut-Daszkiewicz

P74 - Molecular necklaces containing transition metal ions
Iwona Mames, Mateusz Woźny, Bohdan Korybut-Daszkiewicz

P75 - Amphiphilic phthalocyanines by three different substituents on each benzo moiety
Özge Kurt, Ahmet Gül, Makbule Burkut Koçak

P76 - Study of the interactions of PyCHO with SDS and CTACl micelles
J. Antonio Lebron, Manuel Lopez-Lopez, Francisco Sanchez, Eva Bernal

P77 - Mixed-monolayer gold nanoparticles for targeted MRI: synthesis and characterization
Janaína Gonçalves, Miguel F. Ferreira, Paula M. Ferreira, Carlos F. G. C. Geraldes, Lothar Helm, José A. Martins

P78 - Possible overestimation of the site size in fluorescent dye/nucleic acid systems when using the McGhee and von Hippel equation
Tarita Biver, Matteo Lari, Fernando Secco, Marcella Venturini

P79 - Complexation abilities of (1-4, 18-36) neuropeptide K toward copper(II) ions and products of metal-catalyzed oxidation
Marta Pietruszka, Elżbieta Jankowska, Teresa Kowalik-Jankowska

P80 - Monitoring of the Ag complexes interactions with biomolecules: the targets of activity identification.
Iryna Goncharova

P81 - Interaction of anticancer ruthenium complex NAMI-A with apo-transferrin.
Olga Mazuryk, Małgorzata Brindell, Katarzyna Kurpiewska, Grażyna Stochel

P82 - Anticancer Au(III) complexes: synthesis and biological characterization
Julien Pierron, Andreia Almeida, Paul J. Dyson, Angela Casini

P83 - Structure, cytotoxic activity and DNA binding of Pd(II) complexes bearing N'-methyl-1-thiocarbamoyl-3,5-dimethylpyrazole
Carolina V. Barra, Sahra C. Lemos, Fillipe V. Rocha, Olga Novakova, Lenka Zerzankova, Barbora Liskova, Viktor Brabec, Adelino V. G. Netto, Antonio E. Mauro, Regina C. G. Frem

P84 - New copper (I/II) complexes: synthesis, crystal structure and cytotoxic properties
Bárbara Ferreira, Bruno Valente, Margarida Meireles, Marli Santo, Paula Brandão, Teresa Santos, Vitor Félix

P85 - Vanadium and copper Schiff base complexes: evaluation of the interaction with HSA and DNA and its cytoxicity
João Costa Pessoa, Somnath Roy, Sladjana Borovic, Sameena Mehtab, Isabel Cavaco, Nataliya Butenko, Rodrigo F.M. Almeida, Ana Isabel Tomaz, M. Helena V. Garcia, Fernanda Marques, Virtudes Moreno, Isabel Correia

P86 - Interaction between monomers of a double-tailed surfactant derived of the $Ru(bpy)_3^{2+}$ complex, $[Ru(bpy)_2\{bpy(C_{11}H_{23})_2\}]^{2+}$, and different receptors: cyclodextrin and DNA
Pilar López-Cornejo, Manuel López-López, Marta Olivares, María Suárez, Francisco Montilla

P87 - Studies of hydrolytic DNA cleavage activity of $V^{IV}O(acac)_2$
Nataliya Butenko, Isabel Correia, João Costa Pessoa, Isabel Cavaco

P88 - Coralyne induces triplex-to-duplex and duplex-to-triplex transitions in ds-RNA according to a temperature controlled cycle
Begoña García, Francisco J. Hoyuelos, José M. Leal, Tarita Biver, Fernando Secco, Marcella venturini

P89 - Synthesis of new ruthenium arene complex, DNA binding properties and in vitro cytotoxicity
Jesús Valladolid, Natalia Busto, Begoña García, José M. Leal, Gustavo A. Espino

P90 - The $Ni^{2+}$and Zn^{2+} competition in coordination to unstructured fragment of *Helicobacter's pylori* HypA
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P91 - Hemoglobin-based copolymers with potential as blood substitutes: increased molecular weight, reduced prooxidant reactivity
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P92 - [15]aneN_4S as a potential agent for treatment of cadmium intoxications
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P93 - Cytotoxicity of salinomycin complexes with Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions on leukemia tumor models
Juliana Ivanova, Georgi Momekov, Ivayla Pantcheva, Mariana Mitewa

P94 - Ability of Salinomycin and its metal complexes to decrease viability and proliferation of human tumor/non-tumor cell lines
Ivayla N. Pantcheva, Mariana Mitewa, Juliana Ivanova, Radostina Alexandrova

P95 - Promising, highly cytotoxic ruthenium-based complexes with bulky triazolopyrimidine ligand: synthesis, structural characterization and antiproliferative activity *in vitro*
Marzena Fandzloch, Iwona Łakomska, Tadeusz Muzioł, Tadeusz Lis, Julia Jezierska

P96 - Hexafluoroglutarate platinum(II) coordination compound with 5,7-ditertbutyl-1,2,4-triazolo [1,5-a]pyrimidine. Structural characterisation and significant *in vitro* cytotoxicity
Iwona Łakomska, Kamil Hoffmann, Jerzy Sitkowski

P97 - Synthesis, structure and physicochemical properties of Ru(III/II) and Au(III/I) phosphine complexes with pyrazole-based ligands
Monika Richert, Tadeusz Muzioł, Paulina Kaczmarek, Magdalena Kubiak, Marcin Janusz Cieślak, Julia Kaźmierczak-Barańska, Karolina Królewska, Elżbieta Budzisz

P98 - Cytotoxicity of vanadocene complexes substituted in cyclopentadienyl rings
Iva Klepalová, Jan Honzíček, Jaromír Vinklárek, Lucie Šebestová, Martina Řezáčová

P99 – Organoruthenium binuclear thiosemicarbazone complexes as potential anti-tumor agents
Bruno Demoro, Rodrigo F. M. de Almeida, Fernanda Marques, Cristina P. Matos, Cynthia Sarniguet, Lucía Otero, João Costa Pessoa, Dinorah Gambino, Ana Isabel Tomaz

P100 - Iron (II) complex that switches from a diamagnetic to a paramagnetic state upon chemical stimulus: an approach towards responsive MRI probes
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P101 - NO_2A-*N*-(α-benzamido)propionate chelators: new leads for stable, fast labelling, targeted agents for ^{68}Ga(III) PET?
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P102 - Synthesis, *in vitro* and *in vivo* characterization of new chelator DO3AAHA and its derivate $DO3AAHA_{PEG750}$
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P103 - Estradiol based indium complexes towards the estrogen receptor
Filipe Vultos, Susana Cunha, Célia Fernandes, Lurdes Gano, Isabel Santos

P104 - Structure-activity relationship studies for flavonol-derived Ru^{II}(arene) anticancer complexes

Andrea Kurzwernhart, Wolfgang Kandioller, Caroline Bartel, Gerhard Mühlgassner, Maria Novak, Simone Bächler, Michael A. Jakupec, Vladimir B. Arion, Doris Marko, Bernhard K. Keppler, Christian G. Hartinger

P105 - Mono- and dinuclear platinum(IV) compounds containing an ethylene glycol moiety: synthesis, characterization and cytotoxicity
Verena Pichler, Petra Heffeter, Seied M. Valiahdi, Michael A. Jakupec, Vladimir B. Arion, Walter Berger, Markus Galanski, Bernhard K. Keppler

P106 - Tri- and tetraaza macrocyclic complexes of ^{43}Sc, ^{44}Sc and ^{47}Sc radionuclides as precursors of PET diagnosis and therapeutic radiopharmaceuticals
Aleksander Bilewicz, Agnieszka Majkowska, Seweryn Krajewski, Agata Kasperek

P107 - New studies of novel active platinum iodido complexes
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P108 - Cytotoxicity and plasmid DNA cleavage of three vanadyl(IV) complexes containing the oxodiacetate ligand on a human osteosarcoma cell line in culture
Ignacio E. León, Nataliya Butenko, Enrique J. Baran, Isabel Cavaco, Susana B. Etcheverry

P109 - Pyrazolyl-diamine Pt(II) complexes bearing DNA-intercalating moieties: Synthesis, characterization and *in vitro* evaluation
Sofia Gama, Teresa Esteves, Filipa Mendes, Fernanda Marques, Isabel Santos, Joana Coimbra, António Matos, Mauro Ravera, Elisabetta Gabano, António Paulo

P110 - Copper(II) complexes of histidine containing peptides as models of the Cu,Zn-SOD enzyme
Sarolta Timári, Katalin Várnagy

P111 - Targeting the breakpoint in Duchenne muscular dystrophy
Béla Gyurcsik, Anikó Czene, Eszter Németh, István G. Zóka, Emőke Endreffy, Hans E.M. Christensen, Kyosuke Nagata

P112 - Molybdenum substituted rubredoxin from *Desulfovibrio* gigas
C.C.S. Carreira, M.S.P. Carepo, R. Grazina, J.J.G. Moura, I. Moura

P113 - Elucidation of probable responses to molybdate stress in *Desulfovibrio alaskensis* by proteome analysis
Rashmi R. Nair, Celia Silveira, Maria Gabriela Almeida, José J.G. Moura, Maria Gabriela Rivas

P114 - Interaction of polytopic aza-scorpiand receptors with nucleotides and nucleic acids
Jorge González, Enrique García-España, Marijeta Kralj, J. M. Llinares, Ivo Piantanida, Roberto Tejero, Lidija Uzelac

PLENARY LECTURES

Redox metals in neurodegenerative diseases, and therapeutic perspectives

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There can be little doubt that one of the major challenges facing our 21st century society is the progressive increase in neurodegenerative diseases as the life expectancy of the population steadily increases.

We live in an oxygen-rich environment, which paradoxically allows us to generate much more ATP than in its absence, yet the consequence is that we continuously produce oxygen-derived free radicals, so-called Reactive Oxygen Species (ROS), the most dangerous of which is the hydroxyl radical, $OH^{\cdot}$, a short-lived but highly reactive free radical, which causes enormous damage to biological molecules. This is the so-called oxygen paradox – oxygen is an absolute necessity for our energy-economical anaerobic life style, yet it is a potential toxin. There is an increasing body of evidence to support the hypothesis that oxidative stress is a major contributory factor in many neurodegenerative diseases.

Redox-active metal ions, like iron and copper, can generate ROS, notably hydroxyl radicals [1, 2]. These can then initiate lipid peroxidation by attacking polyunsaturated fatty acids in membrane phospholipids, generating a family of reactive aldehydes. In their turn, these aldehydes can undergo Michael-type additions to protein thiol, imidazole and amino groups, which, together with other oxidative modifications, result in the formation of protein carbonyls. Subsequent protein denaturation, and aggregation then overwhelms the ubiquitin/proteasome system, which can no longer eliminate these defective, damaged proteins. generating a family of reactive aldehydes. In their turn, these aldehydes can undergo Michael-type additions to protein thiol, imidazole and amino groups, which, together with other oxidative modifications, result in the formation of protein carbonyls. Subsequent protein denaturation, and aggregation then overwhelms the ubiquitin/proteasome system, which can no longer eliminate these defective, damaged proteins. Aggregates of these ubiquinated proteins are a prominent pathological feature found within intracellular inclusion bodies in specific brain regions in many 'protein conformational' neurodegenerative diseases.

In earlier studies, we have shown that iron chelators are able to cross the blood-brain barrier, and to decrease brain iron in specific brain regions [3]. Using the 6-hydroxy dopamine model of Parkinson's disease, we have shown that the clinically available chelators deferoxamine (DFO), deferiprone (DFP) and deferasirox, whether administered focally or parenterally are able to protet against the neurodegenerative lesion [4]. This has resulted in funding being made available by Imperial College, London to carry out a preclinical trial involving Parkinsonian patients with DFP. The perspectives for chelation therapy in neurodegenerative disorders will be reviewed [5].

Acknowledgement. We thank COST Chemistry Action D34 for supporting our international collaboration.

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Metal ion selective sequestering agents, with selective properties

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Bacteria produce small molecule chelators called siderophores for the selective and powerful sequestration of ferric ion. An early example is enterobactin, a tris catecholamide with a cyclic tri-serine scaffold (Fig. 1). We have used these natural chelators as models for the production of metal ion specific chelating agents in support of new MRI enhancement agents, lanthanide time-resolved luminescence agents and actinide-specific sequestering agents.

The formal stability constant of aqueous Fe(III) with deprotonated enterobactin is 10^{49} [1]. A related recent octadentate macrocyclic ligand for Th(IV) has a stability constant 10^{53} (Fig. 2). How does one measure such enormous constants? Recent examples of such determinations and the applications in areas of biomedical research will be described.

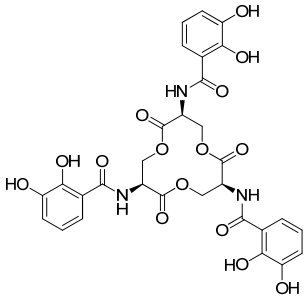

Figure 1. Chemical structure of enterobactin.

a) b)

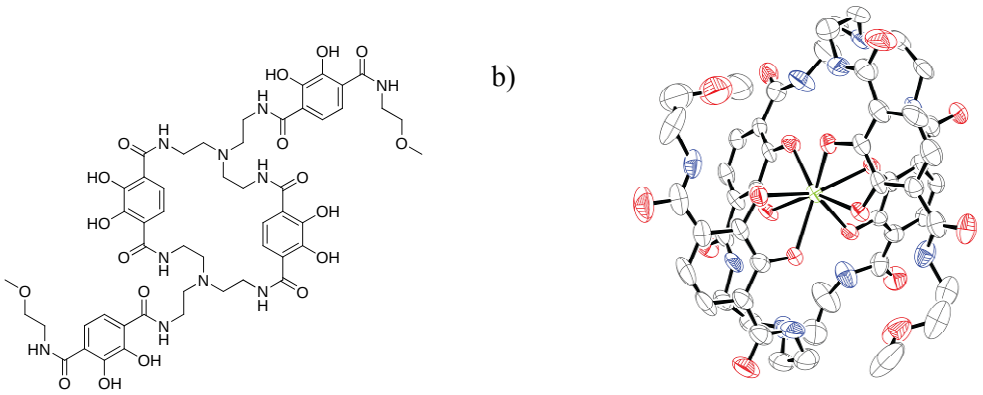

Figure 2. a) Chemical structure of octadentate macrocyclic ligand and b) ORTEP diagram of its complex with Th(IV) (counterions and solvent molecules omitted).

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Therapeutic and diagnostic metal complexes in medicinal inorganic chemistry

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The role of metal complexes as therapeutic and diagnostic agents is burgeoning due to interest from many academic and industrial concerns; the current value of medicinal inorganic chemistry is in excess of $\$10^9$. *Cis*-platin, for example, is the archetypal inorganic drug containing as it does, no atoms of carbon. Principles in the design of metal compounds as drugs will be discussed in detail with examples from work in the speaker's research laboratories presented to illustrate these principles. These examples are taken from our group's work in insulin-enhancing vanadium compounds, diagnostic and therapeutic radiopharmaceuticals, and multifunctional agents for neurodegenerative diseases and malaria.

Metal-based chelates and nanosystems for multimodal molecular imaging applications

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The superb special resolution of Magnetic Resonance Imaging (MRI) has made it a fundamental clinical diagnostic tool. However, its relatively low sensitivity may limit its use in Molecular Imaging. Thus, high relaxivity and specificity of targeted MRI contrast agents (CAs) are currently the most important objectives in the development of such diagnostic imaging tools. The design and relaxivity optimization procedures of Gd^{3+}- chelates as CAs will be discussed, as well as their extension to bimodal (MRI/Optical Imaging) applications. The effect of various molecular parameters of the Gd^{3+}- chelates on the r_1 relaxivity optimization will be illustrated, such as the inner-sphere water exchange rate ($k_{ex} = 1/\tau_M$) [1,2], the rotational correlation time (τ_R) [3] and the number of inner-sphere (q) [2] and second-sphere [4] water molecules. The *in vivo* evaluation of the T_1- contrast effect of some of these systems by DCE-MI in Wistar rats will be shown [5].

The use of nanosized platforms is an effective way to enhance the efficacy of such contrast agents, by increasing the number of imaging agents reaching the target ("cargo effect"). Several types of nanoparticles (NPs) have been explored for this objective. Among the inorganic ones, gold NPs decorated with relaxivity optimized Gd^{3+}- chelates [6] originate high r_1 relaxivities in the MRI imaging frequency range due to the slow rotational dynamics of the NPs and the concentration of many chelates at the NP surface [7]. Silica NPs with surface-bound Gd^{3+}/Tb^{3+} chelates are also interesting examples of bimodal (T_1-wMRI/OI) imaging tools [8]. Other inorganic NPs, with high r_2 relaxivities, originate high negative contrast in T_2-w MRI images, especially at high magnetic fields. Examples of this are Ln^{3+}-containing NPs and core-shell γ-Fe_2O_3@SiO_2 NPs [9,10]. Nature inspired NP platforms, such as lipoplexes and yeast-cell wall NPs (YCWP), are very efficient carriers of multimodal imaging probes which can be exploited as responsive MRI agents and for *in vitro* cell labelling and *in vivo* cell tracking applications [11,12].

Acknowledgements
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Luminescent silica nanoparticles: extending the frontiers of brightness

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Silica nanoparticles are versatile platforms with many intrinsic features, including a low toxicity. Proper design and derivatization yield particularly stable, very bright nanosystems displaying multiple functions, which can be used for either photoluminescence (PL) or electrochemiluminescence (ECL) sensing, labelling or imaging applications. [1,2] For these reasons silica nanoparticles already offer unique opportunities, and further improvement and optimization can substantially increase their applications in fields of high impact, such as medical diagnostics and therapy, environmental and food analysis, and security.

This contribution describes silica-core/PEG-shell multi-component nanoparticles (NPs), tailored for optimization of processes such as directional energy transfer, which provide those systems with extremely valuable functions: high light-harvesting capability, signal-to-noise maximization, multiplex output, signal amplification, [1-5] also for in vivo imaging (figure 1). [4] Very recently, using these nano-architectures we designed new families of sensors for metal cations, offering higher signal-to-noise ratio and selectivity. [3] We have also proved that these NPs doped with Ru and Ir metal complexes can afford high signal intensity in ECL experiments, allowing the enlargement of the color palette of this very interesting technique. [6-7]

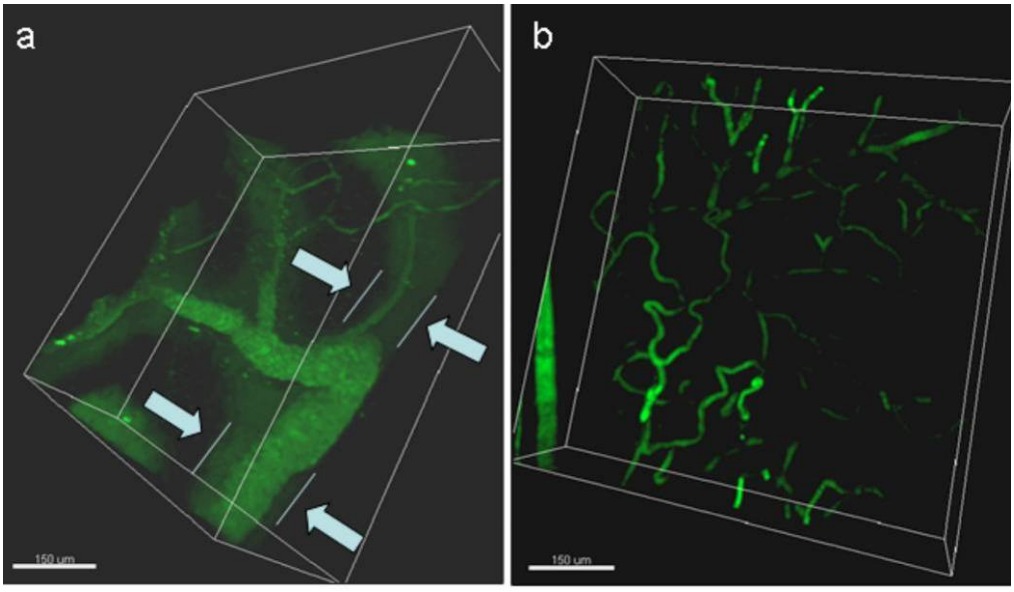

Figure 1: In vivo microscopic images of silica-core/PEG-shell multi-component nanoparticles in tumor (panel a) and in ear (panel b) 10 min, 30 min and 1 hour after the injection of the NPs. [4]

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KEYNOTE LECTURES

The chemistry behind the use of bioassays to assess metal toxicity: pH influence, complexation equilibria

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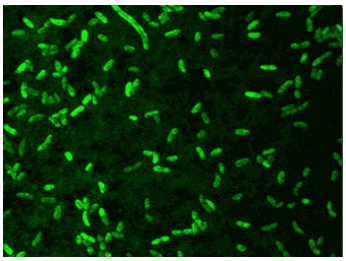
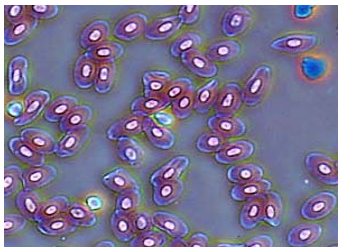
Besides rare but spectacular and media-reported accidents, rapid development of industrial activities and human concentration in industrial areas result in increasing levels of pollution leading to more insidious and gradual contamination of the environment. During the last years, a variety of biological models such as microorganisms, daphnids, fish or cultured cells were adapted to toxicological studies for assessing the presence and risk of environmental pollutants. Practically, the need for rapid screening of chemical toxicity has led to the use of in vitro bioassays, which must be suitable for routine tests in laboratories with medium-range equipment, posing few ethical problems and standardized for reproducibility.



Vibrio fischeri

Daphnia magna



HT29 cell line

Evaluation of environmental samples using microorganisms meets these criteria and may help in the estimation of chemical toxicity in natural and man-modified ecosystems. One of the microbial bioassay, the Microtox® test based on the fading, when in the presence of noxious agents, of light emitted by marine bacteria (*Vibrio fischeri*), can be easily carried out in standard laboratories. This in vitro bioassay has been successfully used to screen the acute toxicity of a large number of chemicals. Toxicity values are routinely obtained after 5 and 15 min exposure and are usually expressed as EC50 values at which a 50% loss of luminescence is obtained.

Metals found in wastewater effluents or in natural water streams may exist as different species. These different forms generally exhibit different physic-chemical properties, and therefore, may exert different effects on biological organisms. It is thus important to know the

species of the metal, its distribution among the various physicochemical forms, to understand its chemical behaviour in the environment as well as its biological toxicity.

Bioassays are carried out in a specific medium that contains all the nutrients and appropriate physical conditions (temperature, pH, ionic strength) required by the microorganism to grow and be alive. For instance, In the Microtox® test, toxicity is measured in a 2% NaCl solution for the osmotic protection of the bacteria and eventhough pH 7 is recommended, the bacteria are alive in the range of pH 5-9. Most of the metal ions form chloro complexes and the chemical speciation of some metal ions can vary as a consequence of pH variation like hexavalent chromium.

In this paper the suitability of bioassays to determine metal toxicity is assessed and discussed. The investigation carried out in our laboratories, on the influence of pH, ionic strength and assay media composition on metal toxicity, demonstrates that most of bioassays neglect the formation of different metal chemical species as a consequence of pH and metal complexes due to the composition of the media.

Structural and thermodynamic aspects of thiol binding to metal ions in excentric proteins

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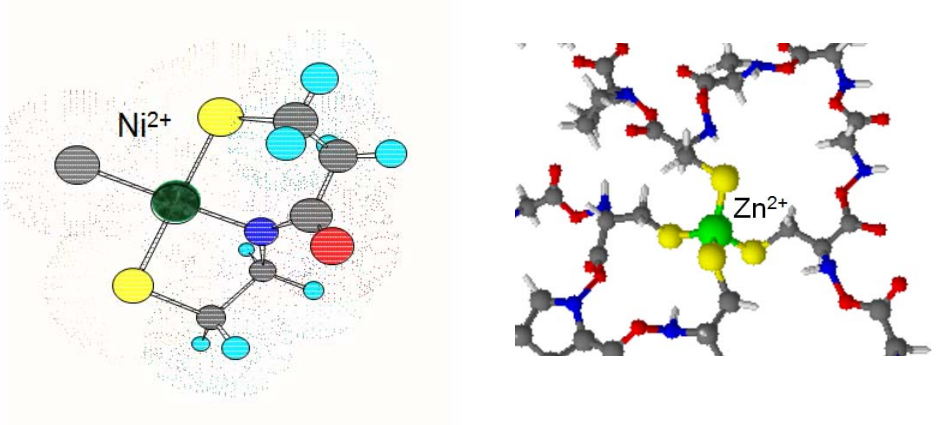

The thiol groups from cysteine residues in proteins are very often involved in processes associated with homeostasis of metal ions. Cysteine-rich sequences play a significant role in the transport and distribution of various metal ions, such as Zn^{2+}, Cu^{+}, Ni^{2+}, Cd^{2+} or even Bi^{3+}. One of the examples where thiols are those of great importance are bacterial chaperones, which are responsible for Ni^{2+} ion homeostasis, crucial for survival of bacteria at low stomach pH. Thermodynamic studies of the C-terminal fragments of Hpn and HspA chaperones that contain a -Cys-Cys- motif clearly proved, that the complexes of Bi^{3+} are much more stable than those of Ni^{2+} [1,2,3]. This result might be an explanation of how Bi^{3+} based drugs, commonly used for the treatment of *H. pylori* infections work.

Thermodynamic studies of the N-terminal multicysteine sequence of the Zn^{2+} specific membrane carrier ZIP 13 revealed a dramatic difference in the stability of such metal complexes [4]. Although all of the cysteines present in the fragment were found to constitute to the metal binding in all of the studied metals, the comparison of the metal complex stabilities indicated that Bi^{3+} complexes are thermodynamically absolutely the most stable ones [4]. What is interesting, comparing analogical species, Zn^{2+} complexes are more than three orders of magnitude more stable than those of Ni^{2+}. Since the stability of the complexes is closely connected with the amount of the metal- bound cysteine sulfurs, competition plots that compare the stability of such complexes are particularily interesting.

In the peptides with a naturally occurring CXXC cysteine motif, the difference in the ZnL and NiL complex stability is over six orders of magnitude [5]. Possesing data about different polythiol complexes containing various metal ions allow to determine or sometimes even predict, the specific binding sites for metals in naturally occurring proteins.

Acknowledgments: This work was supported by the Polish State Committee for Scientific Research (KBN N N204 146537).

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Metal complexes defining aluminium's exposome

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The term exposome has been coined to express the totality of environmental or an environmental exposure. The biologically non-essential and environmentally ubiquitous element aluminium is arguably the most significant metal toxicant in the lithosphere and it is imperative that its exposome is as fully understood as possible. While the most significant biologically-reactive form of aluminium is $Al^{3+}_{(aq)}$ it is its complexes which ultimately determine the delivery of $Al^{3+}_{(aq)}$ to target ligands and systems. Herein I will focus upon one or two metal complexes which are implicated in the toxicity and primarily neurotoxicity of aluminium.

Modeling of molecular properties. Fundamental principles and case studies with transition metal compounds

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The computation of electronic structures of transition metal complexes has been developed in recent years to an extent where a large variety of spectroscopic properties and reactivities of mono- and oligonuclear transition metal compounds can be efficiently and reliably computed and interpreted with ab-initio quantum-chemical and DFT-based methods. These are often based on known structural data, and the interpretation of the electronic structures usually involves the comparison of computed with experimentally observed spectra, stabilities and/or reactivities. The prediction of molecular properties, which eventually may lead to a rational design of novel complexes with given properties, requires as an important additional step a reliable structure prediction. The identification of factors which influence molecular structures of transition metal complexes and the ensuing approaches for a reliable structure optimization are an important basis for electronic structure calculations. In many cases these can and must be done with efficient and accurate molecular-mechanics-based methods, and electronic structure calculations are in some important examples best done with ligand-field-based approaches. Apart from the fundamental principles and possible pitfalls, various case studies from our lab will be discussed, and these may include (i) the Cu^{II} chemistry of natural cyclic peptides and their possible biological function; (ii) the oxidation catalysis of high-valent nonheme iron model systems; (iii) the design, synthesis and characterization of single molecule magnets; (iv) the design, synthesis and characterization of enzyme model systems such as catecholase, catechol oxygenase, carboanhydrase, and purple acid phosphatase.

Cation, anion and ion-pair binding with branched polyamines

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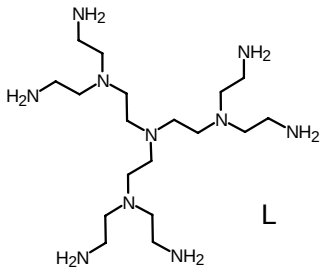
Branched polyamines are known to form stable complexes with transition metal ions. Tren (tris(2-aminoethyl)amine) and penten (1,2-ethanediamine-N',N',N'',N''-tetrakis(2-aminoethylamine)) are classical examples of this type [1]. Protonated forms of such ligands can also be used to bind anions via electrostatic and hydrogen bond interactions [2]. Among branched polyamines, dendrimeric ones are of special interest due to the surge of applications they have already found, or promise to implement, in important scientific and technological areas, including gene and drug delivery, medicinal chemistry, sensing and advanced materials [3]. Dendrimers are three-dimensional compounds formed by reiterated reaction sequences starting from smaller "initiating core" molecules and proceeding via discrete stages referred to as generations (G). For instance, tren is a first generation (G-1) dendrimer obtained from ammonia as the initiating core. Further addition of ethylamino branches to tren gives rise to the G-2 dendrimer **L**, which was firstly synthesized by Tomalia [4]. The binding properties of this dendrimer will be briefly described here.



L

According to its polyamine nature, **L** binds metal ions, such as Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, while its protonated species gives rise to anion complexes with anions such as NO_3^-, SO_4^{2-}, SeO_4^{2-}, HPO_4^{2-} and $H_2PO_4^-$. Stable metal complexes are formed with 1:1 (all metal ions), 2:1 (Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}), 3:2 (Ni^{2+}, Zn^{2+}, Cd^{2+}) and 3:1 (Cu^{2+}) metal-to-**L** stoichiometry. Conversely, despite the branched nature of the ligand, only 1:1 anion-to-**L** complexes were found.

An interesting aspect of the binding properties of this ligand is the ability of protonated mononuclear complexes to bind anions and form ion-pair complexes of considerable stability thanks to the cooperative effect of the oppositely charged partners.

The crystal structures of $[Ni_3\mathbf{L}_2](ClO_4)_6 \cdot 6H_2O$ (**1**) and $[Cu_3\mathbf{L}(OH)_{0.5}(NO_3)_{0.5}ox]Cl_{1.5}(NO_3)_{0.5} \cdot 5.5H_2O$ (**2**) were resolved by X-ray diffraction.

The $Ni_3\mathbf{L}_2^{6+}$ complex cation in **1**, existing in solution as a very stable species, shows two dendrimer units linked together by a bridging Ni^{2+} ion (Figure 1). The distance between the lateral Ni^{2+} ions is 15.049(4) Å and the overall length of the trinuclear $[Ni_3\mathbf{L}_2]^{6+}$ complex is about 28.4 Å.

In **2**, the $Cu_3\mathbf{L}^{6+}$ complex cation (Figure 2), which also exists in solution as a very stable species, gives rise, via bridging coordination of oxalate anions, to polymeric chains which self-organize into two-dimensional sheets. In the two cases, both mono- and two-dimensional aggregation is triggered by the action of ionic species behaving either as functional groups on the dendrimer surface (metal ions) or as the glue (metal ions, oxalate) that sticks together dendrimer units. Two association routes, developing via coordinative force, guide the directional aggregation of dendrimer

units: a) aggregation via metal ions shared by the surfaces of contiguous dendrimer molecules,

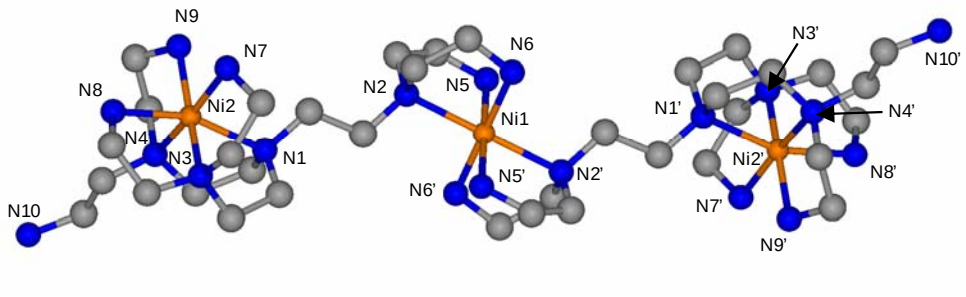


Figure 1. Crystal structure of the complex $Ni_3\mathbf{L}_2^{6+}$.

b) aggregation via chelating ligands bridging surface metal ions pertaining to contiguous dendrimer molecules. These two routes, which are shown here to be effective with a G-2 dendrimer, are expected to function also with higher generation analogues; in particular this applies to the second route which does not require a special flexibility of the dendrimer molecule. Accordingly, they provide non-covalent methods for the creation of novel families of nanostructured functional materials, that could prove useful for the development of the material science-based approach to nanotechnology.

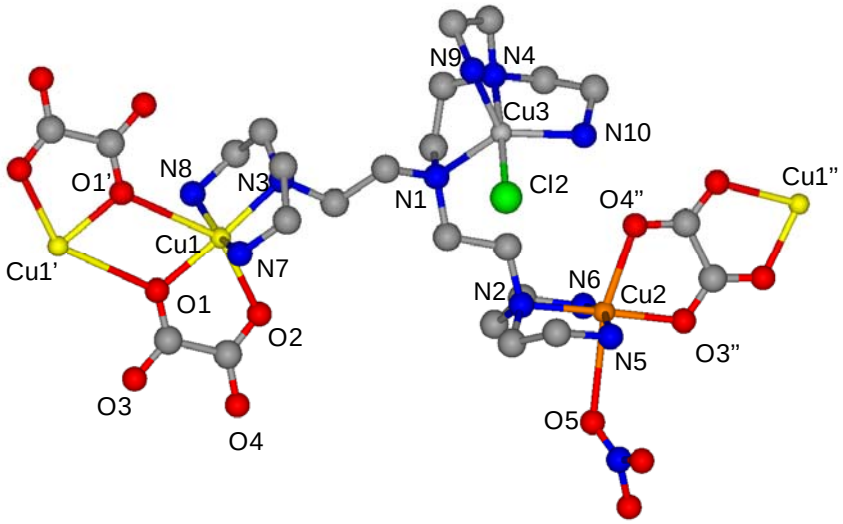


Figure 2. Drawing of the $[Cu_3\mathbf{L}\ (OH)0.5(NO_3)0.5ox]^{2+}$ unit, with metal coordination geometries completed by symmetry related linking groups.

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Macrobicyclic architectures for recognition of anions

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Polyamine macrobicyclic compounds are very versatile architectures. Indeed, in the protonated form these compounds can interact directly with anions, in the neutral form they can coordinate metal ions, and both ammonium groups and metal centres combined can cooperatively bind anions.[1]

In our work we took advantage of the ease modification of the macrobicyclic architecture and by small structural modifications we tried to rigidify their structure in order to increase the preorganization. This was done by using 2,4,6-triethylbenzene as caps instead of tren [tris(2-aminoethyl)amine]. A family of almost unexplored benzene capped polyamine cryptands were thoroughly studied as anion receptors, in aqueous solution and in the solid state. It was not only possible to achieve selectivity between inorganic substrates of similar size and shape but also build new compounds appropriate for the binding of more complicated substrates such as the dicarboxylates and amino acids. Several examples will be presented.[2−7]

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Cation and anion coordination and self-assembling capabilities of 1H-pyrazole containing ligands. Surface modification of nanoparticles

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One of the corner stones of supramolecular chemistry is the design and preparation of highly organized molecular receptors able to discriminate and/or to induce characteristic properties in given substrates. Another corner stone consist of the fabrication of molecular pieces that can self-assemble between them either by weak forces, particularly hydrogen bonding, or by means of coordinative bonds using the coordination geometries imposed by metal ions as an organizing structural element.

1H-Pyrazole constitutes a versatile building block for the construction of organic receptors for metal ions, organic cations or anionic species of different nature. This unit may participate in the binding of organic substrates donating or/and accepting hydrogen bonds through its NH or sp^2 nitrogen, respectively. On the other hand the neutral pyrazole unit can provide coordinative bonds to metal ions as an electron donor through the sp^2 nitrogen. When pyrazole deprotonates to give the pyrazolate anion, it can also act as a bridging ligand between metal centers.[1]

In the first part of this talk some results concerning the metal ion and anion coordination chemistry of pyrazole will be presented. Particular attention will be devoted to molecular pyrazole-based chemosensors for metal ions and organic cations. The capability of pyrazole to arrange hydrogen bonded molecular helices and capsules in solution will be discussed. Finally, our results on self-assembled organic-inorganic cages having metal ions and pyrazolate units as basic building blocks will be presented.

In the search for applicative purposes, recent results on the preparation of modified boehmite or core-shell Boehmite-silica particles will be provided in the second part of this talk. We discuss the preparation of these particles and its modification with different polyamines.

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Interaction of hydroxamic acids with metals: from simple complexes to metallacrowns

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The interaction of hydroxamic acids with metal ions, giving rise to bound forms of increased complexity, is described through three examples, making use of the kinetic approach.

In the first example the results of an investigation on the binding of Ni(II) to salicylhydroxamic acid (SHA) and phenylbenzohydroxamic acid (PBHA) in water [1] and in sodium dodecylsulphate (SDS) solution are presented. Besides observing the so-called "micellar catalytic effect" a change of mechanism has been detected on changing the medium from water to micelle. Actually, while in water the principal path involves reaction (1)

$$Ni^{2+} + L^{-} \rightleftharpoons NiL^{+} \qquad (1)$$

in SDS the main path is represented by reaction (2)

$$NiOH^{+} + HL \rightleftharpoons NiL^{+} + H_2O \qquad (2)$$

where HL denotes the unprotonated hydroxamic acid. The analysis of the results shows that the acid strength of the $Ni(H_2O)_6^{2+}$ ion increases by more than two orders of magnitude on going from water to SDS.

The second example is concerned with a stopped-flow investigation of SHA and benzohydroxamic acid (BHA) with Fe(III) [2]. It is shown for the first time that SHA is able to bind two Fe(III) ions, giving the complex represented in Figure 1.

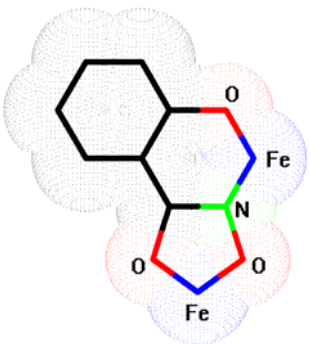

Figure 1: The structure of the dinuclear Fe(III)/SHA complex representing the repetitive unit of a SHA based metallacrown.

The important feature of this complex is the binding of the second Fe(III) ion at the O,N site. This binding implies total deprotonation of SHA, a process not observable with the free acid. Moreover and more important, this complex presents the O-Fe-N-O sequence which characterizes the metallacrown structure. The complex shown in Figure (1) does constitute the fundamental repeating unit of metallacrowns [3].

In the third example are described the main reactive steps that lead to metallacrown formation. The kinetics of the Cu(II)-α-alanine hydroxamic acid metallacrown (12MC4) formation have been investigated by mixing Cu(II) and ligand (L) in the 5:4 ratio. Different stoichiometric ratios do not lead to formation of any complex structure. The kinetic behaviour shows that mononuclear ML an dinuclear M_2L_2 structures are rapidly formed and two dimers, reacting together, form a tetrameric structure which, upon adding further Cu(II) ion, originates the cyclic species 12MC4. In the presence of a slight excess of L and lanthanum, 12MC4 is converted to 15MC5. The binding of La(III) to the cavity of the metallacrown has been investigated as well.

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Mechanistic modelling of An and Ln extraction by ILs: a first step towards a general model

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The mechanism of An or Ln liquid-liquid extraction from acidified aqueous phases towards molecular solvents (dodecane, octanol etc) in which suitable molecular organic extractants (tributylphosphate, calixarenes, malonamides etc) are dissolved has been studied for years and is now well mastered. It is known that extraction proceeds through the formation of a neutral complex of the metallic entity in the organic phase. Depending on the nature of the extracting agent, either neutral (L) or acidic (LH), one of the following equilibria occurs:

$$M^{m+} + mA^- + p\overline{L} \Leftrightarrow \overline{MA_mL_p} \quad \text{(eq. 1)}$$

$$M^{m+} + p\overline{HL} \Leftrightarrow \overline{ML_p} + mH^+ \quad \text{(eq. 2)}$$

Where A^- is a counter-ion present in the aqueous phase, often arising from the acid used, and $\overline{X}$ represents species in the organic phase.

By contrast, the mechanistic understanding of An/Ln extraction from the same acidified aqueous phases towards ionic liquid (IL) phases in which extractants are dissolved is still in its infancy, although an increasing number of experiments offer the potential for general rules to be derived. In the following, biphasic extraction systems will be written as: M^{n+}/HA//L/solvent.

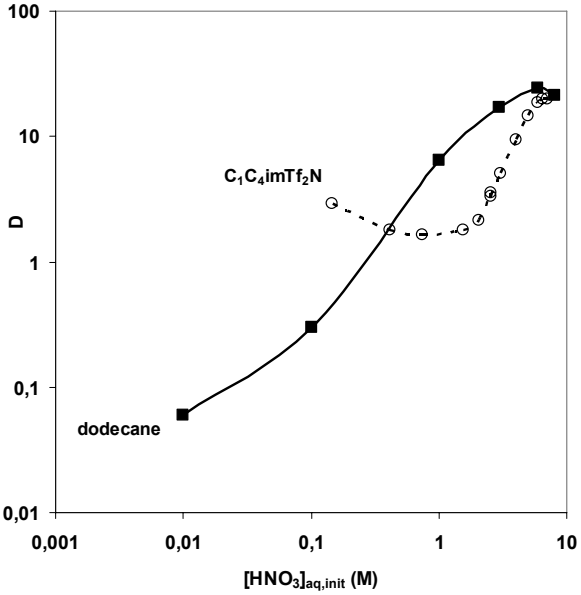

Fig. 1. Distribution ratio of uranyl as a function of the initial HNO_3 concentration of the aqueous phase for the two extraction systems: UO_2^{2+}/HNO_3//TBP/dodecane and UO_2^{2+}/HNO_3//TBP/C_1C_4imTf_2N.

As a matter of fact, the wealth of data already accumulated [1] evidences that the mechanism in IL phases significantly differs from that described through eqs. 1 and 2. This is illustrated in fig. 1 through the comparison of the distribution ratio of uranyl for the two extraction systems : UO_2^{2+}/HNO_3//TBP/dodecane and UO_2^{2+}/HNO_3//TBP/$C_1C_4imTf_2N$, where $C_1C_4imTf_2N$ stands for 1-methyl,3-butylimidazolium bis(trifluorosulfonyl)imide and TBP for tributylphosphate. The "bell shape" of the D versus [HA] plot is typical of molecular organic phases, because, according to eq. 1, an increase in [HA] leads to an increase in the extraction efficiency. At very high [HA] values however, the extracting agent also extracts HA, thus inducing a decrease of D. Similarly, the "boomerang shape" of the D versus [HA] plot observed in the ionic liquid-based extraction system displayed in fig. 1 is typical, with numerous examples to be found in the literature, for various metallic cations, acids, extracting agents and ILs.

We will present and discuss a chemical model aiming at describing cation extraction in IL-based extraction systems. The ability of this model to qualitatively and quantitavely recover experimental data will be demonstrated. The model will be discussed and compared to another model which has been presented recently and which is based on assumptions that substantially differ from those of our model [2]. Practical implications of the two models will be highlighted and means to discriminate between them will presented.

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Chemical speciation in environment and biomedicine: examples to technological development

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Chemical speciation is a broad field including chemical species of given elements as well as their distribution in target systems. Corresponding knowledge is a key factor to interpret material properties as well as related processes. This also includes the design of specific materials, diagnosis of physiological alterations or the environmental impact of a given contaminant. To achieve this key knowledge, appropriate methodologies need to be applied.

In the present lecture, I will introduce broad aspects of chemical speciation with special attention to the methodology for data acquisitioning including both indirect and direct processes.

Examples will be presented concerning environmental and medical systems to illustrate practical significance of this topic. In this concern, specific polluted waters and soils as well as human biomineral materials will take the floor. Finally, special consideration will be paid to some technological applications produced by the use of the generated knowledge

ORAL COMMUNICATIONS

Metal leaching capacity of rainwater in an abandoned lead-zinc mine

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Highly polluted abandoned metal mines often impact the surrounding environments constituting a chronic contamination source due to the pollutants mobility through different ecological compartments [1]. Generally, these migration effects are studied at the surface level. However, such phenomena do also occur through the soil column. Therefore, the main aim of this work is centred on the determination of the metal mobility patterns in both directions, superficial (from above the mine to downhill) and in-depth (from the top to the groundwater pool). This study was carried out in a blende (ZnS) / galena (PbS) mine located in Karrantza's Valley (Biscay, North of Spain).

To achieve this goal, twelve cylindrical cores were systematically collected following the main slope of the hill, from the mine entrance to approximately 300 m downhill. Their depth ranged from 30 cm to 80 cm depending on the soil nature. Once in the lab, the cores were divided in segments of 10 cm, air dried and sieved recovering fractions below 250 µm and between 250 µm and 2 cm of particle size. The first fraction was used to determine: (i) the total soil metal concentration by means of alkaline fusion, (ii) the extractable soil metal composition by microwave assisted extraction (MAE) following EPA 3051 method and (iii) the equilibrium leaching capacity obtained by a mobility test using synthetic rainwater following the DIN 19730 norm. The second fraction was employed to simulate the potential leaching of the soil column itself when submitted to 100 mL of artificial rainwater drop by drop [2]. Major elements and hazardous metals (Pb, Zn, As, Cr, Hg, Tl, etc.) were determined in the whole set of sample extracts by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).

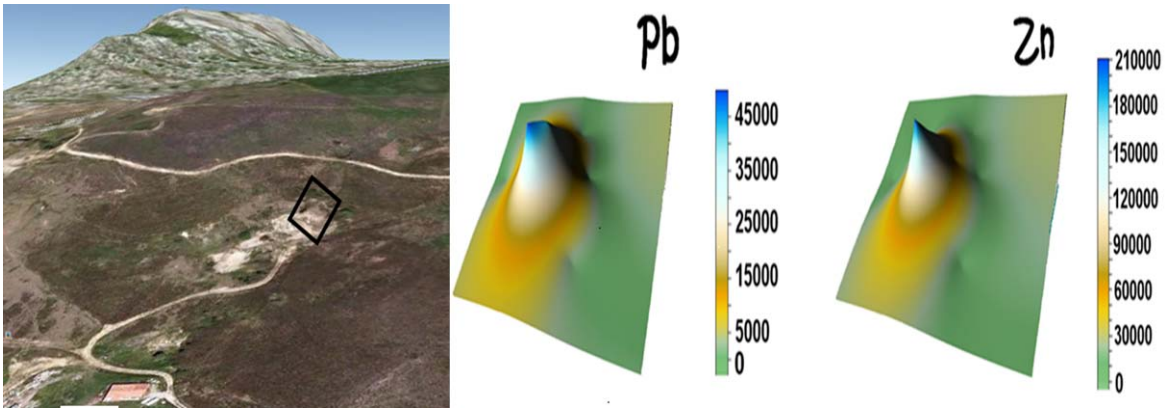

Figure 1: Aerial photo of the abandoned blende/galena mine and the superficial distribution (in mg/g) of Zn and Pb in the studied area.

An example of the superficial distribution of highly pollutant metals such as Pb and Zn in the studied area is shown in Figure 1, where the hot spots are clearly visible close to the mine entrance. This preliminary study allowed us to define different sampling points to collect the cores. Table 1 summarises the concentrations obtained for both elements by means of MAE and in equilibrium with artificial rainwater. According to this table, it seems that Zn has more superficial and in-depth mobility which involves a higher risk to contaminate surrounding environmental compartments. However, another mobility pattern is observed for Pb. In fact, lead does not migrate so easily which ends up in a highly Pb enriched topsoil. These trends were also supported by the analysis of rainwater leaching tests applied to the columns because, in general terms, a bigger rainwater volume was required to mobilise Pb than for the case of Zn.

Table1: Extractable concentration values, determined by means of MAE and equilibrium leaching capacity experiments, of Zn and Pb (in µg/g) of two core samples collected at the mine entrance and 50 m downhill from the mine entrance (RSD < 10%).

		Zn (µg/g)		Pb (µg/g)	
Core Sample	**Depth**	**MAE**	**Equilibrium Leaching**	**MAE**	**Equilibrium Leaching**
Mine Entrance	**10 cm**	8030	31	14428	2.8
	20 cm	11789	76	13233	6.9
	30 cm	4767	61	4171	1.1
	40 cm	4891	39	452	0.5
50 m from the main entrance	**10 cm**	60304	66	102276	7.4
	20 cm	33613	21	31452	2.1
	30 cm	3936	9.5	1414	0.1
	40 cm	799	1.9	235	0.06

According to the obtained results, it can be concluded that although the mine ceased activity some decades ago, the chronic pollution of the area still remains in the whole system, i.e., soil, groundwater, run off, etc. Thereby, the application of ecological and/or health risk assessment protocols is crucial before making any plans for a future use of this area.

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Characterization of the interactions between proteinaceous binders and inorganic pigments in paint reconstructions

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Over the last years our research efforts are focused on the study of the interactions between inorganic pigments and binders in paints and their evolution during aging. The comprehension of the mechanisms and reactions occurring in paint layers is essential to outline a model allowing the valuation of their chemical and physical stability and to plan a correct procedure for their conservation. We took into account both natural binding media such as protein based materials [1], drying oils [2,3], plant gums, as well as synthetic alkyd resins. Part of this research was carried out in the framework of the COPAC project, which concerns the characterization of materials used in modern and contemporary art.

Paints constituents undergo to phisico-chemical modifications which are referred to as "ageing", leading to the formation of new functional groups and intermolecular and intramolecular bonds. Moreover in every paint layer slow chemical reactions can take place between the organic and inorganic materials present. This work aims at characterizing proteinaceous binders, commonly used in tempera painting techniques, and their interactions with azurite ($Cu_3(CO_3)_2(OH)_2$), calcium carbonate ($CaCO_3$), red ochre (Fe_2O_3), minium (Pb_3O_4) and cinnabar (HgS) pigments [1], and as they evolve upon ageing.

The research was carried out on a set of paint replicas on glass slides, which were analysed fresh and after artificial light ageing. Multiple physical-chemical techniques were used, including Thermogravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and Size Exclusion Chromatography (SEC). This analytical approach allowed us to highlight that interactions take place between binder and pigments. For example, it has been possible to reveal that proteins in paint reconstruction are subject to both cross-linking and hydrolysis of the polypeptide chains upon ageing and, to a lesser extent, to oxidation of side amino acid chains. Moreover, we highlighted the occurrence of interactions taking place between proteins and pigments, and we partially investigated into their nature and evolution with ageing.

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Insights on the U(VI) speciation with bacterial isolates from Äspö and Mont Terri

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Since bacteria belong to the most widely spread organisms in nature and are known to have a considerable impact on radionuclide speciation and hence migration in the environment, it is of importance to characterize the interaction of actinides with dominant bacterial strains isolated from sites destined for nuclear waste storage.
In this study we examined the impact of two microbial representatives from actually discussed potential geological formations for nuclear waste storage on the U(VI) speciation. *Pseudomonas fluorescens* CCUG 32456A isolated from the granitic aquifers at the Äspö Hard Rock Laboratory, Sweden, and a novel strain of the genus *Paenibacillus* from clay samples of the Mont Terri Rock Laboratory, Switzerland, which we have recently isolated and been able to cultivate, were investigated. To assess the U(VI) interaction with surface functional groups of theses strains potentiometric titration in combination with time-resolved laser-induced fluorescence spectroscopy (TRLFS) were applied. The characterization of the surface functional groups of *P. fluorescens* in terms of binding site densities and corresponding pK_a values by means of potentiometric titration is described in [1]. The characterization of *Paenibacillus* sp. nov. cells was carried out analogously. To determine the stability constants of U(VI) complexes with bacterial surface functional groups the titration data of cells in contact with U(VI) was fitted using HYPERQUAD [2]. In addition to the pK_a values and site densities of the bacteria the following hydrolytic uranyl species and their stability constants were included in the fit: $(UO_2)_2(OH)_2^{2+}$, $(UO_2)_3(OH)_5^{+}$, $(UO_2)_4(OH)_7^{+}$. The titration curves could be modeled with a very good fit result when the complexes R-COO-UO_2^{+}, R−O−PO_3H−UO_2^{+}, R−O−PO_3−UO_2, and (R-O-PO_3)$_2$-UO_2^{2-} were considered. Using the determined stability constants U(VI) species distributions in presence of both strains in dependence on the pH (Fig. 1) were calculated using the software HySS [3]. These species distributions reveal that at an acidic pH of about 3 U(VI) binds to the cell surfaces primarily via protonated phosphoryl groups. In case of *P. fluorescens* also carboxyl interaction affects the U(VI) speciation significantly. The differences in the U(VI) speciation with both strains and the influencing factors will be discussed in detail.
TRLFS as a well-established direct speciation technique suitable for low, environmentally relevant U(VI) concentrations [4, 5] was used for the verification of the results gained with potentiometric titration. The TRLFS results will be presented and discussed in detail.

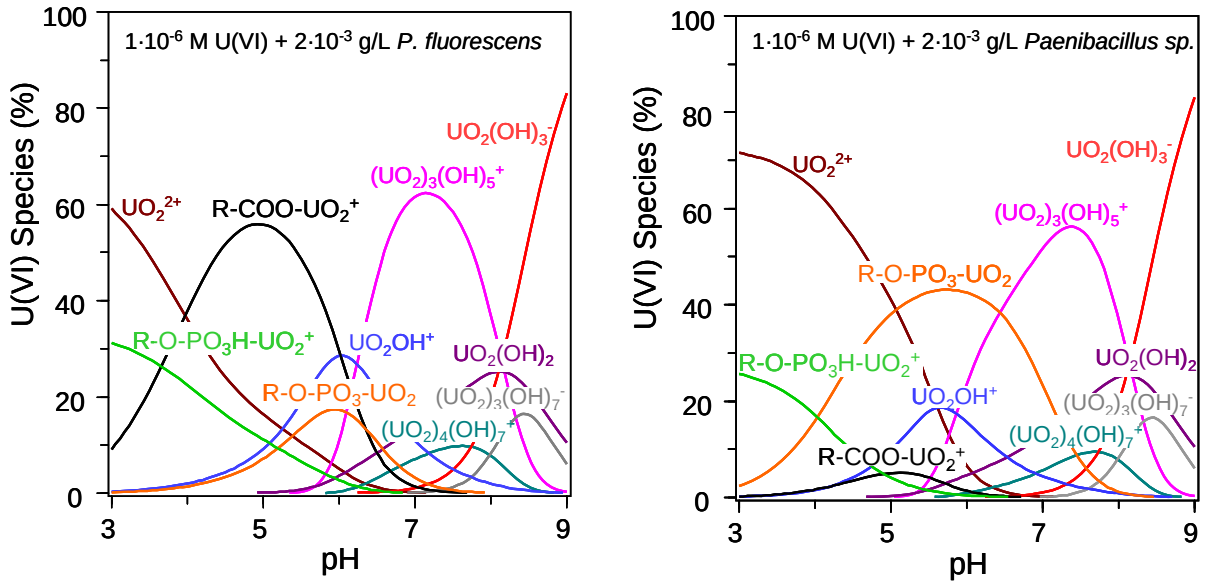

Figure 1: U(VI) species distributions in presence of *P. fluorescens* (left) and *Paenibacillus* sp. nov. (right), [U(VI)] = $1 \cdot 10^{-6}$ M, [dry biomass] = $2 \cdot 10^{-3}$ g/L, I = 0.1 M, N_2 atmosphere.

In general, both strains possess high U(VI) binding capacities, e.g. at pH 6 at $[U(VI)]_{initial}$ of $1 \cdot 10^{-4}$ M 124 $mg/g_{dry\ biomass}$ and 109 $mg/g_{dry\ biomass}$ are bound by *P. fluorescens* and *Paenibacillus* sp. nov., respectively.

Acknowledgement: This work was funded by the BMWi under contract number 02E10618.

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Histidine-rich branched peptides as copper and zinc chelators with potential therapeutic application in Alzheimer's disease

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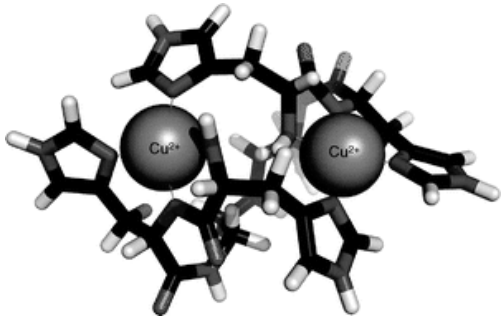
Alzheimer's disease (AD) is the most common cause of age-related senile dementia. It is characterized by cerebral deposits of extracellular amyloid plaques and intracellular tangles. The amyloid plaques comprise mixtures of aggregated amyloid-β peptides (Aβ). Elevated levels of metal ions in these deposits, such as Zn(II), Cu(II) and Fe(III) has been proven. Several studies have shown dyshomeostasis of these metal ions in the brain of AD patients. It was demonstrated that Aβ possesses selective Zn(II) and Cu(II) binding sites that mediate its physicochemical behaviour. In parallel with these findings, the reduction of the aberrant metal-protein interaction by metal-protein attenuating compounds (MPAC), which are molecules able to chelate metal ions, is a possible therapeutic way for AD [1]. Among others the antibiotic *Clioquinol* (5-cloro-7-iodo-8-hydroxiquinoline, CQ) [2] and N^1,N^2-bis(pyridine-2-yl-methyl)ethane-1,2-diamine (ENDIP) [3] with moderate affinity towards Cu(II) and Zn(II) was proven to inhibit metal-induced Aβ aggregation.



Two His-rich peptides with one Lys unit [$(GH)_2K$ and $(HH)_2K$] were designed and synthesised by solid-phase peptide synthesis [4]. Both peptides could keep Cu(II) and Zn(II) in complexed forms at pH 7.4 and bind two equivalents of metal ions in solutions with excess of metal. Both mono- and bimetallic species were detected in the pH range (4-10) studied. The basic binding mode is either a tridentate (N_{amino}, N_{amide}, N_{im}) or a histamine-type coordination which is complemented by the binding of far imidazole or amino groups leading to macrochelate formation. The peptides were able to prevent Cu(II) induced Aβ(1-40)

aggregation but could not effectively compete for Zn(II) *in vitro*. Our results suggest that these His-branched peptides containing potential metal-binding sites may be suitable metal chelators for reducing the risk of amyloid plaque formation in AD.

Acknowledgement:
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Biomimetic analogues of siderophores as structural probes for microbial iron uptake processes

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At the time of increasing number of severe and often lethal infections caused by multiresistant bacterial strains, the research in the field of iron transport in microorganisms seems to be of great importance and has stimulated considerable interest in understanding of the uptake mechanisms of ferric siderophore complexes. The difficulties in synthesis of structurally complicated natural siderophores, has prompted research in the direction of artificial siderophores used as structural probes of microbial iron uptake processes [1]. Rationally designed synthetic analogues, recognizable and utilizable by the same uptake system as the natural siderophore, may provide a unique platform to study recognition motifs, structure variation effects and key factors affecting recognition [1].

Our current research is focused on characterization of novel biomimetic compounds, artificial iron-carriers, in terms of iron complex formation and stability. The interplay between structure and function is studied on biomimetic examples based on Ferrichrome siderophores, containing hydroxamates as the iron binding units. Here we will present a new series of ferrichrome analogues, based on a tripodal template, where the asymmetric hexapeptide ring of the natural ferrichrome is replaced by a much simpler C3 symmetric template, anchored to a quaternary carbon. Three identical arms are comprised of a spacer containing an amino acid (Xaa) and terminated by hydroxamate metal binding moiety (Fig. 1). It has to be underlined, that the apical site (on the quaternary carbon) provides an excellent anchor point to attach fluorescent markers, surface adhesion moieties or antibiotics. Various aminoacid residues are studied, in order to determine the possibility of hydrogen bonds formation and the role of polar side groups (such as amines). Preliminary data show that Fe(III) binding properties of studied analogs are close to natural ferrichrome. Moreover, growth promotion studies show that these biomimetic compounds are able to transfer iron to *Pseudomonas putida* as efficiently as natural ferrichrome, and therefore act like siderophores.

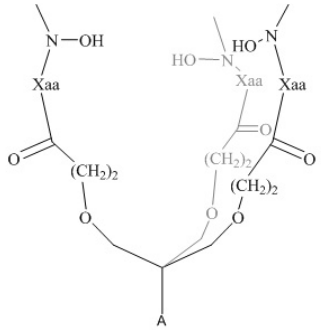

Figure 1. Generalized structure of the ferrichrome tripodal analogs. The epical site (marked as A) is connected to the tripodal template, to which amino acid is attached (Xaa), terminated with the hydroxamate group.

Additionally, monomeric reference compounds derived from the above compounds are used for comparison purposes and to reveal possible intramolecular interactions. Overall, the homogenous series of iron chelators, should help us to underline the influence of chirality, spacer length and the presence of additional groups on Fe(III) binding properties.

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A peptidic turn with high affinity for heavy metal ions

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The Cys-X-Y-Cys is a highly conserved chelating unit in biological systems. This short amino sequence is found in the metal binding site of a wide variety of metalloproteins [1-3] among them those involved in the bacterial mercury detoxification system (MerP) and the copper transport systems from humans, yeasts and bacteria. This short chelating unit is mainly found in loops and therefore, it has high flexibility. In all cases though, the overall structure of the protein scaffold helps to organize the loop and the Cys residues for proper metal binding.

Herein, we report a four amino acid peptide containing two Cys separated by a β-turn inducing template (d-Pro-Pro) [4] and show how this short peptide is a strong chelator for Hg(II). The UV-Vis, CD, ^{199m}Hg PAC and Raman spectroscopic studies indicate the binding of Hg(II) to the two Cys forming the dithiolate-Hg(II) complex Hg(CdPPC). ESI mass spectrometry corroborates the 1:1 complex formation. These results highlight how the simple dPro-Pro unit can mimic the overall pre-organization achieved by the native protein scaffold and pre-organize the two Cys residues for Hg(II) coordination. Using computational modelling we have obtained two possible conformers for Hg(CdPPC) that will be indistinguishable by the spectroscopic techniques employed in this study. The coordination properties of this peptide towards other heavy metal ions will be also presented.

Acknowledgements: This work has been carried out with financial support from FCT (PTDC/QUI-QUI/10/2008, PTDC/BIA-PRO/100791/2008, REDE/1504/REM/2005), the Danish Research Council (DFF|FNU) and beam time at ISOLDE CERN (IS488).

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Microprotonation and Na(I)/Mg(II)-interaction of inositol 1,3,4,5,6-pentakisphosphate: ^{31}P NMR and computational insights

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The *myo*-inositol phosphates (Ins*P*) are ubiquitous biomolecules in eukaryotic cells, which form a broad panel of specific signaling metabolites [1]. Together with inositol hexakisphosphate, inositol 1,3,4,5,6-pentakisphosphate (Ins(1,3,4,5,6)P_5, Fig. 1) is the most abundant member of the family [1]. Although Ins(1,3,4,5,6)P_5 has been related with cellular proliferation, apoptosis, viral assembly, chromatin remodeling and the activity of L-type Ca^{2+} channels, the certain biological roles of this member are far from being elucidated. This has been caused by the unusual and non-intuitive behavior displayed by the highly charged Ins(1,3,4,5,6)P_5 species in the presence of metal ions. Besides the various protonation equilibria, this Ins*P* interacts strongly with metal cations in a complex but poorly described chemistry, encompassing solution complexation and precipitation reactions. The lack of a rigorous description of all these reactions is a significant hurdle for Ins(1,3,4,5,6)P_5 biology.

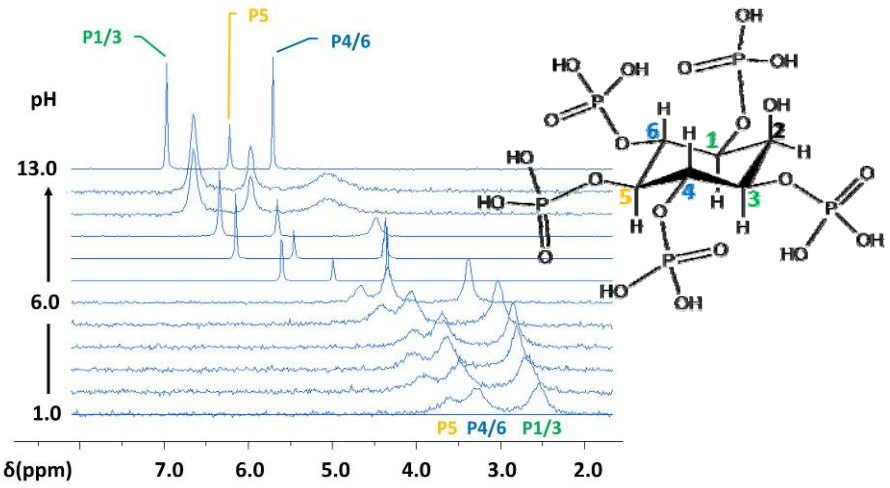

Figure 1. Structure of Ins(1,3,4,5,6)P_5. Superimposed are shown the ^{31}P NMR spectra for a 10.6 mM solution of Ins (1,3,4,5,6) as a function of pH, in 0.15 M NMe_4Cl at 37.0 ° C.

In light of this, we have strived to make a rigorous and at the same time ‘‘biological-user-friendly’’ description of the Ins(1,3,4,5,6)P_5 chemistry with mono and multivalent cations [2]. In this work we expand these studies focusing on the inframolecular aspects of its protonation equilibria and the microscopic details of its complexation behavior towards biologically relevant metal ions. We present here a systematic study of the Ins(1,3,4,5,6)P_5

inframolecular acid–base processes over a wide pH range, analyzing the ^{31}P NMR curves (Fig. 1) by means of a model based on the ‘‘cluster expansion method’’. In addition, we have performed a computational approach to the energetic and structural features of the protonation and conformational change of Ins(1,3,4,5,6)P_5 as the pH varies. Besides, we analyzed how they are disturbed by the presence of two physiologically relevant cations: Na(I) and Mg(II).

Ins(1,3,4,5,6)P_5 contains ten acid protons, $H_{10}L$. We were able to detect the first seven protonation reactions. Our results predict that the predominant species at physiological pH are H_4L^{6-} and H_3L^{7-}. We have determined the ligand protonation sequence and probabilities of each of the microspecies in solution. We have also confirmed, both experimentally and computationally, that the conformational change suffered by this Ins$P$ is triggered by the reaction involving HL^{9-} and H_2L^{10-}. The fit of the spectroscopic data allowed us to detect polynuclear complexes with Na^+ of general formula $[Na_i(H_jL)]^{(10-i-j)-}$ with i:j = (2:2), (3:1) and (4:0). Under conditions close to the cytosol and nucleus, the predominant species with sodium is $[Na_2(H_2L)]^{6-}$. In the presence of Mg^{2+}, species of general stoichiometry $[Mg(H_jL)]^{(10-2-j)-}$ with $1 \leq j \leq 4$ were detected. By means of the spectroscopic data and the information provided by molecular modeling tools, we characterized the structure of the species and analyzed the topological details of the protonation and complexation processes. In particular, for the complex $[Mg(H_3L)]^{5-}$, one of the predominant forms of Ins(1,3,4,5,6)P_5 under cytosolic-nuclear conditions, the magnesium ion is predicted to be in an octahedral distorted environment, linked by two phosphate groups and three coordinated water molecules (Fig. 2).

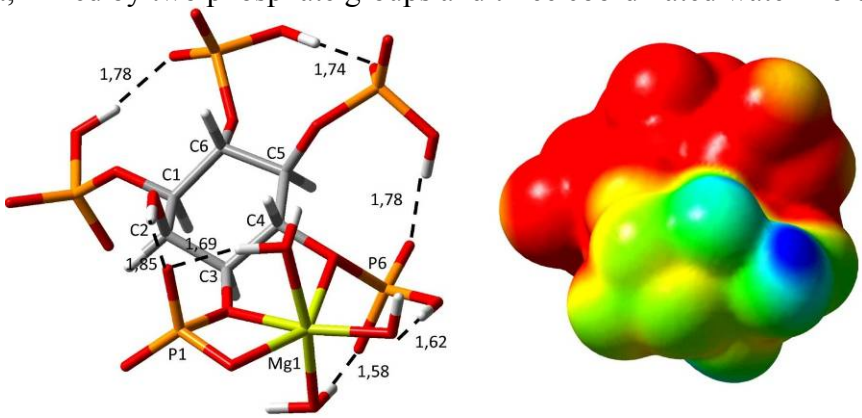

Figure 2. Gas phase RB3LYP/6-31+G* geometry and molecular electrostatic potential for $[Mg(H_3L)]^{5-}$. The intramolecular hydrogen bonds are shown in dashed lines with the corresponding distances in Å.

Acknowledgments: CSIC-Uruguay (Programa de Apoyo a Grupos de Investigación) and ANII

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Siderophores - transport properties and environmental stability

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Siderophores are naturally occuring ferric-specific chelators which are synthesized and excreted by many fungi and bacteria under iron-limiting growth conditions. Production and transport of siderophores in microorganisms is regulated by intracellular sensor proteins that respond to the available extracellular and intracellular iron concentrations. Some plants, like grasses are able to excrete phytosiderophores which behave in a similar manner. A basic property of all siderophores is their high stability constant with ferric iron (10^{20}-10^{49}) which excludes uptake of other trivalent ions and allows recognition of Fe-siderophores by membrane located transport systems. Environmental stability of siderophores means survival in water and soil for longer time periods. Extracts from soil samples yielded about 10 nM ferrichrome compounds, mainly originating from mycorrhizal fungi at the root surface of plants [1]. Other siderophores may have a very short halflife due to the activity of esterolytic and peptolytic enzymes present in organic soils [2]. When pathogenic bacteria or fungi invade the eukaryotic host, siderophores behave as virulence factors by extracting iron from host proteins. Enhanced solubility may improve virulence as seen with the water soluble salmochelins of *Salmonella enterica* and uropathogenic *E. coli* species [3]. Being kinetically labile, siderophores display iron exchange reactions which are generally slow (hours) compared to uptake by transport systems (min), but may eventually establish a dominant microbial population. Finally we know organisms, like *Saccharomyces cerevisiae*, that do not produce siderophores, but have the ability to transport and utilize siderophores from other organisms [4]. We have summarized the above mentioned observations under the title ecology of siderophores which combines individual biosynthetic and environmental factors [5].

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Actinide complexes incorporating environmentally relevant chelators: a structural, thermodynamic, and kinetic prospect

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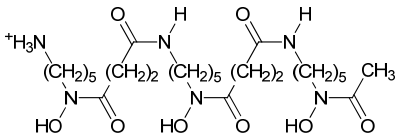
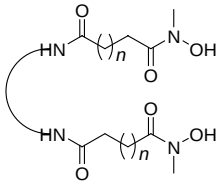
The disposal of radioactive wastes in deep geological repositories, the management and remediation of contaminated fields are societal issues of great concern. Predicting the behavior of actinides under environmental conditions is of paramount importance, but modeling their speciation in waters and soils requires an extensive and accurate knowledge of the thermodynamic and kinetic parameters related to their complex formation and dissociation equilibria. In particular, migration and bioavailability of actinides in the biosphere are highly dependent upon the presence of organic ligands [1]. Because such data are extremely scarce and moreover mostly unreliable in the case of the transuranium cations, considerable research efforts are required.

Our aim is to investigate the coordination chemistry in aqueous media of selected 5f elements (Th, U, Pu, Am) with environmentally-relevant, widespread chelators, namely polyaminocarboxylic and polyhydroxamic acids. Among the first series, linear complexones, such as EDTA, CDTA, and DTPA, are ubiquitous sequestering, extracting, and *in-vivo* decorporating agents in the nuclear industry. Moreover, tons of weakly biodegradable EDTA used as softener in soaps and detergents are released annually to the environment, thus impacting the mobility of metal captions in contaminated areas. In spite of the technological, environmental, and medicinal significance of these polyaminocarboxylic acids, their coordination chemistry with respect to plutonium(IV) and americium(III) is still poorly understood and remains a matter of debate [2,3].

The second class of ligands to be discussed includes naturally occurring and abiotic hydroxamic acids. Siderophores are excreted by most bacteria and some yeasts to supply them with iron(III). However, desferrioxamines and rhodotorulic acid have recently been shown to form stable complexes with various actinides and to efficiently mediate plutonium uptake by several bacterial strains [4].



Desferrioxamine B



(*n* = 1 or 2)

Studied abiotic dihydroxamic acids

The combination of classical potentiometric and spectrophotometric titration techniques with EXAFS spectroscopy and capillary electrophoresis (CE–ICP-MS) enabled us to unravel the uranium(VI), plutonium(IV), and americium(III) speciation in the presence of the aforementioned ligands, as well as the most plausible structures of the major complexes found in solution [5]. Finally, the proton-assisted dissociation mechanism of several uranyl compounds incorporating abiotic dihydroxamic siderochelates or desferrioxamine B will also be presented.

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Computational studies of cesium-137 recognition by cucurbituril

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The accumulation of radioactive Cesium-137 (^{137}Cs) in the environment, particularly in the soil, as a result of nuclear accidents represents a challenging scientific problem [1]. Chemists have developed a number of artificial receptors for the selective recognition of Cs^+ ions which have the potential to both detect and remove this radioactive nuclide from the contaminated environment. In this regard, several years ago Ungaro and co-workers [2] developed a series of calix[4]arenes strapped with crown ether bridges which have the ability to coordinate Cs^+ ions through the formation of Cs–O and cation-arene interactions. Counterions are also important for recognition and, in this regard, a novel series of calyx[4]arene-calix[4]pyrrole hybrid receptors have been recently synthesized by Sessler and co-workers [3]. These novel receptors possess the ability to coordinate Cs^+ ions through the formation of ion-pairs. Another interesting class of versatile macrocycles is represented by cucurbiturils or CB[*n*], with *n*=5-10, a series of pumpkin-shaped molecules which can be synthesized from the condensation of *n* glycoluril monomers [4].

Here we employ modern density functional theory (DFT) methods to investigate the interaction of Cs^+ with CB[6] using as starting point the x-ray molecular crystal structure of $CB[6](Cs^+)_2(H_2O)_6$ [5] shown in Figure 1 (the counterions are not shown and the Cs^+ ions are represented by large balls). One notices that each Cs^+ ion bears three water molecules while interacting with four of the six carbonyl groups lining each macrocycle's portal.

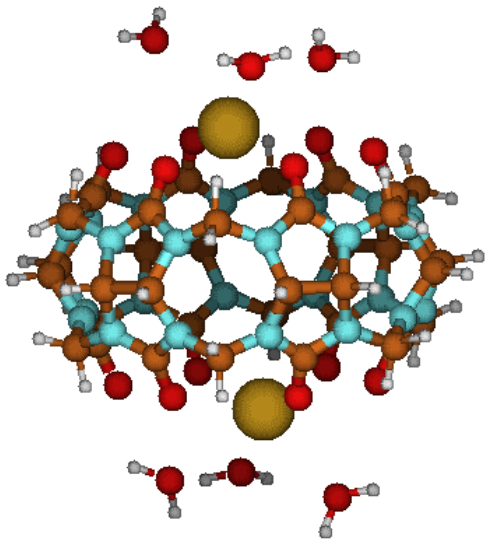

Figure 1. Molecular crystal structure of $CB[6](Cs^+)_2(H_2O)_6$ [5].

The C=O···Cs^+ interactions in the complex originate from the topology of the highest-occupied molecular orbitals HOMO-1 and HOMO of CB[6] both of which are localized on the twelve oxygen atoms, six on the upper portal and six on the lower portal [6]. This orbital-based argument predicts the occurrence of ligand-to-metal charge transfer (CT) which can be characterized with the aid of DFT calculations. Along with the quantitative characterization of CT effects, we also estimate the binding energy (B_e) associated to the interaction of each Cs^+ ion with the macrocycle as well the effects of the solvent (water) and counterions on ion binding. Furthermore, a comparison between the ion-binding properties of CB[6] and those of CB[5] and CB[7] is also performed. These computational modelling studies are expected to shed light on the recognition of Cesium-137 by artificial receptors and to pave the way toward the development of selective and chemically-stable macrocycles for environmental chemistry applications.

Acknowledgements
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Protonation sequence of zoledronic acid: a DFT and QTAIM study

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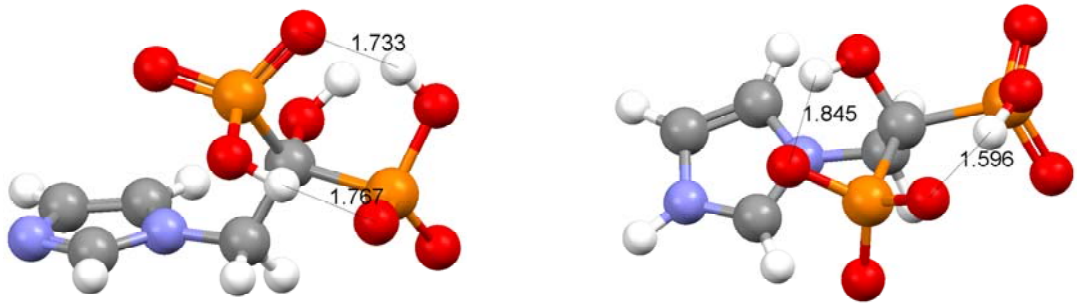
The duel function of the bisphosphonates (BPs) in inhibiting bone resorption (by being adsorbed to mineral surfaces in bone) as well as in interfering with specific biochemical processes must be accounted for to understand their activity in the treatment of bone diseases, including bone cancer. To this effect, the degree of protonation and the placement of protons within a BP is of paramount importance because there is ample evidence that the charge and proton distributions are linked with the BPs mode of action which is still not well understood. For instance,(i) from the solid-state NMR study [1] it was found that both the chemical shift anisotropy and asymmetry cluster as expected for the fully deprotonated state of BPs, but (ii) from the study of interactions of BPs with bone by isothermal titration calorimetry [2] it was concluded that the assumed diprotic form of BPs present in a solution (involving one $–PO_3H^–$ group and a protonated N-atom) is preserved after binding to bone.

We report here protonation constants of the most potent BP, zoledronic acid, ZA (only three constants were reported in the literature [3] and we consider this as highly questionable) and propose the most likely protonation sequence of ZA.

The stepwise protonation constants of zoledronate ($L^{4–}$) were established from glass electrode potentiometric studies at 0.15 M (H,Na)Cl ionic strength, 25° C: log $K_H^{(1)}$ = 10.72±0.05, log $K_H^{(2)}$ = 7.88±0.02, log $K_H^{(3)}$ = 5.69±0.01 and log $K_H^{(4)}$ = 1.79±0.01. From our DFT/QTAIM study (RX3LYP/6-311++G(d,p) in solvent, PCM/UFF), the first step involves a $–PO_3^{2–}$ fragment ($HL^{3–}$ = $^–HO_3P–C(OH,CH_2–Imid)–PO_3^{2–}$ is formed) followed by protonation of the other $–PO_3^{2–}$ fragment ($H_2L^{2–}$ = $^–HO_3P–C(OH,CH_2–Imid)–PO_3H^–$ is formed) fragment. This results in most symmetrical proton distribution in the diprotic form of ZA which is the major species of ZA at blood plasma pH (about 70 % of the total analytical concentration of ZA). Only in the third step the imidazol ring is protonated ($^–HO_3P–C(OH,CH_2–ImidH^+)–PO_3H^–$) and finally a zwitterion is formed (H_4L = $^–HO_3P–C(OH,CH_2–ImidH^+)–PO_3H_2$).

From DFT we found $\Delta G(aq) = G(H_2L^{2–}) – G(*H_2L^{2–}) = –13.7$ kcal mol$^{–1}$ ($*H_2L^{2–}$ has imidazol ring protonated, $^–HO_3P–C(OH,CH_2–ImidH+)–PO_3^{2–}$) – see Fig. 1. Computed ΔG(aq) (equivalent to about 10 protonation constant log units) means that the formation of $*H_2L^{2–}$ (with much larger free energy than $H_2L^{2–}$) is virtually impossible in aqueous solution, contradicting literature reports.

We have also analyzed QTAIM-defined net atomic charges of the phosphonate groups. The net atomic charges obtained for P4, O5, H6, O7, and O8 forming the P4-group in the lowest energy $H_2L^{2–}$ conformer (Fig. 2) are 3.297, –1.388, 0.622, –1.512, and –1.506 *e*, respectively, resulting in q(P4-group) = –0.487 *e*. Note that the net charges of the O-atoms not bonded to H are almost equal (–1.509 ± 0.003 *e*) and larger than the charge of O5 (–1.388 *e*) which is bonded to H6.



H_2L^{2-} $*H_2L^{2-}$

Figure 1. Lowest energy conformers of two tautomers of the diprotic form of ZA: two $-PO_3H^-$ singly protonated fragments are in H_2L^{2-} whereas $*H_2L^{2-}$ has the imidazol ring protonated. Distances shown are in Angstrom.

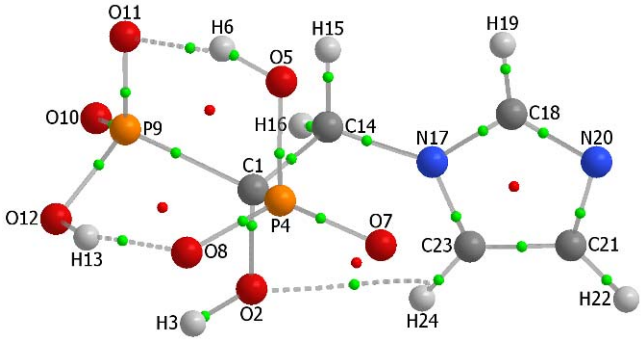


Figure 2. Molecular graph of H_2L^{2-}.

For the P9-group, we obtained net atomic charges of 3.289, –1.510, –1.504, –1.388, and 0.624 *e* for P9, O10, O11, O12, and H13, respectively, *q*(P9-group) = –0.488 *e*. The absolute difference $\Delta|q(\text{P-group})| = 0.001$ *e*.- This resulted in most uniform charge distribution within the $^-OHO_2P–C(OH)–PO_2HO^-$ moiety; similar charge distribution is also observed in the lowest energy conformer of H_3L^-. Three orders of magnitude larger charge difference was found for the lowest energy $*H_2L^{2-}$ conformer, $\Delta|q(\text{P-group})| = 0.750$ *e*. This observation confirms again that the protonation of the imidazol ring should be excluded when diprotic ZA is considered. Crystal structures of HL^{3-}, H_3L^- and H_3L^- / H_4L are also reported and they support the proposed protonation sequence.

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(Thio)pyrone–derived organometallics: an approach for new metal–based anticancer drugs

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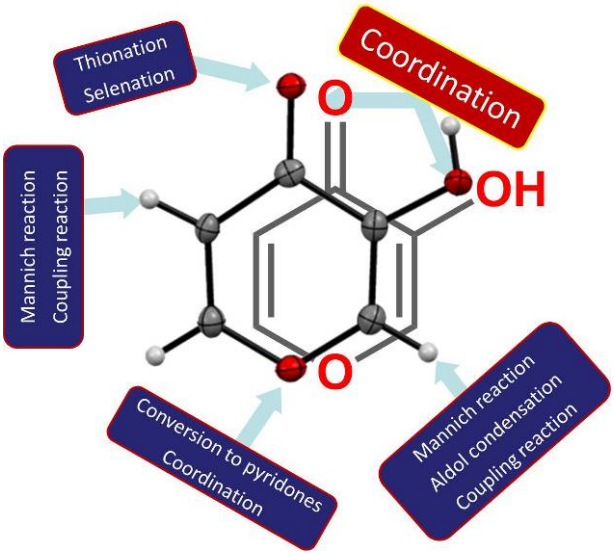
Pyrone scaffolds are often present in natural products and many derivatives exhibit therefore favorable biocompatibility and toxicity profiles. Hydroxypyrones are obtained by isolation from natural sources, are commercially available or can be synthesized by different well established approaches and can easily be converted into the analogous thiopyrones. These features make them well suited for drug development and other biological applications. With the aim to stabilize complexes bearing the (thio)pyrone motif and thereby making them anticancer active, we have synthesized compounds of the general formula [M(arene){(thio)pyrone}X] (M = Ru, Os, Rh; arene = *p*-cymene, benzene, toluene, biphenyl; X = halide).[1] Preliminary structure-activity relationships have been derived from the collected data and will be discussed.



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Solution and biological behaviour of fluoroquinolones metalloantibiotics: a route to counteract bacterial resistance?

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Quinolones are amongst the most widely prescribed families of antibiotics, both in human and veterinary medicine, due to their broad spectrum of activity and safety profile [1]. Their mechanism of action relies on the inhibition of the enzymes responsible for DNA replication (DNA gyrase and topoisomerase IV) [2, 3]. Due to limited activity of the first quinolones (*e.g.* nalidixic acid), structural changes to the basic nucleus were introduced to broaden their antibacterial spectrum of activity namely, the introduction of a fluorine atom at position 6 of the basic quinolone ring, giving rise to fluoroquinolones [4] and a cyclic amino group at C-7. However, their overuse/misuse seems to be the basis of the emergence and dissemination of microbial resistance that results from the bacterial adaptations and compromises antimicrobial efficiency [5]. This increasing menace of bacterial resistance to quinolones, led to the need to improve existing antimicrobial drugs and/or develop new ones, pushing forwards the concept that metal complexes could be an alternative to conventional drugs, as novel derivatives of fluoroquinolones [6, 7]. Numerous studies regarding the interaction between various quinolones and metal cations have been reported and reviewed in the literature. In particular, the study of quinolones–copper–1,10-phenanthroline complexes has become an increasingly important field since they seem to exhibit high affinity towards DNA binding as well as nuclease activity towards plasmid, genomic and internucleosomal DNA [8, 9]

In this work we report the solution behaviour of some fluoroquinolones complexes with copper(II), nickel(II), cobalt(II) and zinc(II) in the presence and absence of 1,10-phenanthroline and the biological effect of the binary and ternary Cu(II) species presented at physiological pH in different Escherichia coli strain.

The values obtained for the stability constants of the binary and ternary divalent metal ion complexes are very high and clearly show that the ternary complexes are more stable than the binary ones, suggesting stabilization due to an intra-molecular interaction between the ligands. Nevertheless, distribution diagrams indicate that only the copper(II) binary or ternary species are stable at physiological concentrations.

Binary copper(II)/fluoroquinolone and ternary copper(II)/fluoroquinolone /phenanthroline complexes were synthesised and characterized by elemental analysis, UV–visible spectroscopy and FTIR or X-Ray crystallographic. The antimicrobial activity of these complexes and of copper(II)/fluoroquinolone and copper(II)/fluoroquinolone/phenanthroline solutions, prepared by mixing of the individual components in the same stoichiometric

proportion and concentration range used for the synthesised complexes, was tested against different Escherichia coli strains.

Although, at a glance, the results point to a possible use of both complexes as metalloantibiotics, a detailed analysis shows that, at biological concentrations, the copper(II) binary complex does not exist and the antimicrobial activity observed is a consequence of its dissociation into free fluoroquinolone (Figure). Consequently, only the ternary complex seems worth pursuing as a possible antimicrobial agent candidate. Moreover, as the biological studies showed, both the synthesised complexes and the solutions prepared by mixing the components exhibited the same behaviour. Hence, a new, faster and accurate methodology to screen metalloantibiotics prior to synthesis of the complexes is proposed.

The overall results are quite encouraging and suggest that the study of the ternary copper complex as a potential new antibacterial agent is worth pursuing. In fact, the hypothesis that microorganisms resistant to pure fluoroquinolones could be sensitive to their metal complex derivatives has previously been put forward.

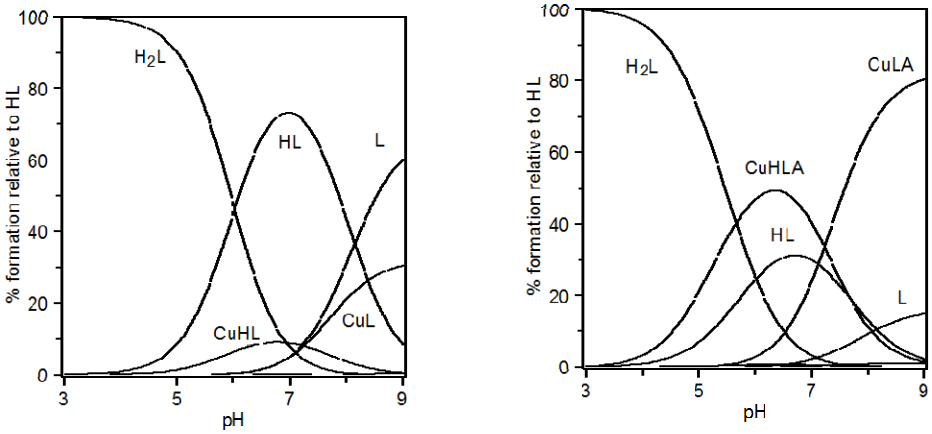

Figure. Species distribution as a function of pH for binary (left) and ternary (right) copper(II) complexes. Calculated from the stability constants listed in Table 1. Concentrations in the range used for MIC determinations.

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Supramolecular chirogenesis with schiff base complexes: a gateway for determination of absolute configurations

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Supramolecular chirality effects are commonly encountered in natural systems such as DNA and metalloenzymes. Nature uses the most elemental building blocks (i.e., amino acids) to create chiral objects in nano-space, and throughout the last decade synthetic chemists have become inspired by these efficient approaches to design new materials with interesting properties [1]. Supramolecular chirogenesis, i.e. the induction of chirality by means of using a chiral substrate that locks a host molecule into a preferred chiral state, is an emerging field of science that has great potential for the determination of absolute configurations of various substrates,[2] enantio-selective catalysis,[3] and use in material science [4].

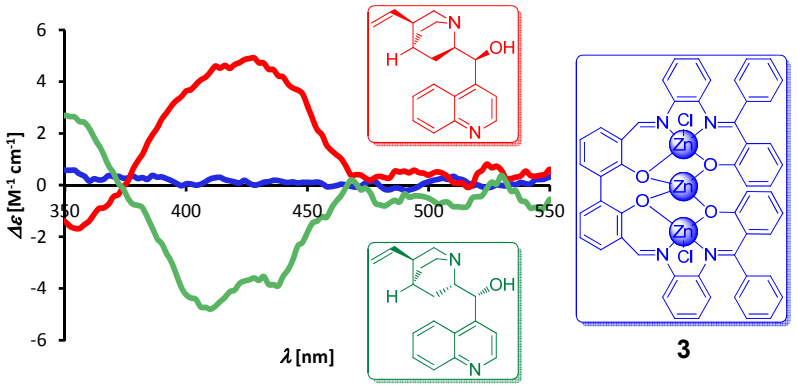

Figure 1: Chirogenesis induced in the trinuclear Zn_3 Schiff base structure **3** using monotopic ligands.

We recently reported a new type of bis-salphen [salphen = *N,N′*-1,2-bis(salicylidene)-diaminobenzene] host molecule incorporating two Zn ions that are connected via a ditopically binding acetate linker [5]. Exchange of the bound acetate for chiral carboxylates results in a preferred population of one of the chiral conformations of the host system as detected by CD spectroscopy. In order to improve the potential of this type of Schiff base structures for chirogenesis effects, we have also designed a second generation host that is "free" of any guest and can be directly combined with various ditopic guests unlike for the first generation host [6]. Furthermore, we found that this new host structure can be made suitable for the

binding of chiral, monotopic substrates by simple cation addition (**3** in Figure 1). As such, the new host structure shows great potential for the determination of absolute configurations for a widespread series of substrates.

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Complex formation equilibria of copper(II) with triethylentetramine and its human acetyl metabolites

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Triethylentetramine (TETA) dihydrochloride is a therapeutic molecule mainly used in the treatment of Wilson's disease, a human disorder characterized by copper accumulation in certain organs [1].

In 1993 Kodama et al. [2] found a TETA metabolite in the urine when TETA was orally administered to healthy humans, which they successfully identified as N^1-acetyltriethylentetramine (MAT) [3]. In a recent study of Lu et al. [4], two major metabolites of TETA were detected in human urine, N^1-acetyltriethylenetetramine (MAT) and N^1,N^{10}-diacetyltriethylenetetramine, the latter being novel. Both metabolites were verified by LC-MS with synthetic standards. The proportion of unchanged TETA excreted as a fraction of total urinary drug-derived molecules was significantly higher in healthy than in matched diabetic subjects, consistent with a higher rate of TETA metabolism in the latter. TETA-evoked increases in urinary copper excretion in non-diabetic subjects were more closely correlated with parent drug concentrations than in diabetic subjects wherein, by contrast, urinary copper was more closely associated with the sum of TETA and MAT. These findings are consistent with the hypothesis that MAT could play a significant role in the molecular mechanism by which TETA extracts Cu^{II} from the systemic compartment in diabetic subjects.

These findings seem to imply a strong interaction of MAT with Cu^{II}, contrary to that reported in the work of Kodama [2], wherein is stated that "the chelating activity of acetyltrien (MAT) is much lower than that of trien (TETA)". This statement is based on a wrong qualitative interpretation of the titration curves of TETA and MAT, both pure and in presence of Cu^{II}, as can be seen by any researcher experienced in solution equilibria studies. Given the strong biomedical importance of the knowledge of the formation constants between copper and MAT and DAT, we performed a potentiometric, and spectrophotometric study of their complex formation equilibria. We furthermore carried out a study of the already know

equilibria between TETA and Cu^{II} in order to provide for comparison the related stability constants derived under the same experimental conditions.

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Metal complexes of the antitumor drug Triapine and related thiosemicarbazones

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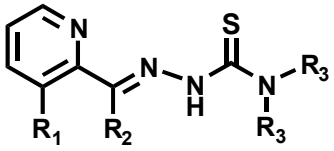
Triapine is the most prominent representative of α-N-heterocyclic thiosemicarbazones (TSCs) as it has been tested in a variety of tumor cell lines in the preclinical setting and is currently undergoing several phase I and II clinical trials [1]. The proposed mechanism of action is based on the inhibition of the iron-containing enzyme ribonucleotide reductase (RNR) and the formation of an iron(II)-Triapine complex is probable, which reacts with molecular oxygen resulting in the generation of reactive oxygen species (ROS). Subsequently, these ROS are responsible for the quenching of the active site tyrosyl radical of the RNR required for the enzymatic activity [2]. The special arrangement of the donor atoms in these TSCs is also suitable for the coordination to other transition metal ions which resulted in the synthesis of complexes with modulated antitumor activity compared to the metal-free TSCs [3].



Triapine: $R_1 = NH_2$; $R_2 = H$; $R_3 = H$

Therefore, the stoichiometry and stability of Fe(II/III), Ga(III), V(IV/V), Cu(II) [4], Zn(II) [4] complexes of Triapine and some related α-N heterocyclic TSCs with potential antitumor activity have been determined by various methods such as pH-potentiometry, UV-vis spectrophotometry, spectrofluorimetry, ESI-MS, ^{1}H and ^{51}V NMR, as well as EPR spectroscopy in partially aqueous solutions (with 30% DMSO), together with the characterization of the proton dissociation processes. Additionally, the redox properties of the iron complexes were studied by cyclic voltammetry at various pH values. The complexation of the α-OH salicylaldehyde TSC was also investigated for comparison.

Our studies are focused on the most plausible species of the metal complexes administered for the biological activity studies emerging in the aqueous solutions at physiological pH and the effect of the substituents (R_1, R_2, R_3) of the TSC backbone on the stability and activity. The knowledge of the speciation and the most probable chemical forms of these complexes in aqueous solution is a mandatory prerequisite for understanding the

mechanism of action and may be useful for the design of more effective and selective chemotherapeutics.

Acknowledgement:

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Equilibrium, kinetic, relaxation and structural properties of H_3DO3A-sulfonamide ligand and its Ca^{2+}, Zn^{2+}, Cu^{2+} and Ln^{3+}-complexes

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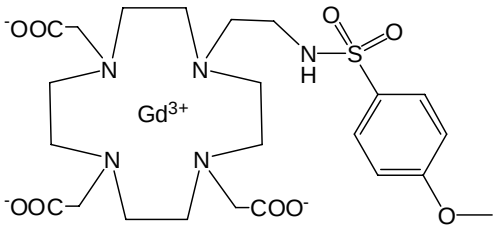
Recently there is a growing interest for *in vivo* monitoring of pathological events (including tumors and cardiovascular diseases) which are associated with alterations of pH homeostasis.[1-3] The goal of the intensive research is to develop non-invasive methods for the *in vivo* pH measurements in local environment of biological systems.[4] The pH sensitivity of the Gd^{3+}-based MRI Contrast Agents is always related to some pH dependent change in physico-chemical, structural or dynamic properties of the agent resulting in substantial alteration of the water proton relaxation rate.

The relaxivity of Gd(III)-complexes of a series of the DO3A-*β*-arilsulfonamide ligands (Scheme 1) has an efficient pH dependence on passing from about 8 $mM^{-1}s^{-1}$ to 2.2 $mM^{-1}s^{-1}$ in the pH range 4.5 – 8.5. It has been demonstrated that the observed decrease of relaxivity is caused by a switch in the number of the inner-sphere water molecules coordinated to the Gd^{3+} from 2 to 0 due to the deprotonation and coordination of the NH-group of the sulfonamide pendant arm.[5]



Scheme 1. Schematic structure of the Gd(III)-complex of the DO3A-*β*-arilsulfonamide ligand (L^1)

We are going to report our new results on the thermodynamic, kinetic, relaxation and structural properties of the Gd(L^1) complex. The protonation constants of the H_3L^1 ligand, the stability and protonation constants of the Ca(II)-, Zn(II)-, Cu(II) and Ln(III)-complexes of L^1 were determined by pH-potentiometry, UV-spectrophotometry and ^{1}H-NMR spectroscopy (Ln^{3+}=La^{3+}, Y^{3+} and Lu^{3+}). The rate of the decomplexation of $GdHL^1$ complex was studied by following its transmetallation reaction with Cu^{2+} in the absence and presence of *β*-cyclodextrin. The formation kinetics of the $CeHL^1$ and $EuHL^1$ complexes were studied by UV-spectrophotometry in the pH range 4 – 6. The structural properties of the $LnHL^1$ and

LnL^1 complexes were investigated by ^{1}H-NMR spectroscopy. The solid state structure of the $CuHL^1$ complex was determined by X-ray diffraction studies.

The stability constants of the Ca(II)-, Zn(II)-, Cu(II) and Ln(III)-complexes of L^1 are very similar to those of the DOTA complexes. The protonation constant of the NH-group of the sulfonamide pendant arm is similar for the free L^1 ligand and the Ca(II)-, Zn(II)- and CuL^1 complexes, whereas the $\log K_{NH}$ values of the LnL^1 complex decrease from La^{3+} to Dy^{3+}, then they increase at the end of the series (GdL^1: $\log K_{NH}$=6.16 (0.02)). The transmetallation reaction between $GdHL^1$ and Cu^{2+} takes place by the dissociation of the $GdHL^1$ via the proton-assisted pathways in the absence and presence of *β*-cyclodextrin. However, the rate constant characterizing the proton-assisted dissociation of $GdHL^1$-*β*-cyclodextrin adduct decreases substantially, it is about half compared to the one of $GdHL^1$. This finding indicates the presence of an intramolecular interaction between the Gd^{3+}-ion and the oxygen atom of the protonated sulfonamide pendant arm, which can be hindered by the "host-guest" interaction between the benzoxy group of the $GdHL^1$ and the cavity of the *β*-cyclodextrin. This kind of interaction has also been confirmed by the ^{1}H-NMR spectra of the $LnHL^1$ and LnL^1 complexes recorded in the temperature range 274 – 353 K.

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Monopicolinate cyclen and cyclam derivatives for stable copper(II) complexation

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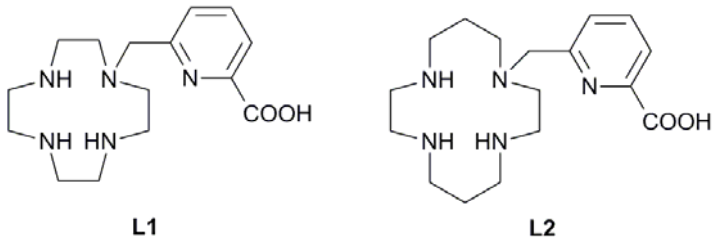

Scheme 1 – Chemical structure of the chelators.

Copper(II) is a very interesting metal cation for applications in nuclear medicine, as some of its radioisotopes have suitable radioactive properties for PET imaging (^{64}Cu) or for radioimmunotherapy (^{67}Cu). Thus, many chelators have been proposed for copper(II) chelation in search of better radiopharmaceuticals, including some allowing for coupling of the radiochelate to a targeting biomolecule to form bifunctional chelates [1]. Among the different types of copper(II) complexes, those based on the well-known cyclen and cyclam tetraazamacrocyclic frameworks have demonstrated to be the most efficient due to their favourable properties of thermodynamic stability and kinetic inertness. For that reason, the development of new cyclen and cyclam derivatives with improved copper(II) chelation properties continues to be a field of intense research effort [1, 2]. Our current research interests also include the design of tetraazamacrocyclic derivatives for stable copper(II) complexation [3].

Now, we have synthesized two new chelators based on cyclen or cyclam containing a picolinate pendant arm, **L1** and **L2** (**Scheme 1**). The thermodynamic stability properties of the chelators and their copper(II) and zinc(II) complexes were studied by potentiometry. Both chelators proved to form thermodynamically strong complexes with copper(II) and less strong ones with zinc(II), but with a striking selectivity for copper(II) over zinc(II) in the case of **L2**. Importantly, the copper(II) complexes of **L1** and **L2** form very quickly from quite acidic pH conditions. The structures of both copper(II) complexes were thoroughly studied in solid state and in solution, showing that the coordination of the complex of **L1** is distinctly pH-dependent unlike the complex of **L2**. Indeed, while in acidic pH both complexes are penta-coordinated with the metal centre bound to all amines of the ligands, at neutral pH the metal in the complex of **L1** is also coordinated to the carboxylic oxygen atom and thus becomes hexacoordinated. These features were consistently found in solution by UV-vis and EPR

spectroscopies, and in crystal structures obtained at low and neutral pH, from which examples are shown in **Figure 1**. The kinetic inertness of the copper(II) complexes was studied by acid-assisted dissociation and cyclic voltammetry assays. In highly acidic media, the complex of

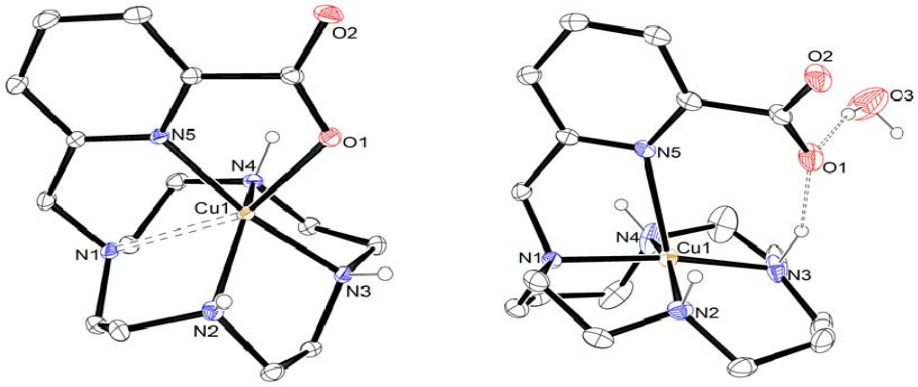

Figure 1 – X-ray crystal structures of the copper(II) complexes of L1 (left) and L2 (right) at neutral pH.

L1 is moderately stable while the complex of **L2** is very stable when compared to other macrocyclic complexes, and a dependence of the counter-anion present (chloride or perchlorate) was also found and is higher for the latter complex. The electrochemical studies showed quasireversible reduction systems for both complexes at neutral pH, while at acidic pH they become irreversible. This demonstrated that, at physiological pH, both complexes are able to avoid demetallation upon reduction of copper(II) to copper(I), with a clear advantage for the complex of **L2**.

In conclusion, we have developed two new chelators that are capable of quickly forming thermodynamically stable copper(II) complexes, which are kinetically inert under very acidic media and also stable upon copper(II) reduction. In particular, the complex of **L2** appears as a promising candidate for applications in nuclear medicine. The thermodynamic, kinetic, and structural properties of the complexes of **L1** and **L2** will be discussed in detail.

Acknowledgements

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Mn(II) chelates with potential interest for MRI

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Magnetic Resonance Imaging (MRI) has become one of the most successful diagnostic imaging modalities. A large number of MRI scans use paramagnetic contrast agents (CA), to enhance the image's contrast. Gd(III), with seven unpaired electrons and a long electronic relaxation time, is the most used metal ion for the preparation of CA. Mn(II) is also a good candidate for MRI contrast agents due to its five unpaired *d* electrons, a favorable electronic relaxation time, and the lability of the coordinated water molecule(s). Presently, there is one approved Mn(II)-based CA, Teslascan® ($[MnDPDP]^{4-}$, $DPDP^{6-}$ = *N,N'*-dipyridoxylethylenediamine-*N,N'*-diacetate-5,5'-bis-(phosphate), Figure 1).

Due to toxicity problems, the paramagnetic ions should be administrated as metal complexes of high thermodynamic and kinetic stabilities. Macrocyclic ligands are known to form such stable metal complexes. Bifunctional ligands can be coupled to targeting molecules (i.e. peptides) with high affinity for biological receptors, preserving the coordination properties of the chelator.

Chelates with hydrophobic moieties can interact with human serum albumin (HSA), the most abundant serum protein. This can be exploited as a strategy to increase the blood retention time of the metal chelate and also to enlarge the relaxivity by increasing the chelate tumbling time (τ_r) [1-2]. The formation of micelles by amphiphilic chelates can also be used with the goal of increasing τ_r.

In this work, we developed three new triazapolycarboxylate ligands for Mn(II), NODAHep (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-heptanil), NODABA (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-bensoate), and NODAHA (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-hexanoate) (Figure 1). These chelators are pentadentate, leaving one coordination site of the metal coordination sphere available for one water molecule. NODAHep has a lipophilic side chain, designed to endow the chelate with the capacity of forming micelles and of interacting non-covalently with HSA. This was expected to increase τ_r and consequently to increase the relaxivity. NODABA and NODAHA are bifunctional ligands that present a free carboxylic group in the pendant lateral chain, allowing their conjugation to targeting molecules.

^{1}H NMRD and ^{17}O NMR studies were performed for the three Mn(II) chelates, showing relaxivity values comparable to those of Gd(III) chelates with one water molecule in the inner coordination sphere of the metal ion. Potentiometric titrations allowed the determination of

the pK_a's of the ligands and the thermodynamic stability constants of the Mn(II) and Zn(II) chelates. The kinetic stability of [Mn(NODAHep)] in the presence of Zn(II) and at different pH values was also studied. The critical micellar concentration of the amphiphilic [Mn(NODAHep)] chelate was determined by fluorescence and ^{1}H NMRD.

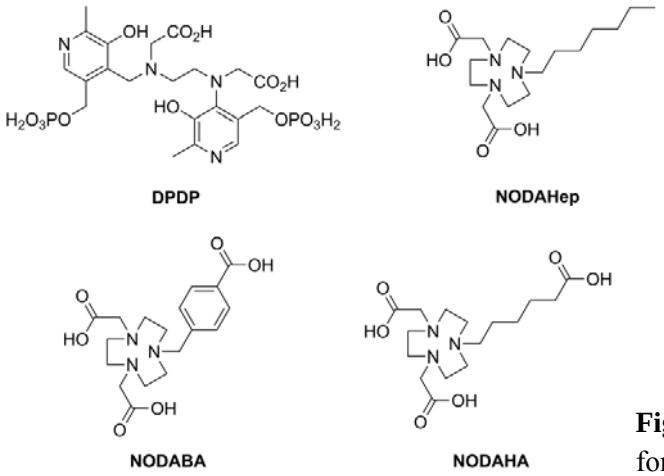

Figure 1 – Structure of the different chelators for Mn(II).

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Binding properties of *p-tert*-Butylcalix[4]arene derivatives and their application in ion selective electrodes

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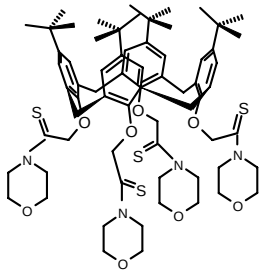
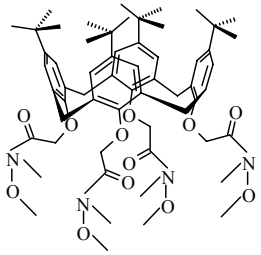
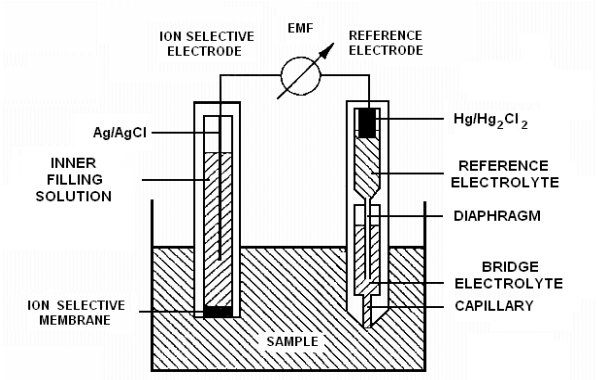
The importance of detecting and controlling the toxic heavy metals, such as Cd^{2+} or Pb^{2+}, in biological or environment samples is extremely important, being a challenge for chemists who design and synthesize selective ligands for these cations. Chemical potentiometric sensors based on ‘‘host–guest” interaction are for the last years in fast progress e.g. decreasing of the sensors size, lowering the detection limits, improvement of the sensor sensitivity and selectivity, and of the response and the lifetime [1]. The relationship between a new ionophores properties and its structure, is of great interest [2]. Due to the remarkable and versatile binding properties, *p-tert*-butylcalix[4]arenes may act as hosts for cations, anions or neutral molecules depending on their functionalization.

We report here the study of calix[4]arene functionalized with amide, thioamides and hydroxamate moieties as potential sensing material for transition and heavy metal cations. Although some examples of calixarene-thioamides applications are known from the literature, only few publications deal with, for instance, stability constants determination which is important in studying new ligands properties [3-5].

The interactions of these ligands with several representative cations (Na^+, Ca^{2+}, Gd^{3+}, Ag^+, Cd^{2+}, Pb^{2+}, Zn^{2+} and Cu^{2+}) were studied using different techniques: liquid-liquid extraction, ^1H NMR, X-ray diffractometry, UV spectrophotometry, potentiometry and microcalorimetry. Results obtained with some calixarene derivatives used as active materials in ion-selective membrane electrodes (ISEs) are presented and discussed.







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BODIPY-phosphane as a versatile tool for an easy access to new metal-based theranostics

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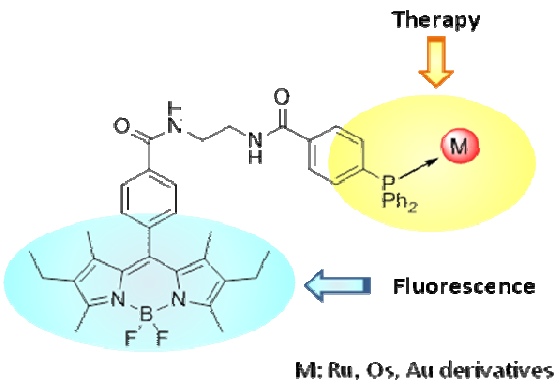
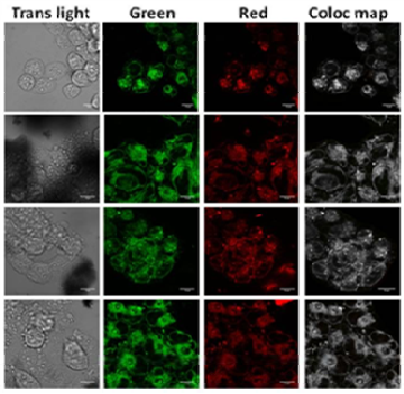
Since the pioneer discovery of cisplatin for biological applications by Rosenberg in the 1960's,[1] metal complexes have become the most currently investigated and used class of compounds in cancer chemotherapy.[2] However in most cases, their mechanisms of action are still poorly understood. Imaging drugs aimed at understanding their mechanism of action and studying their pharmacokinetics is thus one of the key challenges of medicinal chemists today.





To take up this challenge a new BODIPY-phosphane compound was synthesized. It is a versatile tool to image organometallic complexes, and allowed the access to an unprecedented family of theranostics featuring Au, Ru and Os complexes. The compounds were studied for their stability and fluorescence properties in solution. Their cytotoxicity was also tested on cancer cells, and their cell uptake was followed by fluorescence microscopy in vitro.

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Effect of ethanol on gold nanoparticles-induced DNA compaction: thermodynamic, kinetic and conformational aspects of the Interaction

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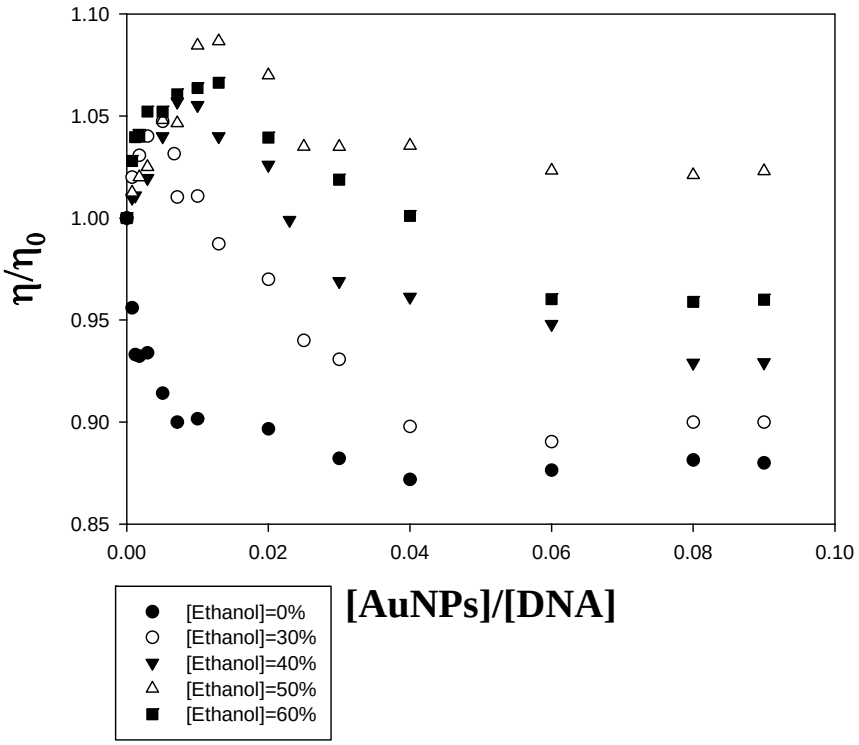
The features of binding and the effect of ethanol on the kinetic and DNA conformational changes induced by N-(2-mercaptopropionyl)glycine gold nanoparticles, AuNPs, were studied in detail by means of fluorescence and circular dichroism (CD) spectroscopy, atomic force microscopy (AFM), viscosimetry and dynamic light scattering (DLS) experiments. From CD titration it was determined that AuNPs displayed a higher binding affinity toward DNA when they were attached to the biomolecule. The rise in the ethanol content is reflected in a great increment of the equilibrium binding constant of the interaction [1]. The kinetic of the interaction has been studied by using stopped flow technique in CD detection mode. The kinetics curves reveal the presence of two different processes whose rates differ by about three orders of magnitude on the time scale. Viscosity experiments were performed at a constant DNA concentration by adding increasing amounts of gold nanoparticles. Figure shows that the measured viscosity increases initially with increasing binding ratio and subsequently decreases after passing a maximum. The biphasic behavior of the viscosity curve remains upon changing the ethanol percentage. Similar trends were registered in fluorescence titrations of solutions containing the DNA and the fluorescence probe, 1-PyCHO, with AuNPs. It is known that the fluorescence emission of 1-PyCHO decreases when it goes from a polar to a non-polar medium such as DNA bases [2]. The increase of the fluorescence emission of 1-PyCHO at low binding ratio, R, indicates the competition of AuNPs with 1-PyCHO in the binding to DNA. Such unexpected behavior can be rationalized by considering that the presence of ethanol promotes AuNPs partial intercalation into DNA bases. The observed decrease of the viscosity is assigned to the formation of aggregates of DNA/AuNPs compacted structures. These results were confirmed by atomic force microscopy and dynamic light scattering technique. Structural and conformational changes of DNA due to the effect of alcohol on AuNPs-DNA binding results may provide useful information to design better anticancer compounds using metal nanoparticles.



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Factors affecting the thermodynamic and redox stability of manganese(II) – and cobalt(II) – hydroxamate complexes

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There are many reasons, why results, what can be obtained by investigation of the different factors, determining the interaction of biogenic metals, including manganese and cobalt, with different hydroxamic acids are interesting. For example (i) both of the mentioned metal ions can be involved in catalytic centers of metalloenzymes and, it is without doubt that the significant inhibitory effect of hydroxamate-based compounds is in direct correlation with the coordination of the hydroxamate function to the metal ion situating in the active centre of the metalloenzyme. As a consequence, if the main factors determining the manganese and cobalt binding ability of hydroxamate based compounds are known, those provide valuable help during development of a new effective inhibitor molecule. Also the results can help to get deeper insight into the mechanism of inhibition. (ii) Mn(II)-hydroxamate complexes can be expected as potential candidates for contrast agent application in medical magnetic resonance imaging. The above are the main reasons, why recently, we have investigated manganese and cobalt complexes of numerous hydroxamic acids, including synthetic compounds and natural siderophores. In this study, thermodynamic stability, redox stability, and in the case of the manganese-containing systems also the relaxivity data of the formed complexes have been determined and evaluated [1,2].

In these works, really noticeable results were obtained relating the redox behaviour of the complexes formed with two natural siderophores, Desferrioxamine B (DFB) and Desferricoprogen (DFC). It was found that under acidic condition, as expected, the M^{2+}-containing species existing under acidic condition were not sensitive to air oxygen, but they became sensitive at neutral and high pH and the formation of the extremely high stability M^{3+}-containing species was supported [1,2]. According to the results (and in the case of DFB complexes, in agreement with recently published literature data [3,4]), the stability of the Mn(III) complexes are close, while that of the Co(III) complexes is higher than the stability of the corresponding Fe(III) species. Whether does it mean the possibility of disruption of the microbial iron-uptake in the presence of these metal ions under certain conditions? This question and also the possibility of the development of pro-drugs with the help of high stability inert Co(III)-hydroxamate based complexes are waiting for answer. To obtain some additional information to these open questions, namely to explore some factors affecting the redox processes, such as the effects of the number of hydroxamic functions, the pH, the presence of additional donor atoms in the chelating molecule, investigations are still going in our laboratory. In addition to the mentioned trihydroxamis acids, also mono-, di- and aminohydroxamic acids are involved into the study by using pH-potentiometry, UV-Vis

spectrophotometry, cyclic voltammetry and ESI –MS methods. The main results are planed to summarize and evaluate in a presentation on the conference.

Acknowledgments
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Kinetic study of metal complexes with tetraazamacrocyclic ligands with carboxylate/phosphonate pendant arms

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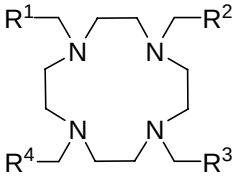
Ln(III) and Cu(II) complexes are utilized in medicine and preclinical research as magnetic resonance, optical or nuclear probes for diagnostics and/or for cancer treatment. For biomedical applications, such complexes should exhibit a high thermodynamic stability as well as kinetic inertness under physiological conditions. Thus, knowledge of their thermodynamic/kinetic properties (e.g. dissociation rate constants for an estimation of kinetic inertness) is important to evaluate their use in these applications.



R^1, R^2, R^3, R^4 = COOH	**H_4dota**
R^1, R^2, R^3 = COOH; R^4 = $P(O)(OH)_2$	**H_5do3ap,**
R^1, R^3 = COOH; R^2, R^4 = $P(O)(OH)_2$	**H_6do2a2p**
R^1 = COOH; R^2, R^3, R^4 = $P(O)(OH)_2$	**H_7doa3p**
R^1, R^2, R^3, R^4 = $P(O)(OH)_2$	H8dotp
R^1, R^2, R^3, R^4 = P(H)(O)(OH)	H4dotp^{H}
R^1, R^2, R^3, R^4 = P(O)(OH)(OEt)	H8dotp^{OEt}
R^1, R^2, R^3, R^4 = P(Ph)(O)(OH)	H8dotp^{Ph}
R^1, R^3 = COOH; $R^2 = R^4$ = H	H4dotp
R^1, R^2, R^3 = COOH; R^4 = H	**H_2do2a**
	H_3do3a

Here, thermodynamic and kinetic properties of Cu(II), Ce(III) and Eu(III) complexes with macrocyclic cyclen-based ligands where acetate pendant arms were substituted by phosphonates (H_4dota, H_5do3ap, *trans*-H_6do2a2p, H_7doa3p, H_8dotp) [1–4] are presented. In addition, the influence of substitution of one acetate/phosphonate of (H_2do2a/H_3do3a/H_4dota/H_5do3ap derivatives) and/or all phosphonate pendant arms (H_8dotp derivatives) was also studied [5-7]. These results show that the kinetic inertness of the metal complexes is influenced by these substitutions and, therefore, this fact should be taken into account in possible *in vivo* applications of the ligands/complexes.

Acknowledgement:

Financial support from the Ministry of Education of the Czech Republic (grants ME09065 and MSM0021620857), and EU programs (COSTs CM 1006, TD 1004, ERASMUS; CEITEC CZ.1.05/1.1.0/02.0068) are acknowledged.

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Novel functional materials as Ionic Liquids based on metal complexes

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The development of smart functional materials that can combine one or more properties is one of the major challenges in the industrial and research modern applications. Several smart materials have been developed in recent years where their properties can be significantly changed in a controlled fashion by external stimuli such as temperature, pH, electric or magnetic fields, among others. Metal complexes can be incorporated for the development of some functional smart materials.

Ionic liquids (IL) are organic salts in the liquid state and are particularly interesting those liquid at room temperature RTIL's. [1] They are constituted by an organic cation and an anion that could be organic or inorganic. Some peculiar properties of ILs, such as, very low vapour pressure, non-flammability, high ionic conductivity, large electrochemical window and chemical stability, capacity of dissolving different organic, inorganic and polymeric compounds, catalytic properties have been attracted the interest of numerous researchers and the field is in growing expansion. Another important aspect is the fact that the physico-chemical properties of IL can be tuned by the appropriate combination of the anions and cations.

In recent years our team reported the use of functional ILs in different contexts such as the preparation of the first intrinsically photochromic ionic liquid [2] or first intrinsically electrochromic (and magnetic) ionic liquid based on metal complexes of the ligand Ethylenediaminetetraacetic (EDTA) with the appropriated cations [3] Some of these compounds can also switch from diamagnetic to paramagnetic upon reduction/oxidation.

Electrochromic materials are the basis of a variety of devices where the discovery of high ionic electrolyte is generally the most challenging component of these devices. Some advantages can be expected with the combination of ILs as good electrolytes and electrochromic scaffolds as cations or anions units.

Encouraging with the preliminary results related with Room Temperature ILs based on Vanadium Oxide, we have developed different Electrochromic based on metal oxides preferentially as anions units and metal complexes with organic or inorganic ligands as well as based on supramolecules structures such as aza macrocycles as cations or anions units. In the case of these structures, the electrochromism lies on the metal center used (vanadium, tungsten, manganese, copper, iron, cobalt, nickel or ruthenium). Different examples of electrochromic ILs and their display devices will be discussed.

The discovery of magnetic ILs was only recently reported which are primarily based on high-spin d5 Fe(III) in the form of tetrachloro- or tetrabromoferrate (III) anions combined with various counter cations. [4]

Some of the Ionic Liquids based on metal complexes can be also used as magnetic ILs according with the selected metal. Potential applications of Magnetic ILs have been described mainly for separations processes as well as chiral extraction and enrichment of chiral compounds.

Novel Magnetic ILs have been developed in our group mainly based in similar structures as described before such as metal complexes with organic and inorganic ligands, supramolecular structures such as aza macrocycles (tri and tetradentate). These scaffolds represent an extraordinary research topic for the complexation with paramagnetic species.

Preferentially, we selected supramolecules that can well-incorporate different paramagnetic transition metals and lanthanides such as iron(III), manganese (II), Chromium (III), terbium (III), dysprosium (III), samarium (III) and gadolinium (III). Depending the ligands or supramolecules selected as well as oxidation state of the metal is possible to create magnetic anions or cations units.

All novel electrochromic and magnetic ILs have been completely characterized by NMR, FTIR, UV/Vis, cyclic voltammetry, spectroelectrochemical studies, Mass Spectra (ESI or MALDI-TOF techniques) or Elemental Analysis. Complementary studies related with their evaluation of physical, chemical and thermal properties have been performed.

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Grafted squaramide nanoparticles systems for sulfate recognition in pure water

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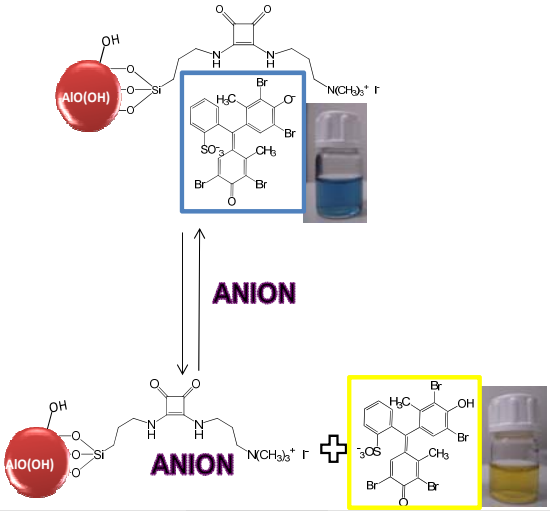
Squaramide ligands have shown good potentiality for the selective recognition of sulfate anions either in non-polar solvents or in alcohol or alcohol-water mixtures with water contents not above 10 % v/v. [1-3]

Additionally, the recognition of sulfate over phosphate in hydroalcoholic medium is based on the regulation of pH since at the acidic pH values where phosphate anions exist in its diprotonated monovalent $H_2PO_4^-$ form; sulfate still persists in solution as the divalent SO_4^{2-} anion due to its higher acidity. [4] However, these systems are not operative in pure water due to the fact that water itself is a good hydrogen bond donor and acceptor and disrupts the hydrogen bonding of the dye and anion with the squaramide function.

In this communication, we describe a very simple system able to operate in pure water in a broad pH-range. Systems formed by a chain containing a squaramide function and a quaternised amine group attached to boehmite or silica-coated boehmite nanoparticles are able to discriminate anions in pure water. To sense this recognition, displacement assays (IDA) in buffered solutions in which an anionic dye bound to the squaramide is displaced to the solution by the target anion have been used as we show in the Scheme below. [5]



We will prove that the attachment of these molecular components to the nanoparticles leads to devices with reproducible responses and long durability for selectively binding sulfate anions in pure water, which is a challenging goal in supramolecular analytical chemistry.

We thank MINECO and GVA for financial support (Consolider Ingenio 2010-00065, CTQ2009-14288-CO4-01 and PROMETEO2011/008 grants)

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Thermodynamics of protonation and metallation of the TPTZ ligand with a variety of cations

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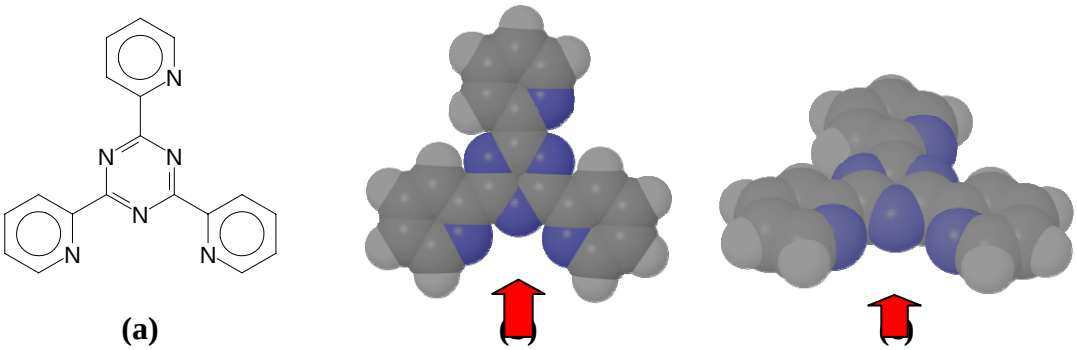
Selective coordination of minor actinides, in particular, the most radiotoxic of them americium and its neighbour in the periodic table curium, is the major unresolved challenge in the way of efficient reprocessing of spent nuclear fuel [1]. The task is far from trivial, as the above mentioned actinides have to be separated from a matrix of numerous lanthanides and other metals. Trivalent lanthanides and actinides are very close in their coordination behaviour, and without removing the former, which unfortunately possess high neutron cross-sections, disposal of Am and Cm isotopes is not viable, as it entails transmutation of these long-living and highly radioactive species to other short-lived isotopes [2]. In addition, spent nuclear fuel contains an array of other elements, some of which, like transition metals, are coordinated much more strongly than lanthanides or actinides by the conventional ligands.

In this work we turned our attention to the polyazine-based ligands, which have become the object of close attention in recent years. It has been shown that polydentate nitrogen ligands can separate both Am(III) and Cm(III) from Ln(III). The most promising candidate ligands of this type reported in literature thus far are 2,6-bis-(5,6-dialkyl-1,2,4-triazine-3-yl)-pyridines (BTPs), which afford Am/Ln separation factors between 50 and 150, when used to extract from 1-2 M HNO_3 [3]. Although vast amount of data has been published on the thermodynamic stability of metal complexes of polypyridine ligands, such as Bpy, Tpy, and their numerous modifications, very little information is available for the complexes of polyazine ligands. The only systematic experimental study in this area that we are aware of is that of the coordination of Ln(III) and Am(III) by Adtpz ligand [4].

In this presentation we report the stoichiometry of equilibrium species detected in aqueous solutions alongside protonation and stability constants of the Tptz ligand and its complexes with a range of metal ions of different nature, determined by the UV-Vis absorption spectrophotometry and refined by means of the Protonic Software applications [5]. In particular, the stability constants of Tptz complexes with alkali-earth: Mg(II), Ca(II), Ba(II), 3*d*-transition: Co(II), Ni(II), Cu(II), Zn(II), heavy: Cd(II) and Pb(II), rare-earth and lanthanide: Sc(III), Y(III), La(III), Ce(III), Sm(III), Gd(III), and Lu(III) metal ions, both in water and in 0.100 M $NaClO_4$(aq) are reported.

Tptz, or 2,4,6-Tri(2-pyridil)-1,3,5-triazine, Scheme (a), is a ligand with a cleft (b-c) that serves as a metal binding site of particular dimension (shown with a red arrow). It reportedly can be protonated in two steps [6] but the values of acid constants were somewhat in doubt. An interesting feature of this ligand is that the triazine nitrogens are practically non-basic,

and, subsequently, almost non-nucleophilic. As we found, this affords weaker binding of metal ions with high affinity towards nitrogen donors (e.g., Ni(II), Cu(II), etc.). On the other hand, enhanced complex stability is observed for metal ions of the "right size", the ones that fit best into the cleft of Tptz (relatively large ions with spherically symmetric closed shell). Resulting uncommon pattern of complex stability and selective binding might be exploited in the reprocessing of nuclear fuel waste (separation of minor actinides from lanthanides), or in treatment of such ailments as the Alzheimer disease and other neurological disorders.



Scheme. Different views of the Tptz ligand.

A brief analysis of rather interesting electronic spectra of Pb(II) and Ce(III) aqua-ions will also be offered.

As anticipated, the stability of the Tptz-M complexes with a covalent type of binding is significantly reduced in comparison to the Tpy analogues, while that of the complexes with predominantely ionic type of binding is notably increased. The peak of stability within the lanthanide series was observed for Sm(III) (it might be on Nd(III), which has not been studied yet), and bodes well for the potential coordination of Am(III).

The work currently in progress on this ligand includes the investigation of binding by it large heavy metal ions, Hg(II), Bi(III), Th(IV), and UO_2(II). The aim is to better understant the nature of interaction of Tptz with large metal ions, resembling Am and Cm in their coordination chemistry.

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Modeling of Sn^{2+} speciation in aqueous solution, with particular reference to natural fluids

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In contrast with organotin(IV) compounds, inorganic tin forms are less considered and are not generally envisaged as biologically and/or environmentally relevant, though their biological activity and their importance from the environmental point of view is documented. Moreover, the formers are commonly formed by (bio)alkylation of inorganic tin in the environment, and the extent of this (and other) process(es) is strictly dependent on the speciation of the latter. Despite this, very few studies are reported on the speciation of inorganic tin forms in aqueous solution and less are those referred to natural fluids. The speciation studies in such systems are particularly difficult, since the knowledge of a lot of thermodynamic parameters is requested for all the components involved in the formation equilibria in those conditions. Moreover, inorganic tin forms are already characterized by some particular chemico-physical solution properties that make their study more difficult than other cations. The 2+ and 4+ oxidation states of tin are both fairly stable and both undergo strong hydrolysis low pH (pH ~ 2 for Sn^{2+}), and the precipitation of sparingly soluble species already occurs in the acidic pH ranges even at millimolar concentrations. In the case of tin(II), it can be also oxidized to tin(IV) by atmospheric oxygen, so that particular attention must be paid during experiments for this cation. These facts are probably the most important causes of the lack of reliable information on the solution chemistry of inorganic tin forms (and Sn^{2+} in particular) and its interactions with various ligands. For this reason, recently our group has undertaken a systematic study of the speciation of Sn^{2+} in aqueous solution, in the presence of inorganic and organic ligands of biological and environmental importance [1-3]. Owing to the objective impossibility of measuring all interactions of tin(II) with all components of real systems, modeling studies are very useful. In this light, tin(II) behavior in natural waters and biological fluids can be assessed by modeling its reactivity towards the main classes of ligands usually present in natural systems (carboxylates, amines, S-donor ligands, phosphates, etc.), of both natural origin or derived from anthropogenic activities, so that particular attention was paid by our group to the study of the interactions of this cation with these ligands, by means of potentiometric, voltammetric and calorimetric techniques. In this contribution, several empirical relationships are presented, for a rough but immediate estimation of various thermodynamic parameters (stability constants / free energies, formation enthalpy changes, quantitative parameters for the sequestering ability, etc.) as a function of different variables, including the structure of ligands and the nature of their functional groups.

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DMT and AGNES: determination of free Zn(II) concentrations in synthetic systems, in river water and in soils

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Toxic or nutritional effects of an element are essentially related to its free metal ion concentration, according to environmental paradigms such as the Free Ion Activity Model (FIAM)[1]. Consequently, there is a significant interest for analytical techniques that can act as selective probes for the free Zn(II) concentration in a large variety of environmental systems, but also in synthetic solutions (e.g. for the determination of stability constants) or food systems. The measurement of free Zn(II) concentration is particularly challenging, because there is no commercial Ion Selective Electrode for this element. Only a very few techniques have a direct access to the free metal ion concentration, while many other popular techniques (such as DGT, Diffusion Gradients in Thin Films) measure operationally defined fractions (e.g. a certain labile fraction). AGNES (Absence of Gradients and Nernstian Equilibrium Stripping)[2] and DMT (Donnan Membrane Technique)[3] provide robust and direct measurements of the free metal ion concentrations. In the literature, AGNES has been applied for the determination of free Zn in seawater, freshwater, humic acid solutions, ZnO nanoparticles dispersions, wine, etc. DMT has been applied to soils, natural waters, etc.

The application of both techniques to the same synthetic and natural systems allows a cross-validation. AGNES and DMT are validated in synthetic solutions of Zn+NTA, yielding results in agreement with each other and with the theoretical code VMINTEQ. A further validation came from analysis of Rhine river water. A critical comparison of the characteristics of both techniques can be performed in terms of time of analysis, limit of detection, required instrumentation, etc. We report the first application of AGNES to different type of soils extracts[4]. The analyses of free Zn in 4 soil extracts gave similar concentrations with both techniques, and consistent with ECOSAT theoretical predictions.

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Molecular reorganisations in polytopic receptors

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Coordinated molecular reorganisations induced by chemical or physical impulsi are central to life. For instance, Ca^{2+} induced conformational changes of the calmoduline family of proteins trigger the activity of different enzymes, ionic pumps and other proteins.[1] The rotational motion of flagella that permits the straight swimming of bacteria constitutes a beautiful example of a pH-driven molecular motion.[2] Previously, chemists have gained inspiration from these sophisticated biological molecular systems to generate much simpler molecular devices able to perform movements in response to chemical or physical inputs.[3] Polytopic ligands having differentiated binding sites represent a landmark for investigating substrate reorganisation within receptor molecules. These motions, whose final stage is under thermodynamic control, can be, however, kinetically guided in its intermediate stages. In spite of this, the number of kinetic studies about molecular reorganisations of substrates in polytopic ligands is small.[4]

Here we report the kinetics of Zn^{2+} and Cu^{2+} reorganisation motions within the polytopic ligands **L1** and **L2**. **L1** has two different coordination sites, a polyamine scorpiand-like macrocycle and a phenanthroline chelating unit. **L2** can be described as a double scorpiand-type ligand in which the tails of two identical scorpiand moieties have been connected through a phenanthroline unit. Therefore, **L2** presents three clearly differentiated binding sites: two macrocyclic units and one phenanthroline site.

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The mechanism of the reaction of gold(III) ion with pyridine-2-azo-p-dimethylaniline in water and SDS

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The gold extraction and recovery from its scraps and waste fluids has attracted considerable attention because of increasing industrial demand of gold in electronics and devices, in biomedicine and catalysis [1,2]. In recent years the research on metal extraction based on micellar system indicates that ligand modified micellar enhanced ultrafiltration (LM-MEUF) can be a promising green technique for the separation, extraction and recovery of metal-ions [3,4,5].

Previous studies from our laboratory on gold extraction with sodium dodecyl sulphate (SDS) have been demonstrated that the use a complexing ligand, as pyridine-2-azo-p-dimethylaniline (PADA), greatly enhances gold(III) extraction yields. Furthermore, in order to understand the fundamental aspects of process, the kinetics of complex formation reaction between gold(III), initially present as AuCl4-, and PADA have been investigated in water, and in mixtures of water and SDS using classical spectrophotometry and stopped-flow technique.

The tetrachloroaurate anion in aqueous solution undergoes multiple hydrolysis forming several chlorogold(III) species.

$$Cl^- + Au(OH)_yCl_{4-y} \rightleftharpoons Au(OH)_{y-1}Cl_{5-y} + OH^- \qquad (1)$$

Our results show that the equilibria represented by equation (1) play a very important role in the kinetics of gold(III)/PADA system. Actually, it has been found that the reaction rates depend in a rather complex way on the acidity and chloride ion concentration. The analysis of the kinetic behavior reveals role of the surface charge of the micellar system on the binding reaction. In effect, in the presence of anionic micelles (SDS), an “anticatalytic effect” has been observed (Figure 1) that should be ascribed to repulsion of the negatively charged gold(III) complexes by the negative SDS micelles.

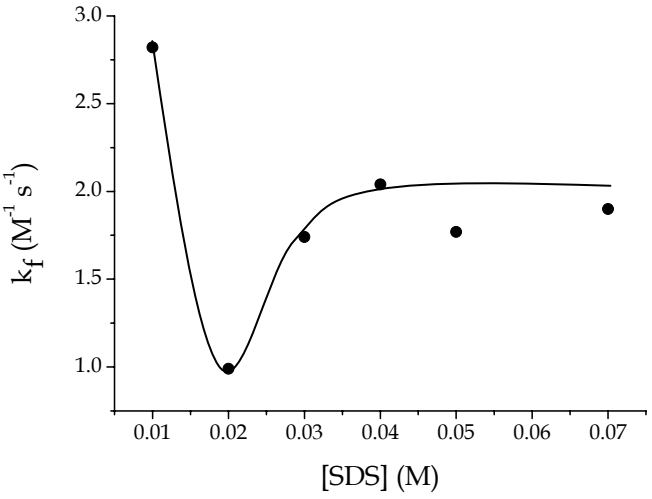

Figure 1. Plot of the rate constant of the slow effect, k_f, vs surfactant concentration for the gold(III)-PADA system at pH = 5; $C_{Au} = 2\times10^{-4} \div 2\times10^{-3}$ M, $C_{PADA} = 2\times10^{-5}$ M, [NaCl] = 0.04 M, T = 25°C.

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New synthesis dinuclear metal complexes which including gold(III), ruthenium(II) and platinum(II), induce apoptosis in cancer cells via activation of mitochondrial pathway

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Around the world scientists try to design successful cures against still incurable diseases such as AIDS, diabetes or especially cancers. It has been known for many years that metal ions such as gold(III), ruthenium(II) or platinum(II) exert wide biological activity, for example against tumor cells.

Human tumors harbor multiple genetic alterations in genes controlling cell growth, differentiation and survival. These genetic changes comprise activation of oncogenes and inactivation of tumor suppressor genes. One of the most frequently activated oncogenes in human cancer is the Ras gene family. So, in humans, about 30% of the tumors carry Ras mutations [1]. Induction of apoptosis in cancer cells is a key killing mechanism for most antitumor therapies including chemotherapy, g-irradiation, immunotherapy, or cytokines [2].

In this respect, extent of study the metal complexes $[Au(L)(B)]PtCl_2$ and $[Ru(L)(B)]PtCl_2$ were synthesised by benefiting from appropriate literature methods for determining the cytotoxic and apoptotic effects. The complexes have been synthesized by using 2,2'-bipyridyl (L) as ligand, and bis-1,4-di[([1,10]fenantrolin-5-il)amino]-2-buten (B) as a bridge molecule. The characterization of the intermediate and final compounds arising from this work was carried out by means of a variety of spectroscopic methods, which include ^{1}H NMR, IR, MS, and elemental analysis. The cytotoxic and apoptotic effects of test compounds were elucidated with normal rat embryo fibroblast-like cells (F2408) and *H-ras* oncogene activated rat embryo fibroblast-like cancer cell line (5RP7). Cytotoxicity was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoium bromide (MTT) assay. Apoptosis was detected by nuclear fragmentation (DAPI staining and DNA laddering assay) and mithocondria membrane polarization (JC-1 staining).

Creating metal complexes as anticancer drugs is really promising but not easy because the accumulation of metal ions in the body can cause undesirable effects. As the main aim of chemotherapy is the destruction of tumor cells without any undue influence on proper cells, it should not be forgotten that although metals cause desirable effects like cell division, they are also potentially carcinogenic [3]. Our results showed that Au(III) compound selectively targeting cancer cells not normal cells. Also significant increases in the levels of apoptosis were observed with increasing exposure concentration. Additionally, Au(III) compound more

toxic and apoptotic than cisplatin and Ru(II) compound at low concentrations. Our results indicate that gold might be a promising candidate for potantial anticancer therapeutic use.

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Tuning the hydrolytic properties of half-sandwich type organometallic cations in aqueous solution

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Half-sandwich organometallic complexes of various platinum metals are promising candidates as anticancer drugs [1-3]. When administered, the $[(\eta^6/\eta^5\text{-arene})M(XY)Z]$ type compounds, where in hexahapto moieties M is Ru(II) or Os(II), in the pentahapto bound units M is Rh(III) or Ir(III) and XY is a chelating while Z is a monodentate ligand, may not remain intact in the body. Depending upon the thermodynamic stability and kinetic inertness, these potential drug molecules can partly or completely dissociate resulting in $[(\eta^6/\eta^5\text{-arene})M(XY)(H_2O)]^+$ or $[(\eta^6/\eta^5\text{-arene})M(H_2O)_3]^{2+}$ cations and, it is beyond doubt, that these cations will interact with different serum components. Therefore, for a better understanding the existing differences in the antiproliferative activity of these metal complexes their biotransformation processes in the body also need to be considered.

Since these half-sandwich metal complexes consist of three moieties in order to improve their antiproliferative activity the hexa/pentahapto bound arene ligand, the central metal ion and the coordinating bidentate ligand can be modified. The steric demand of different arene ligands in organometallic $[M(\eta^6\text{-}arene)]^{2+}$ (M = Ru, Os) or $[M(\eta^5\text{-}arene)]^{2+}$ (M = Rh, Ir) moieties results in typical piano stool geometry of the complexes. Furthermore, previous studies revealed that the size and the electron donating capability of the arene ligand influences significantly the hydrolytic behaviour of the $[(\eta^6/\eta^5\text{-arene})M(XY)(H_2O)]^+$ or $[(\eta^6/\eta^5\text{-arene})M(H_2O)_3]^{2+}$ cations, respectively, together with strength and kinetics of binding of the metal complexes to nucleosides which is believed to be the key step of biological activity [1]. With the systematic variation of the arene ligands in the precursors the strength of the metal-XY chelate may also be influenced.

In continuation of our work on this field [4-7], we have carried out an in-depth study on the hydrolytic properties of $[(\eta^6/\eta^5\text{-arene})M(H_2O)_3]^{2+}$ cations with the systematic variation of the above arenes and using combined pH-potentiometric, ^{1}H-NMR UV-VIS, ESI-TOF-MS methods in aqueous solution as well as DFT calculations. In this contribution the results of the effect of the metal ion (Ru vs. Os) and the size and electron donating capability of the arene ligands on the hydrolytic properties of half-sandwich metal cations will be presented.

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The leaving group of ruthenium arene complexes plays an essential role in biological activity

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Since the discovery of the biological activity of cisplatin, much effort has been devoted to search for other effective metallodrugs that may avoid certain problems associated to cisplatin, such as high toxicity or severe side effects. Ru (II) organometallic compounds are emerging as promising new therapeutic drugs [1]. Cationic Ru (II) arene complexes have shown to display high antitumour activity both *in vitro* and *in vivo* [2].

In this context, recently a new family of arene Ru (II) complexes bearing a diamino-triazine derivative have been synthesized and characterized. The DNA interaction and biological activity of one of these complexes, [RuCl(*p*-cymene)(κ^2-N,N-*2*-pydaT)]BF_4 denoted as Ru-Cl, has been previously described [3]. It was concluded that the Ru-Cl complex undergoes aquation in water and hydroxylation in basic medium, yielding the Ru-H_2O aqua-complex and the Ru-OH hydroxo-complex, respectively. In addition, it has been pointed up that Ru-Cl is a bifunctional complex able to interact with DNA by external and groove binding. However, negative cyto and genotoxicity results were achieved, probably due to the formation of the hydroxo form.

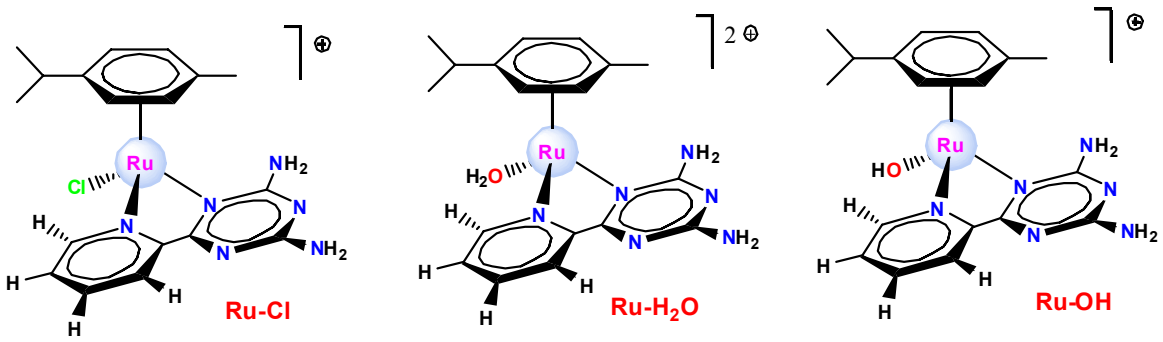

Figure 1. Structures of the Ru (II) arene complexes with general formula RuX(*p*-cymene)(κ^2-N,N-*2*-pydaT)]BF_4. 2-pydaT = 2, 4-diamino-6-(2-pyridyl)-1,3,5-triazine, Ru-Cl (X = Cl), Ru-H_2O (X = H_2O) and Ru-OH (X = OH).

On the other hand, it is well known that the chloride forms in platinum and ruthenium complexes often act as prodrugs, the aqua derivatives being the most active forms [4]. For these reasons, studying the differences related to the leaving group looks a promising challenge. The Ru-H_2O compound has been isolated and purified in our laboratories. The binding mode and its properties are quite different from the chloride counterpart.

The Ru-H_2O interaction with CT-DNA has been studied by thermodynamic and kinetic approaches using a number of techniques: ^{1}H NMR, ^{31}P NMR, viscosity measurements, stopped-flow, UV-vis, fluorescence and circular dichroism spectroscopy. The sets of results gathered have shown that the Ru-H_2O complex interaction mechanism is a complex process with at least three different steps: an electrostatic approximation that favours the diamino-triazine ligand intercalation into the DNA base pairs and a covalent binding, that is, a coordination of the Ru center to the phosphate group that evolves to a guanine N7 coordination.

Due to these findings, it is important to explore the biological properties of this drug by means of the MTT cell proliferation assay with 96 hours exposure time in MCF-7 (human breast cancer) and A2780 (human ovarian cancer) cell lines. In both cases a dose response effect was observed. IC_{50} values (concentration that yields 50% inhibition of cell viability) reveal that Ru-H_2O is more effective in A2780 than in MCF-7. In both cell lines, the effectiveness of the Ru complex depends on pH, being at pH 7.0 lower than at pH = 6.5 due to the amount of the hydroxo derivative formed.

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Synergistic effects of copper(II) complexes and cisplatin: an application of artificial neural networks and experimental design

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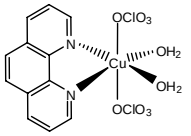
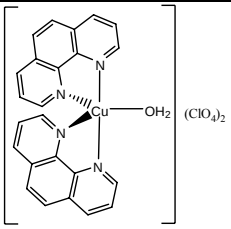
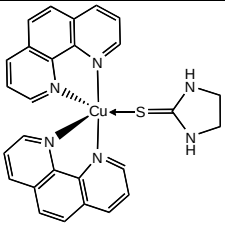
Cisplatin is highly effective in treating a variety of cancers [1] but both inherited and acquired tumoral cell resistance seriously limits its applications [2].

Anticancer drugs are widely used in suitable combinations in order to improve their action [3]. In the cell, associations of two or more drugs may exhibit synergistic, antagonistic or addictive effects. Synergistic, antagonistic or additive type of interaction occurs when the cytotoxicity of the drug combination is respectively greater, lower, or equal to the sum of the cytotoxicity of individual drugs.

Complexes of copper(II) with 1,10-ortho-phenanthroline (phen) are also endowed with cytotoxic and antitumoral effects being capable of cleaving DNA and improving nuclease activity [4]. Recently, we prepared a series of new copper(II) complexes, containing two phen units and N,N'-substituted-imidazolidine-2-thione as auxiliary ligands [5]; these compounds are characterized by a high chemical stability coupled with a high cytotoxic activity against mouse neuroblastoma as well as human hematologic and solid tumor-derived cell lines [6].

In this work we propose a new approach to search for optimal combination of the two compounds for which maximum synergy is observed, by using Artificial Neural Networks (ANNs) and the Experimental Design (ED). The studied compounds are reported in Table 1.

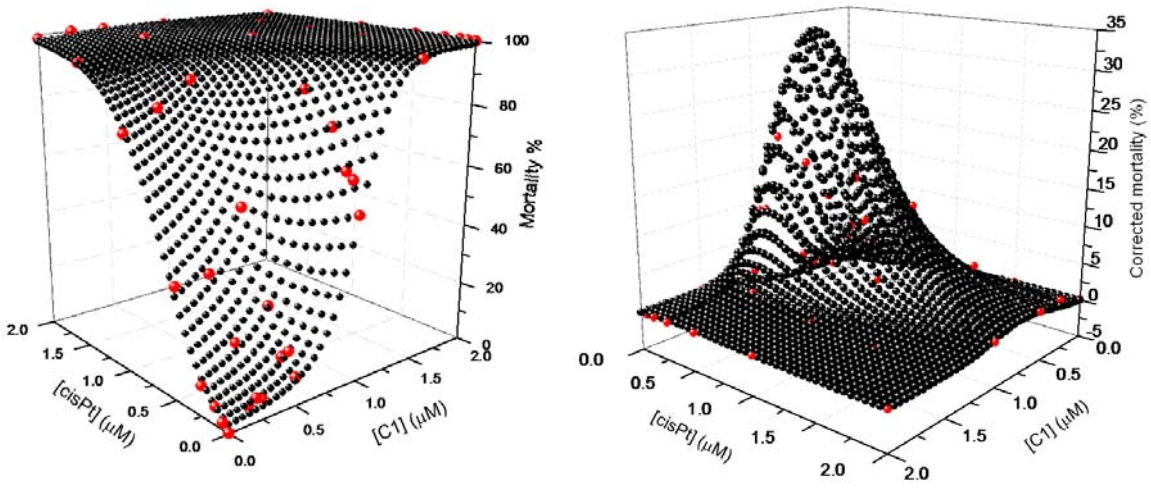
Table 1. Formula and acronyms of the studied compounds

			
1	**2**	**C1**	**cisPt**
$Cu(phen)(OH_2)_2(OClO_3)_2$	**$[Cu(phen)_2(OH_2)](ClO_4)_2$**	**$[Cu(phen)_2$(imidazolidine-2-thione$)](ClO_4)_2$**	**$Pt(NH_3)_2Cl_2$**

We prepared ≈ 40 mixtures of copper complex and cisplatin and measured the corresponding cytotoxicity against CCRF-CEM T-leukaemia cell lines.

A neural network was used to model experiments and then to predict the cytotoxicity values on the whole working space. The values so obtained were corrected for the pure additive effect, putting in evidence the synergistic effect. In Figure 1a and 1b the calculated and corrected response surfaces for the C1-cisplatin system respectively, are shown.

ED-ANN can be considered as a new, efficient and fast method to search for synergy of drug mixtures and/or even for new drugs.



a **b**

Figure 1. Calculated a) and corrected b) surfaces for the system C1-cisPt; mortality against CCRF-CEM T-leukaemia cell lines; black dots ● calculated points, red dots ● experimental points.

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Reliability of protonation constants and chemical model of drugs using SQUAD(84) and SPECFIT/32 regression analysis of pH-UV/VIS spectra

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The resolving power of multicomponent spectral analysis and the computation reliability of the stability constants and molar absorptivities determined for five variously protonated anions of physostigmine salicylate by the SQUAD(84) and SPECFIT/32 programs has been examined with the use of simulated and experimental spectra containing overlapping spectral bands. The reliability of the dissociation constants of drug were proven with goodness-of-fit tests and by examining the influence of pre-selected noise level sinst(A) in synthetic spectra regarding the precision s(pK) and also accuracy of the estimated dissociation constants. Precision was examined as the linear regression model $s(pK) = \beta 0 + \beta 1\ sinst(A)$. In all cases the intercept β0 was statistically insignificant. When an instrumental error sinst(A) is small and less than 0.5 mAU, the parameters' estimates are nearly the same as the bias $\Delta pK = pKa,calc - pKa,true$ is quite negligible. In all four dissociation constants the bias seems to be quite small even though for pKa4 it is a little bit higher, i.e. +0.05 for sinst(A) about 1.0 mAU. In the interval of sinst(A) from 0.1 to 1.0 mAU all four dissociation constants pKi are accurate enough. Of the various regression diagnostics considered, the goodness-of-fit is the most efficient criterion of whether the parameters found adequately represent the data. The magnitude of instrumental error sinst(A) only slightly affects the shape of a Cattel´s scree graph sk(A) = f(k) to determine the true number of light-absorbing species in the equilibrium mixture.

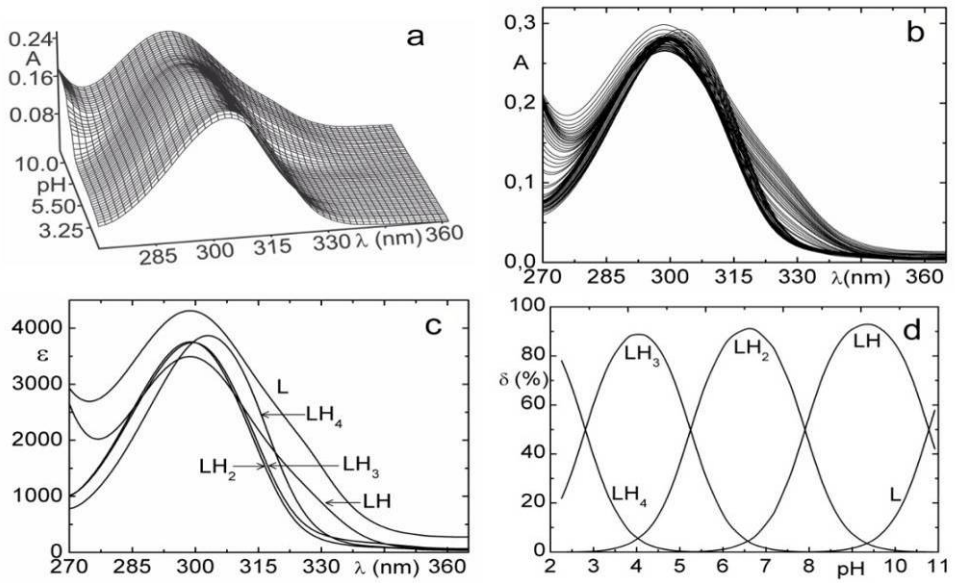

Fig. 1 (a) The 3D-absorbance-response-surface representing the measured multiwavelength absorption spectra of protonation equilibria for physostigmine salicylate depending on pH at 25ºC, (b) Absorption spectra of 7×10^{-5}M physostigmine depending on pH at 25º C; (c) pure spectra profiles of molar absorptivities *vs*. wavelengths for the variously protonated species L, HL, H_2L, H_3L and H_4L; (d) distribution diagram of the relative concentrations of all variously protonated species L, HL, H_2L H_3L and H_4L of physostigmine depending on pH at 25ºC, (SPECFIT/32, ORIGIN). The charges of species are omitted for the sake of simplicity.

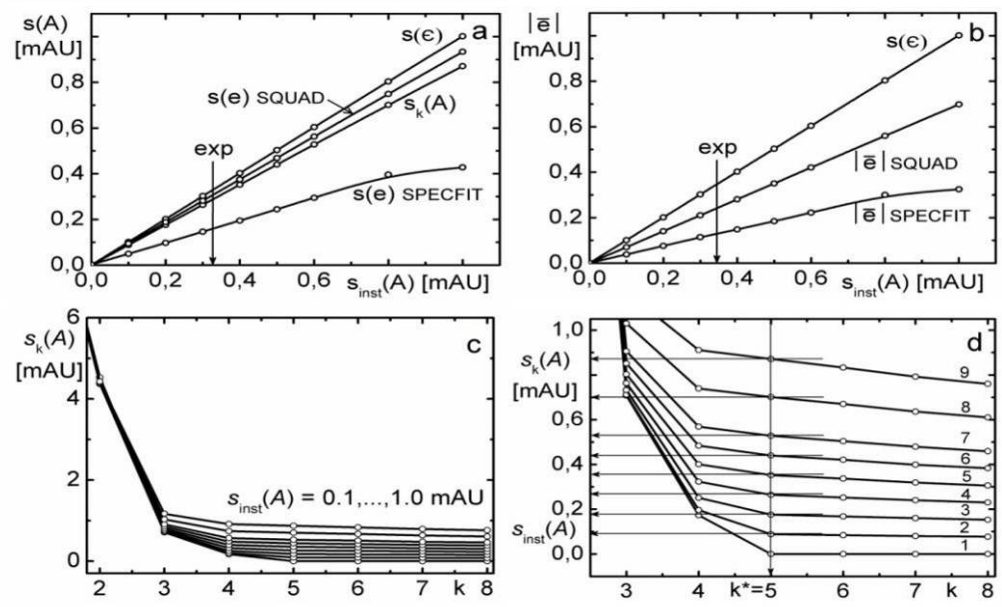

Fig. 2 The influence of the instrumental error $s_{inst}(A)$ on a goodness-of-fit represented with the statistical analysis of random errors ϵ and residuals *e* with the use of (a) standard deviation of random errors *s*(ϵ) and of residuals *s*(*e*), (b) the mean deviation $|\overline{\varepsilon}|$ and residuals $|\overline{e}|$, (c) The Cattel´s scree plot of the residual standard deviation of absorbance $s_k(A)$ depending on the number of the light-absorbing species in physostigmine salicylate equilibria mixture for nine various levels of instrumental noise (d). The detail view on the Cattel´s scree plot enabling an evaluation from simulated spectra of the actual instrumental standard deviation $s_{inst}(A)$ for five components $k^* = 5$, (ORIGIN).

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Aqueous complexation and interactions of Nd(III) and Am(III) with citrate in perchlorate media

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Carboxylic acids have played an important role in the field of separating actinides (An) from lanthanides (Ln) using liquid-liquid extractions to develop effective and economical means to reducing the volume, toxicity, and lifetime of irradiated nuclear fuel in the United States.[1, 2] Studies have now shown that negligent control of the carboxylate concentration in advanced liquid-liquid reprocessing of high-level waste can jeopardize the solubility of Ln and An.[3] Recent bench-scale experiments have demonstrated that the more soluble 3-carboxy-3-hydroxypentanedioic acid (citric acid) is a propitious aqueous complexant that can effectively aid in the separation of transition metals from *f*-elements mixtures using a combined solvent mixture of di(2-ethylhexyl) phosphoric acid (HDEHP) and octyl(phenyl) - N',N',- diisobutylcarbamoylmethyl phosphine oxide (CMPO).[4] The complexation of Ln with anions of citric acid has been previously studied with conflicting results regarding the coordination of metal ions between carboxylic groups, the feasibility of protonated metal complexes, and the formation constants themselves.[5]

Using potentiometric and spectrophotometric measurements as well as specific ion interaction modeling (SIT) we report protonation equilibria of citric acid and its complexes with Nd(III) and ^{243}Am(III) using least-squares fitting of the experimental data. For trivalent metal (M^{3+}) complexation, the best model included mononuclear and protonated species

$$M^{3+} + iH^{+} + jCit^{3-} \rightarrow MH_iCit_j^{3+i-3j} . \quad (1)$$

The calculated formation constants showed enhanced stability relative to other carboxylic complexes with Ln elements which was attributed to some coordination of the α-hydroxyl group of citric acid to the metal ion. Protonated metal complexes demonstrated an overall lower stability than that of the neutral charged $MCit^0(aq)$ species. A comparison of the Nd(III) and Am(III) formation constants with citrate showed very little discrepancy which is consistent given their similar charge, ionic radii, and affinity for hard oxygen-donor ligands.

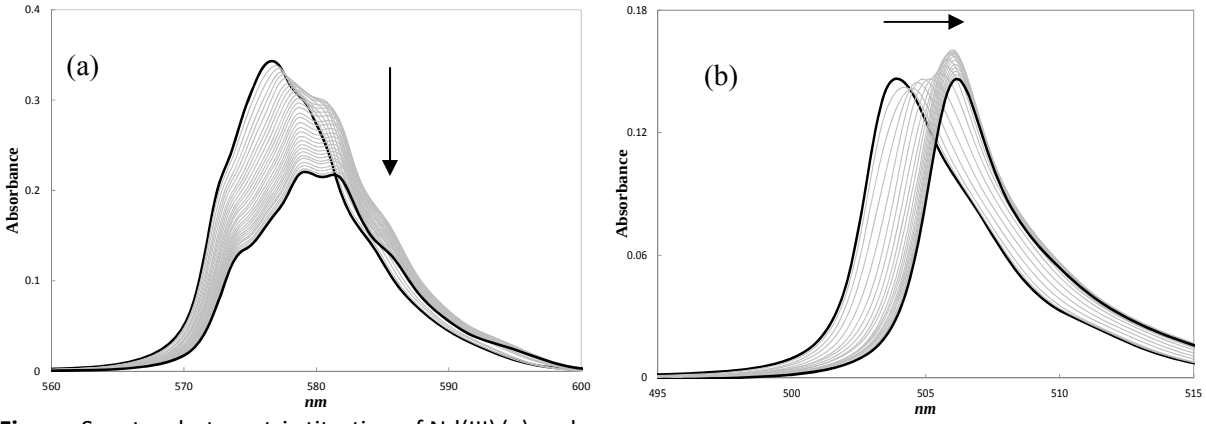

Figure. Spectrophotometric titration of Nd(III) (a) and Am(III) (b), T = 25.0 ± 0.1°C, *I* = 1M sodium perchlorate, V_{init} = 2.0mL, titrant: 0.1665M sodium citrate.

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Neurotoxic effect of nano-alumina on SD rats *in vivo*

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The rapid development of nanotechnology means that the human body has been exposed to nanoparticles through possible four routes: inhalation of airborne nanoparticles, ingestion of drinking water or food additives, dermal penetration by skin contact, and injection of engineered nanomaterials. It is, therefore, needed to answer the questions on their safety issue by performing vigorous toxicological evaluation based on various models [1], and to understand their interaction mechanism as well. Such a toxicological study can provide not only the critical information on the biological applications of nanoparticles, but also help to avoid any undesirable effects [2]. However, only a few studies have evaluated the safety of nano-sized materials and their potential adverse effects on biological systems [3].

In this study, we have focused on the potential toxicity of nano-aluminum (alumina), which consists of potential neurobehavioral changes and the possible mechanisms involved in SD rats. Male SD rats were administrated with various concentrations of alumina by trachea drip method. The animals were administrated in the absence and presence of various concentrations of alumina with mean particle size of about 50 nm. Changes of neurobehavioral, ulrastructural, mitochondrial membrane potential, reactive oxygen species (ROS), lipid peroxidation, DNA fragmentation were analysed by Morris water maze, electron microscopy, JC-1 confocus image assays, flow cytometry, biochemical assays, and TUNEL method. Alumina could decrease the function of neural behaviors, induce cell necrosis and apoptosis observed by electron microscopy and DNA fragmentation. The mechanism was mediated by decrease of mitochondrial membrane potential and ROS, and induction of lipid peroxidation. In this paper, results show a strong induction of cell death effect of alumina on SD rats in vivo. These findings suggest that alumina could be a kind of promising inducer for further neurotoxicology.

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Speciation of vanadyl complexes with simple organic ligands in aqueous solutions

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The chemical speciation of the vanadyl ion (VO^{2+}) and its complexes with some organic ligands (acetate, butyrate, formate, lactate, oxalate and propionate) in aqueous solution has been determined for the first time as a function of pH (1.60 – 9.00) by means of potentiometric techniques, computational analysis, ^{51}VNMR spectroscopy and UV/Visible spectroscopy at constant ionic strength (I=1M NaCl). The protonation, deprotonation and equilibrium constants of vanadyl and vanadyl complexes were measured reliably at different concentrations and ligand (L) to metal (M) ratios (1:1, 1:2, 1:4 and 1:6) potentiometrically and data analyzed using the JESS (Joint Expert Speciation System) computational software [1,2]. In acidic media vanadyl complexes with organic ligands (ML, ML_2, MLOH, ML_2OH etc) were found in higher percentages but at higher pHs the vanadyl hydrolyzed, resulting in formation of mono and binuclear species $(VO(OH)^{+}$, $(VO)_2(OH)_2^{+2}$ etc. ^{51}V NMR chemical shifts and absorption spectral data obtained for various vanadyl complexes in aqueous solution are in good agreement with the potentiometric data. The potentiometric and spectrophotometric characterization of vanadyl complexes with simple carboxylic acid and hyrdoxy carboxylic acids are well explored in an aqueous environment in this paper. The data generated in this study can be used in thermodynamic models for reliably predicting the deportment of vanadium in a range of chemical environments.

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Thermodynamic studies on new copper(I) and silver(I) phosphine complexes with potential antitumor activity

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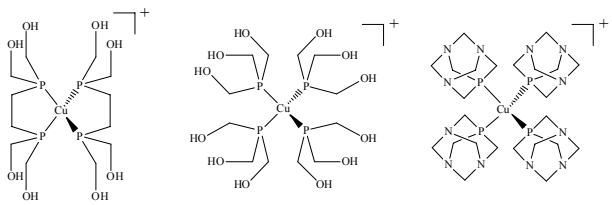
The interest toward copper-based compounds in medicine is due to the fact that copper, unlike platinum and gold, often employed in cancer chemotherapy, is an ubiquitous bioelement involved in several processes of metabolic enzymes in living organisms [1-2]. In addition, it is known that altered levels of intracellular copper are often related both to some genetic disorders [3] and to other serious pathologies such as prostate and lung cancer [4]. On the basis of these evidences, several therapies based on the administration of copper salts in the presence of chelating agents able to transport the bioelement have recently been developed.

Intracellular copper intake in living organisms is tightly regulated by a complex membrane protein system with active transport function. In humans, these proteins, hCTR1, are characterized by several methionine- and histidine- rich aminoacidic sequences, putative binding sites for Cu(I) [2]. Several studies, based on *in vitro* experiments and competition experiments in solution between these substrates and monovalent Cu(I) and Ag(I) and divalent Cu(II) and Zn(II), demonstrated that these transport proteins show a specific affinity for the unstable Cu(I) rather than for the more stable Cu(II) ion [5]. This notwithstanding, most of the research work done in the past on the development of copper compounds with potential antitumor activity has mainly been focused on Cu(II) derivatives. However, in these last years the scientific attention has been devoted also to Cu(I) compounds. In particular, a new class of Cu(I) compounds with hydrophilic phosphines characterized by both high thermodynamic stability and a good solubility in aqueous solution (see figure 1) has recently been proposed [6-8]. Among these compounds, (2) and (3) exhibit good to moderate cytotoxic activity *in vitro*, whereas the activity of (1) and that of the free phosphines are negligible. The cytotoxic activity of copper(I) complexes seems to be linked to the complex abilities of binding biological substrates after dissociation of one or more phosphine ligands. In agreement with this suggestion, some preliminary ESI-MS experiments show that at the high dilutions required by *in vitro* and MS experiments (10^{-5}-10^{-6} mol/L) the chelate complex (1) retains its tetracoordination, whereas complexes including monodentate phosphines (2) and (3) are partially dissociated. This result



(1) $[Cu(bhpe)_2]^+$ (2) $[Cu(thp)_4]^+$ (3) $[Cu(PTA)_4]^+$

Figure 1 Cu(I) – phosphine complexes whose cytotoxicity *in vitro* was evaluated.

points out the importance of obtaining more information about the Structure/Stability-Activity Relationship (SSAR) of these compounds in biological environments.

With this aim, our work has been focused on two main topics: 1) the study of the formation equilibria of Cu(I) complexes with PTA in aqueous solution; 2) the extension of the study to the complex formation of the analogous complexes of Ag(I). This cation is isoelectronic with Cu(I) and might form phosphine complexes with similar cytotoxic activity. In order to carry out the studies, we designed a series of microcalorimetric, spectrophotometric and potentiometric experiments, that allowed us to find the stability constants and the thermodynamic functions (ΔG, ΔH, ΔS) for the formation of both Cu(I)- and Ag(I) - PTA complexes in solution. Results of this study are summarized in Table 1.

Furthermore, in order to gain information about the interaction of Cu(I) and Ag(I) with molecules present in the binding sites of copper-transport membrane proteins hCTR1, we extended the solution studies to the interaction between Cu(I) and Ag(I) and the amino acids methionine and histidine. To date, there are very few studies on this topic [9], however they are essential to acquire the necessary information to clarify the still not fully understood mechanisms of copper intracellular intake.

Table 1 Overall formation constants (logaritmic) and related thermodynamic functions (kJ/mol) for Cu(I), Ag(I) complexes in aqueous environment (T = 298 K, at const. Ionic strength of 1.0 mol/dm^{-3}).

Species	$\log \beta \pm 3\sigma$	$\Delta G \pm 3\sigma$ kJ/mol	$\Delta H \pm 3\sigma$ kJ/mol	$T\Delta S \pm 3\sigma$ kJ/mol
$[Ag(PTA)]^+$	8.19 ± 0.01	-46.75 ± 0.06	-56.3 ± 0.5	-9.6 ± 0.5
$[Ag(PTA)_2]^+$	13.67 ± 0.02	-78.0 ± 0.1	-97.7 ± 0.7	-19.7 ± 0.7
$[Ag(PTA)_3]^+$	17.67 ± 0.02	-100.9 ± 0.16	-135.6 ± 0.9	-34.7 ± 0.7
$[Ag(PTA)_4]^+$	20.35 ± 0.12	-116.2 ± 0.7	-177.3 ± 1.8	-61.1 ± 1.9
$[Cu(PTA)]^+$	6.3 ± 0.6	-36.0 ± 3.3	-53.0 ± 1.7	-17 ± 3
$[Cu(PTA)_2]^+$	12.1 ± 0.4	-69.3 ± 2.5	-110 ± 5	-41 ± 3
$[Cu(PTA)_3]^+$	17.7 ± 0.6	-101 ± 3	-148.0 ± 1.2	-47 ± 3

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Molecular recognition patterns in ternary copper(II) complexes with deaza-adenine and amino-polycarboxylate ligands

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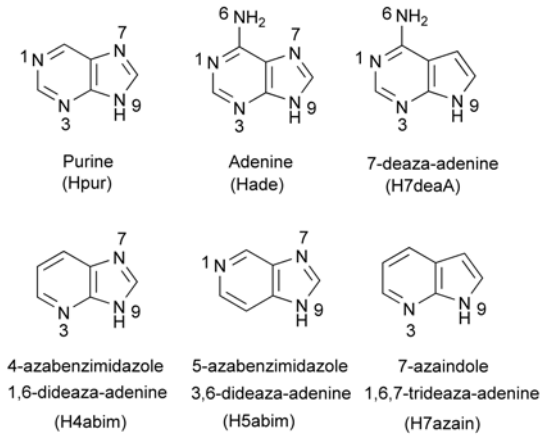
Adenine (6-aminopurine) has probed to be an extremely versatile ligand, either in anionic, neutral or cationic forms, with different metal ions [1]. In order to better understand this behaviour, our group have been developing studies with related N-ligands, addressing a large variety of studies. The aim of this work is to extend previous results [2] on the basis of molecular recognition in ten novel ternary Cu(II) complexes having a deaza-adenine ligands and amino-polycarboxylate chelators.

The four deaza-adenines used in this work have in common the presence of at least one N-heterocyclic atom in each ring of the purine skeleton (see Scheme - right).



The compounds have the formulas: $[Cu(TEBIDA)(H(N9)7azain)(H_2O)]\cdot 3H_2O$ (**1**), $\{[Cu(\mu_2\text{-}FBIDA)(H(N9)7azain)]\cdot H_2O\}_n$ (**2**), $\{[Cu(\mu_2\text{-}CBIDA)(H(N9)4abim)]\cdot 2H_2O\}_n$ (**3**), $[Cu(H_2EDTA)(H(N7)4abim)]\cdot 0.5H_2O$ (**4**), $\{[Cu_2(\mu_3\text{-}IDA)_2(\mu_2\text{-}N7,N9\text{-}(H(N1)5abim)]\cdot H_2O\}_n$ (**5**), $[Cu_2(NBzIDA)_2(H_2O)_2(\mu_2\text{-}N7,N9\text{-}(H(N1)5abim)]\cdot H_2O$ (**6**), $[Cu(IDA)(H(N9)7deaA)]\cdot 2H_2O$ (**7**), $[Cu_2(MIDA)_2(H_2O)_2(\mu_2\text{-}N1,N3\text{-}H(N9)7deaA)]\cdot H_2O$ (**8**, see Figure 1), $\{[Cu(\mu_2\text{-}NBzIDA)(H(N9)7deaA)]\}_n$ (**9**), $\{[Cu(\mu_2\text{-}MEBIDA)(H(N9)7deaA)]\}_n$ (**10**). Nine of the ten novel compounds (**1**-**3**, **5**-**10**) have the own iminodiacetate (IDA) or an N-substituted-IDA ligand, which acts as tridentate chelator. In these complexes, the IDA moiety adopts a *mer*-NO_2 conformation and the N-heterocyclic donor from the appropriate deaza-adenine ligand falls in *trans* to the Cu-N(IDA) bond. The Cu(II) atom exhibits a square base pyramidal coordination, type 4+1, in **1**-**3** and **6**-**10** or a 4+2 coordination in **5**. On the other hand, compound **4** contains the pentadentate H_2EDTA^{2-} anion from the ethylenediaminotetraacetic

acid, displaying one free and one coordinated acetic arms. Herein the Cu(II) coordination is an asymmetrical elongated octahedron, type 4+1+1.

In addition, deaza-adenines reported in this study and its complexes with Cu(II) have been characterized computationally using Density Functional Theory (DFT) methods (M06-L/6-31G* and 6-31++G**) together with the topological analysis of the Electron Localization Function (ELF) [3] (see Figure 2) in order to gain insight on the coordination modes of these heterocycles.

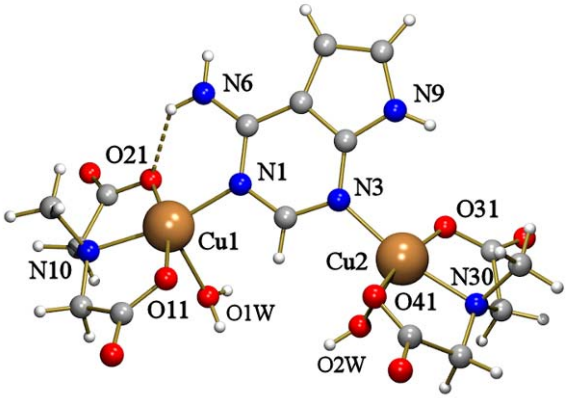


Fig. 1. Dinuclear complex molecule of **8**, $[Cu_2(MIDA)_2(H_2O)_2(\mu_2\text{-N1,N3-H(N9)7deaA})]\cdot H_2O$.

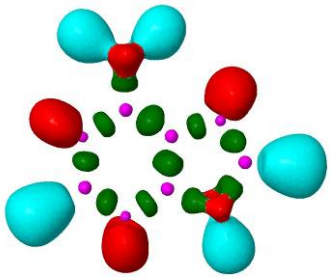


Fig. 2. Isosurface for isolated adenine.

Concluding remarks:

1. Herein, H(N9)7azain, H(N1)5abim and H(N9)7deaA act as a single tautomer, whereas H4abim uses two different tautomers, H(N7)4abim in **3** and H(N9)4abim in **4**.

2. H(N9)7azain and H(N9)7deaA tend to bind Cu(II) by its N3 donor atom, in cooperation with an intra-molecular interligand interaction N9-H···O(coord. carboxy).

3. The bridging mode μ_2-N1,N3-H(N9)7deaA has not been reported previously for purine and related ligands. Indeed, among the novel compounds, **8** is the sole case where the metal binding pattern involves the N1 donor in a Cu-N1 bond.

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MALDI and SALDI TOF mass spectrometry - fast and efficient way to search for supramolecular complex formation and new drug carriers

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Supramolecular chemistry deals with the study of organized molecular systems in which the molecules or ions are held together by non-covalent interactions [1, 2, 3]. The reversibility of such interactions makes supramolecular "dynamic" systems. This is the key principle on which the design of new molecular machines is based. Examples are given in Fig. 1-2.Also, the labile interactions between particular molecules and drug molecule are the way to develop new drug carriers which is nowadays topic of a high importance in medicine. The formation of supramolecular complexes is usually assisted by carrying out their synthesis preparing sufficient amount of the products and examining them by nuclear magnetic resonance (NMR) or other classical analytical techniques. This can be tedious and laborious process and might require rather high quantity of the reagents.

Matrix Assisted Laser Desorption Ionisation (MALDI) and/or Surface Assisted Laser Desorption Ionisation (SALDI) Time Of Flight (TOF) mass spectrometry are traditionally used in Proteomics and Bio-Analytics.

We have applied MALDI and SALDI for the fast screening to find out the formation of supramolecular complexes and/or to search for drug carriers. For this purpose, mass spectrometric analysis was used in combination with combinatorial experiments mixing the reactants, either in aqueous or organic phase and the products were then examined. Reactions can also be done directly on a MS target. In some cases, experimental design (ED) was also used in order to reduce the number of combinatorial experiments.

In this work several examples of supramolecular complex formation using as hosts *cyclic ethers, cyclodextrines, cucurbit[n]urils* etc., and as guests *fullerenes, nanoparticles, or* drugs like *antivirals, cisplatin,* etc., will be given and discussed. The advantage is that the experiments can be done using minimal amount of the chemicals (such as 10^{-5} moles or less) which is important for scarce or expensive substances and materials.

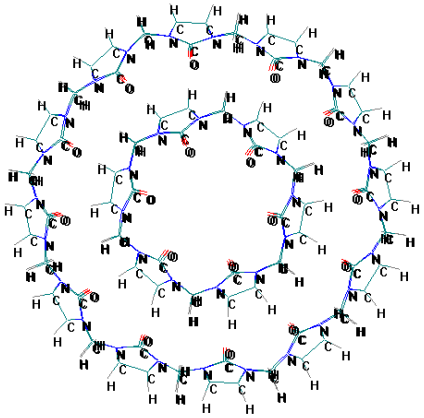

Fig. 1: CB[10]@CB[6] molecular wheel

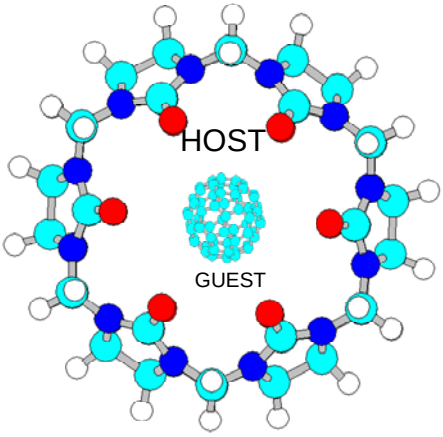

Fig. 2: C60@CB[6] complex

The proposed application of MALDI and SALDI TOF mass spectrometry with ED represents an efficient and economic way to search for the formation of new supramolecular complexes and/or for possible drug carriers.

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Supramolecular systems connecting flavylium moities with metal complexes

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Information processing at the molecular level requires systems capable of switching between several states under control of specific inputs. Examples of such multistate/multiresponsive systems have been developed on the basis of the pH and light dependent network of chemical reactions occurring in flavylium (2-phenyl-1-benzopyrylium) compounds, analogues of naturally occurring anthocyanin dyes.[1,2] Extension of these systems to include redox responsive moieties has been developed by coupling viologen units to flavylium salts.[3]

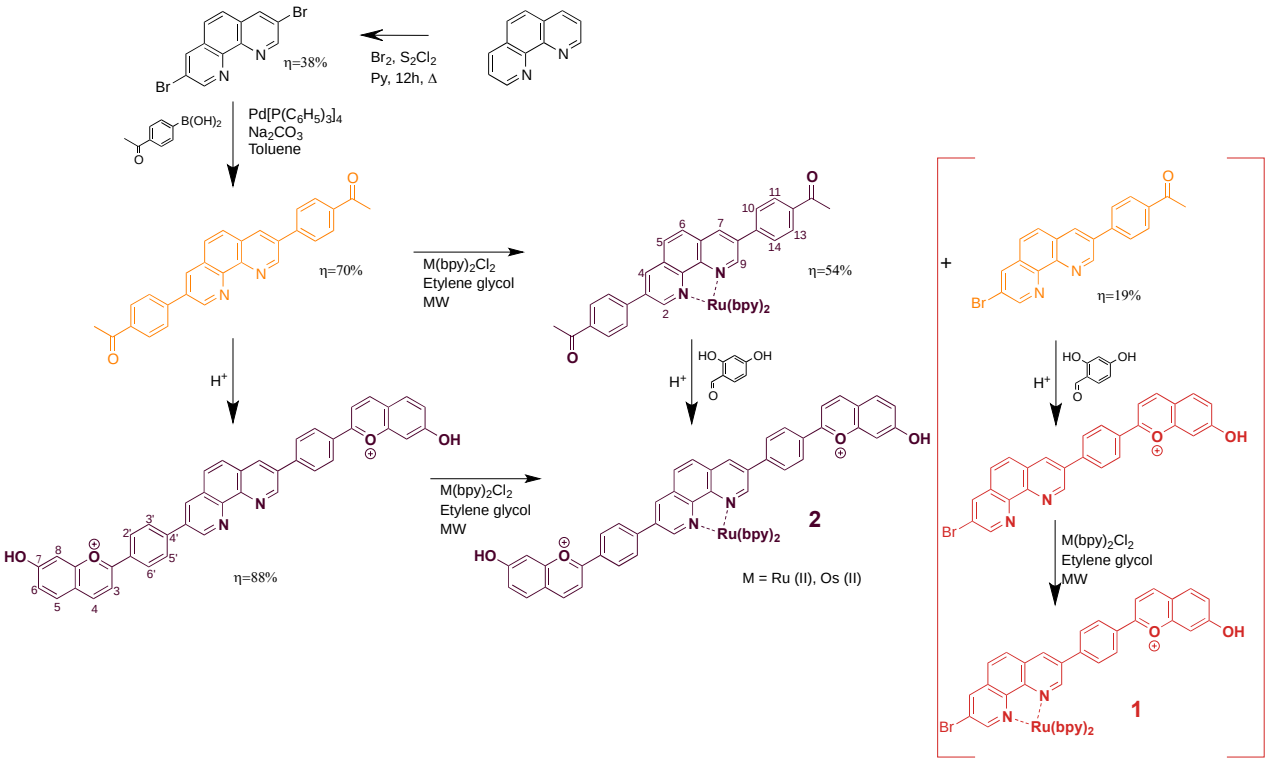

Figure 1: Synthetic strategy leading to dyad **1** and symmetric triad **2** constituted by flavylium moieties covalently linked to a $Ru(bpy)_2(phen)^{2+}$ unit.

In Nature, anthocyanins are stabilised in the vacuoles through an array of supramolecular interactions including π-stacking of the aromatic moieties and complex formation with several metal ions. On the other hand, popypyridine metal complexes have long been employed as building blocks in supramolecular systems where they play the role of

electron transfer components, luminescent moieties or redox relays when cyclic processes are involved. The building of supramolecular dyads and triads involving flavylium cations and popypyridine complexing units opens the possibility of (i) extending the pH and light stimuli to electric inputs and, (ii) study energy and electron transfer processes. Several dyads and triads involving flavylium moieties and polypyridine ligands and respective complexes were synthesised and characterised.

The synthetic strategy leading to dyad **1** and triad **2** is presented in Fig. 1. Palladium-catalysed cross-coupling between 3,8-dibromo-1,10-phenantroline and 4-acetylboronic acid leads to 3,8-bis(4-acetylphenyl)-1,10-phenantroline (70%) and monosubstituted 3-bromo-8-(4-acetylphenyl)-1,10-phenantroline (19%). The former ligand can yield triad **2** through two alternative synthetic pathways while the latter can yield dyad **1**, allowing also further functionalization through the bromine in position 3. Further synthetic procedures leading to 2,2'-bipyridine based triads will also be presented. The thermodynamic equilibria and the kinetics of the chemical reaction network as well as the photochemical reactivity of the respective 2-hydroxychalcones of some of the synthesized compounds will be reported.

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Interaction of vanadate, niobate, molybdate and tungstate oxometalates with calcium pump from sarcoplasmic reticulum: Ca^{2+}-ATPase conformational changes

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Sarcoplasmic reticulum Ca^{2+}-ATPase, is a transmembrane energy-transductor system that is involved in calcium-translocation and muscle-contraction relaxation. Oxometalates, in particular decavanadate and the iso-structural and iso-electronic decaniobate (Fig. 1) inhibit the hydrolytic activity of this pump, with IC_{50} values of 15 and 35 μM, respectively, whereas W and particularly Mo mono-oxometalates, exhibit a much lower inhibitory activity [1].

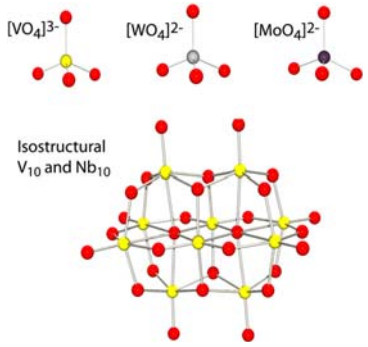

Figure 1. Molecular structures of V, Nb, Mo and W oxometalates [1].

In the present communication, we further investigate the interaction of these oxometalates with the calcium pump, by combining atomic absorption and Raman spectroscopic studies, in order to understand which of the protein conformations, which normally occur during the process of calcium translocation (namely E1/E2) favouring that interaction.

Atomic absorption spectroscopy (AAS), allowed us to determine that decavanadate (V_{10}) binds in the same extent to all protein conformations occurring during the process of calcium translocation by active transport, namely E1, E1P, E2 and E2P. In contrast, it was demonstrated that calcium pump-bound monomeric vanadate (V_1) is favoured only for the E2 and E2P conformations, whereas no significant amount binds to either the E1 or E1P conformations. Moreover, we have compared the conformational changes induced by incubation with the different oxometalates under study with the calcium-induced E1 and E2 conformations forms through Raman spectroscopy experiments in solution. The Raman spectra thus obtained, suggest that decavanadate, decaniobate and vanadate induce similar

conformational changes, but that differ from those observed upon molybdate and tungstate interaction.

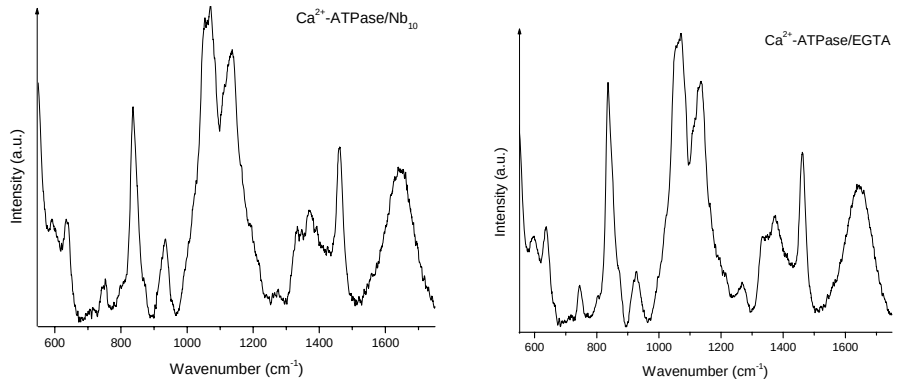

Figure 2. Raman spectra of Ca^{2+}-ATPase in the presence of either decaniobate (left) or EGTA (E2 conformation) (right). Peaks in the region 1000-1200 cm^{-1} are strongly affected upon oxometalate exposition suggesting a membrane interaction.

Whereas molybdate and tungstate oxometalates induce a conformation similar to E2 or E2P (state of lower affinity for Ca^{2+}), all the others oxometalates yield a Raman spectra distinct from that of either E1 or E2. The spectral region from 1000 cm^{-1} to 1150 cm^{-1} is characterized by a peak at 1060 cm^{-1} and a shoulder extending up to 1150 cm^{-1} (Fig. 2). Since the vibrational modes in this interval are highly sensitive to the hydrocarbon (lipid) state, the observed pattern suggests an interaction between decavanadate and decaniobate oxometalates with the membrane, leading to changes in its structure and fluidity. A decreased of the peak at 853 cm^{-1}, normally attributed to E2/E1 conformational changes, was observed upon decaniobate exposure (Fig. 2). In comparison, the intensity of the peak at 853 cm^{-1} is higher when the protein it at the E2 conformation, induced by the presence of EGTA (Fig. 2).
Putting it all together, the present results are consistent with the formation of an adduct between the protein in the E2 conformation, with either molybdate or tungstate. Although both decameric niobate and vanadate should induce similar conformational changes, since they are isostructural, it is however not expected that monomeric vanadate induces an analogous change in the Ca^{2+}-ATPase, particularly at the level of the membrane stability. On the other hand, AAS studies indicate that decavanadate binding with the calcium pump is not dependent on the protein conformation, whereas monomeric vanadate binding is confined to the E2 conformation. There is evidence that different oxometalates presents specific modes of interaction with the calcium ATPase from sarcoplasmic reticulum, a major protein which is responsible for calcium homeostasis and muscle contraction relaxation, with associated relevant cellular implications.

Acknowledgements: MA thanks to CCMAR; LAEBC and MPMC thank QFM-UC for financial support.

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Magnesium and nickel metal ions can induce poly(rU)poly(rA)poly(rU) triplexes formation or quadruplexes stabilization

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There is a growing appreciation that nucleobases can be used to build supramolecular systems with potential applications, for instance as a scaffold for building synthetic trans-membrane ion channels [1]. Besides, recent advances in chemical biology have shown how often non canonical nucleic acids structures (i.e. different from the Watson and Crick double helix form) can play a crucial role in numerous biological processes [2,3].

We have performed a thermodynamic and kinetic analysis on the ability of magnesium(II) and nickel(II) metal ions to stabilise non-canonical structures of the synthetic RNA poly(rA)poly(rU). It has been found that these cations are both able to induce quadruplex and triplexes formation starting from duplex poly(rA)poly(rU). Which of these forms is prevailing depends on the Mg^{2+} or Ni^{2+} concentration. If this is considerably high, the quadruplex structure poly(rU)poly(rA)poly(rU)poly(rA) is stable in solution. On the other hand, below a given metal ion concentration the quadruplex evolves towards a poly(rU)poly(rA)poly(rU) triplex (Figure 1).

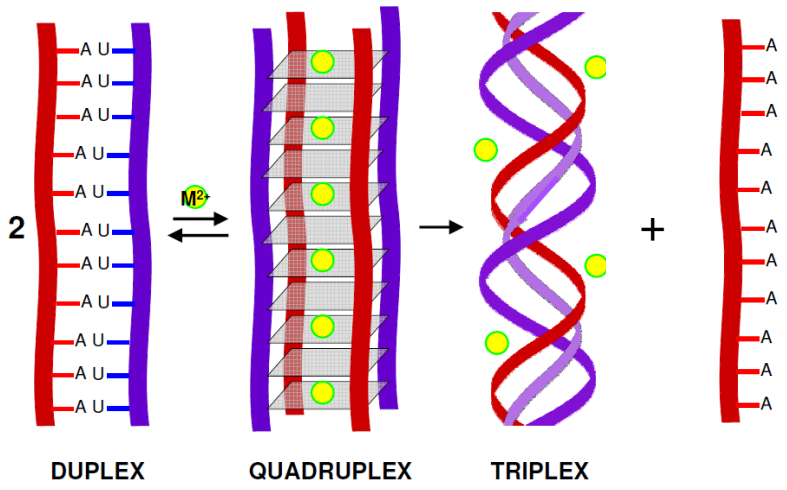

Figure 1: Schematic representation of the ability of Mg^{2+} and Ni^{2+} ions to favour the formation of non-canonical poly(rU)poly(rA)poly(rU)poly(rA) quadruplexes that, depending on the experimental conditions, can either be stable or evolve towards formation of poly(rU)poly(rA)poly(rU) triplexes.

The mechanistic features of the RNA/metal interaction are qualitatively very similar for the two metal ions. However, they are quantitatively very different as a hundred times lower nickel is necessary to produce the same changes driven by magnesium. The analysis of the results shows that the stabilisation of the quadruplex cannot be explained by electrostatics only. On the basis of previous studies on the poly(A) single strand [4], it might be supposed that a considerably high metal ion concentration produces dehydration at the polynucleotide that favours strands aggregation.

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Multinuclear cytotoxic metallodrugs: synthesis and biological properties of novel bimetallic ruthenium-titanium and gold-titanium complexes

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Rosenberg's pioneering discovery of the cytotoxicity of cisplatin against cancer cells in 1969 unquestionably opened the way to metallodrugs in the fight against cancer. Therefore, effort has been focused on the development of other platinum-based drugs as well as metallodrugs containing other metal centers. Interestingly, three non-platinum based complexes have reached Phase II clinical trials, namely the Ru-based KP1019 and NAMI-A, and the MKT-4 formulation of titanocene dichloride. Meanwhile, gold complexes have also appeared as promising anti-cancer candidates in recent years. [2]

We have thus synthesised a series of titanium-ruthenium and titanium-gold bimetallic complexes based on a titanocene-phosphine skeleton (Figure 1).

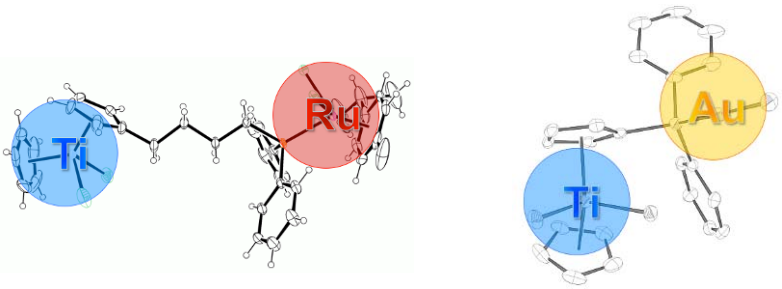

Figure 1. Representative examples of Ti-Ru and Ti-Au bimetallic complexes.

The cytotoxicity of these bimetallic complexes has been evaluated on A2780 ovarian cancer cells and on their cisplatin resistant cell line A2780cisR, showing an activity in the low μM range being markedly more pronounced than those of the monometallic analogues. Studies of cathepsin B inhibition, an enzyme involved in cancer progression and metastasis, will also be reported, as well as complementary ESI-MS studies of the interactions of the most active compounds with the model protein ubiquitin. [3, 4] The mechanistic implications of these results will be discussed and a preliminary trend of the structure-activity relationship will be given.

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New polydentate Ru(III)-Salan complexes: synthesis, characterization, anti-tumour activity and interaction with human serum proteins

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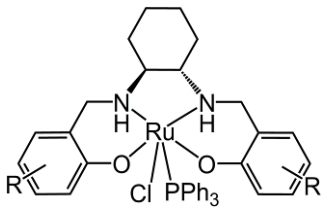
Cancer condition is a health concern with an outstanding global scope. It is still the second largest cause of death in developed countries, and this trend is becoming true in middle-income countries, emerging in the less developed countries as well [1]. Breast cancer is the most frequent in women, the cause for *ca.* 450 thousands of deaths in 2008, and expected to rise over 60% in 2030 according to the World Health Organization predictions [1].

Ruthenium complexes have attracted great interest for their potential use as metallodrugs for cancer treatment, and represent in this field the class of most widely studied non-platinum drugs under development [2,3]. Although Ru^{III}-salen compounds are known for their application in catalysis, and some complexes have been reported to have relevant anti-bacterial action, Ru-Salan complexes are virtually unexplored as prospective metallodrugs in in the field of cancer chemotherapy. Two new Ru(III) complexes bearing tetradentate bis(aminophenolate) ligands (*i.e.* Salan-type ligands) and formulated as $[Ru^{III}(R\text{-Salan})Cl(PPh_3)]$ (R-Salan = 4-methoxy/5-methoxy derivatives of 1,4-bis(salycilidene)cyclohexanediamine, PPh_3 = triphenylphospane) were prepared and characterized by the usual techniques. EPR spectroscopic results indicate a rhombic distortion consistent with a highly asymmetric environment of the low-spin d^5 Ru(III) centers.



Both ligands and the aforementioned complexes were screened for anti-tumour activity *in vitro* against human cancer cell lines, namely ovarian adenocarcinoma A2780, breast adenocarcinoma MCF7 (ERα+) and invasive breast cancer MDA-MB-231. Both complexes exhibited moderate to high cytotoxicity against the cell lines investigated, being up to 7-fold more active against MCF7 cell line than the commercial metallodrug in clinical use Cisplatin. Coordination to the Ru(III) centre was quite beneficial for the anti-tumour activity observed, enhancing the cytotoxicity of each bis(aminophenolate) ligand by at least two-fold [4].

Plasma proteins can exert a significant effect on the distribution and pharmacokinetics of any prospective drug. Albumin (HSA) is the most abundant protein in the human blood plasma, and it is known to accumulate in malignant and inflamed tissue, an effect that can be used to access more efficient tumor-selective drug delivery [5]. In this context, and as an initial approach to the pharmacokinetics of these 'Ru^{III}Salan' complexes, we investigated its interaction with human serum albumin as a vehicle for the transport in the blood plasma.

Steady-state and time-resolved fluorescence data indicate that the interaction of both complexes with HSA occurs by a mixed mechanism, consistent with the mechanism of simultaneous static and dynamic quenching of the fluorescence of the lone Trp214 residue in the protein. These results suggest the formation of {protein-complex} adducts with two different stoichiometries and binding sites, one envolving a specific but 'loose' interaction of the Ru-compound with the protein, and one compatible with binding within the van der Waals distance of Trp214. Binding constants calculated for these systems suggest that this protein might be a transport vehicle in the blood serum for these agents. The cytotoxicity of the protein-bound Ru(III)-Salan complexes was also assessed in the A2780 cell line to evaluate the effect of serum protein binding on the activity of these complexes [4].

These new Ru(III)-Salan complexes are the first compounds of this class studied for antitumor purposes reported in the literature.

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Tuning structure and properties of Pd and Pt camphorimine complexes

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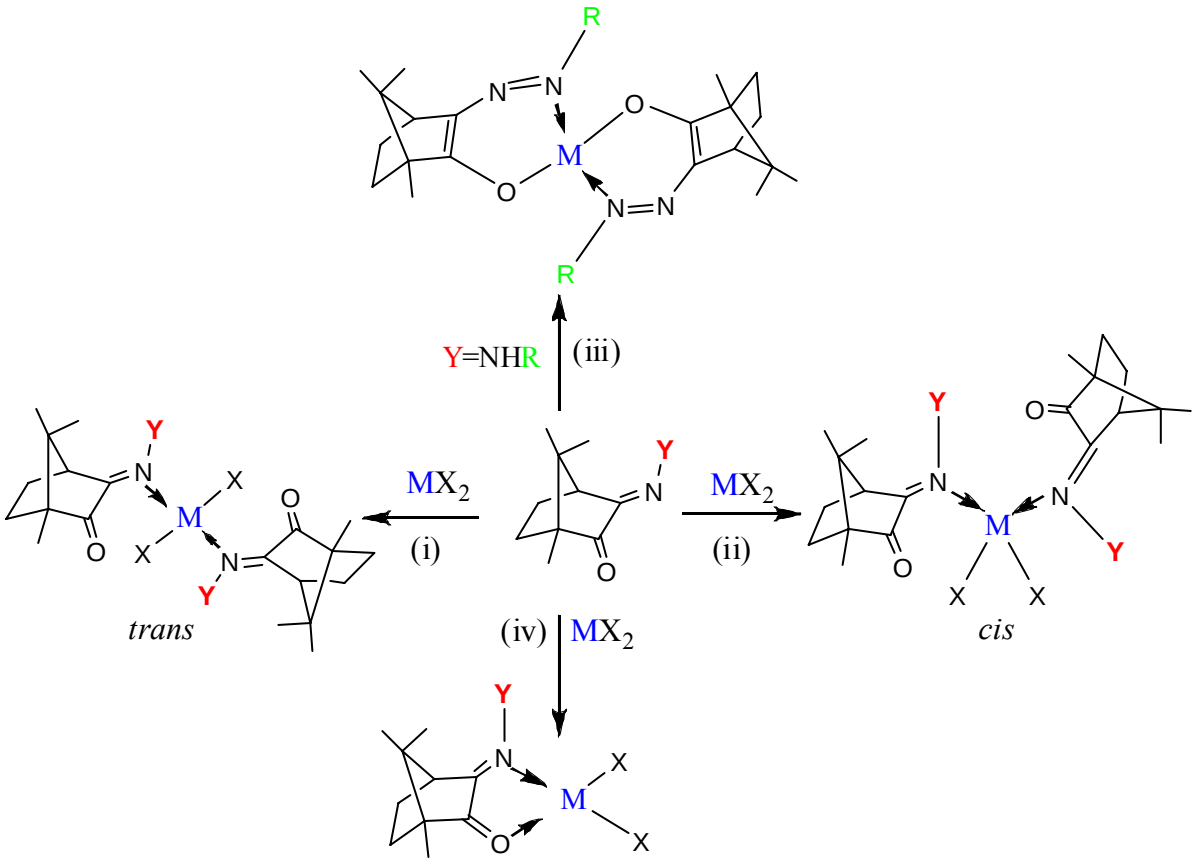
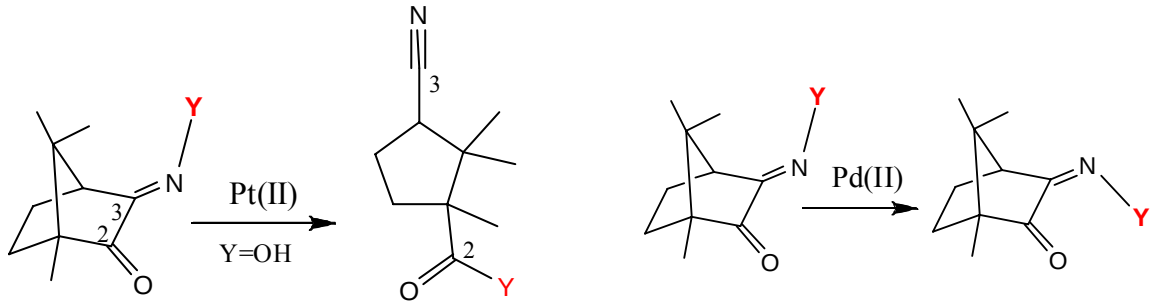
Till now, all camphorimine ($YNC_{10}H_{14}O$) complexes structurally characterized display two camphorimines coordinated to Pd or Pt occupying mutually *trans* positions, such as in *trans*-$[MCl_2(YNC_{10}H_{14}O)_2]$ (M=Pd, X=Cl or Br, Y=NMe_2; M=Pd, X=Cl, Y=NHMe, NH_2, *iso*-Pr, OH, Ph; M=Pt, X=Cl, Y=NMe_2 NHMe, NH_2) (Scheme 1, (i)) [1,2] suggesting that other arrangements were inaccessible. We now demonstrate that is not the case.

By tuning the reaction conditions and/or the characteristics of the camphorimine substituent (Y) we were able to synthesize complexes with ligands in adjacent positions ((ii): *cis*-$[PtCl_2(PhNC_{10}H_{14}O)_2]$) different metal to ligand ratio ((iv): $[\{PdCl(Ph_2NNC_{10}H_{14}O)\}_2(\mu\text{-}Cl)_2]$, promote formation of homoleptic species ((iii): $[Pd(RNNC_{10}H_{14}O)_2]$ (R=Me, Ph) or trigger organic processes in the camphorimines.



Scheme 1 – Reactions: (i) in CH_2Cl_2; (ii) in MeOH, Y=Ph; (iii): with $Pd(OOCCH_3)_2$; (iv) in MeOH, 1:1.

Beckmann type fragmentation (Y=OH, Scheme 2 (a)) or *E* to *Z* isomerisation (Y=NHMe, NHPh, Scheme 2 (b)) were activated in camphorimines ($YNC_{10}H_{14}O$) without isolation of the intermediate complexes.



Scheme 2 – Camphorimine rearrangement by interaction with Pd(II) or Pt(II)

Complexes *trans*-$[MCl_2(YNC_{10}H_{14}O)_2]$ are active and selective catalysts for CC triple bond activation [1,3] while $[Pd(RNNC_{10}H_{14}O)_2]$ (R=Me, Ph) are inactive. Search for the catalytic properties of the other types of complexes is under way.

Acknowledgments
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How CO releasing molecules CO-RMs interact with proteins

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The term CORM (CO Releasing Molecule) has been coined to designate small organic or preferably organometallic molecules that release carbon monoxide, CO, in biological media or living animals for therapeutic purposes [1]. They have been developed in the last decade as described in several patents and publications ([2] and therein). Treatment with these compounds resulted in the cure of many pathological situations induced in animal models of disease suggesting that CORMs may become useful drugs in the clinical armamentarium of the near future. However, achieving this goal requires, inter alia, collecting more knowledge on the still rather unexplored interaction of organometallic carbonyl complexes with biological media and molecules. It is the aim of this work to collect fundamental information on the interaction of CORMs with proteins providing the basis for the future design of more potent and safer CORMs.

Three well characterized CORMs have been studied using LC-MS, FTIR, UV-Vis spectroscopy, together with X-ray crystallography [3-5]: [*fac*-$Ru(CO)_3Cl(k^2\text{-}H_2NCH_2CO_2)$] (CORM-3), $[Ru(CO)_3Cl_2(1,3\text{-thiazole})]$ (ALF850) and $Na[Mo(CO)_3(histidinato]$ (ALF186).

It has been shown that all three metal carbonyl complexes release CO upon protein interaction. Atomic resolution models of hen egg white Lysozyme reacted with different CORMs have been obtained using synchrotron radiation providing valuable information regarding protein-CORMs interaction.

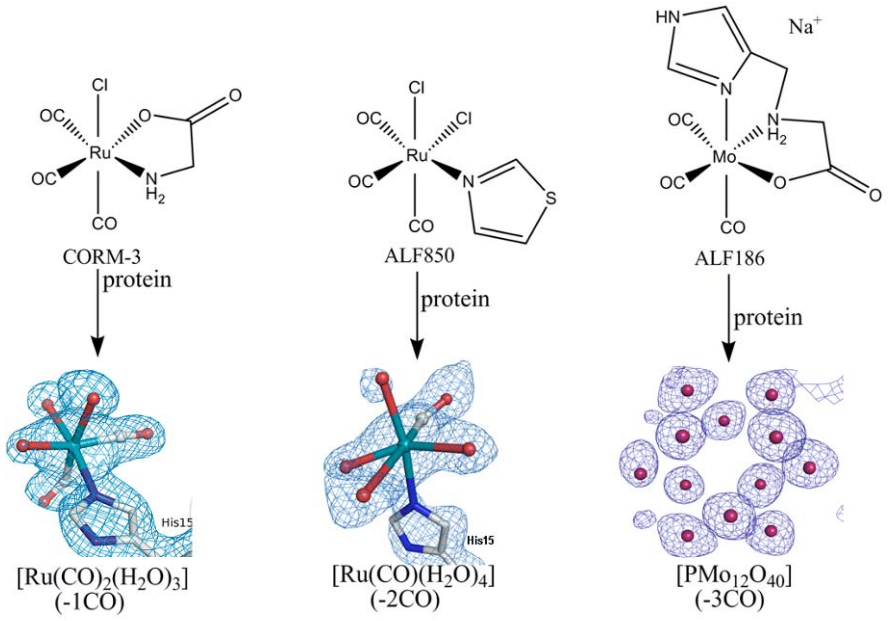

Figure 1: Schematic representation of protein-CORM interactions.

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Mechanism of sulfide ion incorporation into the metal cluster of metallothioneins

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Metallothioneins (MTs) are a large family of ubiquitous, small, and cysteine rich proteins with the ability to bind metal ions. Especially plant MTs are not well examined, neither in structural nor in functional aspects.

Previous investigations on the plant MT2 from *Cicer arietinum* (chickpea; cicMT2) showed the binding of five equivalents of divalent d^{10} metal ions (Zn^{2+}, Cd^{2+}) to all 14 cysteine thiolate groups of the protein. Additional sulfide ion incorporation into this metal-thiolate cluster is accompanied by an increased metal ion binding capacity [1, 2]. The presence of sulfide ions in plant and other MTs has already been reported previously [3, 4], but the mechanism of the incorporation remains still unclear. Here we present a detailed investigation mainly using spectroscopic techniques. The UV spectra shed light on the ligand-to-metal charge transfer (LMCT) bands of the zinc-thiolate bond at 230 nm, the cadmium-thiolate bond at 250 nm, and the metal-sulfide bond at 275 nm.

The dimension of the metal-sulfide-thiolate cluster is depending on the initial available free sulfide ion concentration. The more sulfide ions are present the more sulfide and metal ions can be picked up by the MT. In the case of cicMT2, the cluster can be enlarged to a multiple size of the one without sulfide ions. To study the sulfide ion incorporation into cicMT2 we varied the sequence of sulfide and metal ion addition and indeed were able to observe a dependency of sulfide incorporation efficiency on the order of cluster assembly. (Fig).

A comparative analysis was also performed with the well studied mammalian rabbit MT2A [5]. While the native form of this protein does not contain any sulfide ions, a similar enlargement of the metal ion binding capacity was observed in presence of sulfide ions.

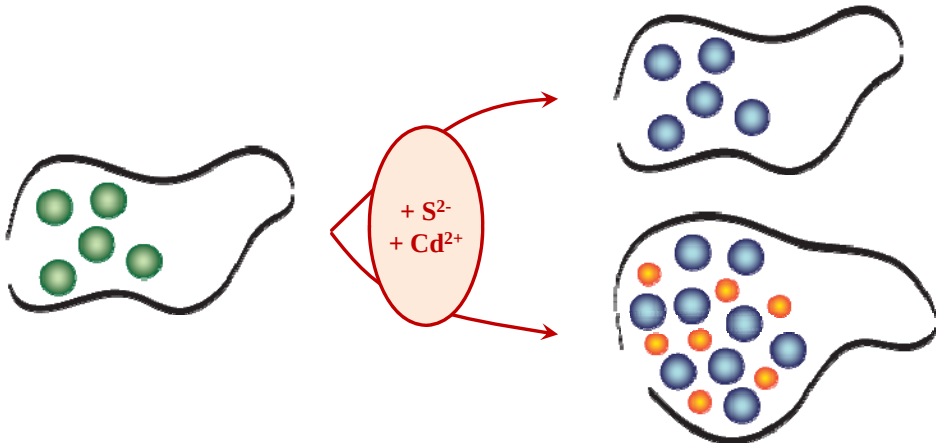

Figure. Incorporation of sulfide ions and hence enlargement of the cluster size depends on the sequence of sulfide and metal ion addition.

Acknowledgements

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Orange proteins in sulphate reducing bacteria: Mo-Cu heterometallic clusters in proteins involved in cell division

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Tetrathiomolybdates (TTMs) are highly reactive and have the ability to form a wide range of heterometallic complexes between molybdenum and other metals such as iron or copper. The antagonism between TTM and copper has been exploited for the treatment of Wilson's disease and breast cancer by dietary supplements on tetrathiomolybdate.

An intense orange color protein (ORP) containing both Cu and Mo in the same cluster, was purified for the first time from *Desulfovibrio gigas*. EXAFS studies revealed the presence of quite unique mixed metal sulfur cluster $[S_2MoS_2CuS_2MoS_2]^{3-}$ [1]. This protein is small monomeric protein of 11.9 kDa. The Uv-visible spectra contains two characteristic absorption maxima at 340 and 480 nm, identified as ligand to metal charge-transfer bands involving Mo. Genomic analysis of *Desulfovibrio* species allowed the identification of other metalloproteins encoded by the same operon and a recent study in *D. vulgaris* Hildenborough have shown that ORP is part of a protein complex involved in sulphate reducing bacteria (SRB) cell division [3]. This is particularly important due to economical impact of SRB in biocorrosion processes.

In this work we present an ORP isolated from *D. alaskensis*. This is a low molecular mass protein of 12.8 kDa, containing a 2Mo:1Cu cluster. This ORP was after heterologously expressed in *E. coli* and purified as apo-protein. The holo-protein was reconstituted *in vitro* using TTM and copper chloride. UV-visible titrations of (ORP + TTM) with Cu^{2+} and (ORP + Cu^{2+}) with TTM were performed and allowed us to identified that the protein favours the 2 Mo:1 Cu ratio. Titrations of the two metals in the absence of ORP were also done in order to investigate the role of ORP in the cluster formation. Real time PCR studies have shown that the expression of this protein is 6 fold increased when molybdate is added to the growth medium. Expression studies also allowed us to identify the presence of two putative ATPases containing iron sulphur clusters in the same operon that encodes for ORP.

Acknowledgements
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POSTER COMMUNICATIONS

Equilibrium and kinetic studies on copper(II) complexes of scorpiand-like ligands

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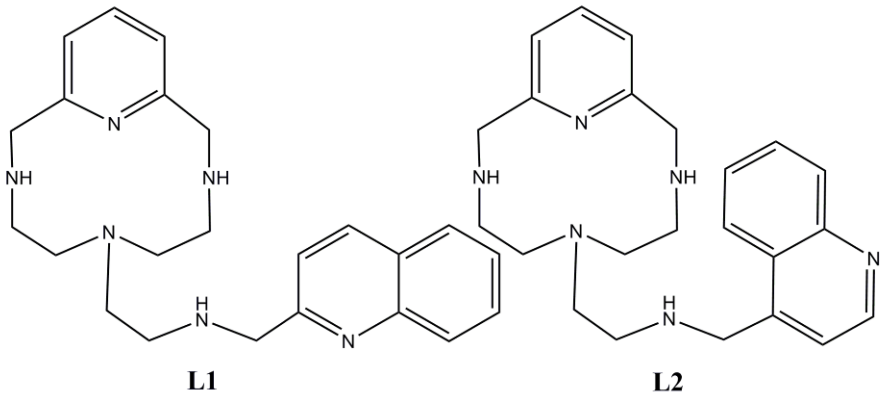
Macrocyclic polyamines with appended tails including additional donor sites have revealed as a very interesting class of receptor. This kind of systems joins the typical high thermodynamic stability of cryptand ligands with fast kinetics, thus facilitating transport processes through organic membranes.

We have previously reported the study of a series of Copper(II) complexes with scorpiand-like ligands that were built up by linking together a tris(2-aminoethyl)amine unit to the 2,6 positions of a pyridine spacer through methylene groups and they were further funtionalized on the hanging arm with a 1-methylnaphthyl unit or with 2- or 3-pycolyl groups.[1,2] These studies revelaled that the folding movement of the arm towards the macrocyclic core could be achieved not only by coordination of Cu^{2+} but also by formation of internal hydrogen bonds.

In this communications, the results of a study conducted with two new Cu(II) complexes of quinoline polyazamacrocyclic ligands (**L1** and **L2,** Scheme 1) will be presented. The aim of this study was obtaining additional information about the effect of the substituent in the dangling arm on the solution properties of the complex.



Scheme 1.

Potentiometric studies indicate the formation of stable CuL^{2+} species with both ligands, the **L1** complex being 3-4 log units more stable than the **L2** complex. The lower stability of the Cu**L2**$^{2+}$ complex and its capability of forming protonated and hydroxo complexes suggest a penta-dentate coordination of the ligand, in agreement with the type of substitution at the quinoline ring.

Kinetic studies on complex formation show the initial coordination of the metal center to the nitrogen atom in the quinoline ring. This is followed by the coordination of the remaining nitrogen atoms, in a process that is faster in the **L1** complex probably because the substitution at the quinoline ring facilitates the reorganization. Kinetic studies on complex decomposition provided also evidence of differences associated with the substitution at the quinoline ring. The occurrence of molecular movement typical of scorpiand-like complexes was observed in the case of the **L2** complex.

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Full characterization of synthetic *pheomelanins*, and its complexation by Cu(II) ion

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Melanin is a natural pigment obtained from the polymerization of the amino acid tyrosine under the action of enzymes and it has received increasing attention recently.[1] In this oligomeric structure there is the presence of chelating groups: catechol (Cat), carboxylic (Ac) groups, quinine imine (QI) and thiol groups. The ultraviolet rays cause increased tyrosinase activity in melanoma cells with melanosomes, which is induced by metal ions.[2] The goal of this study was to determine the affinity of synthetic *pheomelanin* for the Cu(II) ion with IR, XRD, TGA, EDX, CHNS; in aqueous solution was made potentiometric titration for calculation the equilibria constants. In order to evaluate the redox active species in the system by electrochemical methods and also electronic structure calculations were carried out at the DFT level to determine the structures formed.

The elemental analysis: C 45.76%, H 4.30% N 7.71%, S 16.03% and O 26.20%. The IR spectrum showed the absence of bands in 2962cm^{-1} and 2082cm^{-1} on υN-H and υC-H respectively present in the precursor cysteine and *pheomelanin* has a band at 1625cm^{-1} representing the υC=O of carboxylic stretching and another at 1740cm^{-1} related quinone-imine. The ESI-MS analysis (Figure 1) shows a fragment at m / z = 536, with respect to fragments of melaninn trichochromes structures, and a weight loss of 110 refers to the grouping catechol. Also there are other mass lost relating to dimers, trimers and tetramers. Free *pheomelanin* features two redox processes, quinone / semi-quinone, semi-quinona/catecol: E_{pc} = - 0.376 V and $E_{1/2}$ = 0.235 V respectively. The dimeric specie was calculated using Gaussian03 and the optimized molecule shows in Figure 2.

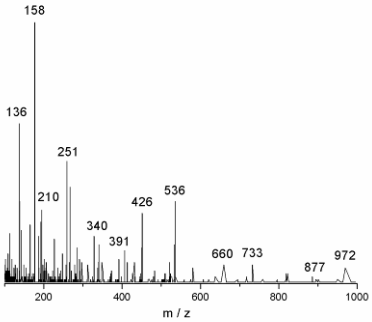

Figure 1: ESI-MS of *pheomelanins*

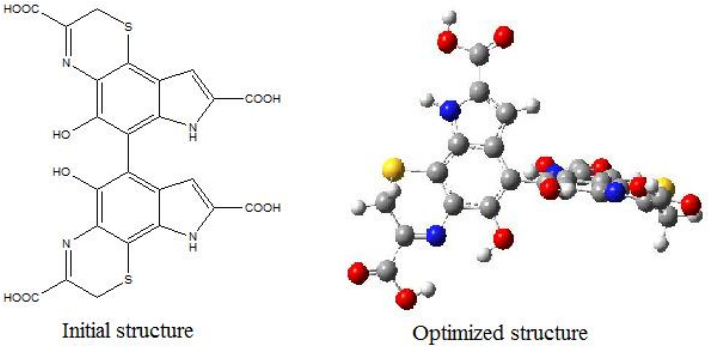

Figure 2: Initial and optimized structure for *pheo* dimer.

For the *pheo*-Cu(II) complexes equilibria studies revels the Cu(II) center start to coordinating with acetate and quinine-imine group in acid pH, with increase the pH have the interaction with thiol and catechol groups. The species distribution as a function of pH is show in Figure 3. The infrared of the complexes isolated in three different pH's confirm the species detected in aqueous solution with the respective shifts in the presence of Cu(II): 1740cm^{-1} by interaction with AC and QI groups and 1005cm^{-1} by interaction with catechol group. XRD spectrum of the free *pheomelanin* and complexes are shown in Figure 4, comparing the diffractograms can be observe a gain of structure with increased pH, similarities in the results occurs at pH 7 and 10 more specifically between 2□ = 16 – 21^{o} by the interaction with the same two groups in this pH ranges. The thermogram analysis shows the difference of free *pheomelanin* degradation temperature T = 214^{o}C and the complex with Cu(II): T = 238,36^{o}C (pH = 4) and 260,06^{o}C (pH = 7); showing the stability of this complexes, its happen due the stoichiometric difference of this species in each pH.

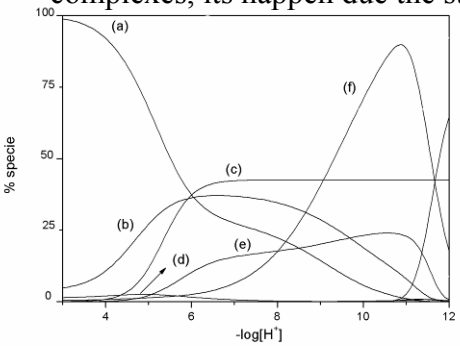

Figure 3: (a) [CuAc]+ = 8,56; (b) [CuQI]+ = 10,30; (c) [$Cu(QI)_2$] = 5,21; (d) [Cu(tiol)]+ = 2,43; (e) [Cu(cat)] = 18,19; (f) [Cu(cat)2] = 10,82.

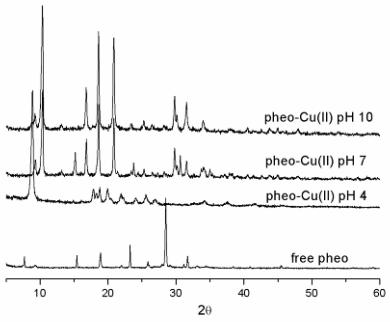

Figure 4: Diffractograms of free *pheomelanins* and they complexes with Cu(II) ion in pH 4, 7 and 10.

The *pheomelanin*-Cu(II) has a quasi-reversible wave $E_{1/2}$ = 0.306 V [Cu (II) / Cu (I)] and one $E_{1/2}$ = -0.073V [quinone / catechol] which is displaced anodically against free melanin, due the stability of the interaction with the metal center.

The main and inedited conclusion of this work is the relationship between the aqueous and solid state species, in acid pH the *pheomelanin* interact with Cu(II) metal ion by carboxilate and quinine-imine groups, and with the increase of the pH has the coordination with catechol and thiol groups. These results are important for many applications like adsorption of metals in wastewaters, induce the metals in melanoma cells and open the gate for study the interaction of this melanins with some cationic drugs.

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Mixed transition metal complexes of model peptides related to the metal binding site of prion protein

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Conformational changes of prion protein (PrP) are responsible for a series of neurodegenerative disorders such as mad cow, scrapie or Creutzfeldt-Jakob disease. It has also been suggested that the aberrant metal binding to the protein can cause conformational changes which are responsible for plaque formation in the brain and that is the typical phenomenon of numerous neurodegenerative disorders. A great number of studies support that histidine containing peptide fragments of PrP and their mutants can effectively bind both copper(II) and nickel(II) ions. It was found that the peptide fragments can bind as many copper(II) ions as the number of independent histidyl residues. The nickel(II) binding capacity of the same peptides is less than that of copper(II) and the histidines outside the octarepeat domain were considered as nickel(II) binding sites. In the case of copper(II), the species bonded at His111 were found to be the most abundant coordination isomers, while His96 was the most common binding site for nickel(II) [1-3]. These results support that the non-coordinating side chain residues around the specific sites (His96 and His111) may also contribute to metal binding.

To understand the role of the specific sequences of the peptides a series of tetra- and octa-peptides has been synthesized both with free amino termini and in the N-protected forms. The ligands include: NH_2-GTHS-NH_2, NH_2-MKHM-NH_2, Ac-GTHS-NH_2, Ac-MKHM-NH_2, NH_2-GTHSMKHM-NH_2, NH_2-MKHMGTHS-NH_2 Ac-GTHSMKHM-NH_2 and Ac-MKHMGTHS-NH_2. These peptides can be considered as the simplest models of the fragments PrP(94-97) and PrP(109-112).

Copper(II) and nickel(II) complexes have been studied by the combined application of potentiometric and spectroscopic (UV-Vis and CD) methods. It was found that the peptides with free amino termini had especially high metal binding affinity towards these metal ions, because their sequence corresponds to that of the ATCUN motif. The same selectivity for copper(II) and nickel(II) binding was, however, observed for these complexes, too. It was also evident that the octaepeptides can form dinuclear complexes, in which the histidyl residues are the primary metal binding sites. As a consequence, the mixed metal complexes of the octapeptides have also been studied and the preference for the formation of various coordination isomers evaluated.

Acknowledgements:

Financial supports from the OTKA-NKTH 77586 and TAMOP 4.2.1/B-09/1/KONV-2010-0007 and 4.2.2.B-10/1-2010-0024 are acknowledged.

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Solution studies on antitumor gallium(III) complexes and their interactions with human serum proteins

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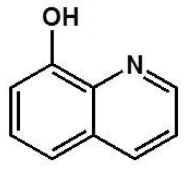
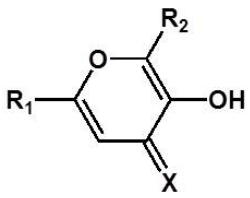
Platinum complexes are used in therapy but serious side effects and resistance of tumors led to extensive investigation of non-platinum antitumor agents. Gallium is the second metal ion, after Pt, to be used in cancer treatment. Remarkably, the simple salt Ga(III)-nitrate exerts antineoplastic activity in particular for the treatment of lymphoma and bladder cancer and exhibits a therapeutic effect in cancer-related hypercalcemia (Ganite^{TM} in clinical use) [1]. However, the applicability of $Ga(NO_3)_3$ as an anticancer drug is restricted by nephrotoxicity (in the case of short infusions) and optical neurotoxicity (in the case of continuous infusions). Orally administered $Ga(NO_3)_3$ or $GaCl_3$ is not sufficiently bioavailabile. An improved therapeutic index is expected to result from permanent low Ga(III) concentration in plasma, that can be assured by application of charge neutral Ga(III) complexes. Accordingly, many compounds have been prepared and tested in vitro and in vivo. Six-coordinate tris-ligand Ga(III) complexes are a promising group of compounds. Tris(3-hydroxy-2-methyl-4H-pyran-4-onato)gallium(III) (gallium maltolate) and tris(8-quinolinolato)gallium(III) (KP46) are the most promising Ga-antitumour complexes undergoing clinical trials [2,3].



8-quinolinol



	X	R_1	R_2
maltol	O	H	CH_3
allomaltol	O	CH_3	H
thiomaltol	S	H	CH_3
thioallomaltol	S	CH_3	H

Both complexes are administered orally, exhibit moderate side effects and can overcome $Ga(NO_3)_3$ resistance. Furthermore thio derivatives have been studied as radiopharmaceuticals for medical imaging [4].

The mode of action of Ga(III) anticancer drugs is probably related to the similarity of Ga(III) to Fe(III) in terms of charge, ionic radius, electronegativity, electron affinity and coordination geometry. The most significant difference between the two metals is the redox inactivity of Ga(III) in contrast to the Fe(III/II) system; hence it can interfere with the cellular iron metabolism but cannot participate in biologically important redox processes inhibiting

the activity of a number of enzymes. Ribonucleotide reductase is supposed to be the primary target, which catalyses the reduction of ribonucleotides to deoxyribonucleotides required for DNA synthesis. Binding of Ga(III) to the iron site of the R2 subunit of this enzyme results in destabilisation of the tyrosyl radical wich is essential for its enzymatic activity. Consequently the impaired DNA synthesis leads to apoptosis through the mitochondrial pathway [5]. Ga(III) is able to bind to the iron sites of transferrin, which promotes the cellular absorption of Ga(III), in particular in proliferating cancer cells with elevated iron demand, however, cellular gallium uptake may also occur by a transferrin-independent pathway.

Our investigations are focused on the solution equilibrium behaviour of Ga(III) compounds (with: 8-quinolinol, 8-quinolinol-5-sulfonic acid, maltol, thiomaltol, allomaltol, and thioallomaltol) as ligands and on the interaction of gallium maltolate and KP46 with the serum proteins human serum albumin and transferrin. These studies were done by pH-potentiometry, UV-Vis spectrophotometry, ^{1}H-NMR spectroscopy, spectrofluorimetry and ultrafiltration-ICP/UV-Vis techniques. The acquired information will help in understanding basic pharmacokinetic parameters and can afford a deeper insight into their modes of action.

Acknowledgement:
This work has been supported by the Hungarian Research Foundation OTKA K77833 and the Hungarian-Austrian Action Foundation. „TÁMOP-4.2.1/B-09/1/KONV-2010-0005 - Creating the Center of Excellence at the University of Szeged". É.A.E. acknowledges the financial support of Bolyai J. research fellowships.

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Coordination ability of small multihistidine peptides

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The copper binding site of the Cu,Zn superoxide dismutase contains histidine imidazole rings to coordinate copper(II) ion in the active centre. To mimic the active site of this metalloenzyme various peptides containing two or three histidine amino acids (HGGH-NH_2, HVVH-NH_2, Ac-HGGH-NH_2, Ac-HVVH-NH_2, Ac-HGGHGH-NH_2, Ac-HAAHGH-NH_2) were synthesized and their copper(II) complexes were studied. Peptides were synthesized by using a microwave-assisted Liberty Peptide Synthesizer (CEM, Matthews, NC) and peptide purity was checked by HPLC and ^{1}H NMR. The solution equilibrium studies of copper(II) complexes were performed by means of pH-potentiometry, UV-Vis and CD spectroscopy.

For terminally protected peptides two or three imidazole coordinated ML complexes are formed in the acidic pH range. Similarly to other three histidine containing small oligopeptides [1-3] the presence of three histidyl residues in the peptide results in enhanced stability of ML complexes and these complexes are present predominantly under slightly acidic pH conditions. This coordination mode, however, cannot prevent the deprotonation and coordination of amide nitrogens and the formation of (N_{Im}, N^-, N^-,N_{Im}) and (N^-, N^-, N^-,N_{Im}) coordinated species can be detected in the basic pH range. On the other hand, the structure of the hexapeptides makes possible the formation of dinuclear complexes, in which the copper(II) ions bind to the C-terminal and internal part of the molecules.

In the case of the tetrapeptides with free terminal amino group the MLH and ML complexes are formed with histamine-like coordination mode. The binding of amino and imidazole nitrogen(s) significantly hinders the deprotonation and coordination of amide nitrogens, which processes take place only above pH 7.

As a consequence, the imidazole (and terminal amino group) coordinated ML complexes of all studied ligands are promising model complexes for further electrochemical and SOD activity investigations.

Acknowledgement: This work was supported by TÁMOP (4.2.1/B-09/1/KONV-2010-0007) and by the Hungarian Scientific Research Fund (K 72956).

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Potentiometric studies and stability constants of manganese(II), cobalt(II), nickel(II) and copper(II) complexes with a ligand derived from 1,2,4 triazole

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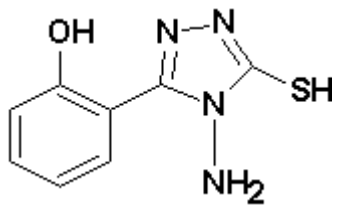
1,2,4 triazole derivatives are associated with diverse pharmacological activities. The ligand 2-(4-amino-5-sulfonyl-4H-1,2,4-triazol-3-yl) phenol (see figure) has been synthesized and characterized by elemental analysis and spectrometric methods.



Formula of the ligand

Its protonation constants and the stability constants of its complexes with Manganese(II), Cobalt(II), Nickel(II) and Copper(II) ions have been determined by potentiometric methods in water-ethanol (90 :10 v/v) mixture at a 0.2 mol/L ionic strength (NaCl) and at 25.0 ±0.1 °C and for 1 : 2 Metal/Ligand molar ratio.
The Sirko program was used to determine the three protonation constants of the ligand (3.7 ; 7.5 and 9.7) as well as the stability constants of both species $[M(HL)]^+$ and [ML] formed in the present experimental conditions .

The species distribution diagrams as function of pH for the ligand and the complexes were also determined and discussed.

The stability order obtained for the complexes is in agreement with Irving-Williams series.

Mixed thiophene-phenanthroline Cu(II) complexes: synthesis, equilibria and cytotoxicity

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The synthesis and the study of new molecules as anticancer agents are a very topical and wide field of research. Copper(II) complexes with phenanthroline (phen) have shown cytotoxic activity against a great number of cancer cell lines [1]. The cytotoxic activity of the metal complexes can be modified by using different auxiliary ligands [2].

The thiophene group has been reported to possess anti-inflammatory, analgesic, antidepressant and anticonvulsant activities [3], and its derivatives are widely used as anti-microbial and anticancer agents, showing a greater resistance to oxidative reactions [4].

In this work, we prepared new mixed compounds inserting into the precursor molecules $Cu(phen)(H_2O)_2(OClO_3)_2$ and $[Cu(phen)_2(H_2O)](ClO_4)_2$ some thiophene derivatives (Fig.1). The obtained complexes have been isolated in the solid state and spectrally characterized, by using FT-IR and UV-Vis techniques. The solution equilibria between the precursor molecules and the thiophene derivatives were studied by spectrophotometric titrations, at pH 7.4, in 0.1 M phosphate buffer, at 25 °C.

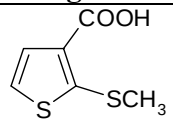
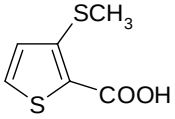
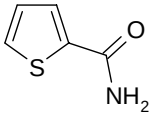
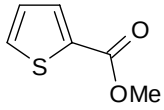
Ligand	IUPAC name
	2-(methylthio)-3-thiophene-carboxylic acid
	3-(methylthio)-2-thiophene-carboxylic acid
	2-thiophenecarboxamide
	Methyl 2-thiophenecarboxylate

Figure 1. Formula and IUPAC names of the studied thiophene derivatives

The potential anticancer activity of these compounds has been investigated measuring the cytotoxic activity against human hematological and solid tumoral cell lines.

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Redox reactions of the peroxomonosulfate ion in the ferroin/ferriin system

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Peroxomonosulfate ion (oxone, HSO_5^-) is a strong, two-electron oxidant. Recently the use of oxone has increased rapidly. Reasons for this are the stability, the simple handling, the non-toxic nature, the versatility of the reagent and the low costs. Experiments involving oxone provide valuable information on the study of reactive intermediates, may confirm mechanistic considerations regarding the autoxidation of various substrates and may explore important aspects of industrial applications.

This poster reports a kinetic study on the redox reactions of oxone in the ferroin/ferriin system (tris-1,10-phenanthroline complexes of Fe^{II} and Fe^{III}), which is frequently used for modeling the redox activity of biologically active compounds. A complex kinetic behavior was observed: under certain conditions, the concentration of ferroin decreases in the first stage of the reaction. However, after reaching a minimum, the concentration increases to a maximum and then decreases again. A similar unmonotonous temporal behavior of the concentration of ferroin was described previously in the reaction of $Fe(phen)_3^{2+}$ with Ce(IV) [1].

Detailed kinetic studies and ESI mass spectrometry confirmed the formation of an 1:1 adduct between the reactants in the initial phase of the ferroin-HSO_5^- reaction. [2] The oxidation product of the ligand, 1,10-phenanthroline-mono-N-oxide was also identified in the reaction mixture by several methods (UV-Vis, ESI-MS, ^{1}H-NMR). The N-oxide is not only formed in the oxidation but also has significant inhibiting effect: upon the addition of the N-oxide to the initial mixture, a slower consumption of ferroin was observed. A kinetic model was proposed for the reaction and independent measurements were carried out with ferriin which is formed in the reaction, too.

Ferriin decomposes in strongly acidic solutions producing ferroin and 1,10-phenanthroline-mono-N-oxide. 1,10-Phenanthroline-mono-N-oxide has a slight autocatalytic effect on the decomposition and increases the rate of ferroin formation. We propose the formation of $Fe(phen)_3^{4+}$ as a minor intermediate in the overall process. [3]

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Cross-bridged cyclen derivative: synthesis, acid-base and metal complexation studies

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12-Membered tetraazamacrocycles functionalized with a variety of pendant arms have an excellent ability to form stable complexes with several metal ions, therefore their study continues to be attractive to many researchers.[1,2] Among tetraazamacrocycles the cross-bridged derivatives are considered a special group due to their increased rigidity, which can led to particular selectivity pattern regarding metal complexation.[3] The strained macrocyclic framework favour their proton-sponge behaviour. These ligands are able to form kinetically inert metal complexes, specially with copper(II), therefore they can be considered for therapeutic purposes (^{67}Cu-radioactive pharmaceuticals) or positron emission tomography (^{64}Cu-labelled macrocycles).[4,5]

In this work two different cyclen (1,4,7,10-tetraazacyclododecane) derivatives were synthesized, containing two methylnitrophenol pendant arms, one of them is a cross-bridged compound. The acid-base behaviour of the two cyclen derivatives was studied by means of spectrophotometric and NMR titrations, in water: dimethylsulfoxide 1:1 medium due to the low solubility of these compounds in water at high pH. The cross-bridged compound behaves as a "proton sponge" exhibiting a very high value for the first protonation constant. The complexes of both ligands with Cu^{2+} and Zn^{2+} were characterized in solution and in solid state. Both copper(II) complexes were also studied by X-band EPR spectroscopy. Data for both compounds will be presented and their behaviour compared.

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Substituent effect on the stability of iron(III)-salicylate complexes. Structure of *trans*-[Fe(H5Nsal)$_2$(H$_2$O)$_2$]Cl·2H$_2$O.

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The solution equilibria of iron(III) with a class of hard ligands (salicylic acid and its nitro-derivatives) have been reliably studied by potentiometric, and spectrophotometric techniques [1]. The effect of the nitro substituent on the binding properties of salicylic acid has been examined. The inductive and resonance properties of the substituent that, as expected, lower the basicity of the phenolic and carboxylic groups, lead to a general decrease in both protonation and complex formation constants. Corresponding to this decrease in stability constants, an increase in pM is observed.

In order to correlate these effects of nitro group on the stability with the structural properties of the formed complexes, we started with the synthesis of the solid, crystal complexes and their X-ray analysis. In this conference we present the structure of a complex with 1:2 iron: 5-nitro-salicylicilate (5Nsal) ratio, which is stably formed in water solution at pH around 5 (Figure 1).

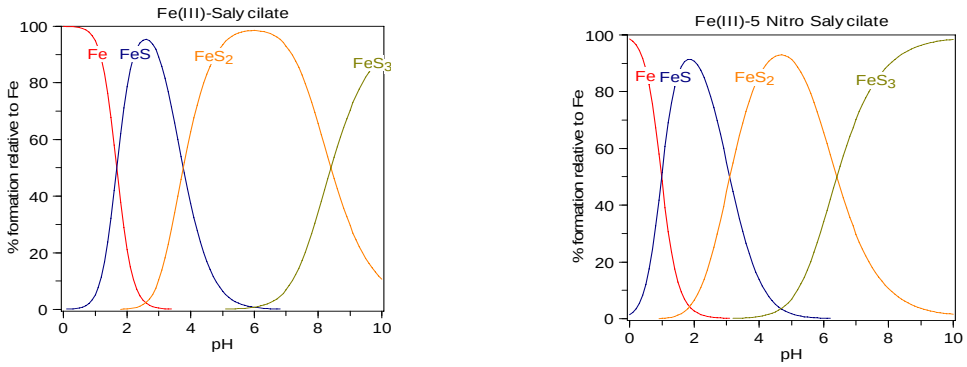

Figure 1: Speciation plots of Fe^{III} 1x10^{-3} M complexes with salicylic acid 3x10^{-3} M (left) and with 5-nitrosalicylic acid 3x10^{-3} M (right). S = salycilate (left) or 5-nitrosalycilate (right) ligands. Protonation and complex formation constants are taken from [1].

The molecular and crystal structure of the novel compound, here reported, corresponds to the title salt, where the cation is an all trans-octahedral complex. This species has two H5Nsal$^-$ bidentate unit and two aqua ligands. The polarizing effect of iron(III) atom on the phenol O-H bonds seems to be large enough to promote their implication in H-bonding interactions with non-coordinated water molecules, going towards proton transfer processes. Such interactions strongly suggest that the actual structure of the compound agrees more to that of an oxonium(1+) derivative, with formula $(H_3O)_2[Fe^{III}(5Nsal)_2(H_2O]Cl$ (Figure 2).

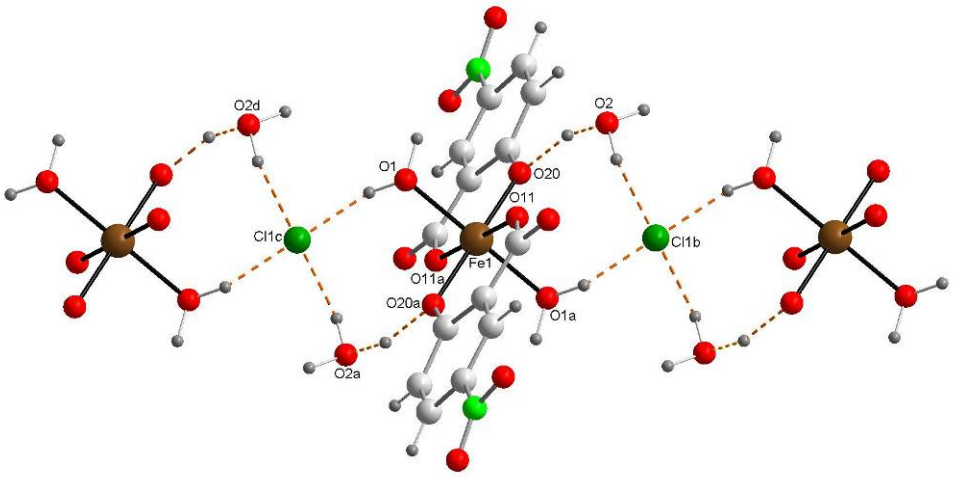

Figure 2: Structure of $(H_3O)_2[Fe^{III}(5Nsal)_2(H_2O]Cl$ showing the all-trans octahedral iron(III) coordination and the O-H···Cl non-classical H-bonding interactions, involving aqua ligands and oxonium cations.

Interestingly, from this point of view, all O-H bonds (both from H_3O^+ cations and aqua ligands) act as donors for H-bonds. The acceptor atoms are an O-non-coordinated carboxylate, an O-nitro and the choride anion. Each Cl$^-$ ion is symmetrically involved in two O(aqua)-H···Cl interactions (2.777 Å, 147.5º) and two O(oxonium)-H···Cl ones (2.804 Å, 116.5º).

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Control of copper(II) complexes speciation and properties by harnessing the flexible nature of peptidic ligands

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Metal ions play a determinant role in the structure and catalytic functions of a great variety of proteins. Their properties are precisely fine-tuned to achieve the desired role by the protein scaffold which controls their geometries and coordination numbers [1, 2]. The final structure of the metal binding site is the result of a delicate interplay between opposing requirements for tight binding and for function, which can involve dynamic changes specially for catalysis. Understanding this relationship is crucial to develop new artificial metalloenzymes with a wide range of reactivities.

We have designed, synthesized and characterized decapeptides containing several histidines and presenting different degrees of flexibility. The coordination properties of these peptides towards copper(II) have been studied using pH-potentiometry and different spectroscopic techniques (UV-Vis, CD, NMR and EPR). The results obtained show how the flexibility of the peptidic scaffold plays a crucial role in determining the formation and geometry of different species in solution. Additionally, the study of their redox potentials by cyclic voltametry reveals different behavior for the equivalent copper(II) complexes.

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The mutual separation of rare earth elements utilizing the reaction of corresponding complexes coordinated by tris(2-aminoethyl)amine with 2-hydroxy-3-methoxybenzaldehyde

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The chemical properties of the trivalent rare earth ions and their complexes in solution are remarkably similar to each other. Although a number of attempts to separate REEs effectively have been made, their mutual separation usually requires tedious procedures. It is important to find a different behavior in the reaction of rare earth complexes for the attempts to separate and purify individual elements effectively.

We reported a series of pseudo-helical, mononuclear rare earth complexes [1,2]. Furthermore, some rare earth complexes with Schiff-base ligands of the type $N[CH_2CH_2N{=}CH(2\text{-}OH\text{-}3\text{-}R_1\text{-}5\text{-}R_2C_6H_2)]_3$ (H_3L^1) have also been reported [3,4]. In these complexes [ML^1], each tripodal heptadentate Schiff-base ligand (L^1) effectively encapsulates the metal ion and enforces seven-coordinate geometry. In the present work, we have tried to prepare the complexes [ML^2] (M = Nd, Eu, Tb, Dy) of a tripodal heptadentate Schiff-base ligand of the type $N[CH_2CH_2N{=}CH(2\text{-}OH\text{-}3\text{-}OMeC_6H_3)]_3$ (H_3L^2). The reaction of dysprosium(III) and terbium(III) ions coordinated by tris(2-aminoethyl)amine with 2-hydroxy-3-methoxybenzaldehyde in methanol resulted in the precipitation of the complexes [ML^2]. (M = Tb, Dy). On the other hand, the complexes [ML^2] (M = Nd, Eu) were not obtained as solid products under the same synthetic condition of those of [ML^2] (M = Tb, Dy). The different behavior of the complexation reaction of these ions were applied to the mutual separation of a pair of rare earth elements, Dy^{3+}/Nd^{3+} and Tb^{3+}/Eu^{3+}.

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Systematic studies of dimeric gold(I)-NHC-complexes

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Photoluminescence can occur due to *aurophilicity*, an idea introduced by *Schmidbaur*.[1, 2]

Mononuclear complexes can show short gold-gold-distances in the solid state and, consequently, display a specific emission band in fluorescence spectra. In contrast, binuclear complexes can form a short intramolecular gold-gold-distance in solution. The position of this emission band is influenced by the choice of the ligand.[2] In consequence, the complexes can be applied to optical components, sensors or graphic displays. Additionally, it is possible to trace the path of a gold(I)-NHC-complex into a cell with confocal fluorescence microscopy.[3]

A gold-diphosphane-complex has been proven to have an effect on cancer cells in mice.[4] Cationic Gold-NHC-complexes are lipophilic compounds, which attack cancer cells very selectively. The lipophilicity can be influenced by the choice of functional groups of the ligands.[5]

This work focuses on a systematic study of conformational changes, existence of gold-gold-bonds, and fluorescence of binuclear gold(I)-NHC-complexes. Aggregation in solution or in the solid state to form supramolecular structures which could be stabilized by gold-gold-bonds or π-π-interactions is analysed additionally.

The complexes consist of a series of binuclear gold cycles with NHC-ligands on the basis of imidazole. All complexes contain an ethyl side chain and bromide as counter ion. They only vary in the length of the alkyl chain which forms the linker between the NHC units. Alkyl linkers were chosen because of their flexibility, which makes is possible to systematically study the influence of the linker length on the conformation of the complex and the possibility and stability of intramolecular gold-gold-bonds.

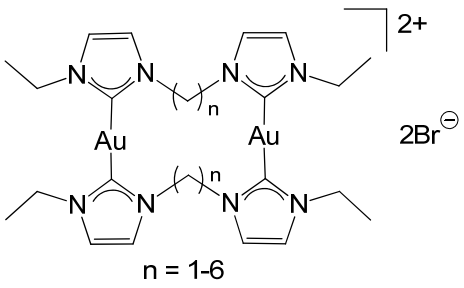

Figure 1: binuclear gold(I)-NHC-complexes.

Molecular structures determined by x-ray single crystal analysis show some structural similarities. Expectedly, the gold-centre always has a linear coordination and the NHCs are

planar. A short intramolecular gold-gold-distance is given with short linkers (n = 1, 2). Complexes with an even n (n = 4, 6) align in a way that intermolecular gold-gold-bonds are possible. NHCs additionally enable π-π-interactions. The complex with the shortest linker (n = 1) is an exception. It forms inter- and intramolecular gold-gold-bonds and π-π-interactions.

The measurements of VT-NMR spectra show the dynamic behaviour in solution. As expected, the ring inversion of the complex with the shortest linker (n = 1) could be accelerated with increasing temperatures while the ring inversion of the other complexes in solution at room temperature results already in an equilibration. The ring inversion of the complex with a short linker (n = 2) is decelerated at lower temperatures. The complex with the longest linker (n = 6) is suspected to aggregate with decreasing temperatures.

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Use of amino–polycarboxylic chelating agents for the sequestration of $(CH_3)Hg^+$ ion in aqueous solution

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Among the mercury organic derivatives, mono-methylmercury (MMHg) is by far the most toxic form of mercury because of its high capacity to enter biological membranes and accumulate in living organisms [1], as shown by the biomagnification factors: ~10^4 from water to edible shell-fish (mussels), and 10^6 –10^8 from water to big fishes (e.g. tuna fish) at the top of food chain [2]. The presence of complexing agents in the environment, which form soluble complex species with MMHg, favours the mobility of the ion in the aquatic ecosystems. Among anthropogenic complexing molecules, the most used ones are the amino-polycarboxylic chelating agents (usually called with the acronym APC) which are employed as metal ions sequestering agents in several application fields [3]. With the aim to assess the sequestering capacity of APCs towards mono-methylmercury(II) ion, we report here the results of a systematic study on the interaction of $(CH_3)Hg^+$ with nitrilotriacetate (NTA), ethylenediamine-*N,N,N',N'*-tetraacetate (EDTA) and diethylenetriamine-*N,N,N',N'',N''*-pentaacetate (DTPA). Moreover, since most of aminopolycarboxylic ligands are little biodegradable [3, 4], including those above mentioned, and their widespread use could be of environmental concern, we investigated also the interaction of MMHg with (*S,S*)-Ethylenediamine-*N,N'*-disuccinic acid (S,S-EDDS) which is, among the APCs, the most biodegradable one. The results obtained in this work show that the stability of MeHg - APC complex species is very similar for DTPA, EDTA and S,S-EDDS (e.g., $\log K_{MeHg(APC)}$ = 10.14, 10.03, 10.14 for DTPA, EDTA and S,S-EDDS, respectively) whereas, as expected, MeHg - NTA complexes are less stable ($\log K_{(MeHg)(NTA)}$ = 9.04).

Stability of $(CH_3)Hg$-S,S-EDDS species show that this ligand can be used successfully as environmental friendly chelating agent alternatively to other less degradable APCs in all their application fields. The sequestering ability of APCs towards $MeHg^+$ ion was studied by calculating the sequestering parameter $pL_{0.5}$ in the pH range (3 to 11) investigated, in NaCl medium and also by simulating the presence of a non interacting medium (NaX), at the same ionic strength of the experiments.

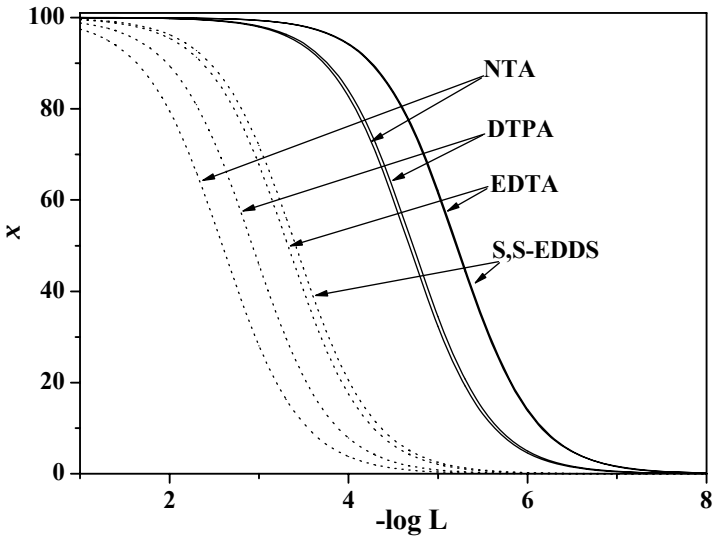

Figure. Fraction (x) of $MeHg^+$ ion complexed by APCs vs. –log[L] (L = NTA, S,S-EDDS, EDTA, DTPA) , at T = 25°C. Experimental conditions: $C_{MeHg^+} = 10^{-12}$ mol·L^{-1} (trace), pH = 7, I = 0.1 mol L^{-1} in $NaCl_{aq}$ (dotted lines) and in NaX_{aq} (continuous lines).

As an example, in Figure are reported the sequestration curves of the complexones towards the $MeHg^+$ ion at pH = 7, in interacting and non interacting ionic media, at I = 0.1 mol L^{-1} and T = 25°C.

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Some solution thermodynamic properties of penicillin derivatives. The effect of ionic strength and temperature on the solubility and acid-base properties of the amoxycillin, ampicillin and 6-aminopenicillanic acid

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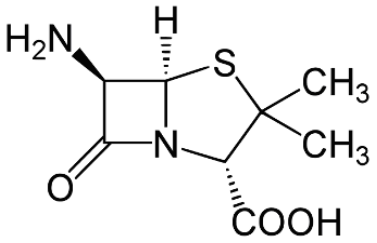
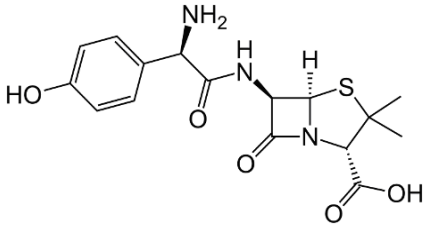
The penicillins are naturally occurring compounds produced by different microorganisms and the first class of antibiotic available for humans. These molecules have a selective anti-bacterial toxicity and perform their activity interfering on the growth processes and on the proliferation of the microorganism. Some penicillins behave inhibiting the cellular wall growth of bacteria, others interfering with their mechanism of the proteic synthesis.

The fundamental part of penicillins is represented by the β-lactam ring which is associated to a thiazolidine molecule (Figure 1). The penicillins differ for the lateral acyl chain condensed with the amino group; the lateral chain and the substituent influence the pharmacokinetic, the biochemical and the antibacterial properties (against both gram-positive and gram-negative organisms) of penicillins. The substituent on the amino group influences the antimicrobial spectra, the susceptibility to the acidic ambient, the sensibility to the β-lactamase and the pharmacokinetic properties. The substitution on the condensed carbon in position 2 increases the stability to the β-lactamase.

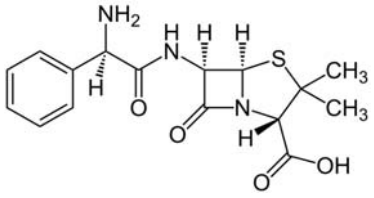
Figure 1



6-aminopenicillanic acid
(6-APA)



Amoxicillin
(Amox)



Ampicillin
(AMP)

The 6-aminopenicillanic acid is an intermediate product with special importance to pharmaceutical industry since is the main starting block for the preparation of numerous semisynthetic penicillins (β-lactam antibiotics) to obtain new derivatives with enlarged spectrum of biological activity, by means of acylation, esterification, amidation and hydroxyamidation reactions, etc. Among the different penicillin types, the amino-penicillins are undoubtedly the most important, since the amino-group is bounded to a large radical that avoid the attack of the penicillinase to the β-lactam ring, and allowing them to have a large anti-bacteria activity.

Amoxicillin and ampicillin are the most important amino-penicillins since are effective against many different bacteria including *H. influenzae, N. gonorrhoea, E. coli, Pneumococci, Streptococci,* and *Staphylococci*.

In different industrial fields, the knowledge of the drug solubility is a very important property for pharmaceutical product design, because it affects the drug efficacy, its future development and formulation efforts, and also influences the pharmacokinetics, such as the release, transport and the degree of absorption in the organism.

Solubility data involving new drugs are frequently not available in the literature. Although some thermodynamic models can be used to predict drug solubility, the availability of experimental data is still fundamental for an appropriate model development and evaluation.

Since many years, our research group has undertaken a systematic study of the modelling of the acid-base properties and solubility of different ligand classes of acidic and basic non-electrolytes and zwitterions in experimental conditions simulating those of natural waters and biological fluids. The information obtained from this kind of investigations allowed us to determine the total solubility of the ligands and of its neutral species, as well as the corresponding activity coefficients determined using the Setschenow equation.

Data regarding their thermodynamic properties appear till now few and quite confusing, and any systematic modelling studies regarding their dependence on the experimental conditions (ionic medium, ionic strength and temperature) is reported. These kind of investigations allow to propose simple semi-empirical equations that allow to model the dependence of the thermodynamic parameters on ionic strength, ionic medium and temperature, and to predict the behavior of the ligands in a wide range of experimental conditions.

In this order, the main scope of this paper is to give an important contribution on the knowledge of the thermodynamic properties (log K^{H}, solubility and formation enthalpies) and behavior of three different biological active molecules (see Figure 1), namely: (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4- thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid or 6-aminopenicillanic acid [6APA]; (2*S*,5*R*,6*R*)-6-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)-acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid or amoxicillin [Amox] and 2*S*,5*R*,6*R*)-6-([(2*R*)-2-amino-2-phenylacetyl]amino) -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid or ampicillin [AMP]) in NaCl aqueous solutions at different temperature and in a fairly wide ionic strength range.

Moreover, since penicillin derivatives are readily inactive in presence of water, alkalis, acids, oxidizers and heavy metals, the hydrolysis of the β-lactam ring was accurately studied as a function of pH, ionic strength and time using both the UV-vis spectroscopy and NMR.

The evaluation of the water infiltration chemical attack in building materials by spectroscopic techniques: Raman and DRIFT

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Building materials suffer several mechanisms of deterioration caused by stressor factors being one of the main consequences the formation of soluble salts. These salts cause disaggregation and loss of original material by hydration/dehydration cycles and dissolution/crystallization processes which provokes the crystallization of salts within the pores and produces internal fractures when solubilised ions, coming from others salts, recrystallize as another salt or the same but with different number of hydrate water. Therefore, identification and characterization of the salts present in the damaged building materials comes prior to the diagnosis of the deterioration causes related to conservation interventions.

This work presents an innovate analytical diagnosis methodology to identify the main source of degradation as well as to establish the chemical processes involved in the different pathologies, combining nondestructive techniques as Raman and Infrared (in diffuse reflectance mode, DRIFT) spectroscopies. In addition, after checking the condition of the building, quantitative analysis of the soluble salts was carried out by Ion Chromatography in order to assess the extent of the impact suffered by the building [1]. Finally, a Chemometric treatment was carried out to complement and contrast the experimental results.

In the case of sandstone and mortar samples, quartz (SiO_2), hematite (Fe_2O_3), rutile (Ti_2O), limonite ($FeO(OH)$), orthoclase ($KAlSi_3O_8$) and vitrified carbon were found as original compounds. Moreover, the analyses revealed the carbonate nature of these stones, in this way calcite ($CaCO_3$), natrite (Na_2CO_3), termonatrite ($Na_2CO_3 \cdot H_2O$) and natron ($Na_2CO_3 \cdot 10H_2O$) were identified. However, these compounds were also found as efflorescences and subefflorescences. This fact indicated a transformation of original compounds due to the influence of water. On the other hand, gypsum ($CaSO_4.2H_2O$) and nitratine ($NaNO_3$) were identified as decaying compounds in the sandstone whereas nitrocalcite ($Ca(NO_3)_2 \cdot 4H_2O$) and niter (KNO_3) were found as main decaying compounds in mortars (the Raman and DRIFT spectra are collected in the Figure and the chemical process are showed in the equations 1-4). The origin of nitrates and sulfates salts was demonstrated to be related to the infiltration waters. Besides, the access of ammonium nitrate (a common decomposition product of the organic matter [2]), to the stones of the wall by capillarity processes was proved by DRIFT. This compound caused the formation of the salts by interactions with join mortars and sandstones. The source of potassium was coming from the hydrolysis of orthoclase whereas calcium and sodium belong to the original carbonates. Moreover, thenardite (Na_2SO_4) was found only in the restored mortars of Portland cement, one of the most harmful salts to the building material, which formation was caused by reactions between the additives (high content of sodium oxide and gypsum) and water.

$$CaCO_3 + SO_4^{-2} + H^+ \rightarrow CaSO_4 + HCO_3^- \;//\; CaSO_4 + 2H_2O \rightarrow CaSO_4{\cdot}2H_2O \quad (1)$$
$$Na_2CO_3 + 2NO_3^- + H^+ \rightarrow 2NaNO_3 + HCO_3^- \quad (2)$$
$$CaCO_3 + 2NO_3^- + H^+ \rightarrow Ca(NO_3)_2 + HCO_3^- \;//\; Ca(NO_3)_2 + 4H_2O \rightarrow Ca(NO_3)_2{\cdot}4\,H_2O \quad (3)$$
$$KAlSi_3O_8 + 8H_2O + NO_3^- + H^+ \rightarrow Al(OH)_3 + 3Si(OH)_4 + KNO_3 + H_2O \quad (4)$$

Finally, a multivariate statistical treatment of experimental results obtained by ion chromatography was performed confirming the spectroscopic results. Moreover, it allowed to the determination of unidentifiable compounds by spectroscopic techniques such as $MgCl_2$.

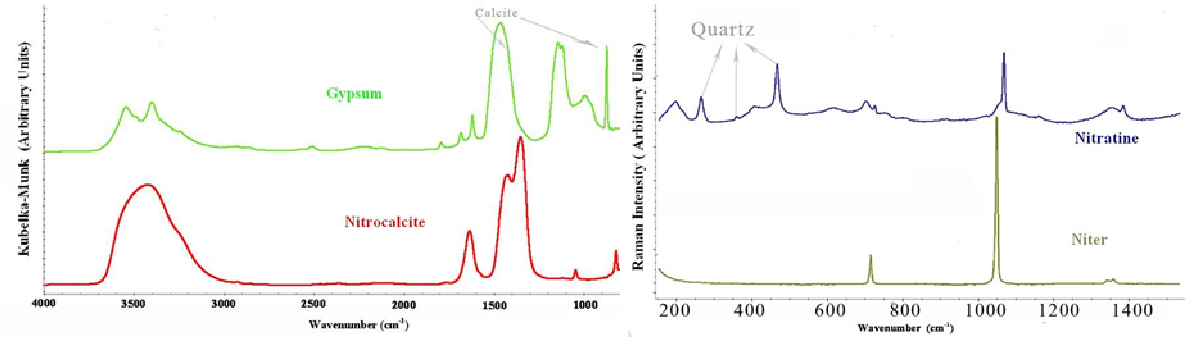

Figure. The image on the left corresponds to the DRIFT Spectra of gypsum and nitrocalcite found as decaying compounds. On the other hand, the image on the right shows the Raman spectra of nitratine and niter identified in the samples.

As conclusion, the multianalytical methodology used allows us to demonstrate that the main source of the decaying process was infiltration water. Moreover, the advantages of the DRIFT in the identification of compounds and location of incoming points of water infiltration were highlighted, as this technique solved the problems presented in Raman spectroscopy by fluorescence effect in some of the samples, making possible the identification of a higher number of compounds. Therefore, this work shows the suitability of this combination of nondestructive techniques as well as their complementarity in the field of Cultural Heritage.

Acknowledgements:

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[1] Prieto-Taboada, N.; Gómez-Laserna, O.; Martínez-Arkarako, I.; Olazabal, M.A., Madariaga, J.M., Optimization of two methods based on ultrasound energy as alternative to European standars for soluble salts extraccion from buildings materials. *Anal Bioanal Chem* **2008**. 391 1361-1370.

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Coordination chemistry of copper(II) complexes with heteroaromatic alcohols. Synthesis, spectroscopic characterization and antioxidant activity studies

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In recent years, many coordination compounds of Cu(II) ions with heteroatomic alcohols have been synthesized in our laboratories [1]. Their stability constans in aqueous solution (Table 1) and single-crystal X-ray diffraction data, spectroscopic or magnetic properties of solid state compounds were reported.

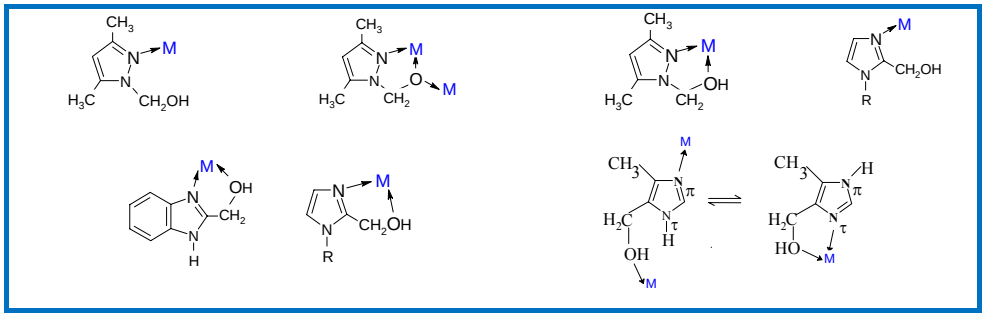
Table 1. Stability constans of imidazole derivatives with Cu(II) ion in aqueous solution at 298 K and I=0.5 mol dm^{-3} (KNO_3) [1]

Ligand	pK_a	log β_1	log β_2	log β_3	log β_4	log β_5	log β_6
1-Me-2-CH_2OHIm[1]	6.98	4.04	7.48	10.08	11.70	12.38	13.57
4(5)-CH_2OHIm[2]	6.67	3.60	7.05	9.53	10.90	-	-
4-CH_2OH-5-MeIm[3]	7.14	3.95	7.26	10.26	11.79	13.00	-
1-Et-2-CH_2OHIm[4]	7.02	4.12	7.58	10.38	12.13	12.68	14.28
1-Pr-2-CH_2OHIm[5]	7.04	4.10	7.55	10.31	11.50	12.10	13.42
1-Bu-2-CH_2OHIm[6]	7.00	4.11	7.62	10.39	11.89	13.18	-
1-Bz-2-CH_2OHIm[7]	6.58	3.34	7.54	-	-	-	-
2-CH_2OHBIm[8]	5.52	2.85	6.26	10.19	-	-	-
1-CH_2OH-3,5-DMePz[9]	3.48	-6.10	2.68				

Abbreviation: 1-methyl-2-hydroxymethylimidazole[1], 4(5)-hydroxymethylimidazole[2]; 4-methyl-5-hydroxymethlimidazole[3], 1-ethyl-2-hydroxymethlimidazole[4], 1-propyl-2-methlimidazole[5], 1-butyl-2-hydroxmethlimidazole[6], 1-benzyl-2-hydroxmethlimidazole[7], 2-hydroxmethylbenzimidazole[8], 1-hydroxymethyl-3,5-dimethylpyrazole[9]

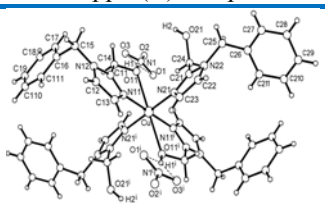
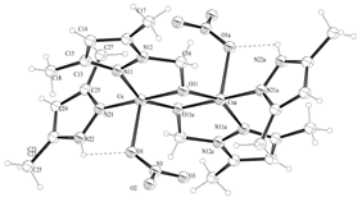
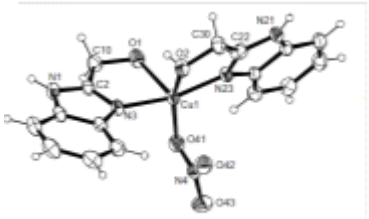
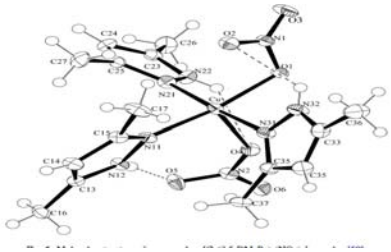
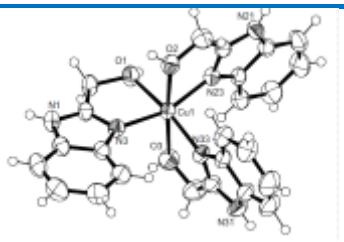
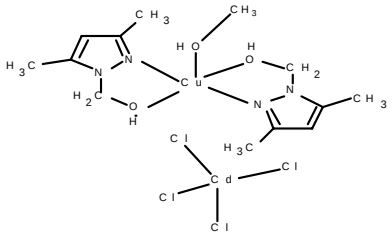
In this work, we want to extend our research into chemistry of hydroxyalkylpyridine Cu(II) complexes (synthesis, analytical and spectral characterization). Additionally, we will report the antioxidant data of these copper(II) complexes, taking into consideration that low molecular weight mimics of SOD, containing Cu(II) ions, have been proposed [2] to overcome the limitation of the use of SOD enzymes as therapeutic agents and pharmaceutical tools.

According to the best of our knowledge, the versality of hydroxyalkyl derivatives of imidazole or pyrazole as ligands, which may act as monodentate or bidentate, either neutral or deprotonated, and which undergo tautomeric equilibrium upon coordination to Cu(II) ions have been discussed and illustrated using relevant examples in Scheme 1:



The data obtained show that solid state chemistry of hydroxyalkylpyrazole and imidazole complexes with Cu(II) ion are very interesting and the kind of complexes obtained in the reaction of Cu(II) salts with heterocyclic alcohols depends on the conditions or solvent used during synthesis (Table 2).

Table 2. Examples of copper(II) complexes with hydroxyalkylpyrazole and imidazole [1]

 [Cu(1-Bz-2-CH_2OHIm)$_2$](NO_3)$_2$	 [Cu(3,5DMePz)(1-CH_2O-3,5-DMePz)(NO_3)$_2$]
 [Cu(2-CH_2OHBIm)$_2$(NO_3)](NO_3)(H_2O)	 [Cu(1-CH_2OH-3,5-DMePz)$_3$(NO_3)$_2$]
 [Cu(2-CH_2OHBIm)3](NO_3)$_2$(H_2O)(i-PrOH)	 [Cu(1-CH_2OH-3,5-DMePz)$_2$(MeOH)][$CdCl_4$]

Acknowledgments: This research was partly supported by the *grantPROGRESS*, which is funded by European Social Found in Poland (Human Capital Programme) (K. Michalska, K. Dumin).

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[1] Barszcz, B.; Coordination properties of didentate N,O heterocyclic alcohols and aldehydes towards Cu(II), Co(II), Zn(II) and Cd(II) ions in the solid state and aqueous solution. *Coord. Chem. Rev.* **2005**, 249, 2259–2276.

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Factors controlling the structures of Cu(II) and Cd(II) complexes obtained *in situ* using 1-hydroxymethyl-3,5-dimethylpyrazole as a starting ligand

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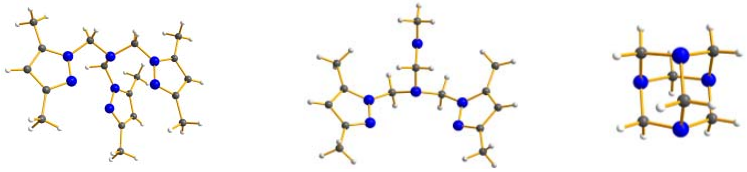
Here we report how a change in a synthetic approach for the redox system, using zerovalent copper (powder), cadmium oxides (CdO), ammonium salts and the starting ligand, 1-hydroxymethyl-3,5-dimethylpyrazole, influenced the type of obtained compounds.
To our system, we incorporated not only zerovalent Cu but also CdO as a cadmium ion source because many current investigations in coordination chemistry are inspired not only by the biological function of Cu(II) ion but also by competition between Cu^{2+} and Cd^{2+} towards relevant donor atoms of protein. Cadmium plays an unusual role as a significant toxic species due to its obvious accumulation in the human body, which may lead to a serious cadmium intoxication [1]. For instance, a possible mechanism of increasing ROS in the cell is caused by displacement of copper by cadmium ions from various intracellular sites. Therefore, we also try to find effective chelating agents for the therapy of cadmium intoxication. However, the principal aim of these studies has been to investigate the dependence of the obtained complexes type and structure on the redox properties of halide anions of NH_4X salts incorporated to our system.
The redox process which accompanies the direct synthesis of complexes [2], can be summarised in the following reaction:

$$Cu^0 + 2NH_4^+ + 0.5O_2 \rightarrow Cu^{2+} + H_2O + 2NH_3$$

In addition, in our system the synthesis processes of cadmium compounds also generated the reactions of condensation of 1-hydroxymethyl-3,5-dimethylpyrazole (L) with ammonia, creating new organic tripodal ligands (Scheme 1) and urotropine.

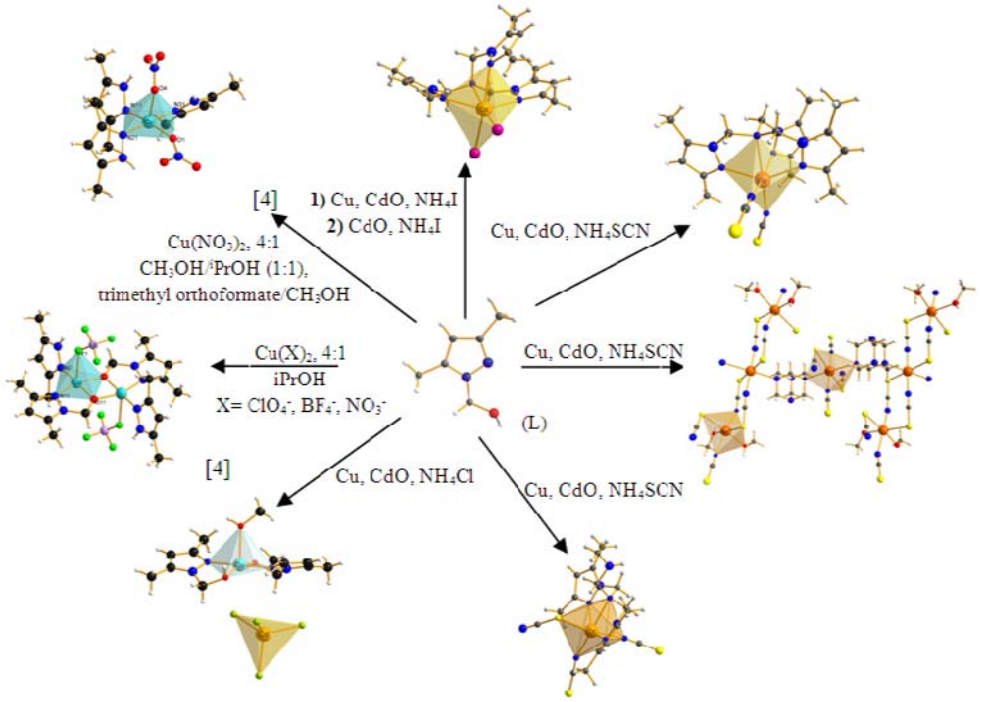


(L^1) (L^2) (L^3)

Scheme 1. Type of ligands obtained *in situ* during direct synthesis of complexes

The ligands obtained *in situ* belong to the new family of the tris(pyrazolyl) tripodal ligands, involving [3] a similar coordination capability to polypyrazolylborate ligands (scorpionate ligands), but instead of boron as the central atom they have nitrogen, phosphorus, arsenic or carbon. The tripodal character of ligands arises from the three pyrazolomethyl arms or two pyrazolomethyl and one CH_3-NH arms surrounding a central amine nitrogen. By designing

such ligands, the steric crowding near the tertiary amine nitrogen sites have been introduced and it results in unique geometry around the metal centers (Scheme 2). It should be pointed out that the type and structure of obtained complexes where conditioned by the redox properties of halide anions of NH_4X salts incorporated to the reacting systems.



Scheme 2. Schematic drawing of each reaction for this work

Acknowledgments: This research was partly supported by the *grantPROGRESS*, which is funded by European Social Found in Poland (Human Capital Programme).

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Interaction of divalent cations with Park9 protein fragments

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Two peptide sequences from Park9 Parkinson's disease (PD) gene, -$P_1D_2E_3K_4H_5E_6L_7$- (**1**) and -$F_1C_2G_3D_4G_5A_6N_7D_8C_9G_{10}$- (**2**) have been tested for Mn(II), Zn(II) and Cu(II) binding. Park9 encoded protein can protect cells from manganese poisoning, which is an environmental risk factor for a Parkinson's disease-like syndrome [1-4]. In fact, Park9 belongs to a family of ATP-ases involved in metal coordination and transportation; familial gene mutations may result in early development of PD. The chosen fragments are located from 1165 to 1171 and from 1184 to 1193 residues in the Park9 sequence, and are highly conserved in a number of organisms, going from yeasts to humans. Potentiometric, UV-vis experiments together with mono- and multidimensional NMR spectroscopy have been used to understand the details of metal binding sites at different pH values and at different ligand to metal molar ratios, showing that the three metals are able to effectively bind the examined peptides.

From NMR measurements Mn(II) and Zn(II) coordination with peptide **1** involves imidazole N_ε or N_δ of His_5 and carboxyl γ-O of Asp_2, Glu_3 and Glu_6 residues. Six donor atoms participate in Mn(II) binding, resulting in a distorted octahedral geometry, possibly involving bidentate interaction of carboxyl groups; four donor atoms participate in Zn(II) binding, resulting in a tetracoordinated geometry. Potentiometric data show that soluble, hydroxylated Zn(II) species are formed in the alkaline pH range. The formation of Cu(II) complexes with peptide **1** starts below pH: only mononuclear complexes have been potentiometrically detected also in the presence of excess of ligand (see Figure 1). Imidazole nitrogen of His residues acts as first Cu(II) anchoring site; as pH is raised, ligand coordination proceeds with deprotonation and binding of neighbouring amide nitrogens of the peptidic backbone. UV-vis spectra agree that the main species at neutral pH is a $\{N_{im}, 2N^-, O\}$ complex, where the oxygen atom most likely belongs to an equatorially coordinated water molecule.

Cu(II), Mn(II) and Zn(II) coordination involves the cysteine residues with peptide **2** and complex-formation invariably starts at lower pH with respect to ligand **1**.

Mn(II) accepts additional ligand bonds from D_4 and D_8 to complete the coordination sphere; the unoccupied sites may contain solvent molecules. When the ligand is in excess, both Zn(II) and Cu(II) ions form bis-complexes. The two metal ions behave in a very similar way and the stoichiometry of main species at physiological pH depends on the metal/ligand ratio: $[ML]^{2-}$ in equimolar solution or $[MHL_2]^{5-}$ for the 1:2 ratio. Potentiometric data suggest for the former a {2S, 2O} and for the latter a {3S, 1O} coordination without any participation of amide nitrogens, as usually found for Cu(II)/peptide complexes.

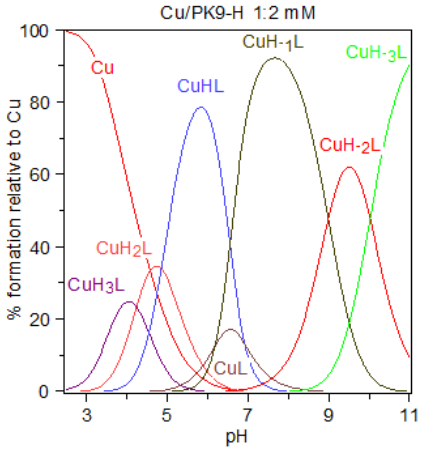

Fig. 1
Exemplificative distribution diagram for the system Cu(II)/peptide **1**

References:

[1] Gitler, A.D.; Chesi, A.; Geddie, M.L.; Strathearn, K.E.; Hamamichi, S.; Hill, K.J.; Caldwell, K.A.; Caldwell, G.A.; Cooper, A.A.; Rochet, J.-C.; Lindquist, S., Alpha-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity, *Nat. Genet.*, **2009**, 41 (3), 308-315.

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Preparation and characterization of the polydentate Schiff base derived from 2,6-diformyl-4-methylphenol and N-aminopyrimidine-2-thione and its metal complexes

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Complexes of macrocyclic ligands derived from 2,6-diformyl-4-methylphenol (dfp) are of great interest as they can mimic the structural features of macrocyclic biological molecules [1] . First row transition metal Schiff base complexes of 2,6-diformyl-4-methylphenol with N_2O_2, NON and NOO coordination sites are well characterized[2,3]. Today, metal complexes are used in many industrial fields, especially for their antimicrobial property is having for use in pharmacology. Research into Schiff base derivatives of Dfp and their metal complexes having various biological effects have increased in recent years[4].

In this study, a new polidentate Schiff base ligand, derived from 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidin-2-thione[5] and dfp[6] was synthesized and characterized. The Schiff base complexes were prepared by reacting ligand and various metal salts in methanol to get a series of mononuclear complexes. The structure of the newly synthesized ligand and its metal complexes were determined using elemental analysis and spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR, LC-MS and UV-Vis. In addition to the spectral techniques mentioned above, molar conductivity, magnetic susceptibility measurements were also used.

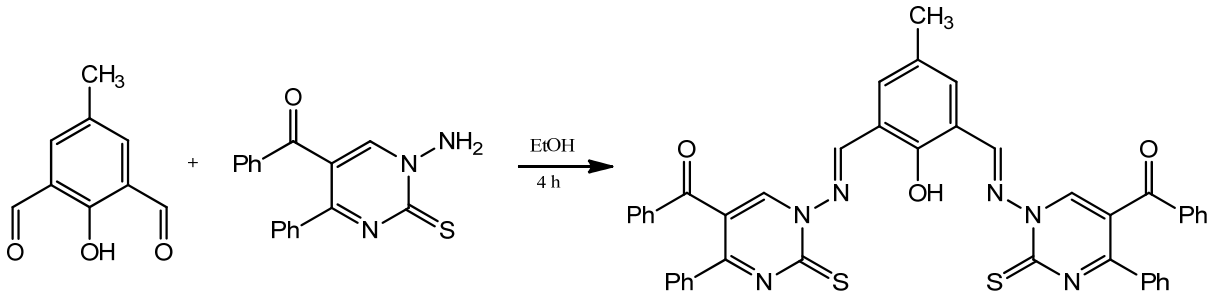

Figure 1 Synthesis protocol of Schiff base ligand

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Kinetics and mechanism of the reaction between a Mn(III) porphyrin and *n*-hydroxyurea in aqueous solution

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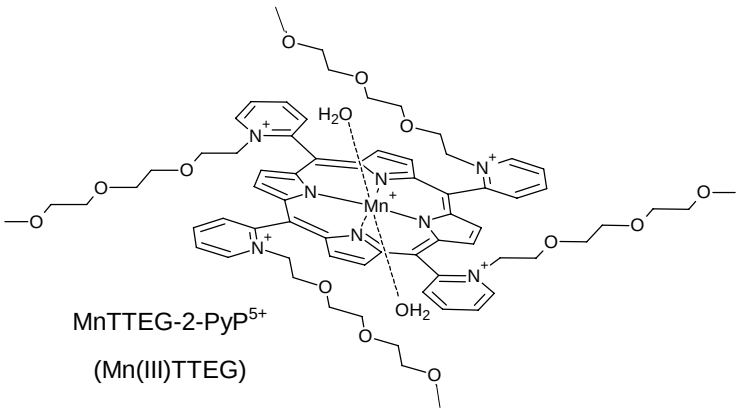
Recently, a number of metalloporphyrins have been developed for therapeutic purposes. Manganese seems to be a favorable choice for the central metal ion as it lacks Fenton-related toxicity. The porphyrin ring provides high complex stability, rich biologically relevant redox chemistry at the metal site, tunable overall redox potential and water exchange rate [1]. Therefore, studying the reaction of manganese prophyrins with N-hydroxyurea (HU), which has been used in human medical therapy for more than 40 years because of its broad antitumor spectrum, seems to be a beneficial strategy for improving medical applications.

In this poster, we present a study of the aqueous autoxidation of HU as catalyzed by Mn^{III}TTEG-2-PyP^{5+}, a synthetic water soluble Mn(III) porphyrin which is also a potent SOD mimic. A proposal for the mechanism of the reaction is based on kinetic studies carried out mostly under basic conditions at pH = 11.7 but also including some pH-dependent observations in the pH range from 9 to 13. Intermediates were identified simultaneously by UV-vis spectroscopy and electrospray ionization mass spectrometry. The reaction sequence starts with a fast coordination of HU to the metal center of Mn^{III}TTEG-2-PyP^{5+}, which is followed by a ligand-to-metal electron transfer to get Mn^{II}TTEG-2-PyP^{4+} and the free radical derived from the one electron oxidation of HU. Nitric oxide (NO) and nitroxil (HNO) are minor intermediates. The major pathway for the formation of the most significant intermediate, the {MnNO} complex of Mn^{II}TTEG-2-PyP^{4+}, is the direct complexation of Mn^{II}TTEG-2-PyP^{4+} with NO. The autoxidation of the intermediates open alternative reaction channels, and the process finally yields NO_2^- and the initial Mn^{III}TTEG-2-PyP^{5+}.



MnTTEG-2-PyP^{5+}

(Mn(III)TTEG)

References:

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Kinetic studies on the light-induced water splitting catalyzed by the Ce(III)/Ce(IV) redox system

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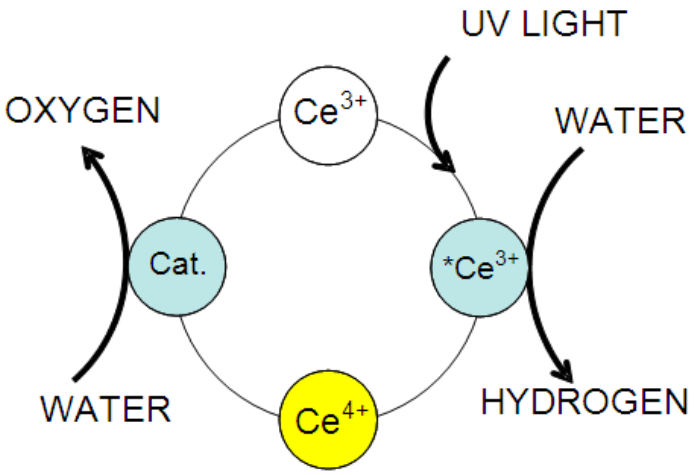
Photochemical water splitting catalyzed by cerium(III) ions is one of the possibilities to utilize solar energy in homogeneous medium. In this process, the net reaction is the photochemical decomposition of water into oxygen and hydrogen gases. The energy necessary for the process is provided by the light and the catalyst of the process is the cerium(III) salt in aqueous medium. Although the reaction itself has been known for more than 50 years [1], there is still no thorough mechanistic information about it.



The first part of the catalytic cycle, *i.e.* oxidation of water by cerium(IV) can be catalyzed by light, or various heterogeneous catalysts (*e.g.* ruthenium dioxide). The other half reaction, namely the formation of hydrogen gas, requires light or other energy source to take place.

Based on earlier literature data, this later step can also be catalyzed. As a catalyst for these two steps, metal complexes without readily oxidizable organic ligands should be chosen since cerium(IV) is a very strong oxidizing agent. Such an agent is the ruthenium(III) aqua ion, but it is important to note that the presence of an organic ligand does not rule out the possibility of application as a catalyst.

To carry out these measurements, a method worked out earlier [2], which uses a diode array spectrophotometer as a photoreactor and analyzing unit at the same time, was employed here. This method uses a special property of the diode array spectrophotometers, namely the high light intensity passing through the sample. This polychromatic UV-Vis light is able to induce photoreactions. The instrument at the same time – being a spectrophotometer – can follow the kinetics of all reactions in the cell which are accompanied by a change of color. To

do this, it is also important to characterize the photometer lamps in detail (including light intensity, light energy spectra, number of photon counts, stability of the lamp and detector).

Photochemical reactions of acidic Ce(IV) aqueous solutions at different pH values containing sulfate ion as ligand were investigated using a HP-8543 diode array single beam spectrophotometer. The dependence of the initial reaction rate on the sample volume, illumination time, Ce(IV) concentration, temperature and Ce(III) concentration was investigated. The volume dependence of the reaction rate is always very important when dealing with photochemical reactions. Our reaction shows a decrease in the reaction rate when the sample volume is increased. Based on these measurements, the reaction order with respect to light intensity was calculated to be 1.

For investigating the dependence of the reaction rate on the illumination time, solutions with different Ce(IV) concentrations were measured. At relatively low Ce(IV) concentration (10^{-4} mol/dm^3), the dependence of the initial rate on the illumination ratio is linear and the quantum yield could be calculated. It was also found that the reaction also runs without any illumination, so the intercept of the initial rate – illumination ratio function is not 0. At a concentration of 10^{-3} mol/dm^3 or higher, the previous function is not linear, but a saturation curve. There was also an initial, unexpected increase in the absorbance values in the first few minutes of the reaction. This can be explained with the light induced formation of some kind of Ce(IV) dimer at this concentration. Measurements carried out in a double beam Shimadzu spectrophotometer show that this instrument cannot initiate the photochemical reaction.

Temperature dependent reaction rate measurements show an increase in rate when the temperature is increased, indicating that the reaction mechanism contains thermally activated steps. Ce(III) ions, which are also the products of the investigated reaction, have a decreasing effect on the reaction rate, but only in a concentration which is comparable to the Ce(IV) concentrations of the solutions.

The same light catalyzed reaction using EDTA as a ligand instead of sulfate ion was also investigated. In this case, strong complexation reactions of both Ce(III) and Ce(IV) change the formal redox potential of the Ce(III)/Ce(IV) system substantially. CV measurements were also carried out to determine the redox potentials experimentally.

Acknowledgements: This work was supported by TÁMOP 4.2.1./B-09/1/KONV-2010-0007.

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Oxidative dehydrogenation of an Fe(II) complex with a scopiand-type ligand

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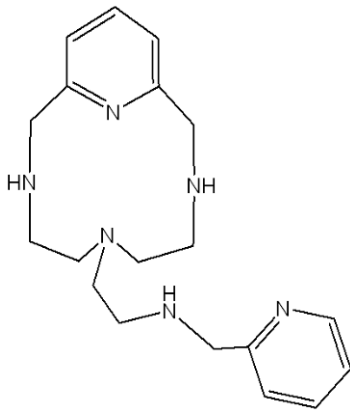
Oxidative dehydrogenation of coordinated ligands is one of the most common problems found when designing complexes able to act as functional models of non-heme oxygenases. Examples of oxidative dehydrogenations leading to coordinated imines have been reported for a variety of metal ions, and for the case of many iron-polyamine complexes several consecutive dehydrogenation processes may occur, [1] and actually there are not many examples in which a single C=N bond is formed. During the course of our work with scorpiand-like ligands, we have found an example of such behaviour and are currently carrying out detailed mechanistic studies. Ligand L (see formula below) forms stable metal complexes with Cu(II) [2] but attempts to isolate a complex with Fe(II) led to isolation of a $[Fe(L\text{-}2H)]^{2+}$ complex, in which L-2H is a ligand resulting of oxidative dehydrogenation of one of the C-N bonds in L. The crystal structure has been solved and reveals the formation of a single C=N bond. Here we report kinetic studies on the oxidative dehydrogenation of the Fe(II)-L complex to form $[Fe(L\text{-}2H)]^{2+}$.



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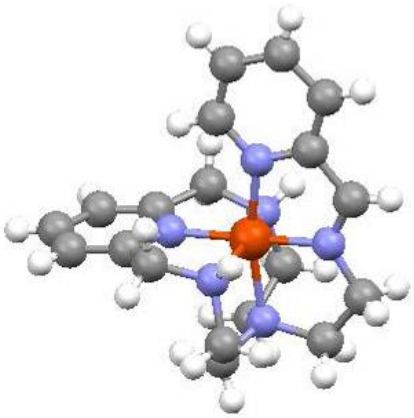
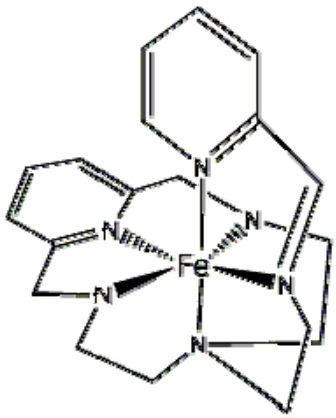
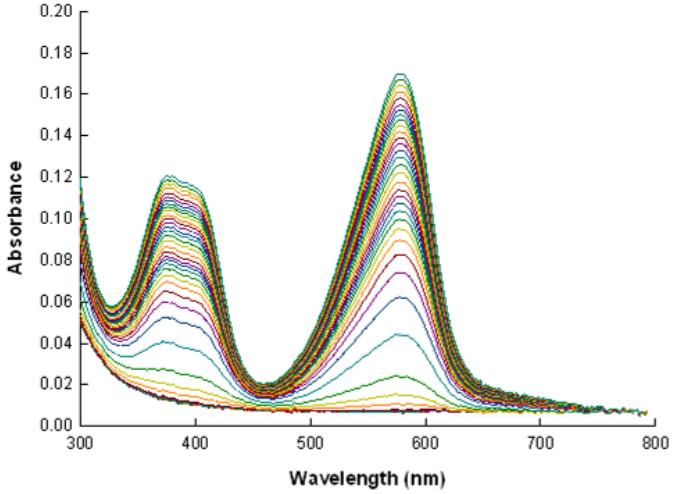


$[Fe(L\text{-}2H)]^{2+}$



$[Fe(L\text{-}2H)]^{2+}$

The Uv-Vis spectrum of $[Fe(L\text{-}2H)]^{2+}$ shows an intense band at 578 nm and two overlapping bands that span from 370 to 400 nm. These bands can be used for monitoring the kinetics of oxidative dehydrogenation, and results under a variety of conditions will be presented. Whereas acidic conditions lead to direct formation of the $[Fe(L\text{-}2H)]^{2+}$ complex without accumulation of any detectable reaction intermediate, more complicated kinetic schemes are observed in neutral solutions. The effects of using H_2O_2 as oxidant and of changing Fe(II) to Fe(III) will be also discussed.



UV-vis spectral changes during formation of $[Fe(L\text{-}2H)]^{2+}$.

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Coordination abilities of mono and multi-histidinic and glutamate peptide fragments towards manganese(II) and cobalt(II)

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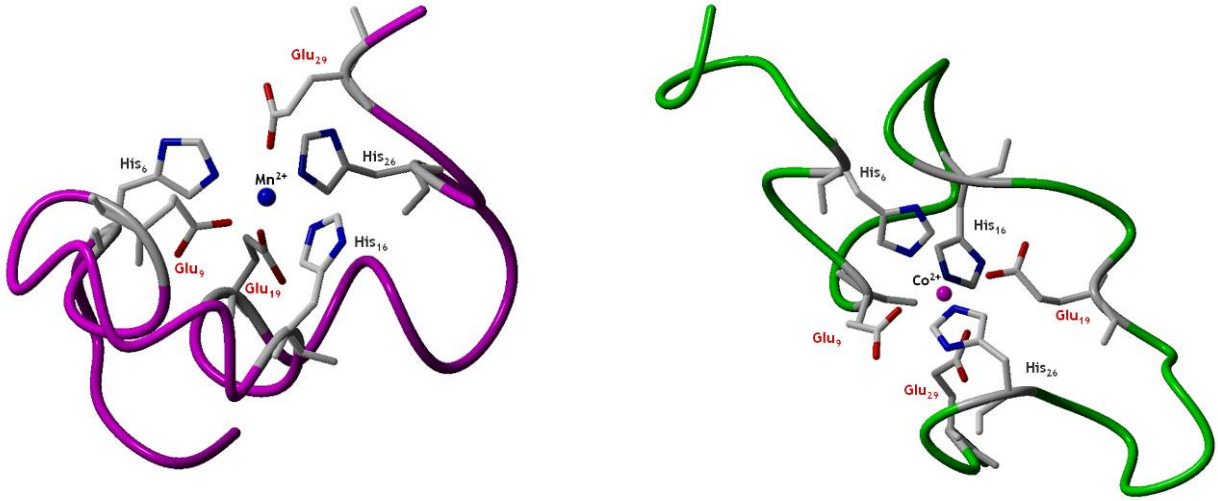
It is known that rich repeat domains in peptides can be of interest as the models for the study of molecular phenomena related to metal ion binding in proteins involved in neurodegenerative disorders. Imbalances in transition metal ions are assumed to contribute to the conversion of the multi-histidinic amyloid β-peptide (Aβ) from its soluble form to an amyloidogenic form, and to Aβ deposition. Of these ions, it has been reported that manganese binding to PrP is detrimental and causes a conformational change in the protein, suggesting that manganese binding could potentially play a role in prion disease progression *in vivo*. It appears that PrP is less stable on binding manganese and quickly converts to a misfolded form. The binding of manganese to PrP potentially results in the conversion of the protein to an abnormal isoform with properties reminiscent of PrP^{sc}. In particular, although PrP can bind the same number of manganese atoms as of copper atoms, the resulting protein becomes proteinase resistant, forms fibrils and loses function.[1,2]

Regarding cobalt, a novel low-affinity binding site for Co(II) was discovered between PrP residues 104 and 114, with residue His_{111} being the key amino acid for coordinating Co(II).[3] Thus, despite the interest in manganese and cobalt binding to PrP, a thorough analysis of the interaction of both metals with proteins related to brain pathies has not yet been reported. The $(T_1R_2S_3R_4S_5H_6T_7S_8E_9G_{10})_3$ fragment from Cap43 protein, which is induced by metal ions, is characterized by a decarepeat domain comprising three decapeptide units with one histidine and one glutamate residue in each repeat. Therefore the study of the interaction of the 30-aminoacid peptide from Cap43 protein with metal ions can contribute to the understanding of the crucial role of multi-imidazol and glutamate sites in the protein coordination processes and the possible role of divalent metal ions in the pathogenesis of prion disease and other related protein pathies.[4-8]

Here we present our recent results on the Cobalt(II) and Manganese(II) complexes of terminally protected mono- and multi-histidine-glutamate peptides studied by combination of potentiometric measurements and spectroscopic techniques (NMR, UV-Vis and EPR). Metal complexation induces important structural changes with the C-terminal portion of the ligand, constraining it to leave its disordered conformation and promoting side chain orientation. Our

results give rise to a molecular model of the induced structure for the peptides complexed with cobalt and manganese.



Models of the most likely coordination spheres of Mn(II) and Co(II) with a multi-histidine-glutamate peptide fragment.

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Synthesis, structural characterization, catalytic and thermal investigations of multidentate Schiff base ligand derived from pyrimidine compound and its metal complexes

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[b]Department of Chemistry, Faculty of Science and Letters, Sütçü İmam University, Kahramanmaraş 46100, Turkey;
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Schiff base complexes containing different central metal atoms have been studied in great detail for their various crystallographic features, enzymatic reactions, steric effects, structure-redox relationships, mesogenic characteristics, catalysis, magnetic properties, and their important role in the understanding of the coordination chemistry [1]. The pyrimidine ring system; present in nucleic acids, several vitamins, coenzymes, and antibiotics; provides potential binding sites for metal ions, and their coordination nature is important in the understanding role of the metal ions in biological systems [2]. Many Schiff base complexes show excellent catalytic activity in various reactions at high temperature (>100 ^{o}C) and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis, hence the need for a review article highlighting the catalytic activity of Schiff base complexes realized [3,4].

In this work, a new multidentate Schiff base ligand, derived from 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidin-2-one [5] and 4-tert-Butyl-2,6-diformylphenol was synthesized and characterized. The Schiff base complexes were prepared by reacting ligand and some metal salts in methanol to get a series of mononuclear complexes. The synthesized compounds were characterized by elemental analysis FTIR, NMR, API-ES and UV-vis spectral techniques. The thermal stabilities of the complexes were also investigated using TGA. Moreover, the study on the catalytic activity of metal complexes towards the oxidation of 3,5-di-tert-butylcatechol (DTBC) were investigated.

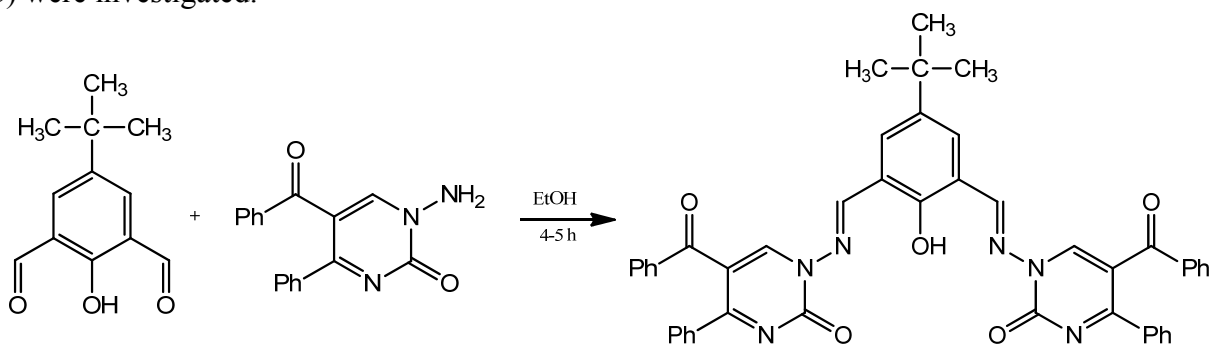

Figure 1 Synthesis protocol of Schiff base ligand

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Structural studies on the interaction of group 12 metal ions with the water soluble 8-hydroxy-sulfo-quinoline

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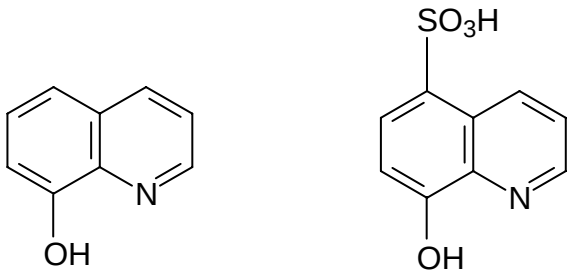
The impact of metal ions on human health and environment has led to the development of novel materials and methods for on-line detection of environmentally hazardous metals, including the divalent metals of group 12 (Zn^{2+}, Cd^{2+} and Hg^{2+}). Because of its unique electronic and structural preferences, Zn^{2+} plays a central role in regulating cellular metabolism. It is present at high concentrations in the human brain, tightly sequestered by proteins. However, alterations of Zn^{2+} homeostasis can lead to disorders of its metabolism and excessive zinc accumulation in the brain may be implicated in neurodegenerative disorders, such as Alzheimer's disease, as also suggested for Cu(II) and Al(III) [1,2]. Cd^{2+} and Hg^{2+} can accumulate in soft body tissues, are also well known for their toxic effects [3].

The high selectivity and sensitivity of optical sensors has led to interest in their development for these applications. The sensor response is characterized by a change in some optical property, such as absorbance or luminescence, as a function of the concentration of the analyte. Metal chelators such as 8-hydroxyquinoline (8-HQ) and its derivatives show considerable potential for sensing as they exhibit *turn-on* fluorescence signalling in the presence of a range of metal ions (e.g. Al^{3+}, Cd^{2+}, Zn^{2+}, Mg^{2+}, Sn^{4+}, Ti^{4+}) [4]. Free 8-HQ is weakly luminescent in solution (Φ_F<0.04), but can form luminescent metal chelates. The luminescence of the metal chelate (emissive state, wavelength, quantum yield) is modulated by metal ion electropositivity, spin-orbit coupling, and the excitation wavelength [5].

Recently, the complexation of 8-hydroxy-5-sulfoquinoline (8-HQS) with Zn(II) was studied [6]. We extend these studies to Cd(II) and Hg(II), using multinuclear NMR spectroscopy (^1H and ^{13}C), DFT calculations and ^{luminescence} techniques to characterize these complexes. DFT results suggest that the ligand geometry around the metal centre is highly dependent on the hard/soft properties of the metal. The 1:2 (metal:ligand) complex of Zn^{2+} with 8-HQS is square bipyramidal, with the two coordinated water molecules mutually *trans*, and the remaining positions occupied by the donor groups of the two coordinated 8-HQS ligands [9]. The corresponding 1:2 complexes of Cd^{2+} and Hg^{2+} with 8-HQS show an increasing distortion of the positions of the two water molecules around the metal centre. Along the group 12, there is a pronounced tendency of the two water molecules to adopt mutually *cis* positions, which is related to the increasing soft acid properties of the metal. In addition, 8-HQS shows a marked increase in the intensity of the fluorescence band compared to the fluorescence of the free ligand on binding to metal ions. This is accompanied by

marked changes in the absorption spectra, in line with previous studies, These observed changes are likely to be particularly important for the potential application of 8-HQS as a luminescent sensor for the detection and remediation of Zn(II), Cd(II) and Hg(II) in surface waters and biological fluids. In addition they may be useful for applications in organic light emitting diodes (OLEDs).



8-HQ **8-HQS**

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Liquid chromatography combined with elemental and molecular mass spectrometry for analysis of phytosiderophores and metal-phytosiderophore complexes in the context of strategy II iron acquisition by plants

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Iron deficiency in crop plants is a widespread problem and the efficient mobilization and uptake of iron by plant roots is crucial for maintaining agricultural production and sustainable iron nutrition of human beings.

Phytosiderophores are exuded by crop plants of the Poaceae plant family (e.g. wheat, barley, rice and maize) to mobilize iron from soil via the formation of highly stable iron-phytosiderophore complexes. Phytosiderophores are non-proteinogenic amino acids consisting of hexadentate ligands with aminocarboxylate and hydroxycarboxylate functional groups. The three major compounds are mugineic acid (MA), 2'-deoxymugineic acid (DMA) and 3-epihydroximugineic acid (epiHDMA). In the root-soil intertface, i.e. the rhizosphere, phytosiderophores can efficiently scavenge iron from a range of ironbearing compounds including iron oxides [1]. The iron deficiency induced synthesis and exudation of phytosiderophores, and the subsequent uptake of iron–siderophore complexes has been described as the ''strategy II'' iron acquisition mechanism [2]. While the mechanisms and regulation of phytosiderophores synthesis by plants is well understood, the rhizosphere biogeochemistry of phytosiderophores and phytosiderophores iron acquisition is largely unknown.

In the analytical part of in our interdisciplinary research project, we are aiming at the development and implementation of LC based separation methods, and their combination with both, molecular and elemental mass spectrometry for analysis of free phytosiderophores and iron-siderophore complexes as well as other important transition metal complexes in soil and plant related samples and in the plant soil interface. We will present two novel methods based on LC-ICP-MS and LC-ESI-MS, respectively. First results from pot experiments, root exudate collectors as well as batch experiments including natural soils and synthetic phytosiderophores will be presented.

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Kojic derivatives: a promising class of iron(III) chelators.

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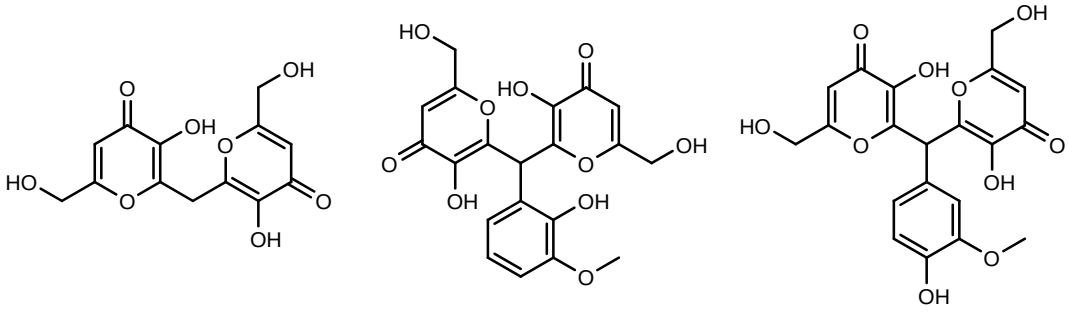
In the last two decades there has been an increasing interest in the use of chelation therapy for various medical conditions involving iron and aluminium [1]. Reagents in current use, such as desferal, deferiprone and deferasirox, are based on hydroxamic groups, hydroxyl-substituted pyridinones or aromatic ring systems. With the aim to design new chelators we presented the equilibria of kojic acid and some its derivatives (Scheme 1).



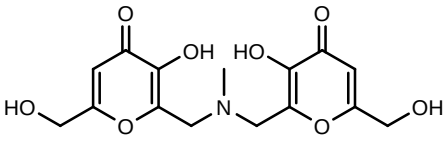
1 **2** **3**

Scheme 1

In a previous work, evidence was given on the formation of MeL, MeL_2, and MeL_3 complexes of both metal ions with kojic acid, confirmed by the X-ray structure of a FeL_3 complex, and of diverse protonated Me_2L_2 and MeL_2 complexes of ligand **1** (Scheme 1) [2]. On the basis of the extremely good pFe value (23.1) characterizing ligand **1**, and of its ability to scavenge iron from inside cells, we extended the investigation to related compounds in which vanillin and *o*-vanillin substituents are placed on the linker that joins the two kojic units. The found pFe values (18.9 for ligand **2** and 22.2 for ligand **3**), despite lower than that for desferal (26.6) but surely comparable with that of deferiprone (20.7), are very encouraging [3]. These ligands are relatively easy and cheap to produce, as the starting materials, kojic acid and vanillin are not expensive. Hence, they deserved further examination to determine their toxicity and their capacity to remove iron and/or aluminium from intra-cellular sites in living organisms.

In Me_2L_2 complexes formed with ligands **1**-**3**, each metal ion is coordinated by two CO-C(OH)-chelating moieties, one from each coordinating molecules. Actually, the length of the linker between the two kojic units prevents metal ion coordination by both kojic units on the

same molecule. Therefore, aimed at improving that interaction, we have designed and synthesized a new set of bis-kojic ligands whose linkers (between the kojic chelating moieties) are differentiated both in terms of type and size (Scheme 2). In this communication we will present the synthesis and the characterization of the three derivatives **4**, **5** and **6** in Scheme 2.



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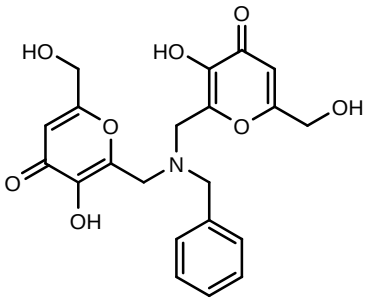

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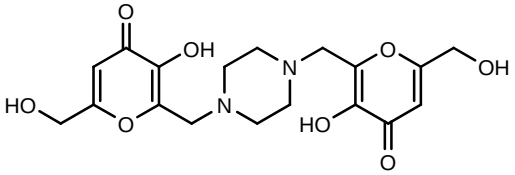

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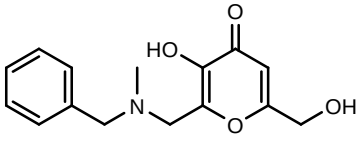

7

Scheme 2

The description of the protonation and complex formation equilibria by potentiometry, UV-Vis spectrophotometry and ^{1}H NMR spectroscopy will be described and discussed.

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Alkylamine-bearing *N*-heterocyclic chelators for *hard* metal ions

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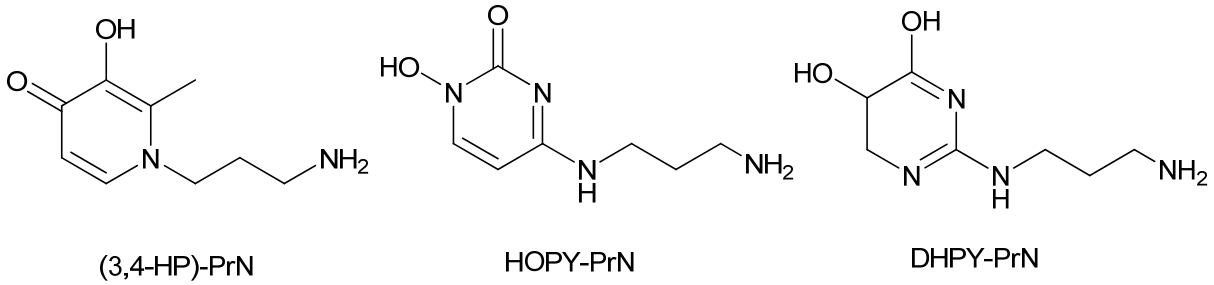
In healthy conditions, the body is provided with homeostatic mechanisms and buffers to maintain low concentrations of free metal ions, therefore avoiding episodes such as anomalous decompartmentalization and release or trafficking of metal ions. Besides iron overload diseases, such as hematochromatosis or β-thalassemia associated transfusional hemosiderosis, the main reasons for the abnormal accumulation of metal ions in the body can be environmental exposure (e.g. Al, actinides) and the administration of metallodrugs in therapy or diagnosis. In fact, metallodrugs can create biometal competition, oxidative stress and enzyme deregulation thus provoking several pathologies.

One of the goals of medicinal inorganic chemistry has been the design of nontoxic orally active chelating agents adequate for hard metal ions. Several hard ligands were developed, such as polyaminocarboxylic acids (e.g. EDTA, DTPA), cathecols and hydroxamates, but problems arose such as low oral bioavailability and lack of selectivity (Zn depletion). After the disclosure of deferiprone (DFP) for iron overload, approved as a second-line therapy for thalassemia patients, several bidentate hydroxypiridinones (HPs) have been proposed as pharmaceutical drug candidates. Although the bidenticity of these ligands is associated with the formation of more labile complexes than the hexadentate ones, such as the tris-hydroxamate DFO, the high pM values exhibited by HPs at the physiological pH are a guarantee that complex dissociation is not likely to occur during the administration protocols.

Our group has developed several 3-hydroxy-4-pyridinone (3,4-HP) derivatives [1], compounds which high basicity of the hydroxyl group renders them neutral at the physiological pH and with higher affinity for hard metal ions than for soft biologically relevant bivalent metal ions (e.g. Zn(II)). Besides HP derivatives, we have also studied hydroxypyrimidinones (HPMs), which revealed high chelating affinity towards hard metal ions, both in solution or when grafted to solid matrices [2-4]. HPMs are hard bidentate ligands, typically heterocyclic hydroxamates, with higher acidity and higher water solubility than 3,4-HPs. Following our search on hard metal chelators we have recently developed a new *N*-heterocyclic chelator, a dihydroxypyrimidine (DHPY).

Herein, we present a comparative study on the chelating properties (solution and *in vivo*) of a set of analogous of those chelators, which were bifunctionalized with alkylamine moieties for further skeleton attachment. Therefore, three alkylamine-bearing *N*-heterocyclic chelators, one HP ((3,4-HP)-PrN), one HPM (HOPY-PrN) and a 2-(3-aminopropylamino)-4,5-dihydroxypyrimidine derivative (DHPY-PrN), are studied in terms of acid-base properties,

complexation behavior towards Fe(III) and Ga(III). They are also *in vivo* assayed (^{67}Ga biodistribution) for evaluation of their capacity to remove hard metal ions from an animal model previously administered with gallium.



(3,4-HP)-PrN HOPY-PrN DHPY-PrN

DHPY-PrN showed improved chelating capacity towards Fe(III) and Ga(III), when compared to (3,4-HP)-PrN, HOPY-PrN or even DFP, although (3,4-HP)-PrN showed better results in terms of *in vivo* studies, revealing enhanced urinary excretion leading to an increased ^{67}Ga removal from the soft tissue.

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Bifunctional iron-chelators with protective roles against neurodegenerative diseases

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Alzheimer´s disease (AD) is a devastating neurodegenerative disorder characterized by the progressive and irreversible loss of memory followed by complete dementia. Since the main hallmark of the disease is the deposition of extracellular amyloid plaques, the dysfunctional beta-amyloid (Ab) has been the pivotal pharmacological target for AD. The AD etiology is not well known, but there is an amount of evidences about its multifactorial nature, namely because AD brains display metal dyshomeostasis and increased oxidative stress [1]. So, although the approved therapy is mainly for improving the memory impairment and cognitive deficit, through acetylcholinesterase (AChE) inhibitors, quite often also coadjutant drugs have been used, including anti-oxidants [2] and metal-chelators [3]. The benefits of its conjugation have also been proposed to mitigate the associated neurotoxic oxidative stress.

As part of an ongoing research,[4,5] we have designed and developed a series of polyfunctional compounds, bearing a benzothiazol (BTA) unit, as an Ab targeting sensor, but including also either an antioxidant moiety or a tacrine unit for the AChE inhibition. Herein, we present new results on the design and study of new conjugates which also include the BTA unit that is conjugated with a 3-hydroxyl-4-pyridinone (3,4-HP) moiety, in its free or O-benzyl protected form, to provide iron chelating or –pro-chelating roles, respectively. Alkyl-aryl-amide based spacers between these two groups (BTA and 3,4-HP) were modulated to provide a good binding interaction with the AChE active site, besides positive contributions to the anti-oxidant activity and the iron chelating capacity.

The selected compounds were prepared and characterized by standard techniques [5]. Representative compounds were assessed for their iron-chelating efficacy, lipo-hydrophilic and antioxidant properties (DPPH), as well as their activity against AChE. Modeling studies allow shedding some light on the rationalization of the results, namely in comparison with others previously reported. For the most promising compounds, further studies are envisaged to assess their interaction with beta-amyloid peptide and also with neuronal cells to evaluate protection/rescuing roles.

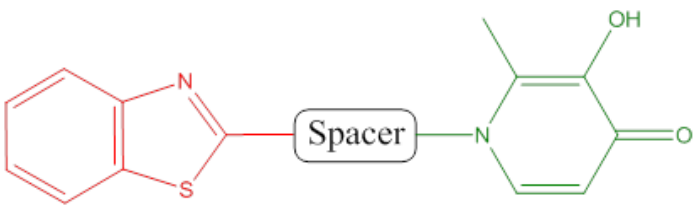

Figure: Schematic representation of the new bifunctional iron-chelators

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A Tripodal Hydroxypyrimidinone-Gd chelate for Potential Diagnostic Use

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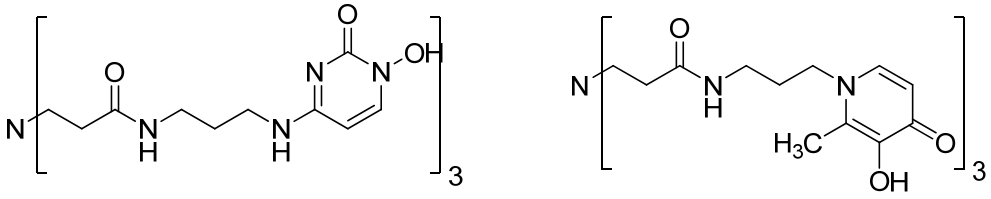
Metal complexes can be used as diagnostic tools and in the last 20 years the research effort has been mainly focused on Gd-chelates for magnetic resonance imaging (MRI). The most common commercially available metal-based imaging probes for magnetic resonance (MR) are based on poly(amino)carboxylate chelators derived from DTPA, NOTA or DOTA [1,2]. Though they are strong chelators, their Gd(III) complexes present disadvantages in terms of MR image-enhancing capability because they are eight-coordinated to the ligands (hydration number 1), a limitation for relaxivity and imaging resolution [1], and DTPA complexes have been shown to dissociate and release metal under physiological conditions.

Due to the pointed drawbacks, another class of MRI agents appeared, based on Gd complexes with hydroxypyridinones (HPs)[3]. In particular, the oxygen donor hexadentate compounds seem to be adequate since they match the oxophilicity of Gd(III), they have high chelating efficacy and the ligand coordination number is 6, which allows a higher number of bound waters, with consequent increase in relaxivity and image resolution. Concerning the type of chelating unities, our group have recently used 3-hydroxy-4-pyridinones (3,4-HPs), which high basicity of the hydroxyl group renders them neutral at the physiological pH and with higher metal affinity [4]. In fact, studies already performed [5] with a tripodal tris 3,4-HP chelator (II) revealed positive results (strong chelating affinity and two inner-sphere water molecules).



(a) (b)

In order to develop new imaging probes, a great deal of research has been directed towards the enhancement of the hydration number or also the slowing down of molecular tumbling by attachment to macromolecules, but the results obtained are still far from optimum. Therefore, the design of efficient MRI probes continues to be a challenging area.

Herein, we present a set of solution studies concerning the Gd(III) complexation properties with a new tripodal tris-chelator, resulting from the attachment of three hydroxypyrimidinone (HPM) units to nitrilotripropionic acid (a). The introduction of HPM

units in this anchoring scaffold can represent an interesting alternative to the HP-analogue since these units have also high chelating capacity for hard metal ions [6], but are more water-soluble and acidic as well as less toxic due to the presence of an extra *N*-atom in the ring. The analysis of the results of solution studies is made in comparison with those of the tris-(3,4-HP) derivative (b), as well as other bidentate HP and HPM ligands. To aid the anticipation on the number of water-molecules coordinated to the Gd(III), molecular modeling studies based on DFT calculations have also been performed. The performed studies reveal that compound (a) is a more potent chelator towards Gd(III) than (b). This important feature, together with the above mentioned physico-chemical properties indicating a well balanced lipo-hydrophilic character, encourage the pursuing of further studies on the relaxometric properties of its Gd complexes.

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The effect of N-methylimidazole on the reactivity of a model complex for compound II. A combined experimental and theoretical study

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In the catalytic cycles of heme enzymes such as catalase, peroxidase and cytochrome P450, it is assumed that high-valent iron(IV)-oxo species (abbreviated as Cpd I and Cpd II) are the key intermediates in oxygenation reactions of organic substrates. The varying catalytic activity of these enzymes is mainly ascribed to structural differences in the structure of the prosthetic group in which different amino acids coordinate iron in a proximal position (tyrosine in catalases, histidine in peroxidases and cysteine in P-450). Due to a very high reactivity of Cpd I, many studies were devoted to elucidate the influence of the axial ligands on their reactivity [1]. However, to the best of our knowledge there are no experimental studies concerning the influence of axial ligation on the reactivity of the biomimetic model of Cpd II.

In this context, we present the results of a detailed kinetic study of high-valent iron(IV)-oxo species with selected organic substrates in the presence and absence of N-methylimidazole (N-MeIm). The model for Cpd II was generated *in situ* in the reaction of hydrogen peroxide with water-soluble iron (III) porphyrin, [*meso*-tetrakis(2,4,6-trimethyl-3-sulfonatophenyl)porphinato]iron(III) – Fe^{III}(TMPS) in alkaline (pH =10) aqueous solution. The products of substrate oxidation were analyzed by application of HPLC technique. In the course of direct kinetic measurements, we could demonstrate a complete catalytic cycle in which the Cpd II analogue oxidizes the selected substrates leading to the almost complete reformation of the catalyst (Figure 1). The performed studies display that the N-methylimidazole axial ligand *trans* to the oxoiron(IV) bond does not significantly affect the oxidation capability of the Cpd II mimic towards selected organic

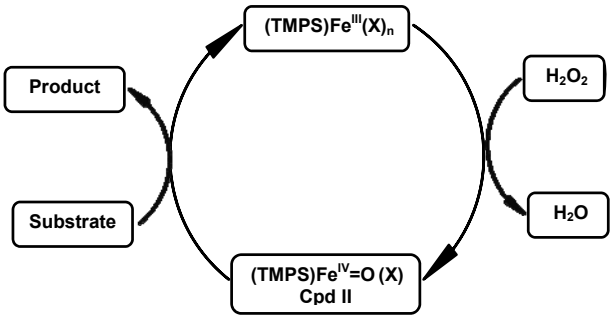

Figure 1. General reaction scheme for the production of iron(IV)-oxo, and their subsequent reactions with various substrates (4-methoxybenzyl alcohol and 4-methoxybenzaldehyde). Note that the iron(III)–porphyrin complex is denoted as (TMPS)$Fe^{III}(X)_n$, in which X = OH, n = 1 or N-MeIm, n = 2.

substrates.

The experimental data were further supported by quantum chemical calculations using Density Functional Theory (DFT) as implemented in the Turbomole package. The performed calculations aimed at identification of the active species involved in the catalytic cycle and were done for both truncated (bare porphyrin ring) and full (taking into account the whole TMPS ligand) models of the catalyst. Geometries and electronic structures of the studied catalyst were computed with hybrid B3LYP functional with the def-TZVP basis set. The obtained results are discussed in terms of bond lengths, valence angles, charge and spin populations.

The influence of the nature of the axial ligands (OH^-, H_2O, N-MeIm) on the stability of various possible coordinative forms of the catalyst was studied. The performed calculations indicate that N-methylimidazole substituted model Cpd II with the *trans* iron(IV)-oxo group is energetically stable in opposite to the analogous complex with a H_2O molecule in the axial position which is not stable, and thus does not participate in the studied reaction. The bulky substituents of the porphyrin ring affect the axial ligand binding, mostly due to steric interactions.

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Synthesis, photophysical properties and DFT calculation of bright-blue luminescent of Zn(II) complex with 7-amino-2-methylchromone

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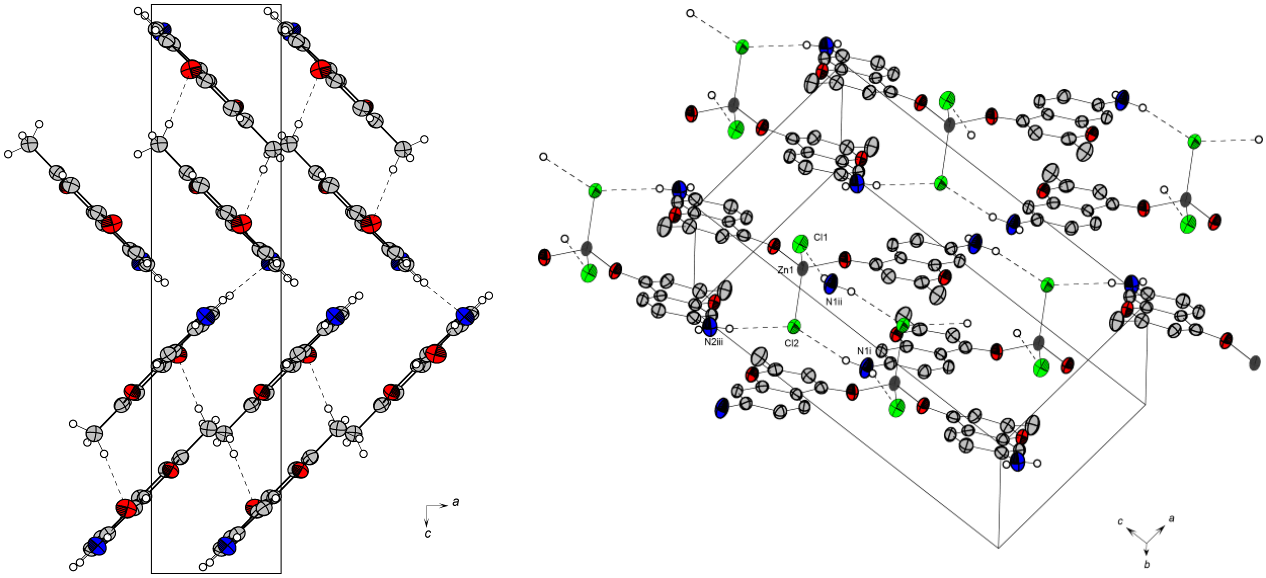
The metal coordination compounds exhibiting fluorescence have received much attention due to their important applications as fluorescent sensor in solution and solid state light emitting diodes. Among transition metals zinc is physiologically important trace element thus the highly selective and sensitive detection of Zn(II) ions is of great importance [1]. On the other hand zinc complexes can be used as an effective white light emissive and electron transport material in electroluminescence device [2].

Here we present results of synthesis, structure study and photophysical properties of Zn(II) complex with simple molecule – 7-amino-2-methylchromone as ligand. The ligand and complex were characterised by ^{1}H, ^{13}CNMR, IR and MS spectroscopy and by quantum chemical calculations using density functional theory (DFT). The relationship between solid-state fluorescence and molecular packing of ligand and complex as well as the effect of solvent polarity on their emission and excitation spectra in solution were examined.

The 7-amino-2-methylchromone (L) is bifunctional molecule containing both electron donor group $–NH_2$ and electron withdrawing group C=O. In complex with Zn(II) this ligand acts as monodendate neutral O donor and forms complex ZnL_2Cl_2.

The 3D fluorescence spectrum of ligand in solid state consist of two emission bands with comparable moderate intensity: the short-wavelength one with a 146 nm Stokes shift value after excitation at 244 nm, and the second shifted long-wavelength band (λ_{em}=500 nm) with excitation at 440 nm. The 3D spectrum of complex with Zn(II) shows one broad with two maxima at 282 and 370 nm. Under the excitation at 282 nm the complex exhibit very intensive broad blue emission band at 420 nm and about 3-fold less intensive narrow band at green region (λ_{em}=562 nm). The differences in solid-state fluorescent characteristic of ligand and complex result from different crystal architecture (Fig.1). Ligand crystallizes in the orthorhombic space group P-1 with four formula units in the unit cell. The molecules are arranged in two, rotated by 90 ° parallel layers linked via two weak hydrogen bonds (Fig.

1A). The complex ZnL_2Cl_2crystallizes in the triclinic space group P-1 with two formula units in the unit cell. The molecules arrange themselves into two layers rotated by 180° to each other which build double-stranded chains along the diagonal of the cell (Fig.1B). They are connected via three N-H···Cl hydrogen bonds.



A B

Fig 1. View of the unit cell along the b-axis, showing the three dimensional network of the packing of ligand (A) and Zn(II)-complex (B). Hydrogen bonds are shown as dashed lines. Displacement ellipsoids are drawn at the 50% probability level.

The fluorescence properties of ligand were measured in the different solvents as acetonitrile, methanol, dichloromethane, DMSO and PBS buffer at the room temperature. The magnitude of ligand fluorescence before and after addition of Zn(II) depends strongly on the nature of solvent. In aprotic solvent acetonitrile the emission spectra of ligand show a maximum at 395 nm after excitation at 348 nm. Addition of Zn(II) to the acetonitrile solution of ligand leads to batochromic shift of maximum (to 440 nm) and significant enhancement of emission intensity. Sensing of Zn(II) was also achieved in mixed acetonitrile/water solutions. Selectivity of ligand towards Zn(II) was also measured.

Acknowledgements

Financial support from the Medical University of Lodz (Grant 503/3-066-02/503-01) and Collegium Medicum UMK (PDS 411) is acknowledged.

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NMR and density functional theory characterization of the structures of oxoperoxo vanadium(V) complexes of L-malic and L-tartaric acids

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In recent decades, *in vivo* and *in vitro* studies of the biological effects of vanadium have revealed important properties. These include the ability to inhibit certain enzymes, the possibility of mimicking the effects of insulin,[1] the capacity to reduce cholesterol biosynthesis,[2] in addition to antitumorigenic properties.[3] Peroxo V(V) complexes in particular show antitumorigenic and enhanced insulinomimetic activity compared with the anionic salts of the high oxidation states of vanadium. Additionally, these complexes have been studied as functional models for the haloperoxidase enzymes, and they are efficient oxidants for a variety of substrates. Peroxovanadium complexes with α-hydroxycarboxylic acids are of particular relevance in biochemistry, since the anions of many of these exist in biological media and are involved in a number of fundamental physiological processes. Here we report a comparative multinuclear (^{51}V, ^{13}C and ^{1}H) NMR and Density Functional Theory (DFT) study of the structures of oxoperoxo complexes of L-malic and L-tartaric acids in aqueous solution. Previously,[4] we have studied the V(V)–L-malic acid–H_2O_2 system in aqueous solution using multinuclear NMR spectroscopy. Seventeen oxoperoxo complexes involving the acid have been identified and structures were proposed for the major species. The solid state structures of two DL-malic,[5] one DL-tartrate [6] and one L-tartrate [7] oxoperoxo complexes are also known. In this work we provide further characterization of the structures we have proposed in solution by calculating their gas-phase and solution optimized geometries using DFT methods. In particular, we have applied the DFT B3LYP/SBKJC method, which we previously validated for related systems.[8,9] From these results, the ^{51}V NMR chemical shifts were calculated for the theoretical geometries in all-electron DFT calculations. The theoretical chemical shifts were then compared with the experimental solution values to assess the quality of the proposed structures. We have studied the oxoperoxo complexes formed in the V(V)–L-tartaric acid–H_2O_2 system in aqueous solution using a similar strategy. The two systems will be compared and differences will be discussed.

Acknowledgments: The authors thank the Laboratory for Advanced Computing, of the Department of Physics of the University of Coimbra, for the computing facilities (Milipeia cluster) and the Rede Nacional de RMN (REDE/1517/RMN/2005) for spectrometer facilities. LLGJ thanks FCT for the postdoctoral grant SFRH/BPD/26415/2006.

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Determination of the number of complex in equilibrium mixture

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Potentiometry and spectrophotometry are often used to study solution equilibria. In the study of solution equilibria, it is not only necessary to determine the stability (protonation or dissociation) constant of each species, but also to find out how many such species are present. The expression "chemical model" means the number of species in mixture, their stoichiometry, values of protonation constants and values of other physical constants (e.g. molar absorption coefficient).

(a) In spectrophotometry we can determine the number of light-absorbing species using a factor analysis of absorbance-response surface. Algorithm INDICES [1] in program S-PLUS contains 12 methods of factor analysis. Precise methods are based on knowledge of the instrumental error of the absorbance data $s_{inst}(A)$, on the other hand if we don´t know $s_{inst}(A)$ we use approximate methods.

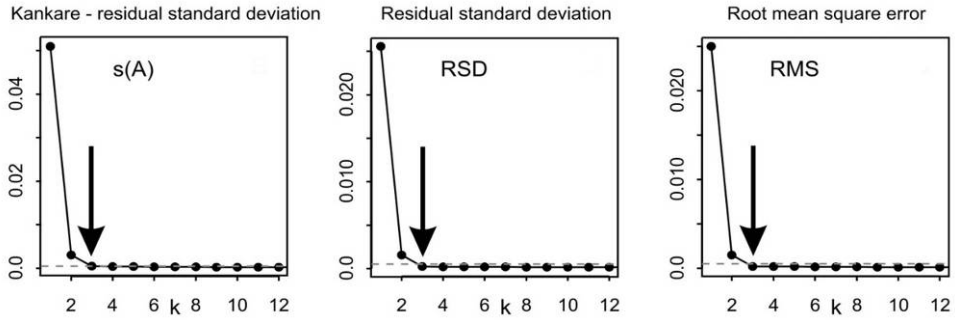

Figure 1: Precise methods of FA to determination of light-absorbing species. (S-PLUS)

(b) In potentiometry we can determine the number of complex species also with the method of factor analysis. The first step in to transform the titration curve into the form of normalizes variables $Z = f(\mathrm{pA})$, where the free equilibrium concentration of component A is usually measured potentiometrically as pA = -log [A] and Z represents the average number of one component (A) bound per another component (B): $Z = (c_A\text{-}[A])/c_B$. Each curve Z can be measured for different total concentration of component B to give finally the matrix **Z**. The rank of **Z** gives directly the number of complex species in solution [2].

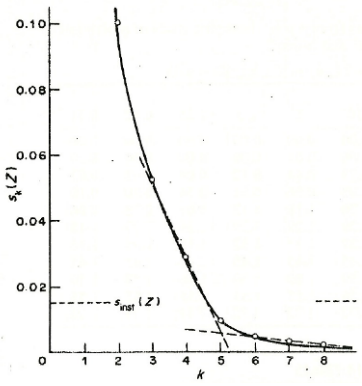

Figure 2: Graphical determination of the number of complex.

The last method for determination the number of species useable for both spectrophotometric and potentiometric data is searching of chemical model using the

minimization process. When the minimization process of a regression analysis terminates in the minimum of the residual square sum function *U*, some diagnostic criteria are examined to determine whether the results should be accepted or rejected: the physical meaning of estimated parameters, physical meaning of the species concentrations, parametric correlation coefficient, goodness-of-fit test (standard deviation of absorbance, Hamilton *R*-factor). The minimization process is repeated for various hypothesis of chemical model and the lowest *U* value obtained indicates the most probable model (Table 1) [3, 4].

Table 1: The search for a protonation model of methotrexate with the SQUAD(84) analysis of A-pH spectra at 25ºC and an ionic strength $I = 0.0012$. The standard deviations in the last valid digits are in brackets.

Model hypothesis	L, LH	L, HL, H_2L	L, HL, H_2L, H_3L
k, $s_k(A)$ [mAU]	2, 4.00	3, 0.52	4, 0.46
pK_{a1}	5.532(7)	3.813(18)	3.086(167)
pK_{a2}	---	5.639(2)	4.403(63)
pK_{a3}	---	---	5.675(6)
s(A) [mAU]	4.68	0.87	0.65
s(e) [mAU]	4.68	0.87	0.65
$\lvert\bar{e}\rvert$ [mAU]	3.24	0.58	0.42
g_1	-0.53	-0.07	-0.28
g_2	4.29	3.21	3.32
R [%]	0.97	0.18	0.13
Model is	rejected	rejected	accepted

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DFT study of the interaction of heavy metal ions with thioethers.

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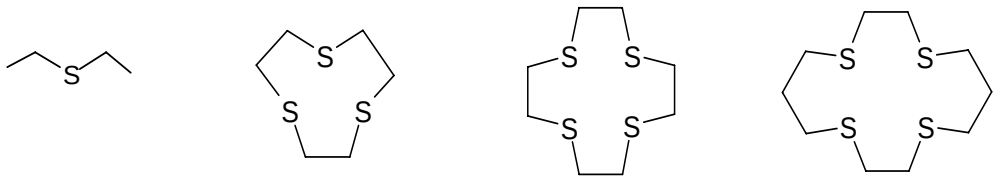
The continuing interest in the coordination chemistry of heavy metals such as cadmium(II) and mercury(II) stems not only from the widespread agricultural and industrial use of their compounds but also from their inherent toxicity and hazardous effects to human health [1]. Therefore, the recognition of these metals is of fundamental importance to many areas of chemistry and biochemistry but the factors underlying the stability and selectivity of a given ligand/receptor are often not of straightforward interpretation.

Recognition process may depend on a series of factors that include the nature of the donor atoms and their spatial arrangement, the backbone structure of the ligand and its rigidity, the eventual formation of chelate rings of variable size. In the case of macrocyclic or encapsulating receptors the ability to bind the metal ion in its preferential coordination geometry is to be taken into account to predict preferential recognition.

Metal - sulphur bond is a fundamental interaction in biochemical systems and in selective separation applications for the heavy and precious metal extraction from liquid phase. For example, numerous macrocyclic structures containing sulphur donor atoms (thiols, thioethers, thioureas…) have been employed as selective extractants in a range of solvent extraction and bulk membrane transport studies [2-3].



Et_2S TTCN 12AneS4 14AneS4

Figure 1. Linear and macrocyclic thioethers

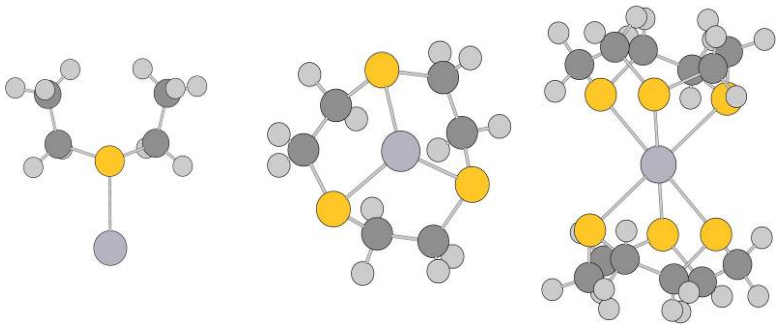
In this work theoretical studies are used to interpret at molecular level the thermodynamics of complex formation for which data have been previously obtained [4].

DFT calculations have been used to study the structure and energetics of the interaction of the metal ions with the sulphur containing ligands Et_2S and TTCN. Since there is a limited number of theoretical works on the interaction of metal ions with thiols and tioethers [5-7] it seemed interesting to test the performance of different exchange-correlation functionals in predicting structures and energies. In our case we tested the B3LYP, PBE and M06 functionals available in Gaussian09 program. For metal ions the Stuttgart Dresden pseudopotentials have been used while for the rest of the atoms two sets of Gaussian basis functions were tested, a small one 6-31+G(d) and a larger 6-311++G(d,p). Stationary points were characterized by

vibrational mode analysis. We limited the study to the interaction of TTCN and Et_2S due to the availability of experimental data [4] for these two ligands.

Solvational effects have been studied by considering the dissociation of acetonitrile molecules upon ligand coordination. We also checked the effect of introducing continuum solvent model to include the polarization due to the bulk solvent. Results clearly indicate how the observed ligand affinity is a balance of binding and solvent dissociation process. Qualitatively, the different functionals give the same indications on the relative affinity of the thioethers for the metal ions while the larger basis set gives much better prediction of the $M(TTCN)_2^{2+}$ structures when compared to the available counterparts [8].

Figure.2 Optimized structures of $Hg(Et_2S)^{2+}$ $Hg(TTCN)^{2+}$ and $Hg(TTCN)_2^{2+}$ complexes in gas-phase.



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Using the MS-Excel™ spreadsheet in potentiometric studies of complex formation equilibria: PKPOT_L1 functions

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At present, there are different computer programs for the determination and refinement of dissociation and complex formation constants from potentiometric data [1-3]. An evolution of the most known is given in the web page: http://www.hyperquad.co.uk/a_time_line.htm. In a general way, the main tasks of these programs are performed by the routines for data and model reading, calculation of mass-balance equations, optimization of the equilibrium constants, and presentation/output of results.

The work presented here is based on a different approach, as the different routines have been implemented as Macro and user-defined functions (UDF) in the MS-Excel™ spreadsheet. This allows using the worksheet for data edition and preprocessing, printing, graphic presentation of results, etc. The developed functions have been tested in different Excel versions: 2003 and 2007 for MS-Windows , and 2011 for MacOSX.

The main routines have been developed from the described previously in the program PKPOT [4], and they have been rewritten in VBA (Visual Basic for Applications) to run in Excel. They consist of two UDF and three Macros:

- i_mbc (function): it calculates the mass balances for a single data point from the total concentrations of components and a set of guessed equilibrium constants. The result is the calculated free concentration of the measured component.

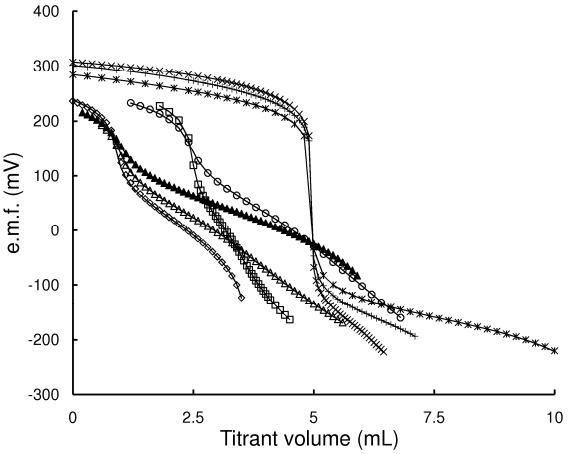
- weight (macro): calculates the statistical weights of each data point from the estimated errors in volume (σ_V) and e.m.f. (σ_E) and the slope of the titration curve. The weights are calculated as: $w_i = \{\sigma_E^2 + (\partial E / \partial E)^2 \sigma_E^2\}^{-1}$.

- ref_GN: this is a standard optimization routine based on the Gauss-Newton method. As usual, it refines a set of parameters in order to minimize an objective function defined as: $U = \sum_{i=1}^{n} w_i (X_{\exp,i} - X_{calc,i})^2$. Where n is the number of total data points, and $X_{exp,i}$ and $X_{calc,I}$ the experimental and calculated magnitudes, respectively (for example, mV or pH).

- calc_conc (macro): it calculates the total species concentration for a selected group of initial total concentrations and a given set of equilibrium constants. It uses a modified version of the i_mbc function, named **s_mbc**.

The procedure has been applied to experimental data corresponding to three different systems: the determination of the dissociation constants of glycine and complex formation with Ni(II) ions [4], the complex formation between In(III) and chloride ions [5] , and the complex formation between Cu(II) and phosphonoacetate [2]. Details about the results corresponding to the Ni(II)-glycine system are commented below.

The experimental data set consisted of eight potentiometric titrations in two groups: three for determining the dissociation constants of glycine, and five for complex formation studies. The refinement of the dissociation and complex formation constants was carried out in three steps: first, two titrations (one of each group, 73 data points) were analyzed simultaneously to get the approximate values of the all formation constants; starting values were (as $\log\beta_{MLH}$): $\log\beta_{011}$=9; $\log\beta_{012}$=12; $\log\beta_{110}$=3; $\log\beta_{120}$=6; $\log\beta_{130}$=9. The refined constants were used as input values in the step 2, and refined using all the experimental data (8 titrations, 382 data points). In the last step, the constants were again refined, together with the electrode standard potentials in each titration (13 parameters to be optimized). The figure at right shows the good agreement between the experimental (symbols) and calculated data (lines). The final results are indicated in the following table, where the estimated standard deviations are given between parentheses, in last digit units.



	$\log\beta_{011}$	$\log\beta_{012}$	$\log\beta_{110}$	$\log\beta_{120}$	$\log\beta_{130}$
Step 1	9.660(5)	12.083(7)	5.630(20)	10.352 (18)	13.718 (29)
Step 2	9.658(2)	12.072 (4)	5.622(5)	10.345 (7)	13.720 (12)
Step 3	9.663(4)	12.082 (9)	5.634(5)	10.366 (7)	13.743 (13)
Values from [4]	9.657(3)	12.070(5)	5.620(5)	10.346(14)	13.708(39)

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Protonation sequence of risedronic acid: experimental and theoretical studies

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Bisphosphonates (BPs) were first synthesized in the late 1800s; however, their clinical use has been relatively recent and nowadays they are the major drugs used to treat bone-resorption diseases and they act by preventing osteoclastic bone resorption, inhibiting the enzyme farnesyl diphosphate synthase. In this work our attention is on Risedronic acid (1-hydroxy-1-phosphono-2-pyridin-3-yl-ethyl phosphonic acid, RA). RA is indicated for the prevention or treatment of postmenopausal and glucocorticoid-induced osteoporosis and Paget's disease. There is a great interest in developing methods to prospect the nature of the bisphosphonate–bone mineral recognition and binding mechanisms, for this reason thermodynamic data are required to allow prediction of important technological and pharmacological equilibria. In this work, the acid-base properties of RA are reported, in particular, protonation constants were determined by potentiometric measurements in a wide ionic strength range [$0 < I$ / mol·L^{-1} ≤ 5] in aqueous NaCl solutions and at T = 298.15 K. Results were analyzed in terms of their dependence on the ionic strength using different thermodynamic models [Debye-Hückel type [1] and SIT (Specific ion Interaction Theory) [2,3]. Therefore, the values of protonation constants at infinite dilution and the relative interaction coefficients were calculated. Data obtained in this contribution were critically compared with those reported in the literature [4,5].

The degree of protonation and the placement of protons within a BP are of paramount importance when understanding of the duel function of BPs (in inhibiting bone resorption and interfering with specific biochemical processes) is concerned. To this effect, we performed a full conformational analysis of all possible protonated forms of RA. A large number of conformers of different tautomers of HL^{3-}, H_2L^{2-} and H_3L^{-} (where L^{4-} is a fully deprotonated form of risedronic acid, $^{-2}O_3P$–C(OH,CH_2–Pyridine)–PO_3^{2-}) was energy minimized at the RB3LYP/6-311++G(d,p) and RX3LYP/6-311++G(d,p) levels of theory in two solvation models, PCM/UFF and CPCM/UAKS. From the Density Functional Theory (DFT)-based calculations a protonation sequence of RA is proposed and compared with known experimental data. Further theoretical studies are suggested to resolve significant differences observed between the DFT-based protonation sequence reported here and generally excepted the NMR-based model reported in the literature.

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Novel N,O-chelated rare earth metal complexes with luminescent activity: DFT analysis of structure luminescent properties relationship

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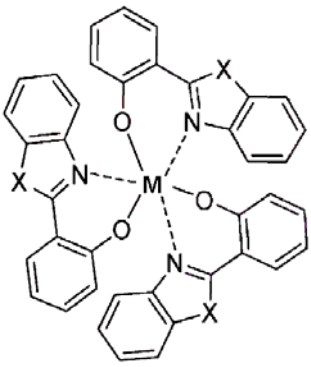
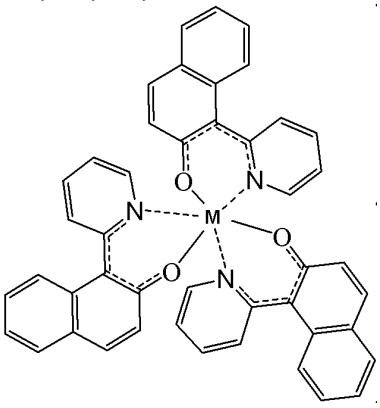
Novel homoleptic N,O-chelated complexes of rare earth metal were synthesised in aprotonic solvents [1-3] to prevent entering of proton-containing solvent molecules in coordination sphere that greatly impair luminescent properties of complexes. The geometry and electronic structure of the complexes $M(Lx)_3$, x=O (2-(2-benzoxyazol-2-yl)phenolate), x=NH, 2-(2-benzoimidazol-2-yl)phenolate, x=S (2-(2-benzothiazol-2-yl)phenolate); M=Sc, Y, La, Ce, Pr, Nd, Eu, Gd, Tb and the 1-(2-pyridyl)naphtolate complexes $M(L)_3$, M=Sc, La, Nd, Gd, Tb



$= M(Lx)_3$



$=M(L)_3$

in ground and first excited states were studied using density functional theory (DFT) approach to focus the problem of theoretical description of their luminescent properties.

All calculations were based on nonempirical PBE functional. The energies and oscillator strengths of optical transitions were calculated with the time dependent density functional theory (TD-DFT). The extended full four-component basis: Ln [30s29p20d14f6g/9s8p6d3f1g], Sc [21s16p11d5f/6s5p3d1f], S [15s11p3d/4s3p1d], C,N,O [10s7p3d/3s2p1d], H [6s,2p/2s1p] was used for an all-electron calculation in scalar relativistic approximation, which is based on the Dirac equation with spin–orbit effects separated out. This level of theory allows well to describe the coordination of ligands around Ln-center in contrast to nonrelativistic calculation with the extended basis set of the same quality using pseudopotential with inner shell relativistic effects included, which lead to large errors for Ln-ligand bond lengths up to 0.5 Å [4].

The arrangement and geometry of calculated complexes are in good accordance with available X-ray data [1,2]. The experimental UV absorption spectra and luminescent spectra of the complexes studied agree with the calculated characteristics of $^1\pi$-π * and $^3\pi$-π * states of coordinated ligands. The ligands contain strongly absorbing chromophores and they can be conveniently used to sensitize lanthanide emission at lower energy. The molecular structure has the great effect on the luminescent properties of rare earth metal complexes. Particularly, it was found that lanthanide complexes studied with large metal ion radii have favourable

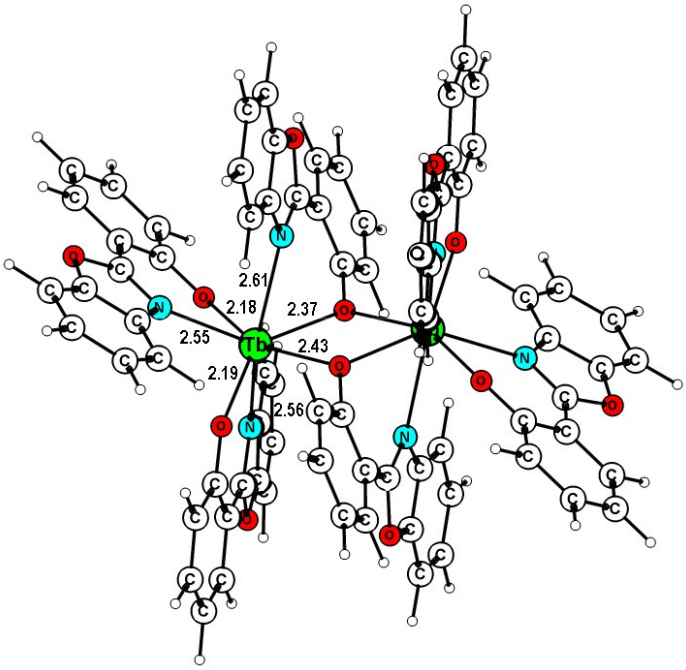


Fig.1 The structure of complex $Tb_2(LO)_6$.

thermodynamics of dimerization in contrast to Sc complexes. See for example the structure of complex $Tb_2(LO)_6$ in the Fig. 1.

The magnitude of distortion of the first coordination sphere under $S_0 \rightarrow T_1$ excitation has the great effect on the luminescence yield. For the Tb_2Lx_6, complexes, x=NH, O, S, with similar coordination polyhedron in ground state the maximal values of metal-ligand distance distortions in T_1 state are rather different, 0.025, 0.087 and 0.172 Å, respectively. So, only for the case of smaller metal-ligand distorsions most of energy stored in the ligand excited state is transferred onto lanthanide ion. The reason is that for large distortion the zeroth vibration level of the $^3\pi$-π^* excited state will be located below intersection point of the $^3\pi$-π^* term and the term with f-shell excitation, and energy transfer will occur only as long as higher vibrational levels are populated. This conclusion is in accordance with presence of luminescence for $Tb_2(LO)_6$ and $Tb_2(LNH)_6$ and its absence for $Tb_2(LS)_6$ complexes.

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Ruthenium complexes in different oxidation states. Synthesis, crystal structure, spectra and magnetic characterization

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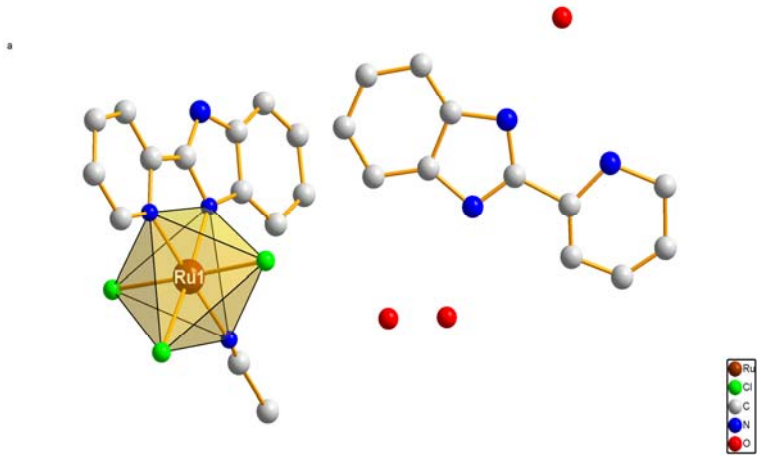
The chemistry of ruthenium complexes is currently receiving a lot of attention, primarily because of their applications in medicine and industry. Ruthenium compounds are usable as catalysts in olefin metathesis. The development of well-defined metathesis catalysts combining high activity with an excellent tolerance to a variety of functional groups has been key to the widespread application of olefin metathesis in organic synthesis and polymer chemistry [1]. Some of Ru(II) and Ru(IV) complexes are applicable as molecular switches and wires [2]. Additionally, compounds of ruthenium have some of the most promising biological properties [3]. They can be used as metaloorganic drugs, antibiotics and other pharmaceuticals in treatment of many infectious diseases caused by parasites. These compounds exhibit a high inhibitory effect against pathogenic bacteria and fungi. Among these, ruthenium complexes are believed to be the most promising alternatives to Pt antitumor drugs.

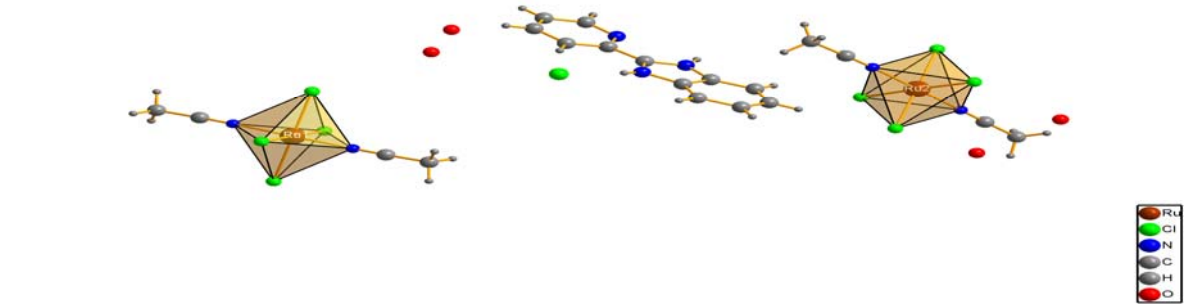
To the best of our knowledge, the application of ruthenium complexes correlates with oxidation states of the central ions which depend on the nature of ligand. So the main goal of our research is to synthesis new $[RuCl_3(CH_3CN)L]\cdot 3H_2O\cdot L$ (**1**), $[RuCl_4(CH_3CN)_2]_3\cdot 6H_2O\cdot 2LH^+ \ 2Cl^-$ (**2**) ruthenium complexes in different oxidation states with 2,2'-bipirydylobenzymidazole (2,2'-PyBIm) and 2-hydroxymethylbenzimadazole (2-CH_2OHBIm).

The obtained complexes have been characterized using elemental analysis, IR, Raman spectroscopy, magnetic study and single crystal X-ray diffraction. The molecular structures of compounds are shown in Fig. 1. Complex **1** crystallizes in the monoclinic space group *C* 2/c. Five ligands (one molecule of 2,2'-PyBIm, one molecule of CH_3CN and three chloride ions) are bound directly to the metal ions to give a RuN_3Cl_3 chromophore. 2,2'-PyBIm acts as N,N-bidentate chelators forming five-membered chelate ring with the ruthenium centre. The most interesting features of the lattice packing are existence of protonated 2,2'-PyBIm in the space which plays role as counter ion. The coordination geometry around ruthenium cation resembles distorted octahedral. Complex **2** crystallizes in the triclinic system ($P\ \bar{1}$). The crystal structure of **2** includes in the unit cell two symmetry – independent ruthenium complexes. Central ions are surrounded by two molecules of acetonitrile and four chloride anions and is hexa-coordinated by N_2Cl_4 chromophores. Protonated 2,2'-PyBIm which are engaged in hydrogen bond with Cl^- ion are located between the molecules of complex in the crystal lattice. The shape of the coordination anion polyhedra can be described as distorted

octahedron. The chloride anions form based plane which is slightly distorted. Apical positions are occupied by nitrogen atoms from two molecules of acetonitrile.



$[RuCl_3(CH_3CN)L]\cdot 3H_2O\cdot L$



$[RuCl_4(CH_3CN)_2]_3\cdot 6H_2O\cdot 2LH^+ \ 2Cl^-$

Fig. 1. The molecular structures of complexes 1 and 2.

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Solid-state studies of manganese(II) complexes with chelating alcohol and aldehyde. Crystal structure, spectroscopic, magnetic and thermal behaviors.

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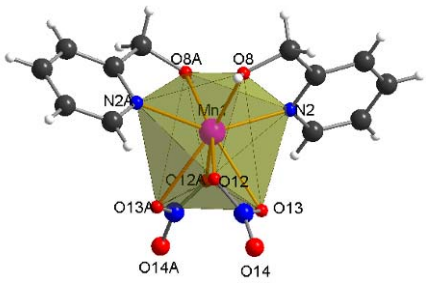
Interest in the coordination chemistry of manganese ions has been driven by a significant involvement of these ions in metal-catalyzed oxidation as one of the most important transfer reactions in chemistry and biology [1, 2]. Due to this role, efforts have been focused on the preparation and characterization of smaller inorganic analogues that would mimic physicochemical properties and activities of Mn-dependent biomolecules.

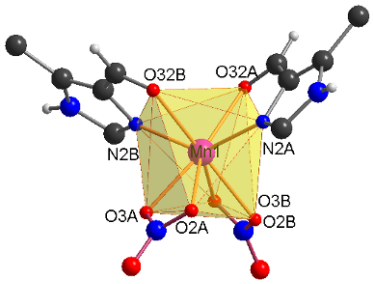
Bearing in mind that imidazole, pyrazole and pyridine derivatives increase recognition of the biological role, and that ligands involving an oxygen donor were used in modeling an active site of metalloproteins, we use two N,O-donor, biologically relevant ligands: 2-hydroxymethylpyridine (2-CH_2OHPy) and 5(4)-carbaldehyde-4(5)-methylimidazole (5(4)-CHO-4(5)-MeIm) in our research. We report here the syntheses and structural characterization of five new manganese(II) complexes with 2-CH_2OHPy and 5(4)-CHO-4(5)-MeIm, as elucidated by spectroscopic (IR, Raman, EPR), X-ray crystallographic methods, magnetic and thermal studies. In isolated solid complexes: $[Mn(2\text{-}CH_2OHPy)_2(NO_3)_2]$ **(1)** and $[Mn_2(\mu_2\text{-}Cl)(2\text{-}CH_2OHPy)_4]Cl_2{\cdot}2H_2O$ **(2),** $[Mn(2\text{-}CH_2OHPy)(SO_4)(H_2O)]$ **(3)**, $[Mn(4\text{-}CHO\text{-}5\text{-}MeIm)_2(NO_3)_2]$ **(4)** and $[Mn(4\text{-}CHO\text{-}5\text{-}MeIm)_2Cl_2]$ **(5),** 2-CH_2OHPy and 5-CHO-4-MeIm coordinate to the Mn(II) centers in a bidentate fashion.

The coordination chemistry of manganese(II) is dominated by the coordination number six. Coordination numbers five- and seven- are less frequently observed, whereas in small inorganic molecules coordination numbers higher than seven are rarely encountered. According to this knowledge we want to emphasize that two complexes obtained by us : $[Mn(2\text{-}CH_2OHPy)_2(NO_3)_2]$ **(1)**, $[Mn(4\text{-}CHO\text{-}5\text{-}MeIm)_2(NO_3)_2]$ **(4)** are eight-coordinated compounds. The structural data for **(1)** indicated that two molecules of 2-CH_2OHPy and two nitrate ions are bound as bidentate ligands, giving a complex with chromophore $\{MnN_2O_6\}$ (Fig. 1a). Compound **(4)** is also an eight-coordinated monomeric Mn(II) complex. Two 4-CHO-5-MeIm molecules and two nitrate ions are coordinated in a bidentate fashion forming $\{MnN_2O_6\}$ chromophore (Fig. 1c). In contrast, in dinuclear complex **(2)**, each Mn(II) ion (CN=6) assumes distorded octahedral geometry in which it is surrounded by two N,O-chelating 2-CH_2OHPy ligands and two bridging chloride anions forming a $\{MnN_2O_2Cl_2\}$

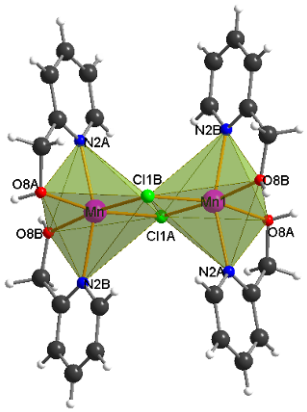
chromophore (Fig. 1b). Two Mn(II) ions are doubly-bridged by two chloride anions, with a Mn···Mn distance of 3.65 Å and Mn-Cl-Mn bridging angle of 92.81°. According to X-ray crystallographic analyses, the structure of **(5)** consists of mononuclear molecules in which Mn(II) ions have the same six-coordinated environment: $\{MnN_2O_2Cl_2\}$ (Fig. 1d).



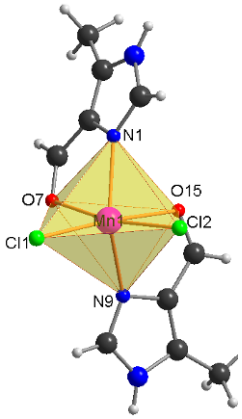
a) $[Mn(2\text{-}CH_2OHPy)_2(NO_3)_2]$ **(1)**



c) $[Mn(4\text{-}Me\text{-}5\text{-}CHOIm)_2(NO_3)_2]$ **(4)**



b) $[Mn_2(\mu_2\text{-}Cl)(2\text{-}CH_2OHPy)_2]Cl_2{\cdot}2H_2O$ **(2)**



d) $[Mn(4\text{-}Me\text{-}5\text{-}CHOIm)_2]Cl_2$ **(5)**

Fig. 1 Molecular structures of synthesized Mn(II) complexes.

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Comparison of crystal structure of Ca(II) complexes with heterocyclic alcohol, aldehyde and carboxylate ligands and their cadmium analogues

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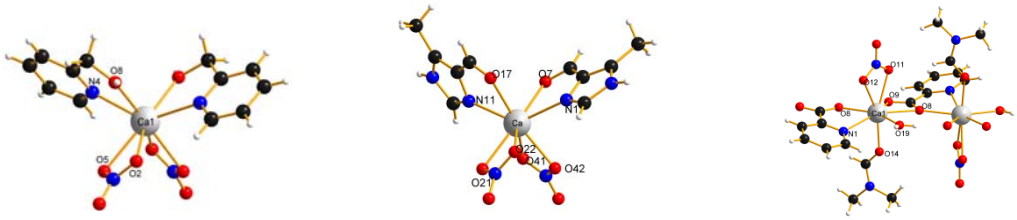
From a bioinorganic point of view, heterocyclic alcohol, aldehyde and carboxylate are of great importance as ligands containing N,O donor atoms which can be used to modelling binding modes of Ca^{2+} ions in the biological system. Thus calcium performs numerous biological functions in all life forms. Over 98% of the total body calcium is present in bone, of which about 1% appears to be freely exchangeable with extracellular fluids through both physicochemical and cell mediated mechanisms [1]. Additionally, calcium homeostasis is maintained within a narrow range 2.10-2.60 mmol/l, so this extracellular calcium concentration can be easily disturbed by a toxic metal ion e.g. cadmium. Even at a low degree of environmental exposure, Cd^{2+} might promote skeletal demineralization, which may lead to increased bone fragility and an increased risk of fractures.

This work describes the synthesis, thermal (TG/DTG, DSC) and spectral (IR, Raman, ^{1}H, ^{13}C NMR) properties of calcium(II) compounds with chosen heterocyclic alcohol (pyridine-2-methanol, **2-CH_2OHpy**), aldehyde (4-methyl-5-carbaldehydeimidazole, **4-Me-5-CHOIm**) and carboxylate (pyridine-2-carboxylate, **pic**). Additionally, the crystal and molecular structures of all compounds were determined by the X-ray method. The design of model complexes in studies of how the chemistry of Ca(II) and Cd(II) ions is modulated by their coordination environment is a key area of research because a comparison of structural data for metal complexes formed by both metal ions ought to provide an explanation for cadmium ability to mimic Ca^{2+} ions in biological systems.

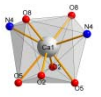
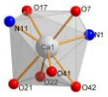
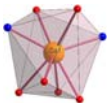
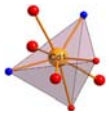
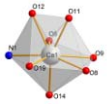


$[Ca(NO_3)_2(2\text{-}CH_2OHpy)_2]$ $[Ca(NO_3)_2(4\text{-Me-5-CHOIm})_2]$ $[Ca(NO_3)(DMF)(H_2O)(pic)]_n$

Fig. 1. Molecular structure with the atom numbering scheme of synthesized Ca(II) complexes

Therefore, in this work we additionally compare the X-ray results obtained for Ca(II) complexes with the structures of previously described compounds of cadmium ion with the same ligands. Some details of comparison are presented in Table 1.

Table 1. Crystal structure details of Ca(II) and Cd(II) complexes with heterocyclic alcohol, aldehyde and carboxylate

Complex	Chomophore (CN)	Shape of polyhedron	M-N (Å)	M-O (Å) ligand	M-O (Å) nitrate
$[Ca(NO_3)_2(2\text{-}CH_2OHpy)_2]$	CaN_2O_6 (8)		2.5165	2.3566	2.5000 2.3566
$[Cd(2\text{-}CH_2OHpy)_2(NO_3)_2]$ [2]	CdN_2O_6 (8)		2.3119	2.3669	2.5671 2.4593
$[Ca(4\text{-}Me\text{-}5\text{-}CHOIm)_2(NO_3)_2]$	CaN_2O_6 (8)		2.487 2.506	2.420 2.524	2.420 2.542
$[Cd(4\text{-}Me\text{-}5\text{-}CHOIm)_2(NO_3)_2]$ [3]	CdN_2O_6 (8)		2.2521 2.2616	2.5426 2.6121	2.357 2.679
$[Cd(4\text{-}Me\text{-}5\text{-}CHOIm)_4]^{2+}$ [4]	CdN_4O_4 (8)		2.292 2.298	2.700 2.745	-
$[Ca(NO_3)(DMF)(H_2O)(pic)]_n$	$CaNO_7$ (8)		2.5582	2.4246	2.5129 2.6100

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Nickel speciation in xylem sap of endemic and facultative species of serpentine soils

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Inside plants nickel is believed to be mostly bounded to nitrogen or oxygen ligands depending the nature of the ligands on the location within the plant and its age. Most studies deal with nickel chelation in other plant compartments rather than in xylem sap. Xylem sap represents a single and specific compartment and a better understanding of the mechanisms of nickel transport, allocation and tolerance surely involves knowledge of nickel binding by the relevant ligands present in the xylem sap.

We report a nickel speciation study in the xylem saps of Holm oak (*Quercus ilex*) the dominant tree growing on the serpentine soils of northeast Portugal [1, 2] and *Alyssum serpyllifolium* ssp. *lusitanicum*, a Ni-hyperaccumulator endemic on those soils [3]. The xylem sap was collected from plants growing in its native habitat, characterized in terms of nickel, calcium, magnesium [4], carboxylic and amino acids content and nickel speciation was studied in model and real solutions of xylem sap by voltammetric techniques.

The results revealed the importance of carboxylic acids in nickel complexation of xylem sap from both endemic and facultative serpentine plants and the central role of magnesium in the kinetics on nickel complexation by carboxylic acids in the xylem sap of Holm oak. The net result is a retardation of complexation reactions that can be more important for intrinsically slow-reacting metals as is the case of nickel. This may render nickel more easily available to xylem tissue, like bark and wood, due to exchange reactions, and so explaining, in a kinetic point of view, the reason why the levels of nickel in the bark and wood increase in plants living in serpentine soils

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The use of chemometrics for classification and calibration of seawater using the H^+ affinity spectrum

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Seawater is a complex aqueous media whose composition is affected by many processes. Models of seawater speciation can be built up with the help of computer programs integrating equilibrium constants databases and the ability to make complex calculations and plots of the results.

Using the MEDUSA [1] computer program the H^+ affinity spectrum of seawater can be constructed. This spectrum is defined as the plot of the first derivative of H_{Bound}, β, ($H_{Bound} = H_{Tot} - [H+] - [OH-]$) vs, i.e., pH and it is calculated numerically by the program.

In a previous work [2] some questions aroused that were left partly unanswered:

(1) Is the variation of the spectrum shape linked with seawater composition and thus, could we use the spectrum to classify seawater samples?

(2) Given the constancy in the proportions of major seawater components, could we use spectrum obtained at different salinities to *calibrate* the composition of these constituents?

To try to answer these questions, The Unscrambler software was used [3].

According with Marcet's principle, also called the principle of constant proportions, the relative proportions of the major seawater constituents are constant. Taking into account this principle, there would be no way to classify seawater samples. However, we have tried to see if subtle differences in these proportions were enough to classify seawater. For this, 14 samples along the coast of Biscay were taken in summer and some replicas in winter. After determining their properties and composition, a Principal Component Analysis (PCA) was made with the H_{Bound} spectrum of the samples (Fig. 1), because the first derivative (β) was too noisy.

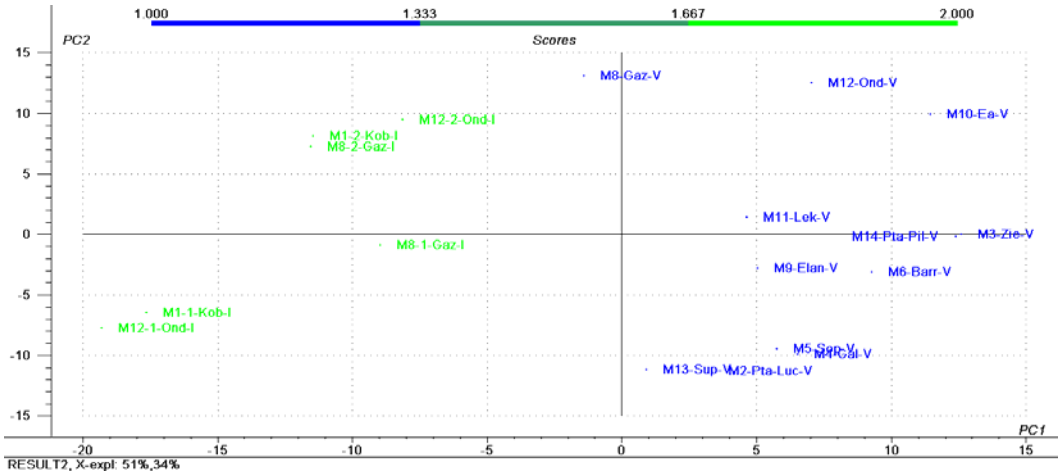

Figure 1: PCA of coastal samples. Green samples are from winter and blue samples from summer.

In this figure, it is possible to see that the place where the samples were taken doesn't have any influence in the cluster formation; however, there are two clusters according with the season in which the samples were taken, summer and winter. Therefore, this proves that it's possible to distinguish in which season the samples were taken using the buffer capacity of the seawater and multivariate analysis.

To try to solve the second question, a *natural calibration* was made to get a calibration set with different salinities. For this, different samples were taken at different times of the tide in two different estuaries, Butroi and Nerbioi-Ibaizabal, and in three different places in each one, and, again, in summer and in winter. In summer, the samples were collected during two tidal cycles every three hours getting a three point calibration. In winter, the samples were taken from low tide to high tide every hour getting a seven point calibration. In all the cases, the major constituents which affect the buffer capacity of the seawater were measured: alkalinity, total carbonate concentration, fluoride, chloride, sulphate, calcium and magnesium as well as the H_{Bound} spectra. According, again, with Marcet's principle, if the constituents proportion is constant, it should be possible to make a calibration by means of the PLS regression of the H_{Bound} spectrum vs. any constituent (i.e. vs. Calcium concentration, as in Fig 2).

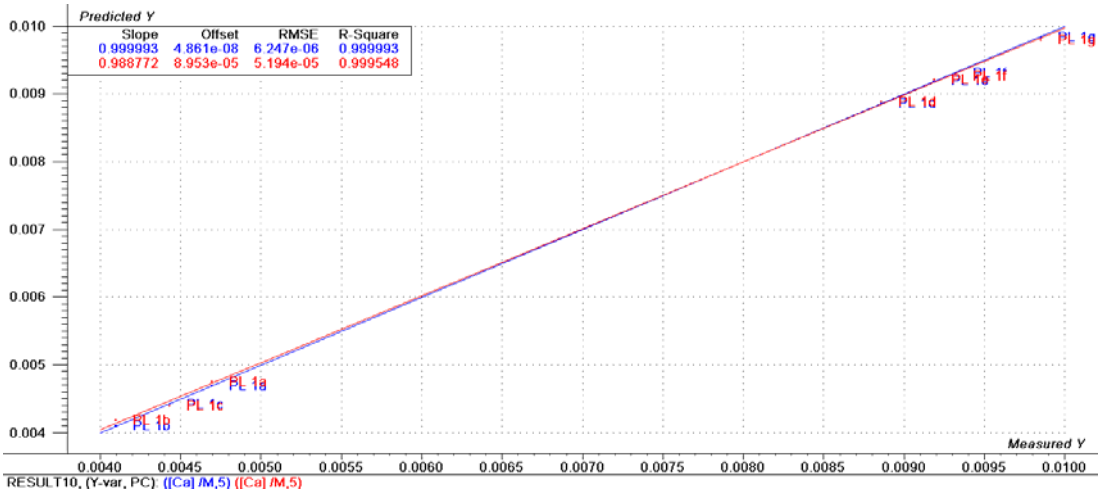

Figure 2: Result of the PLS1 regression of the buffer capacity spectrum vs. Calcium concentration for one of the positions of the Butroi estuary in the winter sampling.

As it can seen in this figure, it is possible to use the seawater H^+ affinity spectrum to calibrate the major constituents of seawater using a natural calibration set at different salinities.

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The interaction mechanism of gold(III) with the metal extractant PADA in DTAC micellar medium and applications to gold(III) extraction

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The kinetics of binding of Au(III), initially present as $AuCl_4^-$, to the azo-dye ligand pyridine-2-azo-p-dimethylaniline (PADA) in dodecyltrimethylammonium chloride (DTAC) micellar solution have been investigated as a preliminary study on gold micellar extraction and recovery. PADA (Figure 1) is endowed with excellent hydrophobic properties, which make it an ideal carrier for the transport of the metal ions from water to micelle, allowing the metal extraction process to be carried out [1,2].

The kinetic study enables the mechanism of the binding reaction to be worked out under different investigated medium conditions, showing that in the presence of the DTAC micellar pseudo-phase the reaction is strongly accelerated (catalytic effect) compared to water. The results concur in suggesting that differently oxydrilated forms, originated from the starting $AuCl_4^-$, are reactive and, in DTAC at low pH, also the aquoform $AuCl_3(H_2O)$ reacts with PADA, whereas the tetrachlorocomplex apparently does not react, except that in water at relatively low pH.

The characteristics of the water/micelle system have been also exploited, for the purpose of extracting and recovering gold, by applying the micellar enhanced ultrafiltration (MEUF) procedure. Using MEUF the negative $AuCl_4^-$ ion is extracted with yields near to 100% by DTAC, owing to direct adsorption on the micelle surface. The recovery step has been accomplished adding an electrolyte (NaCl) solution, which lowers the surface potential of the micelle, thus favoring the recovery process. Ammonia has been also added in order to convert the gold(III) chlorocomplexes into the ammonia complex, which is repelled from the positively charged DTAC surface and can be recovered. A recovery yield of 86% has been achieved, which provides a promising basis for the extraction of gold from water using the surfactant DTAC.

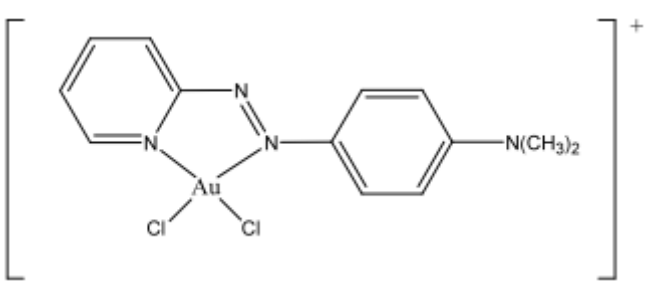

Figure 1: The ligand pyridine-2-azo-p-dimethylaniline (PADA)

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Speciation and bioavailability of Cd in freshwater bivalves – Effect of the TiO_2 nanoparticles

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The increasing and widespread application of manufactured nanoparticles (NPs) through several areas of great economic importance has led to a larger release of these materials into the environment. Some of the special properties that make nanomaterials useful, including their high surface reactivity, are properties that might be expected to cause hazards to humans or the environment. In fact the knowledge about the potential adverse effects of NPs has increased in recent years, and, indeed, it has become a top priority in most governments and private/public sectors. TiO_2 is one of the most used NPs in industrial applications and it is expected to be present in different environmental compartments such as in natural freshwaters. The highly reactive surface of a NP in combination with the properties of an oxide surface, in the case of TiO_2 NPs; provides a large capability for the adsorption of trace metals like Cd, a known environmental hazard.

In this work the effect of the presence of (1 ppm) anatase TiO_2 NPs on the (1×10^{-6} M) Cd dynamic speciation was quantified by using the voltammetric technique scanned stripping chronopotentiometry (SSCP). Furthermore, the relevance of the various speciation parameters for bioavailability and biouptake was assessed by performing bioaccumulation experiments during 10 days in absence and presence of 0.1 – 1.0 ppm of TiO_2 NPs with the freshwater bivalve *Corbicula fluminea*. All studies were performed under relevant environmental conditions of pH and ionic strength.

A decrease of the free Cd present in solution immediately after the addition of the TiO_2 NPs was observed; approximately 10 % between pH 6.0-7.0 and 20 % at pH 7.5-8.5. This decrease was more pronounced after 48 h of equilibration time (about 50% of free Cd). Analysis of the SSCP data obtained at pH larger than 7.5 indicated an increase of the heterogeneity degree of the Cd-TiO_2 system. A linear increase of the internalized Cd was observed as function of the time until the 5th day regardless of the TiO_2 presence, being bioregulated afterwards. However, a decrease of the Cd internalization rate by the bivalve was observed in presence of the NPs even for the lowest TiO_2 concentration.

Our results indicate that the presence of the Ti NPs in the aquatic media thus have an effect on both Cd speciation and bioaccumulation.

Dissolution and aggregation of various ZnO nanoparticles – effects of pH, ionic strength and concentration

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Manufactured zinc oxide nanoparticles (ZnO NPs) have been in the past recent years employed in several areas of economic, health and environmental interest. This had resulted in a large increase of these compounds in the aquatic environment leading to an emergent concern mainly related with the potential impacts in the aquatic biota. It is now understood that these impacts should be ascribed not only to the NPs *per se* but also to their dissolution products. However, most of the recent published works examines the NPs toxicity without characterizing their fundamental properties such as the dissolution and aggregation under environmentally relevant conditions.

The voltammetric technique scanned stripping chronopotentiometry (SSCP) and the fluorescence correlation spectroscopy (FCS) were used to determine the dissolution and aggregation, respectively, of various ZnO NPs: i) NApwd - in a powder form without any stabilization and with a nominal size of 20 nm from NanoAmor Inc.; ii) VN - in aqueous form with a sodium polyacrylate derivative as a stabilizer and with a nominal size less of 20 nm from ViveNano Inc.; and iii) NAaq - in aqueous form with a sodium hexametaphosphate as a stabilizer and with a nominal size of 40 nm from NanoAmor Inc.. The effects of various ZnO concentrations, pH, ionic strength and equilibration time were evaluated.

The NPs dissolution increased with the decrease of pH for all three different ZnO NPs. Total dissolution was obtained for the NApwd NPs at the pH range 4.5 - 6.5, whereas for the VN and NAaq NPs were obtained 83 and 60 % of dissolved Zn, respectively, at pH 4.5. At the highest pH value (pH = 8.5) the quantification of the metal is problematic because of a clear shift in potential that is observed in the SSCP wave, indicating that the metal is being complexed even for the non-stabilized ZnO NPs. This is not an unexpected result due to the well-known complexation properties of the oxides surfaces. No significant differences were obtained for the ZnO NPs from NanoAmor Inc. (approximately 49 % of minimum dissolved Zn), with a slight lower value (40 %) for the VN NPs.

The dissolution of the ZnO NPs is dependent of their concentration; higher dissolution was observed for the lower ZnO NPs concentrations, leading to almost total dissolution of NPs.

For the conditions where the ZnO NPs were not totally dissolved the aggregation was evaluated. The aggregation of the various ZnO NPs increased for pH values that were far from the zero point of charge. At a given pH, an increase in ionic strength generally resulted in increased aggregation.

This study is of great importance, from an ecotoxicological point of view because it suggests that the dissolution of ZnO NPs in the natural aquatic environment might occur to a

greater extent than previously predicted, even for stabilized NPs. Parameters such as pH, ionic strength, equilibration time and NPs concentration are essential to be controlled in order to correctly interpret the toxicological data.

Stability of CdTe/CdS quantum dots – role of pH and small organic ligands

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The increasing use of nanomaterials in consumer products has led to increased concerns about their potential environmental and health impacts. These impacts should be ascribed not only to the nanoparticles (NPs) *per se* but also to their dissolution products. Quantum Dots (QD) are available in various compositions, such as CdSe, CdTe, ZnSe, or PbSe cores surrounded or not by a Zn or CdS shell, and have been extensively used on optoelectronic devices and on biomedical applications. The significance of the dissolution process of the QD is 2-fold: first, dissolution strongly affects the postsynthesis stability of QD and therefore is of great importance for their long-term use in all solutions-based applications. Second, understanding dissolution behavior is of great importance for the rational design of efficient synthesis routes for high-quality QD.

The objective of this work was thus to evaluate the stability of a CdTe/CdS QD stabilized with a sodium polyacrylate derivative (PAA), from ViveNano Inc. (with a nominal diameter of 6-10 nm). Special emphasis was placed on i) precisely quantifying the dissolution of the QD by using the voltammetric technique scanned stripping chronopotentiometry (SSCP), ii) determining the role of pH on the dissolution of the QD, and iii) determining the effect of the presence of small organic ligands, such as histidine (His), glycine (Gly), and citric acid (Cit) on the dissolution of the QD.

The QD dissolution was quantified as function of time (0-48 h) and pH (4.5 – 8.5) with a total ionic strength of 0.01 M. An increase of the dissolved Cd as function of the equilibration time was observed, mainly at pH 4.5. The largest dissolution was obtained at pH 4.5 (more than 20% of minimum dissolved Cd at pH 4.5 vs. less than 10% at the other pH values), which can be explained by the solubility of the CdS shell. Unexpectedly, a higher percentage of dissolved Cd was obtained at pH 8.5 than at pH 7.0 and 6.5. The SSCP results at this pH show the largest shift in the wave potential indicating that the metal is being complexed. This indicates that the PAA that is used as a stabilizer is inducing a greater dissolution of the QD under these conditions.

The SSCP results obtained in presence of the ligands were fitted by using the thermodynamic model Visual MinteQ. Surprisingly, the histidine and glycine SSCP results at the highest pH value couldn´t be explained by the thermodynamic calculations indicating that the presence of these ligands lead to a larger QD dissolution than the one obtained for the QD-only case.

The thermodynamic data couldn´t explained the SSCP results in presence of the citric acid not only at pH 8.5 but also at pH 6.0. The results suggest a greater dissolution of the QD in presence of the citric acid even at pH 6.0. The results obtained can be explained by using the solubility equilibrium and the p*K*a of the ligands present in the QD dispersions.

The use of multiple analytical techniques is essential since no single approach can provide an unambiguous characterization of the NPs. Size changes of the QD were characterized by using atomic

force microscopy and transmission electron microscopy. Photoluminescence (PL) was used to study the surface phenomena in the inorganic part of the QD. Evident surface changes, revealed by the displacement of the maximum wavelength of the emission peaks for lower values, were obtained with the decrease of the pH, time and presence of the small organic ligands.

These results showing the dissolution of the QD under unexpected conditions are of great importance because the QD are not only used in optoelectronic devices but are also being applied in biomedical imaging, for gene targeting and drug delivery. The stability and processability of QD are far from ideal and it is essential to well characterize their properties to improve these processes. Moreover, in toxicological studies, and given the high potential for toxicity of the possible released ions, it is fundamental to quantify both particle dissolution and whether or not the intact QD have their own effect independent of the soluble ions.

Thermodynamics and kinetics of the dissolution of ZnO nanoparticles followed by AGNES

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There is a growing concern on the possible toxic effects of engineered nanoparticles (NPs) in natural waters. In the specific case of ZnO, one must also consider the important dissolution process, which is highly dependent on pH. Some authors even ascribe the toxicity of ZnO NPs to the relatively high free Zn(II) concentrations, rather than to the NP form[1]. Apart from pH and salinity, dissolved organic matter (DOM) plays a key role in the stability of NP suspensions, because adsorption of organic matter, such as humic acids or fulvics acids, onto the NP surface can dramatically vary its surface charge.

The technique AGNES (Absence of Gradients and Nernstian Equilibrium Stripping)[2] is specially suited for studying ZnO dissolution, given that it provides a direct and robust determination of the free Zn concentration. AGNES has been applied for the determination of free Zn in seawater, freshwater, humic acid solutions, quantum dot dispersions, wine, etc. DGT (Diffusive Gradients in Thin Films)[3] provides dynamic information on the fluxes arriving to an ion exchange resin[4]. AGNES[5] and DGT have been applied to dispersions of ZnO NPs from different sources to gain information on equilibrium and dynamic release of zinc ions from the particles under different environmental conditions (pH, DOM, size of NPs , etc.). The results were compared with thermodynamic and kinetic theoretical models. We conclude that both analytical techniques can contribute to the knowledge of the properties of ZnO NP dispersions, which are relevant for environmental impact and toxicity assessment.

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Boron removal from aqueous solutions using alginate gel beads in fixed-bed systems

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Boron occurs naturally throughout the environment, and it is commonly found in the oceans. Boron is an essential element as a trace element for plant growth and human health but in excess it will influence human reproduction and cause disease of the nervous system. The presence of boron in the environment may be due to natural or anthropogenic origin. It is found in the environment mainly as boric acid or borates. Boric acid reacts with water, as given by Eq.1, to reach an equilibrium concentration of the $[B(OH)_4^-]$ anion. The equilibrium constant for this reaction is $K_a = 5.80 \text{ X } 10^{-10}$ mol L^{-1} being the proportion of boric acid in near neutral pH dilute solutions > 99% [1].

$$B(HO)_3 + H_2O \leftrightarrow B(HO)_4^- + H^+ \qquad (1)$$

Calcium alginate was chosen as adsorbent because it is a polymer rich in hydroxyl groups. The presence of OH^- groups makes possible the formation of complexes by reaction of boron compounds. In this work presents the dynamic study of boron adsorption onto alginate gel beads in fixed bed-systems. Ten experiments were carried out at different alginate mass (m), column height (Z), pH, column diameter (d_c) and superficial flow velocity (Q), (Table 1). The initial concentrations of boron solutions used for the performance of work were 10 and 50 mg/L. Column data obtained at different conditions were described using empirical model, Bohart-Adams model and Thomas model [2-4].

The results show that calcium alginate gel beads are efficient at removing boron from dilute solutions. Sorption capacities of 10 mg g^{-1} have been obtained at pH_0 11 when the initial concentration of boron was 50 mg l^{-1}. The maximum adsorption percentage (59.8 %) was obtained when the column with larger diameter was used (column 4), Figure 1.

Table 1. Influence of experimental conditions on adsorption capacity and adsorption

Column	pHo	m (g)	Co (mg/L)	d_c (cm)	Z (cm)	Q (ml/min)	q_d (mg/g)	**% Ads**
1	6	0.5	50	1.6	15	0.9	3.0	**24.2**
2	6	0.5	10	1.6	14	0.3	0.4	**2.0**
3	6	1.5	10	1.2	22	0.2	0.2	**2.9**
4	6	4.8	10	5.5	11	0.2	2.5	**59.8**
5	11	0.4	50	1.6	12	0.9	10	**30.7**
6	11	0.5	50	1.6	15	0.9	10	**38.0**
7	11	3.5	10	2.6	18	0.9	0.6	**38.0**
8	11	3.5	10	2.6	18	0.2	0.5	**32.5**
9	11	1.4	10	1.6	18	0.9	0.5	**52.0**
10	11	1.4	50	1.6	18	0.9	1.8	**26.0**

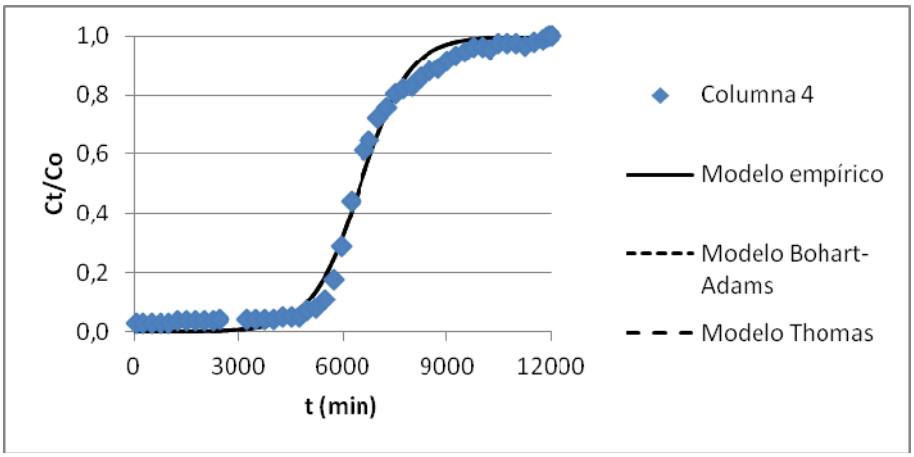

Figure 1. Experimental data and plot of the empirical, Bohart-Adams and Thomas models for column 4.

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Role of surface biomolecules in the heavy metals sequestrant capacity of lactic acid bacteria. A Vibrational Spectroscopy study

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INTRODUCTION: Toxic metals are not degradable and tend to accumulate in the exposed organisms causing serious health effects. The use of inactivated microbial biomass as adsorbents (biosorption) has become an efficient tool to remove such metals from different substrates (*i.e.* water, food, etc.) [1,2]. For this purpose, several species of microorganisms, including lactic acid bacteria, have been successfully employed. However, the molecular bases involved in this process have not been properly explored. For this reason, the aim of this work was to evaluate the bacteria/heavy metal interaction from a chemical point of view.

MATERIALS AND METHODS: *Lactobacillus kefir* strains CIDCA 8348 and JCM 5818 were cultured in MRS broth [3] for 48 h at 30 ^{o}C (stationary phase). One millilitre of cultures in the stationary phase was harvested and washed twice with ultra pure water (Milli-Q plus; Millipore Cop., USA). The pellets were resuspended into 1 ml milli Q water containing Pb^{+2} [from $Pb(NO_3)_2$], Cd^{+2} [from $Cd(NO_3)_2$] or Ni^{+2} [from $Ni(NO_3)_2.6H_2O$] ranging from 0 to 0.9 mM. The suspensions were further incubated for 1 h at 30^{o}C (pH 5.5) and then centrifuged for 4 min at 6600 g. The pellets were kept to register the Raman spectra.

Raman Spectroscopy: The Raman spectra of both bacteria containing the adsorbed heavy metals and nontreated bacteria (controls) were measured by placing them onto an aluminium substrate and then under a Leica microscope integrated to the Raman system (Renishaw 1000B). The wavelength of excitation was 830 nm and the power irradiation over the samples, 45 mW. Each spectrum was registered with an exposure of 30 s, two accumulations, and collected in the 1800-200 cm^{-1} region (spectral resolution: 2 cm^{-1}).

S-layer proteins preparation: Bacterial cells harvested in the stationary phase were mixed with 5 M LiCl and the S-layer proteins were extracted and purified as described previously [4]. S-layer proteins were suspended in 1 ml milli Q water containing 0.3 mM $Pb(NO_3)_2$, $Cd(NO_3)_2$ or $Ni(NO_3)_2.6H_2O$. The suspensions were incubated for 24 h at 30 ºC and then, centrifuged for 4 min at 6600 g. The pellets were used for the FTIR determinations.

FTIR spectroscopy: 30 µl of the S-layer pellets were put on a CaF_2 window and further dried for 15 min at 45 ºC to get a transparent film, used for FTIR experiments. FTIR spectra were recorded in the 4000-500 cm^{-1} range in transmission mode. The IR spectra were obtained co-adding 128 scans at room temperature (spectral resolution: 4 cm^{-1}).

Deconvolution of amide I band and assignment of protein secondary structures was carried out as previously reported [4].

RESULTS: The Raman spectra of both nontreated *L. kefir* strains (controls) were compared with those obtained after the treatment with each heavy metal. The main differences observed between controls and bacteria/metal samples clearly denoted the sites where metals are attached. Modifications of both νCOO^- s (1445 cm^{-1}) and νCOO^- as (1655 cm^{-1}) bands indicated that bacteria/metal interaction occurs through carboxylate groups. The band at 1260 cm^{-1}, related with phosphate groups disappeared after the treatment with metals and in the region 1000-850 cm^{-1}, ascribed to polysaccharides, further changes were observed.

The outmost structures in *L. kefir* strains are the S-layer proteins. They are macromolecular paracrystalline arrays that completely cover the bacterial cell surface [5,6]. They are attached to the underlying cell wall by non-covalent bonds and usually may be dissociated and solubilized into protein monomers by chaotropic agents (*i.e.*: LiCl).

Considering this background, the S-layers of the two strains under study were purified and the S-layer/heavy metal interaction was analyzed using FTIR spectroscopy. The metal/protein interaction occurred mainly through the COO^- groups of the side chains of Asp and Glut residues, with some contribution of the NH groups of the peptide backbone. The frequency separation between the νCOO^- as and νCOO^- s vibrations in the spectra of the S-layers in presence of the metal ions was found to be *ca.* 190 cm^{-1} for S-layer CIDCA 8348 and *ca.* 170 cm^{-1} for JCM 5818, denoting an unidentate coordination in both cases [7].

The secondary structure of the proteins was also altered after the interaction with heavy metals: a general trend to increase the amount of β-sheet structures and to reduce the amount of α-helices was observed. These changes allow the proteins to adjust their structure to the presence of the metal ions at minimum energy expense.

CONCLUSION: This analysis allowed obtaining a deeper insight on the molecular interactions involved when heavy metals are attached to bacterial surfaces.

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Metal-sorption Based on Hydroxypyrimidinone Functionalized Solid Supports

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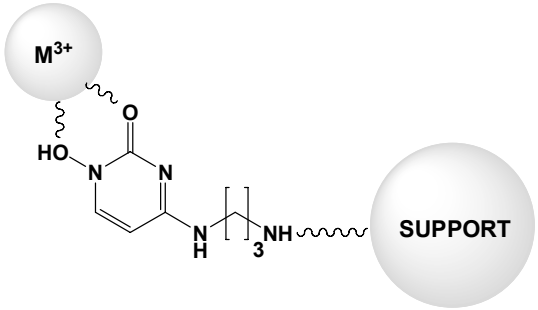
The use of solid supports chemically modified, with chelating capacity for the removal of toxic metal ions from wastewater streams, has motivated great interest in terms of environmental and biological applications. [1]
In recent years our group has developed a series of chelating sorbents for hard metal ions, namely Fe(III), Al(III) and Th(IV) (as a Pu(IV) model), by immobilization of hydroxypyridinone and hydroxypyrimidinone (HPM) units in sepharose and silica matrices. [2-4] We were able to obtain new functionalized sepharoses and silica that demonstrated high stability in a mild basic acidic pH range, very good sequestering capacity for hard metal ions (pH 3-7) and ability for reutilization. [2-4]
Therefore, we have decided to pursuit those studies on HPM solid sorbents aimed at expanding the applications of our research to other kind of solid supports, such as mesoporous silica and Merrifield polystyrene resins. In a first stage we synthesized and characterized three mesoporous silica and one Merrifield polystyrene resin with the ligand 4-(3-aminopropylamino)-1-hydroxy-2(1*H*)-pyrimidinone previously developed. [5] Herein we report the latest results about the optimization of these new chelating matrices in terms of ligand density and Fe(III) and Al(III) chelating capacity.



In general we obtained higher values of ligand density with the Merrifield polystyrene resin than with the mesoporous silica, which is in accordance with a higher number of active sites before coupling to the resin. The results also suggest an enhanced metal chelating ability for the functionalized Merrifield resin when compared to that of the functionalized mesoporous silica.

Acknowledgments

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Application of cork as sorbent of azo-dyes in coloured effluents.

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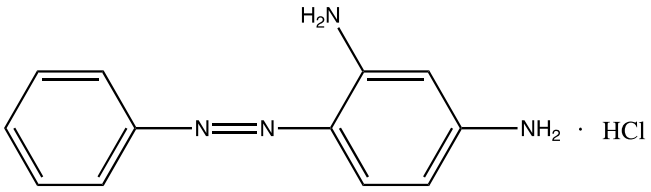
Among the various techniques (chemical coagulation, electrokinetic coagulation, oxidation and ozonation) sorption of both metal ions and of organic molecules from water by biomass has been found to be an effective removal method, due to its efficiency, simplicity, and easy applicability. Cork, thank to the different chelating groups on its surface, behaves as a strong sorbent towards most of the polluting metal ions and it presents good perspectives for organic compounds [1-3].

Azo-dyes, molecules characterized by the presence of the azo-group (–N=N-), are widely used in the textile, leather, rubber, plastic, and food industries. Water-soluble azo-dyes are greatly resistant to biodegradation, and are characterized by a high thermal and photo-stability due to their complex structures. The release of these molecules into the environment is of crucial concern due to their toxic, mutagenic and carcinogenic characteristics. Large volumes of colored effluents are discharged into environmental water sources: the colored wastewater may in some extent inhibit vital photosynthetic processes, and, furthermore, produces an unpleasant environmental impact. Thus, removal of azo-dyes from wastewaters is a fundamental environmental issue.

In this work we present a study on the sorption of chrysoidine, a synthetic azo-dye widely used in the textile industry. Chrysoidine undergoes reduction followed by a chain of reactions leading to formation of toxic compounds. Oral administration of Chrysoidine results in liver-cell adenomas, carcinomas and leukemia in animals, and some case studies also suggest its carcinogenicity. Various researchers have studied the adsorption of this dye on various materials. Activated carbon has been found effective, having both high surface area and high adsorption capacity. However, its relatively high operation costs hamper its large-scale application. Therefore, a number of low-cost adsorbents have been examined [4-7]. Cork has been here investigated as sorbent for the removal of Chrysoidine from wastewater. Chrysoidine, was purchased from Aldrich. It is highly soluble in water (0.213 g/l at 25°C) and has an adsorption maximum (λ_{max}) at 461 nm.



1,3-benzenediamine, 4-(phenylazo)-monohydrochloride (M.W. 248.72)

A stock solution of the dye was prepared in double-distilled water. Batch sorption studies are based on the fact that sorption at the solid–liquid interface changes the

concentration of test solutions. In our experiments, a series of Falcon™ 50 ml tubes containing 40 mL of adsorbate solution of different concentrations were prepared at fixed pH values. The proper amounts (0.5 g) of cork of two different particle sizes (20-40 and <20 mesh) were also added to each tube. These solutions were stirred for 24 hours on a mechanical shaker operating at a constant speed. The solution was then filtered by use of Whatman filter paper, and the filtrate was analyzed by measuring the absorbance at 461 nm to calculate the resulting concentration of the dye.

The adsorption capacity at 25 °C and at different pH values has been obtained from Langmuir equations for both the two different sizes of cork. A spectrophotometric study of the protonation properties of chrysoidine will be furthermore presented.

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Arsenic sorption onto natural, modified and synthetic sorbents

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Pollution with arsenic is an important global environmental problem [1]. Drinking water supplies in polluted areas often contains arsenic in excess of 10 μg/L - the maximum level recommended by the World Health Organization [1].

Arsenic is predominantly present as inorganic species – trivalent arsenite As (III) and the pentavalent arsenate As (V) – in natural waters. As (V) is a thermodynamically stable form and generally predominates in surface waters, but under reducing conditions, e.g. anaerobic ground waters are more favourable for arsenite compounds. In the pH range 6.5-7.5 of most natural waters, As (III) predominantly exists in uncharged ($H_3AsO_3^0$) speciation form and thus it is very difficult to be removed by the conventionally applied physicochemical treatment methods [2].

Arsenic in natural waters and soils is associated to the iron oxo(hydroxides) thus being arsenate and arsenite strongly sorbed onto the surfaces of Fe oxides, forming inner- or outher-sphere surface complexes. These complexes are defined by the presence or absence of hydration sphere of the adsorbate molecule [3]. Therefore iron containing sorbents based on different natural materials have found widespread application in water treatment. Despite of of many synthetic sorbents, production of new sorbents based on natural materials is perspective, because they are relatively cheap, recyclable and can be utilized in an environmentally friendly way. In this respect, peat is a prospective matrix for such sorbent development. Search for peat-based sorbents is topical considering the available significant peat resources in Northern countries and also it could be economically beneficial to produce material with high added value.

The aim of this study was to investigate and compare arsenic sorption onto peat, modified peat and synthetic sorbents.

Two different peat modification methods were used. In first method peat was impregnated with iron hydroxide (modified peat I), but in second method peat impregnation was performed using iron salts (modified peat II). The investigation of arsenic sorption onto two different iron hamates was done. For preparation of iron humates I, commercially produced potassium humate from Ploce peat bog was used (Intelecco SIA, Latvia). Humic acids from Ploce bog (Latvia) and iron (III) chloride were used for synthesis of iron humate II. For comparison synthetic (AN-221) and modified synthetic sorbents (Amberlite-Fe) were used. Arsenic was used in two inorganic forms As (V) and As (III) and one organic form – cacodylic acid ($C_2H_7AsO_2$).

In order to investigate the obtained sorption isotherms, Langmuir and Freundlich sorption models were analysed. Higher determination coefficient was observed for linear form of Langmuir isotherm ($R^2 = 0.998$) in comparison to linear form of Freundlich isotherm ($R^2 = 0.71$).

Sorption results indicate that peat modification with iron allow to enhance sorption capacity (Fig. 1), possibly due to the formation of As-O-Fe bonds [4]. Sorption capacity of arsenic onto modified peat I is comparable with sorption capacity of commercially produced sorbent (AN 221).

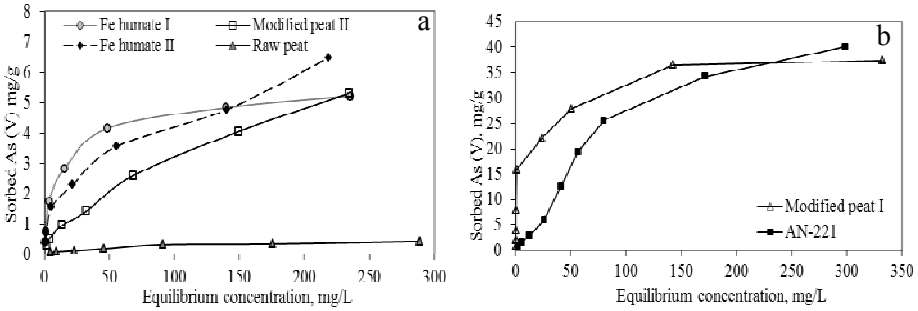

Fig. 1 Sorption isotherms of As (V) onto peat based sorbents and Fe humates (a), modified peat I and synthetic sorbent AN-221 (b).

The modification method had a great impact on arsenic sorption capacity. Since the iron content in both modified peat sorbents was almost identical, the differences in sorption capacity may be affected by the form of iron present in the sorbents, which performs different arsenic binding ability. Similar explanation could be adapted also for arsenic sorption onto iron humates.

The fate and behavior of arsenic in environment could be significantly influenced by physicochemical conditions such as pH. Maximum binding of As (V) for modified peat samples was observed at pH ~ 7. In this pH range between 6 and 8 the predominant species in solution are $HAsO_4^{2-}$ and $H_2AsO_4^-$.

Temperature is one of the factors that can influence sorption capacity. Variation in arsenate sorption onto modified peat at four temperatures (275, 283, 298 and 313 K) showed that sorption capacity increased with temperature. The sorption process was spontaneous ($\Delta G^\circ < 0$) and endothermic, (ΔH° = 41.43 kJ/mol), with a positive standard entropy (ΔS° = 214 J/mol K) that showed increasing randomness at the solid/liquid interface during the sorption of arsenic ions onto modified peat.

To conclude, arsenic sorption character onto unmodified peat and peat modified with iron were different. Peat modification with iron compounds significantly enhanced arsenic sorption capacity supposedly due to formation of As-O-Fe bonds. The best sorption properties for arsenic removal displayed modified peat I and it showed a good sorption capacity either for arsenates, arsenites and organic arsenic. Variation of sorption with pH was mainly influenced by arsenic species in solution. Arsenate sorption capacity increased with increase of temperature and arsenic sorption has spontaneous and endothermic character.

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Effect of pH on Cu(II) and Cr(VI) removal by using exhausted coffee in a batch reactor

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Effluents issued from finishing industries usually contain Cu(II), Cr(VI) and other metal ions whose concentrations are much higher than the permissible levels. During the last decades, biosorption has been an alternative to the costly effluents treatments for metal removal [1] and among the low cost biomaterials, exhausted coffee has been tested as a good biosorbent for Cr(VI) in small stoppered glass tubes[2]. In this work, exhausted coffee has been used for the removal of Cu(II) and Cr(VI) from single and binary mixture solutions in a 5L stirred batch reactor (Figure 1). The effect of pH on Cu(II) and Cr(VI) adsorption and Cr(VI) reduction to Cr(III) was evaluated.

In all the experiments 4 L of 0.2 mM Cu(II) and Cr(VI) in single and binary mixtures were contacted with 10 g of exhausted coffee (particle size 0.5-1.0 mm) under continuous agitation until equilibrium was reached. Experiments were carried out at room temperature (20±2°C) and solution pH was adjusted at different pH values (2, 3, 4 and 5).

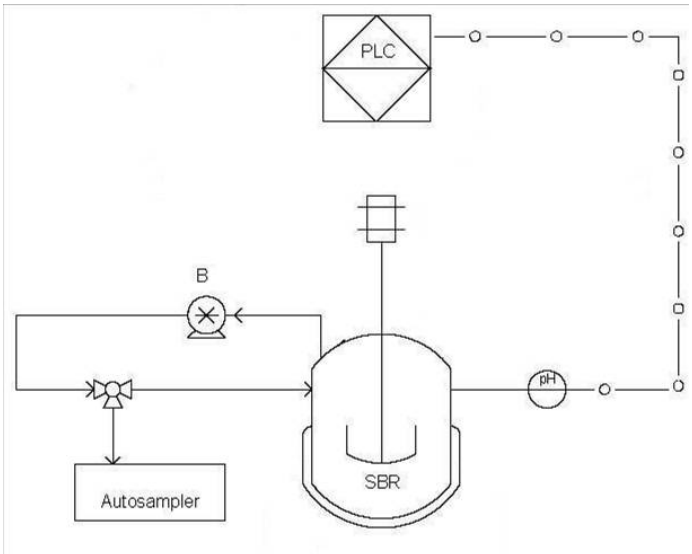

Figure 1. Experimental set-up

The obtained results from single metal solution showed that, the biosorption of Cu(II) reached equilibrium very fast because of the quickly ion exchange between calcium in the biosorbent and copper in the solution. In the case of Cr(VI), it was first, quickly reduced to Cr(III) thanks to the presence of easily oxydable groups on the exhausted coffee and protons in solution; and then slowly sorbed as Cr(III) on the sorbent surface. The best condition for Cu(II) removal was pH 5 (46% Cu(II) removed in 20 minutes) while the best condition for Cr(VI) were pH 2 and 3 (91% chromium removed in 1 and 3 days, respectively). The slight increase of solution pH after Cu(II) sorption may be due to the sorbent protonation, whereas the similar increase of pH solution after Cr(VI) sorption was mainly due to proton

consuming for chromium reduction reaction. When solutions of Cu(II) and Cr(VI) in binary mixture will be further investigated, it is expected to find higher removal yields for both metal ions provoked by a synergism effect to each other.

The results of the present work indicate that exhausted coffee can be successfully employed for the removal of Cu(II) and Cr(VI) both in single and binary mixture solutions in a batch reactor.

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Chromium (VI) sorption onto granulated cork from *Quercus suber* and *Quercus cerris*

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In recent years lignocellulosic materials have gained importance in metal removal from aqueous environments because of their abundance and cost advantage [1].Chromium is found in the industrial wastewaters and is of particular concern because of its high toxicity. Therefore, finding effectives and economical alternatives based on low-cost sorbent materials for chromium removal is of great importance.

In the present study, chromium (VI) adsorption on two different types of cork sieved at 40-60 mesh, namely heat treated *Quercus suber* at 300°C and untreated and heat-treated *Quercus cerris* at different temperatures (200°C, 250°C, 300°C and 350°C) were investigated. In addition, the chromium (VI) reduction to chromium (III) by the chemical composition was also studied. As metal adsorption onto lignocellulosics is a process pH and adsorbent type dependent (structure and chemical composition) the optimal pH for chromium VI removal was determined.

The highest adsorption values were obtained with untreated *Q.cerris* cork at pH 3 and heat treated *Q.suber* cork at pH 2. It was observed that heat treatment of *Q.cerris* cork resulted in a decrease of the total amount of chromium removed and Cr(VI) reduced. The adsorption isotherms were fitted to Langmuir model [2] showing similar maximum uptakes: 21.69 mg/g for untreated *Q.cerris* and 22.98 mg/g for heat treated *Q.suber*.

FTIR spectra indicated that lignin plays a significant role on sorption of Cr (VI) onto both *Q.suber* and *Q.cerris*. Suberin and polysaccharides also contribute to metal binding onto *Q.cerris*. Finally, SEM–EDS analysis showed that chromium was homogeneous distributed in the cork granules.

The overall results indicate that cost effective and environmentally friendly cork granules could be used in purifying chromium charged industrial waste waters.

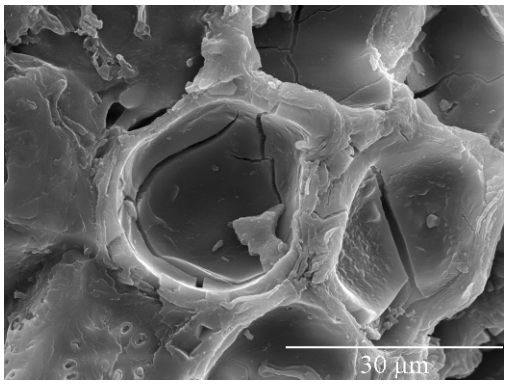

Fig.1A. *Q.cerris* cork cell treated with 1000 mg/L cromium solution

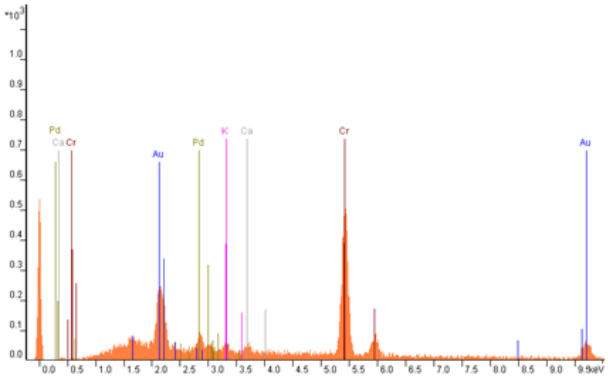

Fig. 1B. EDS spectra *of Q.cerris cork*

Acknowledgments

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Supramolecular receptors in solid phase: developing sensors for anionic radionuclides

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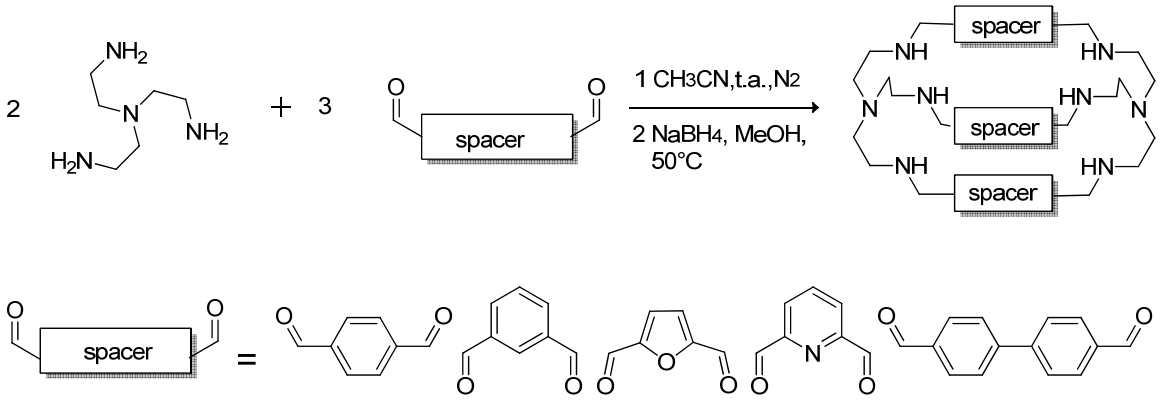
The proposed work is a response to the to the cogent need of receptors for the selective binding, separation and extraction of of perrhenate and pertechnetate (TcO_4^- and ReO_4^-).

The most significant source of ^{99}Tc, in the form of TcO_4^-, is from the nuclear fuel cycle. This anion possesses high solubility in water, good mobility and easily enters the food chain. Thus, there is a great demand for receptors that would permit the detection, monitoring, selective extraction and separation of pertechnetate from radioactive waste or, more generally, environmental media [1]. Moreover, ^{99m}Tc and ^{188}Re are used as diagnostic agents in nuclear medicine. For clinical use, technetium and rhenium were prepared immediately before use in medical centres. In both cases the radionuclides are available as oxoanions in isotonic solution, and it appears highly desirable to directly complex $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ as they exist in the generator eluate itself. Unfortunately, the large size and low density of such anions hinder the design of receptor-selective. Actually, to date, most of the materials and methods used for ReO_4^- and TcO_4^- separation and extraction fail to display high selectivity and, moreover, require the use of environmentally unsafe solvents. For this reason, receptors able to bind strongly and selectively the two anions are of great interest. The efficiency in anion recognition can be optimized by using macrocyclic and macrobicyclic receptors [2]. Polyamino cryptands, in protonated form, are known to display good affinity for ReO_4^- and TcO_4^- and they have already been applied in liquid-liquid extractions. In this work bistren-type systems, in which two tripodal tetra-amine subunits are covalently linked by spacers are considered (Figure 1)[3].

Figure 1



At this preliminary stage, the nonradioactive perrhenate anion will be used as a model. Due to its similar geometrical features to pertechnetate, perrhenate is typically considered to be a nonradioactive chemical analogue.

Receptors displaying higher selectivity in solution are functionalized and then fixed on polymeric matrixes (natural or synthetic polymers) in order to obtain sorbents that can be employed in the solid phase extraction (SPE) of the anions considered.

The first tests, performed as a screening on the performances of the prepared materials, were carried out starting from synthetic solutions at known content of ReO_4^- , and evaluating the efficiency of removal, the % of recovery and the selectivity of the polymers.

The project is currently underway and in this work we presents some preliminarily results that have made possible the identification of some promising solid phases.

The objective of future experiments will be the optimization of the procedures in order to obtain a selective method suitable for routine analysis in clinical and environmental laboratories.

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Synthesis of a water soluble naphthalimide modified 3-hydroxy-4-pyridinone metal ion sensor

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Metal ions are crucial for supporting all forms of life. Alterations in their cellular homeostasis are thinly related to many disorders, including cancer, diabetes and neurodegenerative diseases. For example, Zn^{2+} and Cu^{2+} play vital roles in biochemical pathways like catalysis, transport or biosynthesis. On the other hand, various heavy metal ions, such as Cd^{2+} and $Hg^{2+,}$ are potentially carcinogenic or mutagenic agents and several others affect the toxicity of organic xenobiotics via interaction with metabolizing enzymes or proteins. [1]

The development of highly sensitive and selective metal ion sensors is thus crucial in chemistry, biology, and environmental science, and consequently there is a raising number of groups working in this field of research. [1, 2]

Following our interest on the design of novel metal ion chelators based on 3-hydroxy-4-pyridinones (3,4-HPO) [3] we are currently developing a new group of fluorescent chelators that may act as chemosensors for biological and environmental relevant metal ions. Herein we report the synthesis and optical properties of the fluorescent chemosensor, N1-3,4-HPO (Figure 1). This sensor was synthesized by linking a 4-amino-1,8-naphthalimide platform, characterized by its planarity, fluorescent properties and water solubility, to a 3-hydroxy-4-pyridinone bidentate chelating unit. The synthetic approach was based on a microwave-assisted palladium catalysed amination of the 4-bromo-1,8-naphthalimide derivative with 1,6-dimethyl-2-aminomethyl-3-benzyloxy-4-pyridinone, followed by hydrogenolysis. The resulting N1-3,4-HPO exhibits intense fluorescence in pH physiological conditions. Fluorescence intensity is significantly quenched in the presence of Cu^{2+}, Zn^{2+} and Fe^{3+} (Figure 1).

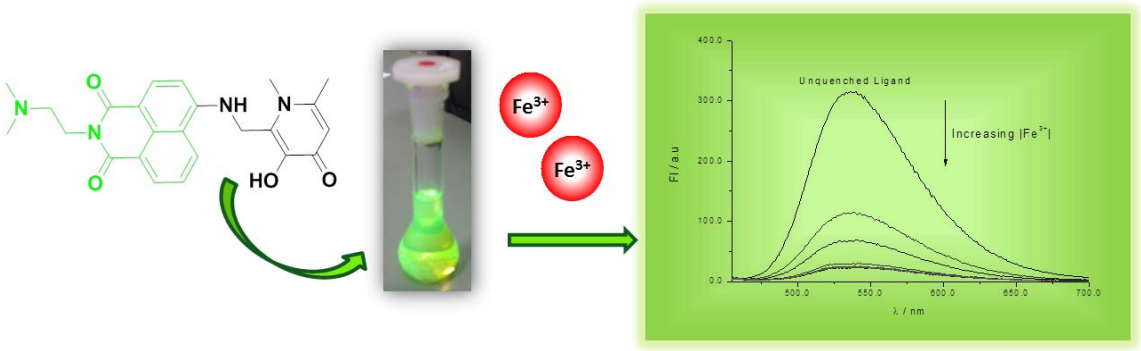

Figure 1

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Kinetic gas-phase studies on the reaction of ferracyclobutadienes with alkynes

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Metallacyclobutadienes belong to an intriguing class of organometallic compounds, which are mostly known as intermediates in alkyne metathesis.

Only a small number of compounds could be synthesized and characterized so far, as these compounds are usually very reactive [1].

In 2002 the group of Filippou has developed a novel method for the synthesis of a new class of metallacyclobutadienes containing iron (Figure 1) [2].

An interesting aspect of the isolated, closed-shell 16VE ferracyclobutadienes of the general formula $[Fe(CO)_{3-n}L_n(C_3R_3)]^+$ (n = 0 - 3; L = CO, phosphane, isonitrile, nitrile; R = NMe_2, NEt_2) and the products $[FeL_n(C_3R_3)]^+$ (n = 0 - 2) generated thereof by ligand dissociation, is their isolobal analogy with the fragments $[Fe(CO)_{4-m}]$ (m = 0 - 2). This suggests, that the ions $[FeL_n(C_3R_3)]^+$ (n = 0 - 2) may exist in a single or triplet electronic state, which in turn is expected to have a strong effect on their reactivity.

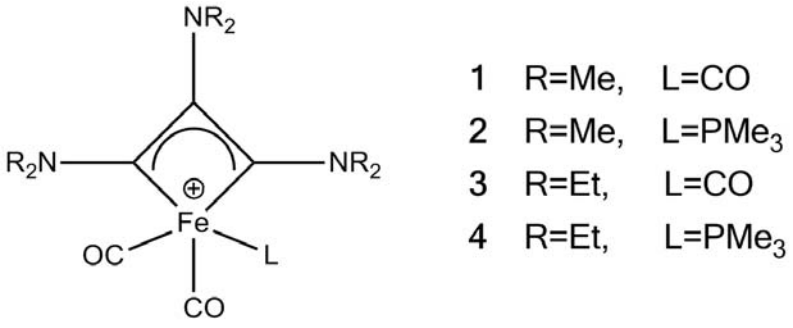

Figure 1: Examples of studied ferracyclobutadiene cations.

Studying reactions of metal complexes in the highly diluted gas-phase in a FT-ICR mass spectrometer is ideally suited to directly observe the effects of substitution and ligand sphere of a complex on the reaction. The absence of solvents or counter ions in the gas phase allows the determination of the intrinsic properties of the ions.

As the ferracyclobutadienes are positively charged, the ionization method of choice is electrospray ionization (ESI), which is among the softest ionization methods and allows the analysis of the intact ion.

Starting from the intact 16 VE ferracyclobutadiene cations $[Fe(CO)_{3-n}L_n(C_3R_3)]^+$, the very interesting highly unsaturated species $[FeL_n(C_3R_3)]^+$ can be generated either by collision induced dissociation (CID) or infrared-multiphoton-dissociation (IRMPD) in the gas phase. Both lead to ligand expulsion, which allows the determination of relative bond-dissociation energies. These are confirmed by quantum chemical calculations.

A set of carefully chosen ferracyclobutadiene cations was reacted with a selection of small alkynes. The analysis of the gas phase reactions under single-collision conditions turned out to be very challenging, as the coordinately unsaturated ferracyclobutadienes react extremely fast and are involved in complex reactant/product equilibria.

The exemplary analysis of the ion $[Fe(PMe_3)(C_3(NMe_2)_3)]^+$ shows that the small singlet-triplet gap provides us with two reactive species, which do react in two completely different ways.

Species one adds only 1-butyne in the gas-phase leading to an equilibrium. Species two on the other hand does not display the direct addition of 1-butyne, but reacts with the alkyne under loss of 1-3 H_2 molecules.

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Optimization of the spectrometric determination of Cr (III) with a SIA system combined with a Dilutor-Autosampler

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The determination of Cr(III) and Cr(VI) besides that of total chromium, is required in decontamination studies of chromium in waste waters, due to the different degree of toxicity of both chromium species. In the case of Cr(III), the analytical method most commonly used is based on calculating the Cr(III) concentration as the difference between total chromium and Cr (VI) concentration. These two values are determined well with specific techniques: AAS, ICP for total chromium and absorption spectrometry UV-VIS for Cr(VI). But this method has the disadvantage of great cumbersome (the samples should be measured in different instruments), and the result accumulates the error of the two techniques executed. [1, 2].

Our research group has presented in previous works a new method for the simultaneous determination of the two species of chromium with a Sequential Injection Analysis system (SIA) [3]. This technique is based in a continuous flow of a carrier solution where sample and reagent segments are injected. The reaction is produced by diffusion in the interface of the segments. After reaction the fluid goes to the detector where the absorbance of the passing solution is measured. For analysis of the two chromium species two aliquots of sample are injected sequentially into the system. In the first aliquot Cr(VI) in the sample reacts with diphenylcarbazide (DPC) and produces a pink coloured complex of great absorbance at 548 nm. In the second aliquot, Cr (III) is oxidized to Cr(VI) with Ce (IV), then, DPC is injected which reacts with the all the Cr(VI) present (the original and the produced in the oxidation) yielding a second peak of absorbance.

In the previous study, detection limit for Cr (VI) and Cr(III) were found to be 0.04 mg L^{-1} and 2 mg L^{-1}, respectively; the precision for Cr(VI) is lower than 5% nevertheless higher values were found for the precision of Cr(III) and in general the results found for Cr(III) determination were not enough good to give a reliable analysis of this species. The main reason for these results must be attributed to the fact that two reactions are involved in Cr(III) analysis (oxidation and DPC reaction) creating two "diffusion interfaces" along the flow tube, which makes difficult the interaction of reagents.

Therefore, in this work different methodologies of the one used in our previous works for the determination of Cr(III) are tested in order to improve the analytical result. Like in our previous works the analysis is based on the DPC colorimetric method and the same type of automatized system has been used. A Dilutor-Autosampler Gilson 223 has been coupled with the SIA system, so a manifold has been designed that allows making the reactions in either the dilutor or in the SIA system or in both of them. The reactions in the dilutor take place in glass test tubes where sample and reagents can be well mixed and reaction completion can be ensured. In addition, the 3-ways valve disposed in the robotic arm allows the sample (or the reaction mixture) going to the SIA system to be analysed.

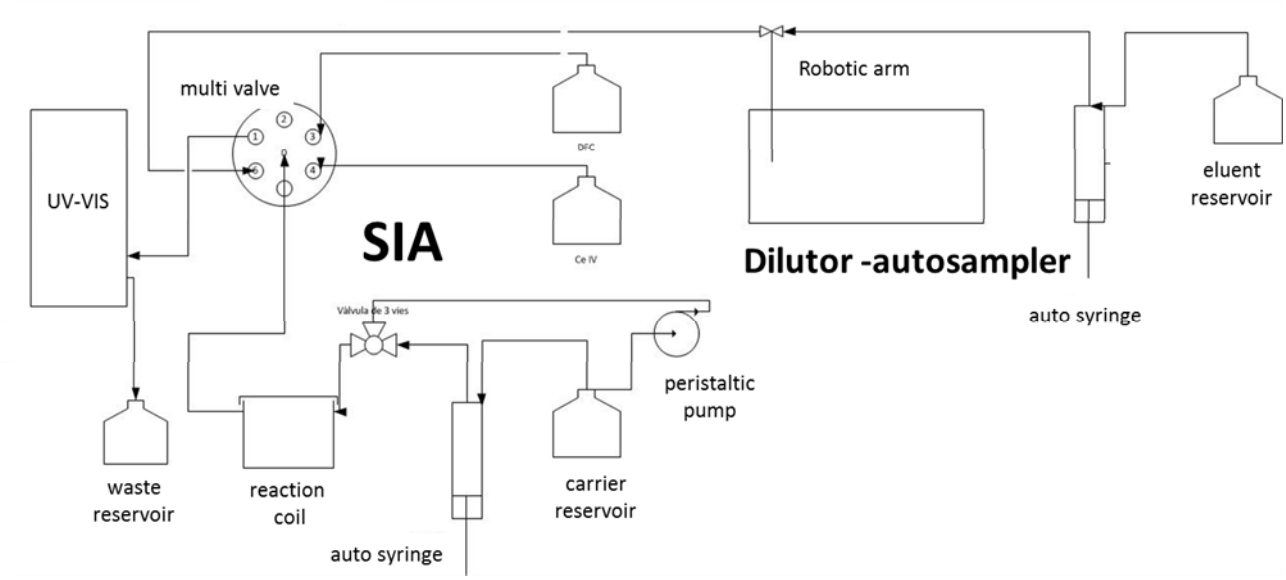

Figure 1. SIA – Dilutor manifold

The tested methodologies are the following:

1. Making all reactions in the dilutor and the spectrometric measurement in the SIA system (Batch Method).

2. Making the reaction of Cr (III) and Ce(IV) in the dilutor and the reaction with DPC and the corresponding spectrometric measurement in the SIA system (Mix Method).

3. Making all reactions in the SIA system (Continuous Method). In this case, several ways of injecting the sample and the reagents have been tested.

For all tested methods, the optimal working conditions were determined (reagents concentration, time of reaction, injection volumes, flow speed). Also the figures of merit and the analysis time per sample were calculated.

Acknowledgement: This work has been financially supported by Ministerio de Ciencia e Innovación, Spain, Project CTM2008-06776-C02-01.

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Ferrocene-glutatione conjugates as electrochemical sensors for human Glutathione S-transferase P1-1

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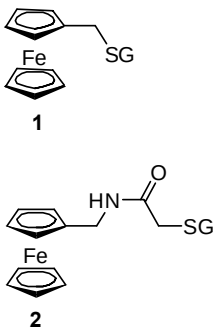
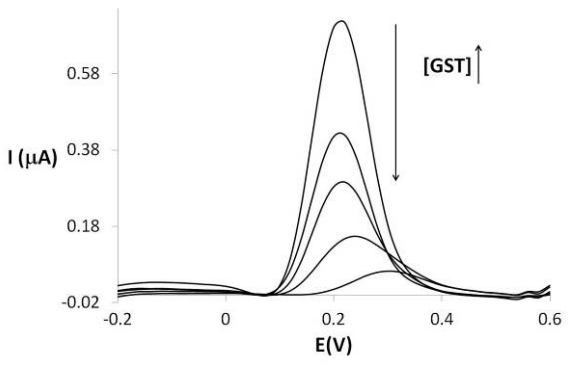
Electrochemical-based protein sensors offer sensitivity and selectivity, making them very attractive tools for protein detection. Thus, compounds containing ferrocene and bearing molecular recognition binding sites have received much attention due to the possibility of building redox-switching or sensing molecular or supramolecular systems, which can be controlled through the application of external stimuli [1]. Therefore, medicinal application of ferrocene is an active research area and many reports have shown that ferrocene derivatives have a highly promising activity *in vitro* against several diseases [2]. A major problem in the treatment of cancer with chemotherapy is the development of resistance of the cancer cells toward the cytostatic drug used. This resistance is in part caused by an increased metabolic detoxication of the drugs in the cancer cells caused by enzymes such as the human Pi glutathione S-transferase (GST P1-1). Moreover, a common feature, demonstrated in a number of different human cancer cells, is elevated levels of this human enzyme relative to their concentration in the corresponding normal tissue [3]. Thus, the design of GST P1-1 inhibitors and sensors can emerge as promising therapeutic agents for managing the development of resistance amongst anticancer agents.

In this work, we have synthesized and studied the sensor properties and inhibition of two electroactive ligands that consist in glutathione attached to one cyclopentadienyl ring of ferrocene ($FcCH_2SG$, **1**) and an amide derivative of this compound ($FcCH_2NHCOCH_2SG$, **2**), to GST P1-1. The two ferrocene-glutathione conjugates studied here bind simultaneously to G-site (by GSH moiety) and to H-site (through ferrocene moiety) of GST P1-1.





These binding interaction studies have been carried out by activity assays, isothermal titration calorimetry (ITC), spectroscopy fluorescence, and differential pulse voltammetry (DPV). Such ferrocene conjugates result to be strong competitive inhibitors of this enzyme with an enhanced binding affinity relative to the natural substrate glutathione. Moreover, the conjugate having the amide group (**2**) exhibits an affinity for GST P1-1 approximately one order of magnitude higher than **1** ($K_{d,(1)}$ = 0.7 μM, $K_{d,(2)}$ = 4.4 μM). The obtained thermodynamic parameters indicate that, when bound, ferrocene moiety of **2** can establish more interactions with residues of the hydrophobic H-site, possibly due to higher length of spacer arm between ferrocene and GSH moieties, compared with **1**. Moreover, the presence of amide group in **2** may also be favourable for the higher affinity of this conjugate. Activity assays results also indicate that inhibitory capacity of **2** is higher than that obtained for ethacrynic acid-glutathione conjugate (EA-SG), a great GST inhibitor, which EA moiety also binds strongly to H-site of GST P1-1 ($K_{d,\ EA\text{-}SG}$ = 5.1 μM) [4]. Furthermore, thermodynamic results do not indicate profound conformational changes upon **2** binding, and no evidence for ligand binding cooperativity was observed. In addition, voltammetric measurements show a strong decrease of the peak current intensity upon binding of ferrocene-glutathione conjugates to GST P1-1. Such voltammetric studies have shown that both ferrocene-glutathione conjugates can be used as electrochemical sensors for the detection of GST P1-1, and that compound **1** exhibit better sensing ability, expressed by the sensitivity parameter, than **2**.

Acknowledgments

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Development of catechol-based fluorescent chemosensors. Synthesis and evaluation of metal ion sensing behaviour

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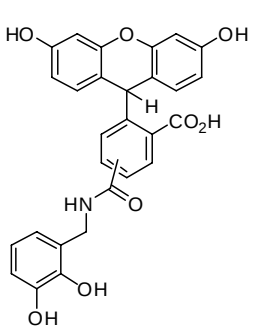
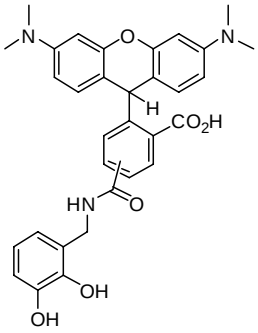
The design of fluorescent chemosensors for a broad range of environmental and biological analysis is an expanding field of research. A fluorescent chemosensor is defined as a device that detects the presence of a target analyte through changes in its physico-chemical properties. There is a larger number of chemosensors but fluorescent metallosensors are gaining special attention due to their high sensitivity and selectivity, quick response, simplicity of measurement and quantification of metal ions affinity.[1] Usually, fluorescent sensors are composed by a fluorescent molecule and a chelating unit (ligand). The fluorescence quantum yield, metallosensors chelating capacity and sensibility are determinant parameters to be considered in order to obtain a good performance.

Recently we reported the preparation of a fluorescein-based dye containing a catechol chelating unit - **Cat1**- and the study of its photophysical properties. The results point to a potential application of this catechol derivative as an ion sensor in biological media, particularly for iron(III).[2]



Cat1



Cat2

Now, we are presenting the synthesis, characterization, UV-Vis and fluorescence spectra of a novel rhodamine-based dye containing the same catechol chelating unit - **Cat2**. This compound was prepared through conventional and microwave-assisted amide coupling of the catechol derivative with the rhodamine scaffold, followed by treatment under a hydrogen atmosphere over 10% Pd/C.

The behaviour of this new compound - **Cat2** - in the presence of metal ions of biological importance (Fe^{3+}, Al^{3+}, Cu^{2+} and Zn^{2+}) was monitored by optical spectroscopy (at physiological pH and 25ºC) (see Fig 1 and 2) and compared with the performance of **Cat1**.

Photophysical characteristics of **Cat2** such as UV-Vis absorption, emission fluorescence intensity and fluorescence quantum yield and it´s affinity for metal ions were studied and compared with **Cat1**. It is expected that **Cat2** might be more soluble in organic solvents than **Cat1**. On the other hand, it is important to have information on the different species present in solution, at different pHs, in order to understand the behaviour of **Cat2** in solution. These comparative studies will be determinant for a future analytical application of these

compounds in the development of a flow based method for the detection of metal ions in natural water.[3]

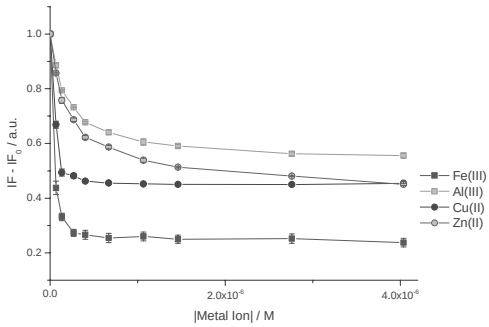


Fig 1. Emission fluorescence intensity quenching of 1.5μM **Cat2** in MOPS (10 mM, pH 7.4), with increasing concentrations of Fe^{3+}, Al^{3+}, Cu^{2+} and Zn^{2+}.

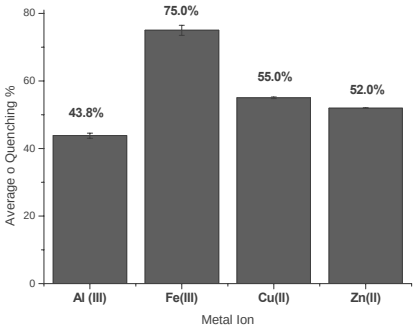


Fig 2. Influence of Fe^{3+}, Al^{3+}, Cu^{2+} and Zn^{2+} on the emission fluorescence intensity of **Cat2**. The results were obtained in a 1.5 μM **Cat2** solution (10 mM MOPS (pH 7.4)) with a fixed 1:1 molar ratio for all the different metal ions understudy.

Acknowledgments:

Financial support from FCT through project PTDC/QUI/67915/2006 is gratefully acknowledged. We also thank Dr. Andrea Carneiro from CeNTI, V.N. Famalicão, for making available a CEM Discover microwave reactor. The Bruker Avance II 400 spectrometer is part of the National NMR network and was purchased under the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and (FCT).

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"Turn-on" sensor based on the opening of the spirocyclic form of rhodamine B

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Iron and copper play important roles in biochemical processes and regulation of their metal ion concentration is crucial for life. Consequently one of the main goals in the field of chemical sensors is the detection and quantification of these relevant metal ions.

Fluorescence spectroscopy is a non-destructive technique, highly sensitive and allows real information on the localization and quantification of the analytical targets. In the last years several fluorophores with different photophysical properties have been used to identify and measure metal ions in varied matrices. Dyes of the xanthene family are amongst the most used sensors due to their excellent properties, such as high extinction coefficients, quantum yields and photostability. Most of the sensors presently in use are based on the measurement of the quenching observed in fluorescence intensity due to the presence of the referred metal ions. These methodologies usually require the use of a de-quencher agent to validate the results and do not provide a positive signal in microscopy methods.

More recently, a strong effort has been put on the design of "turn-on" sensors, in which silent molecules are activated in the presence of metal ions. The spirocyclic derivatives of rhodamine have proved to be useful sensing platforms since the ring-opening process leads to a turn-on fluorescence ligand. [1]

In this work we present the synthesis and characterization of a new ligand based on the lipophilic rhodamine B molecule whose fluorescence is triggered in the presence of iron and copper metal ions which induce the opening of the spirocyclic form.

The structure of the ligand was obtained by X-ray diffraction and is depicted in figure 1. Fluorescence studies in different solvents and in aqueous solution at variable pH and metal/ligand ratios are presented.

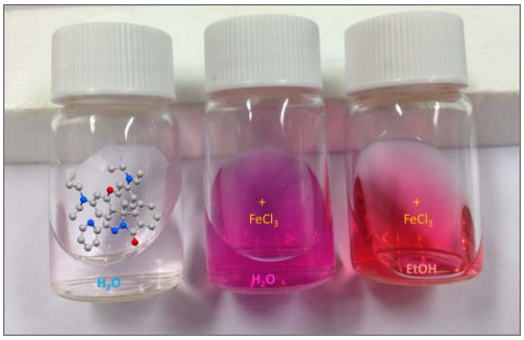

Figure 2. Ligand behavior in water, without and with $FeCl_3$, and ethanol with $FeCl_3$.

Acknowledgments:

Financial support from FCT through project PTDC/SAU-MET/113011/2009 is gratefully acknowledged. The Bruker Avance II 400 spectrometer is part of the National NMR network and was purchased under the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and (FCT).

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Microwave-assisted synthesis of catechol-based rosamines for metal sensing

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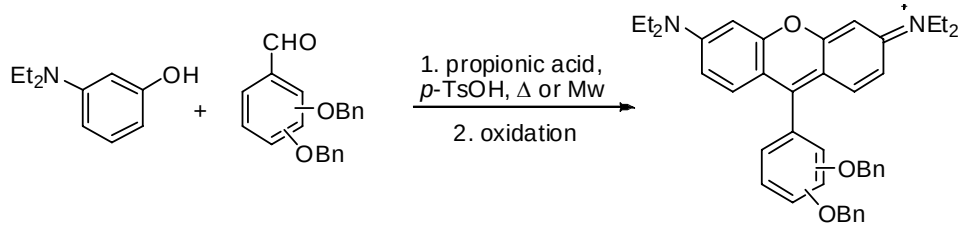
Chemical sensing refers to the continuous monitoring of the presence of chemical species. High sensitivity and selectivity, quick response and simplicity of measurement are the main issues for sensor development.[1] Therefore there is a pressing need for the development of new metal ion sensors that may be of use in several fields including chemistry, biology, clinical biology and environmental sciences. For example, metal ions like Zn(II), Cu(II) and Fe(III) are essential in the human body and play important roles in biological and environmental processes.[1, 2] Consequently, a large number of fluorescent sensors have been developed for monitoring the presence of the latter metal ions.[3]

The purpose of the present work is to synthesise new functionalized fluorescent molecules, whose fluorescence properties change in presence of the metal ions mentioned above. To achieve this goal, two fluorescent catechol based-rosamines were prepared. The mechanism for fluorescence involves the interaction of the metal ion with a catechol ligand that is part of the π-system of the fluorophore (rosamine skeleton). The methodology employed to obtain the desired rosamines is based on the condensation of 3-diethylaminophenol with an appropriate substituted benzaldehyde, using both conventional heating and microwave irradiation approaches, following by oxidation with chloranil and deprotection. Higher yields and a remarkable shorter period of time (10 min) were achieved by using a microwave irradiation protocol under close vessel conditions (80ºC), as shown in Table 1.

Table 1. Results obtained in oil-bath (Δ) and microwave (MW) synthesis of rosamine derivatives.



R	Method	Temp (ºC)	Time	Yield (%)
2,3-OBn	oil bath	65	16 h	36
2,3-OBn	MW	80	10 min	38
3,4-OBn	oil bath	65	16 h	12
3,4-OBn	MW	80	10 min	61

In order to evaluate the potential application of these rosamines as metal ion sensors, the characterization as a function of pH and behaviour in the presence of different metal/ ligand ratios for Zn(II), Cu(II) and Fe(III) were performed by using NMR, UV-Vis and fluorescence spectroscopies.

Acknowledgments:

Financial support from FCT through projects PTDC/QUI/67915/2006 is gratefully acknowledged. We also thank Dr. Andrea Carneiro from CeNTI, V.N. Famalicão, for making available a CEM Discover microwave reactor. The Bruker Avance II 400 spectrometer is part of the National NMR network and was purchased under the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and (FCT).

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Zigzag 1D-copper(II) polymer with alternating bridging units of two different ligands: Synthesis, crystal structure and properties of $\{[Cu_2(\mu_2\text{-trans-1,4-CDTA})(\mu_2\text{-4,4'-bipy})(H_2O)_2]\cdot 4H_2O\}_n$

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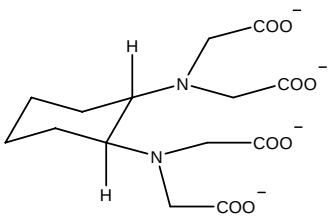
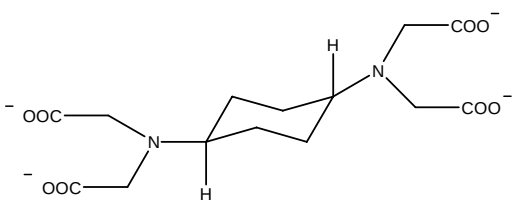
A large variety of polymeric structures with different dimensionalities can be constructed using bridging ligands. The essential strategy is to use metal complexes where the main ligand does not satisfy the coordination requirements of the metal centre. Therefore they can be connected by appropriate bridging ligands. For borderline first-row transition metal(II) ions (Mn-Zn), suitable μ_2-bridging ligands are those having two appropriately spaced N-heterocyclic donor atoms (borderline Pearson bases). Examples of such ligands are pyrazyne (pz), 4,4'-bypyridine (4,4'-bipy), 1,2-bis(4-pyridyl)ethane or purines, among many others.

A previous work [1] reports the structures of four compounds built by copper(II)-(trans-1,2-CDTA) chelate units and pz or 4,4'-bipy as μ_2-bridging ligands (trans-1,2- H_4CDTA = trans-cyclohexane-1,2-diaminotetraacetic acid). Therein highlight two 4,4'-bipy derivatives with formulas [(trans-1,2-H_2CDTA)Cu(μ_2-4,4'-bipy)Cu(trans-1,2-H_2CDTA)]·4,4'-bipy·$2H_2O$ (**1**) and $\{[Cu(\mu_2\text{-trans-1,2-CDTA})Cu(H_2O)_3(\mu_2\text{-4,4'-bipy})]\cdot 8H_2O\}_n$ (**2**).

Compound **1** consists of a binuclear complex molecule with 4,4'-bipy as μ_2-bridging ligand as well as solvate. In this compound, the partially protonated trans-1,2- H_2CDTA ligand only acts as tetra-dentate chelator, thus having two free acetic arms. In **2**, the trans-1,2-CDTA ligand plays two different roles: (i) it acts as hexa-dentate chelator for a Cu^{II}A centre and (ii) as a bridge between two non-equivalent metal centres (CuA and CuB) by means of a syn,anti-carboxylate group. Each Cu^{II}B centre is hexa-coordinated by two N-atoms from two 4,4'-bipy ligands, three O-atoms of aqua ligands and one O-trans-1,2-CDTA atom from its bridging carboxylate group. Hence, 1D zigzag polymeric chains are built in **2** by alternating μ_2-4,4'-bipy ligands between $Cu^{II}(B)(H_2O)_3$ units that are further connected to Cu^{II}(trans-1,2-H_2CDTA)



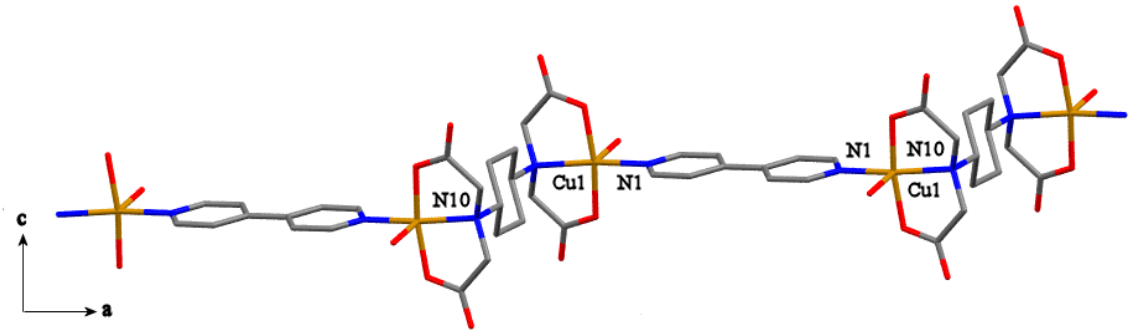
e,e-Trans-1,2-CDTA (4-) ligand



e,e-Trans-1,4-CDTA (4-) ligand

units. Note that μ_2-4,4'-bipy ligands only connect CuB centres, whereas trans-1,2-CDTA ligands only chelate CuA centres.

In order to build a polymer where both chelator and 4,4'-bipy ligand can act as bridges between equivalent copper(II) centres, we used the spacer-chelator trans-1,4-CDTA [2] instead of the most common isomer trans-1,2-CDTA (see scheme above). To this purpose, we reacted $Cu_2CO_3(OH_2)$ (0.25 mmol) and trans-1,4- H_4CDTA (0.5 mmol) in water, heating and stirring under moderate vacuum (to remove CO_2, main by-product). To the resulting clear blue solution, 4,4'-bipy (0.25 mmol) was added and the reaction mixture was stirred till complete solution of reactants. After filtration without vacuum in a crystallization device, the solution was slowly evaporated to promote the crystallization of $\{[Cu_2(\mu_2\text{-trans-1,4-CDTA})(\mu_2\text{-4,4'-bipy})(H_2O)_2]\cdot 4H_2O\}_n$ (**3**), with a yield of 76 %. The compound crystallizes in the monoclinic C2/m space group and the structure was refined to a final parameter R1 = 0.038. It consists of polymeric chains of complex molecules and non coordinated water. The 1D chains exhibit a zigzag topology and extend along the *a* axis (see figure below). In the studied polymer, there is only one kind of Cu(II) centre and both trans-1,4-CDTA and 4,4-bipy ligands acts as bridging ligands in an alternating manner.



Each copper(II) atom has a distorted square-base pyramidal coordination, type 4+1. The four shortest bonds involve a tridentate iminodiacetate moiety (Cu1-O11 = Cu1-O11# 1.935(2) Å, Cu1-N10 2.003(3)Å) and one N donor of a half 4,4'-bipy ligand (Cu1-N1 1.987(3) Å). The apical/distal donor belongs to an aqua ligand (Cu1-O1 2.365 Å). The Addison parameter, that measures the basal distortion, is τ = 0.10. Elemental analysis, electronic and FT-IR spectra and thermal analysis information of the novel compound are available.

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Recognition properties of polyazapolyoxa heteroditopic macrobicyclic compounds

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Macrobicyclic architectures have been used in molecular recognition since the very beginning of Supramolecular Chemistry.[1] Polyamine macrobicycles, in particular, were the first type of compounds to be explored in anion recognition and have been extensively used since then. The reason behind the success of this class of compounds stems from both the binding properties of the ammonium group and the encapsulating abilities of the macrobicyclic architecture.[2-3]

In the continuation of our studies on anion binding by macrobicyclic receptors,[5-8] two polyoxapolyaza heteroditopic macrobicyclic compounds ($btpN_4O_3$ and $t_2pN_5O_3$) were synthesized through a [1+1] "tripod-tripod coupling" strategy, in moderate to good yields. Both compounds where designed to have separate polyamine and polyether compartments, under the expectation that they could be used as dual receptors for anions and cations, and consequently as receptors for zwitterionic amino acids. The receptors have in common a tren derived subunit as the anion binding moiety and differ from each other in the polyether cation binding compartment. $btpN_4O_3$ has a 2,4,6-triethylbenzene derived polyether subunit whereas $t_2pN_5O_3$ has a triethylamine derived one.

The acid-base behaviour of the compounds was studied by potentiometry at 298.2±0.1 K in H_2O/MeOH (50:50 v/v) and at ionic strength 0.10±0.01 mol dm^{-3} in NMe_4TsO. The acid-base studies revealed that the tren subunit of $btpN_4O_3$ is fully protonated at pH ≈ 6.2 whereas $t_2pN_5O_3$ exhibits a more complicated protonation behaviour, in which the tertiary amine of the polyether compartment is protonated before the complete protonation of the tren subunit, rendering the compound inappropriate for amino acid binding. The binding studies between $H_nbtpN_4O_3^{n+}$ and the amino acid substrates in the very competing medium used led to association constant values in the range 1.85–3.33 log units, with $H_nbtpN_4O_3^{n+}$ showing a preference for amino acids containing tetrahedral anionic groups.

Acknowledgements: This work was supported by Fundação para a Ciência e a Tecnologia through grant PEst-OE/EQB/LA0004/2011. The NMR spectrometers are part of the National NMR Network and were purchased in the framework of the National Program for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and Fundação para a Ciência e a Tecnologia (FCT). Pedro Mateus thanks FCT for the grant (SFRH/BD/36159/2007).

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Lanthanide cation binding properties of homooxacalixarenes bearing pyridyl pendant groups at the lower rim

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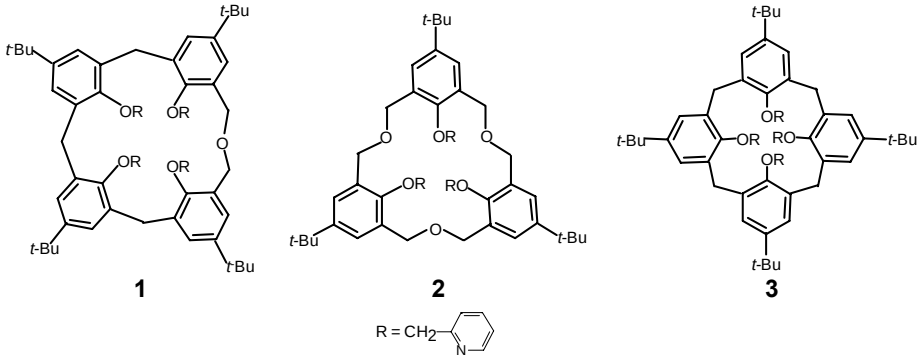
Recent research in host-guest chemistry has shown the remarkable ability of calixarenes to act as selective binders when substituted with appropriate functional groups. Many studies have been devoted to the binding capacity of calixarenes containing carbonyl groups at their lower rims to bind metal ions, in particular mono- and divalent cations [1]. Besides these, research work with trivalent cations, namely lanthanides, has also been increasingly reported [2]. The growing interest in these elements is mainly due to their use in materials for catalysis, optics and electronics, in luminescent probes, in biology and in medicine as contrast agents for magnetic resonance imaging.

In the course of our studies of binding properties of dihomooxacalix[4]arenes bearing pyridyl pendant groups at the lower rim towards alkali, alkaline earth, transition and heavy metal cations [3], we have recently extended our research into lanthanide ions [4, 5].

We present in this work the binding properties of (2-pyridylmethoxy) derivatives **1** and **2**, derived from *p-tert*-butyldihomooxacalix[4]arene and from *p-tert*-butylhexahomotrioxacalix[3]arene, respectively, towards lanthanide cations. **1** was obtained in the cone conformation and **2** was obtained in the cone and partial cone conformations, which were separated and both studied. Extraction studies of metal picrates and stability constant measurements in acetonitrile based on UV absorption spectrophotometry were performed. The affinity of the ligands for certain cations was also investigated by proton NMR spectrometry. The results are compared to those obtained with *p-tert*-butylcalix[4]arene tetra(2-pyridylmethoxy) **3** and discussed in terms of size and conformational effects of the macrocycles.



1 **2** **3**

Authors thank *Fundação para a Ciência e a Tecnologia*, Project ref. PTDC/QUI/69858/2006

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Transition and heavy metal ions complexation by *p-tert*-butylhexahomotrioxacalix[3]arene tri(2-pyridylmethoxy) derivatives

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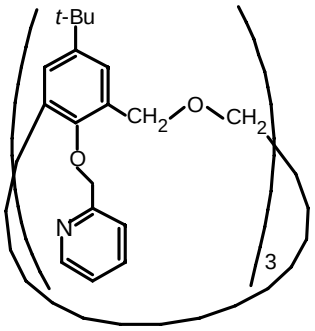
Homooxacalix[n]arenes represent a class of macrocyclic receptors analogous to calix[n]arenes where some or all methylene bridges between the aromatic rings are replaced by CH_2OCH_2 moieties [1, 2]. Due to the presence of additional oxygen and carbon atoms, homooxacalix[n]arenes are larger and more flexible molecules and are expected to host larger cations. The ability of carbonyl containing substituents on the narrow rim of dihomooxacalix[4]arenes to bind metal cations has been extensively studied [3-5]. The replacement of carbonyl groups to substituents containing softer donor atoms, such as nitrogen, showed good affinity for soft heavy metal ions [6]. To extend our knowledge of the behaviour of these derivatives, we studied new hexahomotrioxacalix[3]arene compounds.

We report here the binding properties of *p-tert*-butylhexahomotrioxacalix[3]arene tri(2-pyridylmethoxy) derivatives, in cone and in partial cone conformations, towards some transition (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}), heavy (Ag^{+}, Pb^{2+}, Cd^{2+}, Hg^{2+}) metal cations and Na^{+} and Ca^{2+}, as an example of alkali and alkaline-earth cations. Thermodynamic parameters (stability constants, complexation enthalpies and entropies) have been determined in acetonitrile using UV absorption spectrophotometry and microcalorimetry. Liquid-liquid extraction experiments from an aqueous phase containing the metal cation into an organic phase of dichloromethane containing the ligand were also performed. Proton NMR spectroscopy was used to assess the affinity of the ligands for certain cations. Ab initio computational simulations, using DFT methods, were also carried out for some systems to analyse the structure and the electronic properties of the complexes formed.



The results are compared to those obtained with the corresponding calix[4]arene and dihomooxacalix[4]arene. The influence of the condensation degree, of the number of oxygen atoms and of the conformation is discussed.

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A new policentred heptacopper(II)/adenine complex: synthesis and characterization of $[Cu_7(\mu_2\text{-}O)_6(\mu_3\text{-}O)_6(adenine)_6](NO_3)_y.xH_2O$

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The synthesis and characterization of polynuclear 3d-metal clusters with various nuclearities, structural patterns and unusual metal topologies are of contemporary importance. This is due not only to their intriguing structures and magnetic properties [1, 2], as well as the biological relevance of some of these type of compounds [3, 4]. To date, many structural topologies bearing trinuclear partial cubane, tetranuclear cubane and trigonal-prismatic hexacopper(II) clusters have been synthesided and their magneto-structural trends have been investigated by both experimental and theoretical methods [1, 2]. High-nuclearity clusters of transition metal ions have attracted considerable attention because of the possibility of the occurrence of large number of interacting paramagnetic centres in a single cluster. On the other hand, although a handful of heptanuclear copper(II) clusters are reported, we note that double-cubane-type clusters are the predominant structural topology known [5-8].

Thus it is a great challenge to construct new heptacopper(II) clusters. Because of our interest in biologically useful compounds, for example, as to possess cytotoxic and/or anti-tumoral properties we are much engaged in polinuclear structures with Cu(I/II) and DNA bases-type ligands.

We report here a new example of a heptacopper(II)-7 cluster with adenine, that appears to us an unusual supramolecular, different from the "classical" vertex-sharing double-cubane compounds.

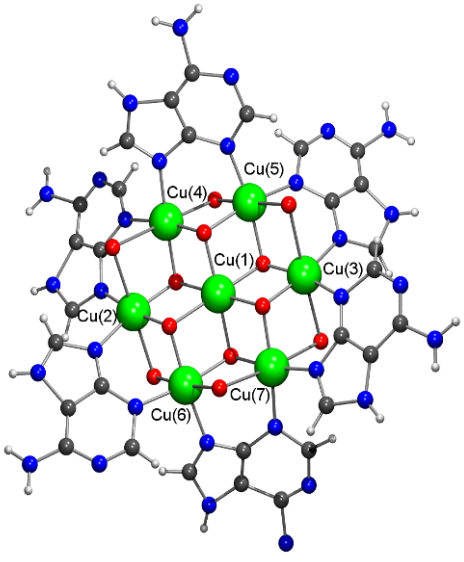

Figure 1 View of the molecular structure of $[Cu_7(\mu_2\text{-}O)_6(\mu_3\text{-}O)_6(adenine)_6](NO_3)_y.xH_2O$. Solvent water molecules and NO_3^- counter ions were omitted for clarity.

The crystalline structure of the heptacopper(II) cluster was determined by X-ray single crystal diffraction. It crystallizes in monoclinic system, *P21* space group, with a = 9.9212(5) Å, b = 24.6150(1) Å, c = 14.9478(7) Å, V = 3634.3(3) $Å^3$ and Z = 2. This compound shows a poli-copper(II) tri-cubane type, with all the copper atom centres linked by bridging μ_3-O and μ_2-O atoms. One of the copper atoms, Cu(1) (see Figure 1) is surrounded by 6 O atoms (Cu-O distances between 1.988(10) Å and 2.131 (11) Å), whereas the remainder copper atoms are N,N-adenine coordinated (Cu-N distances ranging from 1.934(13) to 2.019(14) Å) and 4 bridging oxygen atoms (μ_2-O with Cu-O distances varying from 2.418(11) Å to 2.542(12) Å and μ_3-O with Cu-O bond distances similar to Cu(1)-O). All copper centres, except the central Cu(1), exhibit distorted octahedral coordination with axial elongations due to Jahn–Teller distortion.

The magnetochemical properties of this complex are under evaluation.

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Different crystallization modes of dinuclear copper(II) complexes of an azacryptand containing *1H*-pyrazole units, depending copper salts, solvents and pH

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Pyrazole is a heterocyclic unit that offers different coordination possibilities. In its neutral form behaves as a monodentate ligand towards metal ions and on the other hand , it can donate and or accept hydrogen bonds. In its anionic pyrazolate form, it behaves as a bis(monodentate) or exo(bidentate) ligand towards metal ions while it can behave as a double hydrogen bond acceptor.[1]

This cryptand **L**, has the capability to form [2] bis(□-pyrazolato)-bridged dinuclear complexes with Cu(II) ions. When **L**:Cu(II) molar ratio is 1:2, it forms dinuclear copper complexes $[Cu_2H_{-2}L]^{2+}$ involving two pyrazole units.

In this work, we have used six different Cu(II) salts with different solvents and pH to form the dinuclear complexes. The result shows different crystallization modes.

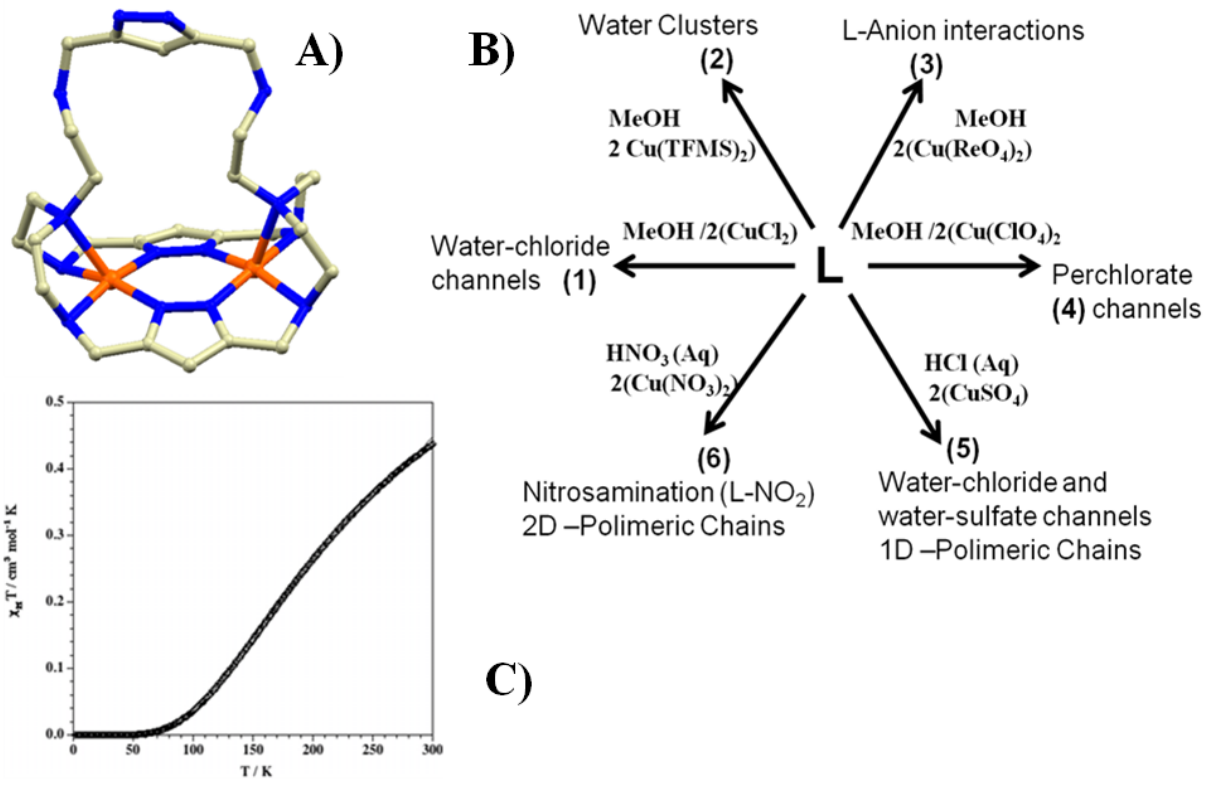

Figure 1: A) Molecular structure of $[Cu_2H_{-2}\mathbf{L}]^{2+}$. B) Cu(II) salts and conditions used. C) Plot of χMT vs. T for the complex **(5).**

The fit of the experimental data to the appropriate susceptibility expression for the complex **(5)** leads to J = -310(5) cm^{-1} and g = 2.08(1). The observed J values lie in the upper range of the magnetic interactions found for related bis(μ-pyrazolato)-bridged dinuclear complexes.[3]

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Design of Co(II) metal - organic frameworks

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In recent years, metal-organic frameworks (MOFs) and other so-called soft materials have received much attention due to their high specific surface area and pore volume. This new class of functional materials that can be rationally constructed by employing the concepts of supramolecular chemistry and crystal engineering [1-3]. The modularity of design strategies, the diversity of prototypal structures, and the dynamic features of networks have afforded great advantages over traditional materials syntheses. The use of rigid and angular organic ligands along with transition metal clusters gives rise to a wide variety of novel metal-organic architectures ranging from zerodimensional nanostructures to three-dimensional frameworks. MOFs materials show peculiar physical-chemical properties (sensing, magnetic, NLO, adsorption of small molecules) and therefore have an immediate practical application (eg. storage H_2) [4,5]. They usually are constituted by anionic or neutral ligands derived from carboxylic acids or amines, to bridge between metal centers. In our project we have designed several complexes and characterized by means of X-ray diffraction (XRD), scanning electron microscopy (SEM), thermogravimetric analysis (TGA) and IR spectroscopy. The compounds reported in Figure 1 and 2 were hydrothermally prepared by reacting in stainless steel autoclave under autogenous pressure at 130°C for 72h, cobalt(II) chloride solution with equimolar amounts of 4-bromobenzoic acid, L, in order to obtain *complex* ***1***, and 4,4'-bipyridine, L', (added as solid) and L, in order to obtain *complex* ***2***.

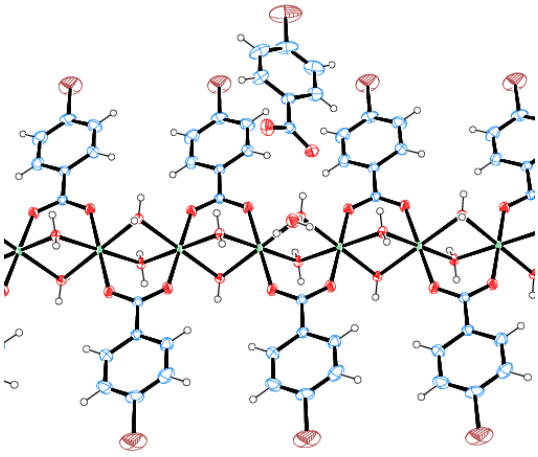

Fig. 1. *The crystal structure of complex* ***1*** *[Monoclinic, C2/c] consists of linear 1D polymeric chain. Cobalt atoms are bridged bonded by 4-bromobenzoic anion and two water molecules. The crystal packing is stabilized by several hydrogen bonding of 4-bromobenzoic anion and water molecules. Co-Co, 3.116(1) Å; Co-O, 1.992(2) Å; Co-Ow, 2.169(3) Å.*

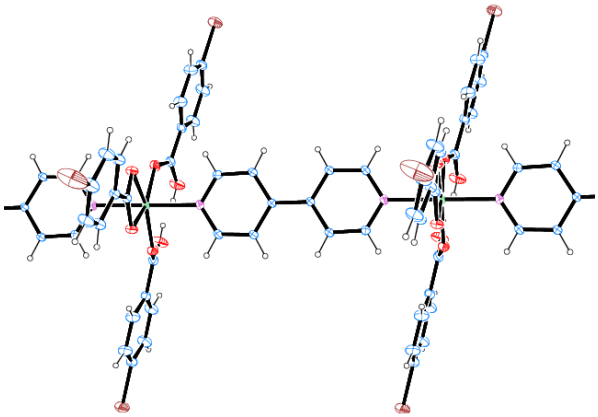

Fig. 2. *The crystal structure of complex* ***2*** *[Monoclinic, C2/c] consists of linear 1D polymeric chain. Cobalt atoms are bonded to the bidentate N,N 4,4'-Bipyrimidine [Co-N, 2.025(3)Å] in a linear arrangement; two monoanionic and a neutral BrPhCOOH completed the exa-coordination of metal atoms [Co-O, 2.023(2) Å, 2.159(2) Å].*

The *complex **2*** was also easily prepared by adding to a boiling solution of L and L' (1:1 ratio) a suitable amount of $CoCl_2$, obtaining a pink insoluble compound.

Infrared analysis. The IR spectra (2000-600 cm^{-1}) of *complex **2*** obtained by both methods were registered, and a perfect overlap of the meaningful frequencies was verified. From this evidence we can deduce the identity of both compounds.

Thermogravimetric analysis. The thermal stability of the samples has been studied in air environment by an heating ramp of 10 °C/min in a temperature range 20-600 °C.

*Complex **1*** – At temperature ranging between 50 and 200 °C the sample (constituted by asymmetric unit $CoLL_2H_2O.H_2O$) starts the decomposition showing a loss in weight of 15.0% (theor. 15.6%) by releasing the bromine present in the no-bounded ligand L. In the temperature range 200-450 °C the sample undergoes an important decomposition, losing a total of 64.5% of its mass. Decomposition stages were identified by using the first derivative curves which are orderly: contemporaneous loss of the no-bounded water and of the second bromine of the linked ligand (34.7%, exper., 33.6% theor.); loss of residual benzoic acid from L (58.1%, exper., 55.8 % theor.); loss of two bounded water (64,5%, exper., 65,1% theor.). In the range 450-530 °C the sample releases the benzoic acid linked to cobalt (exper. 86.6%, theor. 88.5%). The sample weight remains constant at upper temperatures.

*Complex **2*** – In brief, the first decomposition stage ends at 260 °C showing a weight loss of 37.2%, corresponding to the removal of two bromobenzene (theor. 38.6%) in the unit cell $CoLL_2L'$. The sample releases a total of 56.7% from 260 °C up to 350 °C, denoting the loss of the third bromobenzene (57.6% theor.). The mass loss ends at 480 °C and corresponds to a global 76.2% decrease: it is attributed to the losing of the three carboxyl groups linked to Co (74.1% theor.). The complete demolition of the structure occurs at 570 °C with a total mass loss of 89.9%, attributed to the releasing of 4-4' dipyridyl (theor. 92.8%). At upper temperatures no weight change is observed.

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Study of metal cyano "supercomplexes" with a new macrocyclic bipyridinophane

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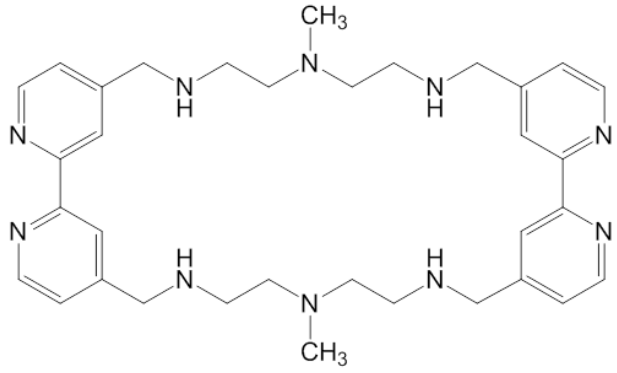
Polyamine macrocyclic ligands have been largely studied as chemosensors. for metal cations, protons, anions and nucleotides. Incorporation of heteroaromatic subunits such as 2,2' bipyridine or 1,10-phenantroline into macrocyclic structures brings together the special complexation properties of macrocycles with the photophysical and photochemical features of the metal complexes formed with these groups. [1-3]

In this work we have synthetized a new polyaza macrocycle (L, scheme 1) containing bipyridine units, where the heteroaromatic nitrogen atoms point outside the macrocyclic cavity. The acid behaviour of the ligand was studied by pH-metric titrations, NMR and UV-Vis techniques. The formation of cyano Fe, Co, Ru and Pt "supercomplexes" was investigated by potentiometric techniques, UV-Vis absorption and emission spectroscopies. The crystal structure of supercomplex L.Ru(CN)$_6$ was also obtained by single crystal X-ray diffraction.



Scheme 1.

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Rotaxanes and catenanes containing units of azamacrocyclic complexes of Cu(II) and Ni(II)

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Motor proteins and synthetic molecular machines belong to interdisciplinary research area on the boundary of supramolecular chemistry, physics and biology. Many of such devices are mechanically-interlocked molecules.[1]

Here, we present the results of our work on the synthesis of new rotaxanes and catenanes, which contain electroactive azamacrocyclic units of Cu(II) and Ni(II) complexes, as centers of π-π interactions.[2] Rotaxanes and catenanes were synthesized by 'classical' methods (**Figure 1, 2**), as well as under thermodynamic control, exploiting the methodology known as dynamic covalent chemistry (**Figure 3**).[3]

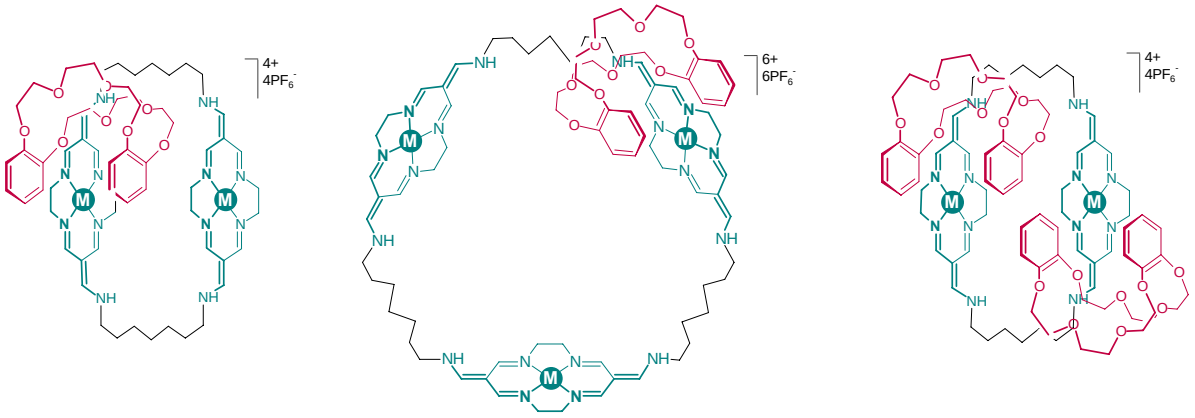

Figure 1. Structure of catenane products of the synthesis of Ni(II) or Cu(II) complex containing macrocycles, carried out in the presence of dibenzo-24-crown-8 (M = Ni^{2+} or Cu^{2+}).

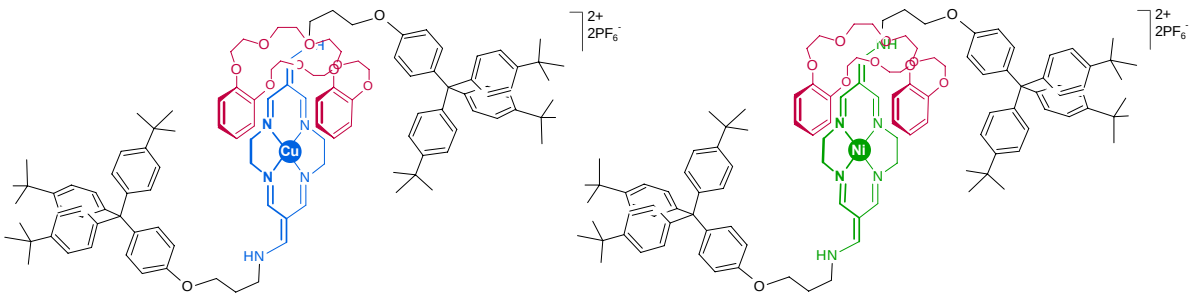

Figure 2. Structure of rotaxane products of the synthesis of Ni(II) or Cu(II) complex containing axis, carried out in the presence of dibenzo-24-crown-8.

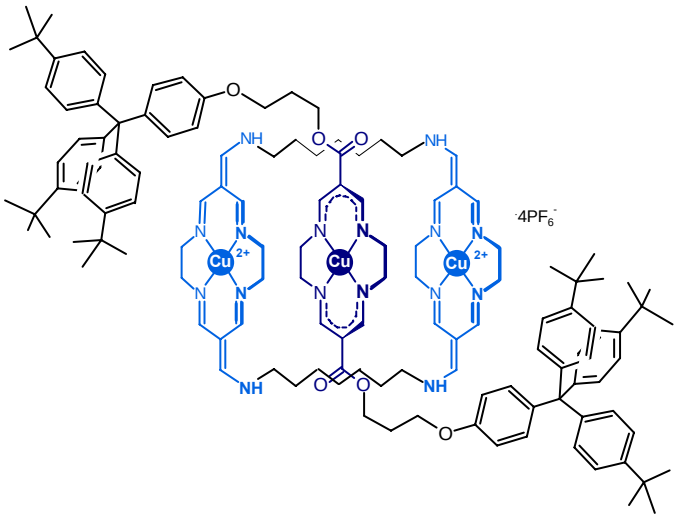

Figure 3. Structure of rotaxane based on π-π interaction between π-acceptor cationic ring and axis containing a unit of neutral Cu(II) complex. Presence of this molecule in the dynamic reaction mixture – containing pure ring, pure axis and catalytic amount of 1,7-heptanediamine – was proven by mass spectroscopy.

The ultimate goal of our research is the design of a model nanodevice – molecular switch, where the process of reversible switching between available translational states, relies on electroactivity of Cu(II) and Ni(II) complexes, and controlled by an electrochemical potential signal. We are also interested in studies on the possibility of building such structures in form of the monolayer self-assembled on the gold surface.[4,5]

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Molecular necklaces containing transition metal ions

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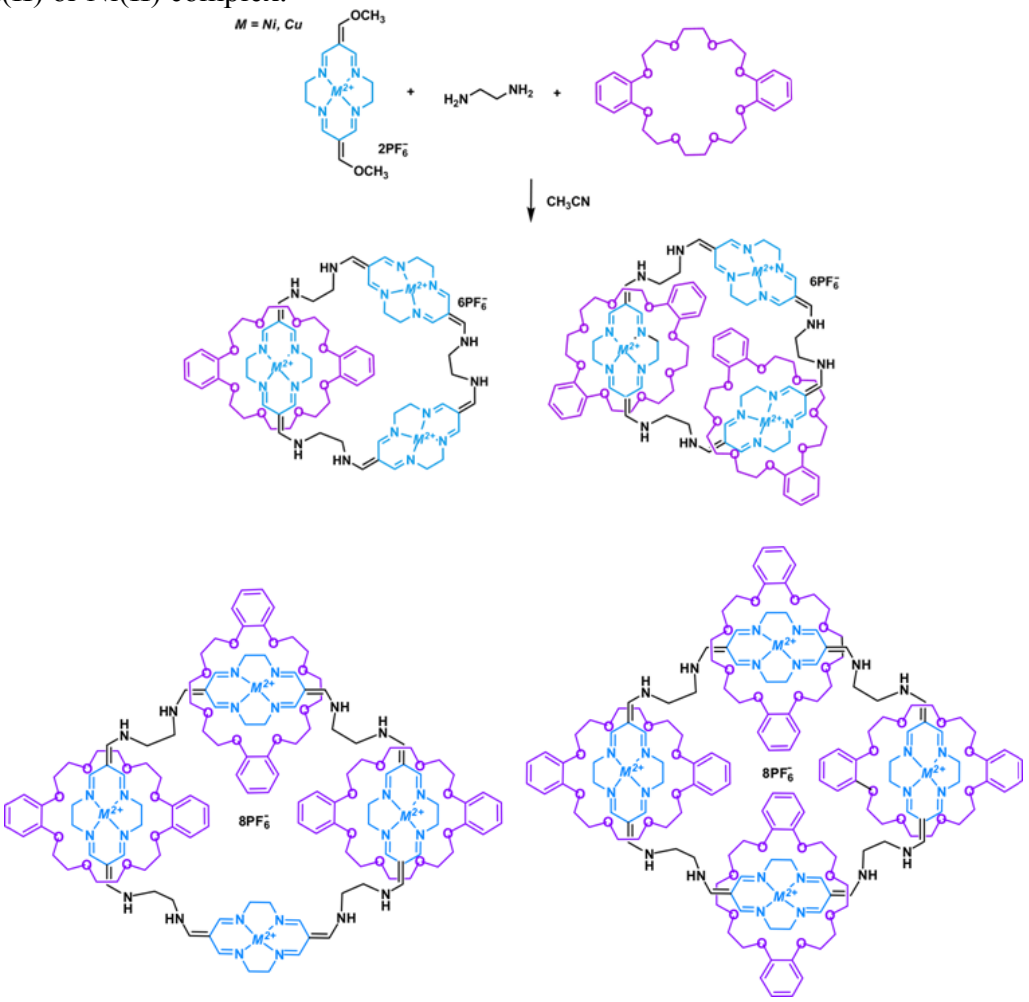
Our study showed that cations built from units of macrocyclic complexes of copper(II) or nickel(II), connected by polymethylene linkers of an appropriate length, form host-guest complexes with electron-rich aromatic molecules.[1] We have exploited this observation in the synthesis of mechanically-interlocked molecules containing above mentioned components.

Self-organization of these systems is possible due to strong π-π interactions between the electron donor, which is the crown ether, and a redox-active ring of electron deficient moieties of Cu(II) or Ni(II) complex.



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Amphiphilic phthalocyanines by three different substituents on each benzo moiety

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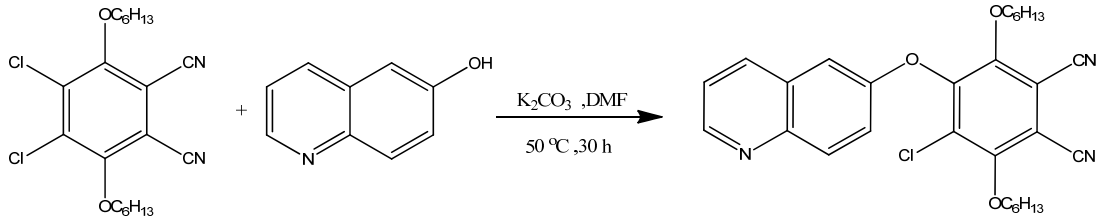
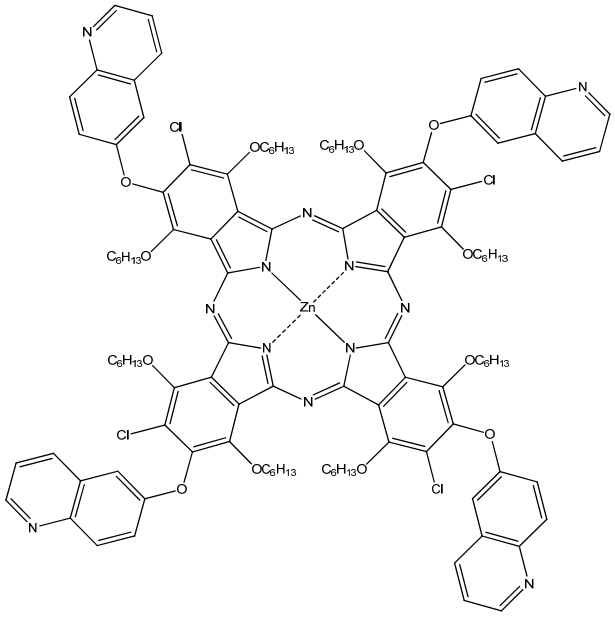
Phthalocyanines (Pcs) and their derivatives are a class of organic functional materials that display interesting catalytic, electronic, and optical properties in addition to their widespread use as blue and green colorants. Due to their fascinating properties, Pc-based materials find applications in a variety of new technological fields such as semiconductor devices, liquid crystals, Langmuir–Blodgett films, sensors, catalysis, and as photosensitizers in photodynamic therapy of cancer (PDT) [1]. However, the use of these materials is limited by their low solubility in common solvents. Additionally, intermolecular aggregation in both solution and solid state causes a drastic decay of their optical properties. In particular, the aggregation behavior of Pcs can greatly affect the photodynamic activity through reducing the active absorbing excited-state lifetime [2,3]. The solubility of phthalocyanines can be improved by introduction of bulky substituents on the peripheral or nonperipheral positions of the molecule by hindering the aggregation of the planar molecules [4,5].

In this work, a new phthalonitrile derivative bearing hexyloxy groups in nonperipheral positions and 6-quinolinoxy and chloro groups in peripheral positions has been synthesized.



The new hexadeca-substituted zinc phthalocyanine with three different substituents on each benzo unit was obtained by cyclotetramerisation of this phthalonitrile derivative in the presence of anhydrous zinc salt $\{Zn(CH_3COO)_2\}$ by microwave irradiation in n-pentanol. The novel compounds have been characterized by using UV-Vis, FT-IR, ^{1}H NMR and MS spectroscopic data.



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Study of the interactions of PyCHO with SDS and CTACl micelles

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A classical procedure for the study of interaction between a receptor and a ligand is measurement of static fluorescence. In the case of ligand having a short lifetime, this procedure gives the binding constant (K) corresponding to the ground state of the ligand.

On the other hand, in the study of reactivity (quenching processes) of ligands in the presence of receptors (SDS and CTACl micelles) it is observed that the trends in reactivity follow the so-called Pseudophase Model. However the binding constant obtained from quenching studies (K_{app}) is different from the binding constant obtained from static fluorescence measurements.
In previous papers [1,2] a treatment was developed which explained quantitatively this difference. Recently, we have extended this treatment, for the case where there are two receptors in the solution (monomers present at concentrations corresponding to c.m.c and micelles). Assuming that the changes between monomers and water are rapid and that the exchange between micelles and water is slow the following equation is obtained for the K_{SV}:

$$K_{SV} = \frac{(K_{SV})_{cmc} + (K_{SV})_b K_{app}[receptor]}{1 + K_{app}[receptor]} \qquad (1)$$

where $(K_{SV})cmc$ is :

$$(K_{SV})_{cmc} = \frac{(K_{SV})_f + (K_{SV})_m \frac{(k_r)_m}{(k_r)_f} K_m^*[cmc]}{1 + (K_{SV})_m \frac{(k_r)_m}{(k_r)_f} K_m^*[cmc]} \qquad (2)$$

(a)

$$K_{app} = K(a_b / a_f) \qquad (b)$$

and (a_b / a_f) :

$$(a_b / a_f) = \frac{(I_{em})_b}{(I_{em})_f} \qquad (3)$$

This treatment was checked calculating K_{SV} from equation 1 and plotting the $(K_{SV})_{calc}[I^-]$ versus (I_0/I)-1 (figure 1). Notice that:

$$K_{SV}[I^-] = (I_0 / I) - 1 \quad (4)$$

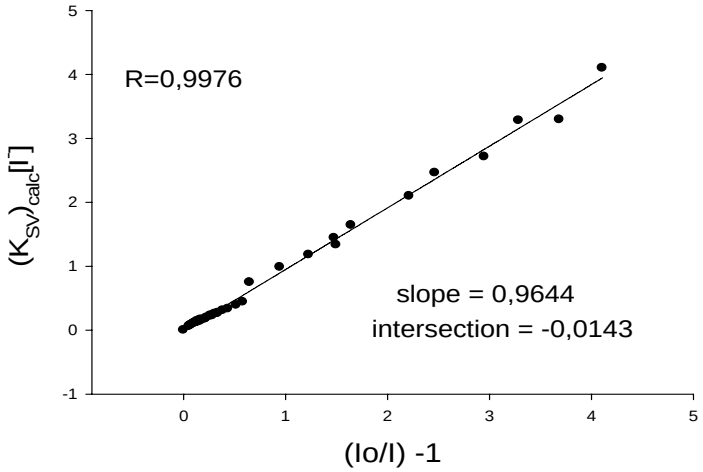

Figure 1. (I_0/I)- 1 versus $(K_{SV})_{calc}[I^-]$

In the case of CTACl micelles, the quencher as well as the fluorofore interact with the micelles. The binding constant for the quencher

$$I^- + M \leftrightarrow I^-/M \quad (5)$$

was obtained following the treatment of Encinas et al. [3].

Once this binding constant for the I^- had been set, the apparent binding constant for the PyCHO was obtained from equation 6:

$$K_{SV} = \frac{(K_{SV})_f + (K_{SV})_b K_{app} K'[M]}{1 + (K_{app} + K')[M] + K_{app} K'[M]^2}$$

once again it is found that $K_{app} = K(a_b / a_f)$.

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Mixed-monolayer gold nanoparticles for targeted MRI: synthesis and characterization

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Nanotechnoloy is the new paradigm in Science. Nanostructures (nanoparticles, quantum dots, carbon nanotubes, fullerenes, graphene, viral capsules) are prone to find many (more) applications in biomedicine. Multifunctional nanostructures allow integrating properties inherent to nanosize with characteristics of biological systems and barriers.[1] Gold nanoparticles (Au NPs) are ideal platforms for developing multifunctional medical imaging agents: consensually accepted biocompatibility; facile preparation; possibility of tuning size, shape and surface properties by changing preparation conditions; detection sensitivity enhancement by reporter clustering. Gold Mixed-Monolayer Nanoparticles (Au MMNPs), containing reporters and targeting epitopes, offer the possibility of integrating multimodal imaging (MRI, X-ray, fluorescence), targeting, and therapy (hyperthermia). Au NPs functionalized with Gd^{3+} chelates are promising Contrast Agents (CA) for Magnetic Resonance Imaging (MRI). Chelate multimerisation can lead to spectacular relaxivities per nanoparticle (high density of relaxivity) despite low relaxivity enhancement per Gd^{3+} chelate. We have reported recently the preparation and characterization of Au NPs functionalized with Gd^{3+} chelates displaying fast water exchange and high stability, as a novel high relaxivity (29 $mM^{-1}.s^{-1}$, 30 MHz, 25 ºC) CA potentially safe for in vivo MRI.[2] Biodistribution and MRI studies in rats revealed that the NPs (~ 3-4 nm diameter) are readily eliminated by renal filtration with very low hepatic up-take. Thus, medical relevant applications, especially tumor imaging, requires decorating the NPs with targeting epitopes. The folic acid receptor is well characterized and its (over)expression profile in normal and in cancer cells is well documented.[3]

The folic acid construct **1** was designed as targeting vector for decorating Au NPs functionalized with Gd(DO3A-*N*-(α-11-mercaptoundecanamido)propionate) chelates (**2**).

In this communication we report the synthesis of folate conjugate **1** and the preparation of Au MMNPs containing folate vectors and Gd^{3+} reporters for MRI.

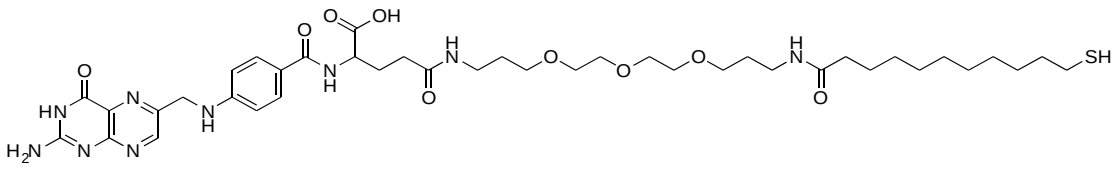

Figure 1: Folate vectors

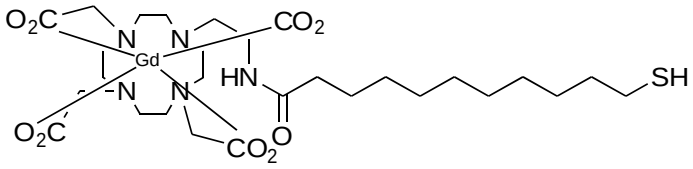

Figure 2: Gd^{3+} chelate

Two different methodologies were studied for preparing MMNP: Brust´s method and the ligand substitution methodology. The Au NPs prepared by both methods were characterized by UV-Vis, DLS, TEM, ICP and by relaxometry. The merits of both methods will be discussed.

Acknowledgements: We thank the support from the F.C.T. Portugal (project PTDC/QUI/70063/2006 "Targeted Nanoconstructs for Multimodal Medical Molecular Imaging". J.Gonçalves thanks the support from the I.N.AB.E, Angola.

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Possible overestimation of the site size in fluorescent dye/nucleic acid systems when using the McGhee and von Hippel equation

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In the analysis of the binding of small molecules (D) to polynucleotides (P) to give a complex PD, the evaluation of the site size (defined as the number of monomer units of the polymer involved in the binding of one dye molecule under conditions of complete saturation) is of primary interest [1]. For such systems, wide use of spectrophotometric and spectrofluorometric measurements is made [1]. In particular, titration data, plotted according to Scatchard representations, are commonly analysed by means of the McGhee and von Hippel equation (1) [2] to evaluate the binding constant (K) and the site-size (n).

$$\frac{r}{[D]} = K\frac{(1-n\times r)^n}{[1-(n-1)\times r]^{n-1}} \qquad (1)$$

In equation (1) $r = [PD]/C_P$ where C_P is the total polymer concentration.

We have performed spectrofluorometric titrations of the intercalating dye of the cyanine family Cyan40 with natural DNA, at different initial dye concentration (C_D). It is found that the McGhee and von Hippel analysis has to be done with care as the very low extent of monomer units occupation obtained with the low dye amounts generally used in fluorescence measurements can yield misleading overestimated results as concerns the site size. This should be a constant parameter characteristic of the analysed system; instead, the apparent value of n estimated by equation (1) is found to depend on C_D with n increasing as the dye loading is decreased (Figure 1).

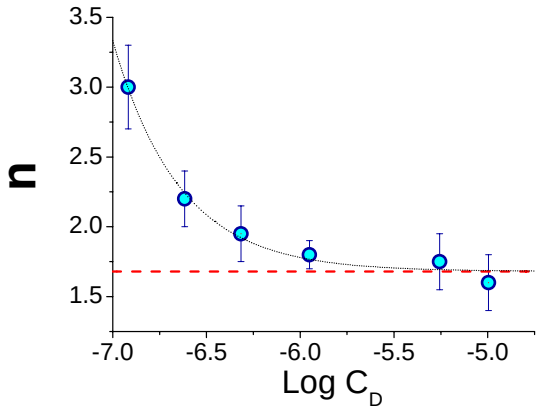

Figure 1: Dependence of the site size, n, on the values of the total dye concentration, C_D, for the Cyan40/DNA system, pH = 7.0, T = 25 °C; (A) I = 2.5×10^{-3} M, (B) I = 1.0 M. The value of the asymptote yields the value of n under complete saturation condition.

The reliability of the analysis can be improved by increasing the polymer saturation, i.e. using considerably higher dye concentrations (tendency to a constant value for the highest C_D in Figure 1). However, under such conditions, positively charged dye self-aggregation on the negative polymer backbone can occur. A method is proposed that, from a set of titrations at different total dye concentration, estimates the parameters K and n, together with the aggregation constant of the dye on the polynucleotide (K_D).

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Complexation abilities of (1-4,18-36)Neuropeptide K toward copper(II) ions and products of metal-catalyzed oxidation

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Tachykinins are bioactive peptides that regulate the functions of many organs and systems. They are mainly synthesized in the nervous system. [1] These peptides are characterized by a C-terminal consensus sequence Phe-X-Gly-Leu-Met-NH_2. [2]

One of the peptide in this family is neuropeptide K (NPK). The primary structure of the NPK was found to be: Asp-Ala-Asp-Ser-Ser-Ile-Glu-Lys-Gln-Val-Ala-Leu-Leu-Lys-Ala-Leu-Tyr-Gly-His-Gly-Gln-Ile-Ser-His-Lys-Arg-His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2. This N-terminally extended form of NPK is present in a high concentration in the brain. [3] NPK functions as a neurotransmitter in the central nervous system of several species. [4]

Copper can also catalyze the production of reactive oxygen species (ROS) such as hydroxyl radicals in the Fenton reaction. [5] ROS would initiate the oxidative damage of many biological targets and can play an important factor in many diseases such as cardiovascular disease, cancer, Parkinson's disease, inflammation, and rheumatoid arthritis.[6]

The interaction of copper(II) ions with the (1-4, 18-36) fragment of NPK and its N-acetylated derivative were studied. To determine the stoichiometry, stability constants and coordination mode of the metal ions in the complexes formed, the potentiometric and spectroscopic (Uv-vis, CD, EPR) and spectrometric (MS) studies were performed. We also determine product of Cu(II)-catalyzed oxidation at physiological pH 7.4.

Copper(II) ions form with (1-4, 18-36) fragment of NPK the CuH_3L, CuH_2L, CuHL complexes in pH 7.4.The CuH_2L complexes dominate with the coordination mode 3N {NH_2, N^-, $2N_{Im}$}. The (1-4, 18-36) fragment of NPK and its N-acetyl derivative may form the polynuclear complexes. These peptides were studied at different from 1:1 to 4:1 metal-to-ligand ratios for the (1-4, 18-36)NPK while only 1:1 for the (1-4, 18-36)NPK because of precipitation.

The acetylated derivative of the fragment of (1-4, 18-36)NPK forms in solution at pH 6-10 (including physiological 7.4 pH) the 4N complex where copper(II) ion is coordinated by two amide and two imidazole of histidine residues nitrogen atoms.

To determine the products of the copper(II)-catalyzed oxidation of (1-4, 18-36)NPK and Ac(1-4, 18-36)NPK the liquid chromatography mass spectrometry method (LC-MS) and the Cu(II)/H2O2 as a model oxidizing system were employed. For the Cu(II)-peptide-H_2O_2 system oxidations of the methionine and histidine residues, and cleavage of the peptide bonds near binding of the copper(II) ions were detected.

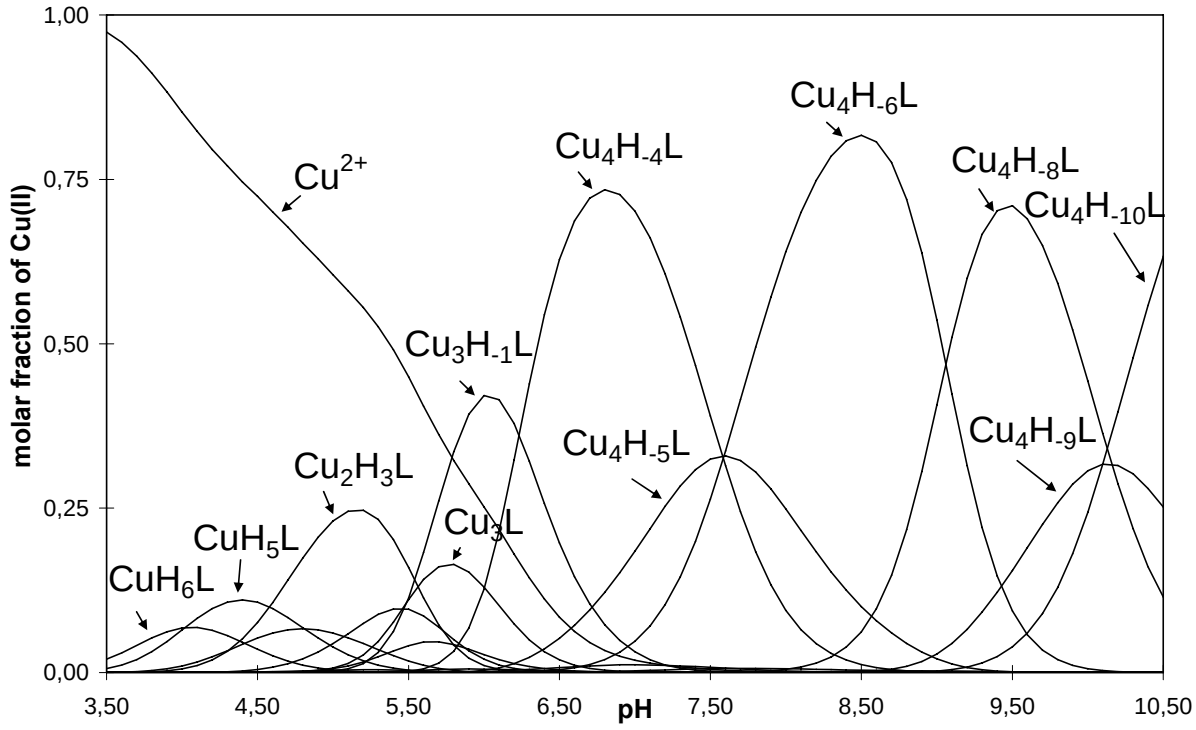

Figure. Species distribution diagram for the Cu^{2+} – (1-4, 18-36)NPK system at the 4:1 metal-to-ligand molar ratio; [Cu(II)] = 0.001 M.

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Monitoring of the Ag complexes interactions with biomolecules: the targets of activity identification

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The origin of the bioactivity of silver compounds is currently unknown; possible ways of their interactions with a cell are speculated on [1]. Moreover, the fact that silver compounds do not destroy mammalian cells, only bacteria, fungi, and some viruses, make them one of the most prospective agents in drug design [1, 2]. Silver complexes have been described as more effective as therapeutic agents than silver salts. These facts have currently aroused considerable interest in the coordination chemistry of Ag complexes with biological or medicinal functionalities [3-5]. It has been reported that complexes of Ag have superior antimicrobial activity when compared to the activities of silver ion and ligand alone. Complexes of silver with various heterocyclic ligands containing S- N- or/and O- donors have exhibited selective antibacterial as well as antifungal activities [1, 3-7]. The biological functions of these complexes have been proven, but their selectivity as well as structural and spatial characteristics have been reported only scarcely.

In presented study we used electronic and vibration circular dichroism measurements along with complementary UV-Vis and IR spectroscopy methods to investigate the structures and the conformations of the Ag complexes with L-, D- amino acids and hydroxy acids in both solution and solid state. Monitoring of their interactions with biomolecular components of bacterial cells and viruses were made to compare with the Ag^+ ions action.

Two ways of the antibiotic actions of Ag complexes were tested: the inactivation of the cell proteins and the inhibition of DNA transcription. Interactions of the Ag complexes with the first possible target of silver antimicrobial action, the thiol groups, were studied in the systems with cysteine, its derivates, enzymes, and proteins. We found that studied complexes with amino acids caused more pronounced changes in structure than alone silver ions. Investigation of the Ag complexes interactions with alone nucleosides and DNA have led us to conclude that Ag complexes were bound preferentially on the DNA bases, not for sugar or phosphate residues, and caused changes of the DNA structure which differ from the changes caused by alone Ag^+ ions.

The second major aim of the study was filling the vacancy of the chiroptical characteristics of the coordination polymers in solutions in comparison with their properties in the crystals structure.

In view of the obtained results, the correlation between chiroptical properties and the certain structure of the studied complexes, their spatial arrangements in solution, and the possible antibacterial properties were investigated.

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Interaction of anticancer ruthenium complex NAMI-A with apo-transferrin

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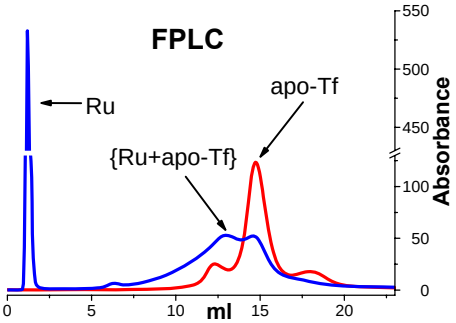
NAMI-A i.e. (ImH)[*trans*-$RuCl_4$(dmso)(Im)] is a novel ruthenium(III) complex with remarkable antimetastatic activity and low general toxicity, that makes this compound incredibly interesting candidate for studies towards elucidation its mechanism of action [1]. Moreover, it was classified for phase II clinical trial [2].

The NAMI-A complex is very unstable at physiological conditions. After intravenous administration NAMI-A undergoes rapid hydrolysis sequentially losing chloride ions and dmso ligand leading to formation various aqua, hydroxo and oxo derivatives [3]. Also in the presence of an ascorbic acid the reduction of ruthenium(III) to ruthenium(II) complexes can occur [3].

The main forms in which this complex occurs in blood are ruthenium adducts with serum blood proteins, mostly with albumin and transferrin (more than 95 %) [1]. The role of these protein adducts remain unknown, but several studies suggest the possibility of using transferrin as a selective ruthenium transporter into cancer cells due the overexpress of transferrin receptors in malignant cells. Apart from that, ca. 70% of transferrin is present in blood as apo-form, which can be used to bind different ions at the same specific sites as iron [4]. Other *in vivo* and *in vitro* studies have shown lower biological activity of ruthenium-protein adducts in comparison to NAMI-A administrated alone [5] and reduction of intracellular uptake of ruthenium in such cases [6]. This can implicate negative influence of binding ruthenium complexes to plasma proteins on its biodistribution and bioavailability.



As our contribution, the binding between apo-transferrin and NAMI-A and its reduced form under physiological like conditions was investigated. The fluorescence spectroscopy was used to determinate the association constants for apo-transferrin-Ru adducts. The FPLC (fast protein liquid chromatography) technique together with ICP-MS (induced coupled plasma mass spectrometry) studies were applied to get information on the stability and extent of formed adducts. The performed studies had shown that apo-transferrin forms stable adducts with NAMI-A and its reduced derivative with association constants ca. 10^4 M^{-1}. Our data also demonstrated that the reaction of Ru(II) derivatives with apo-transferrin is ca. 10 times slower than with the corresponding Ru(III) species.

Acknowledgments

Financial support from the National Science Center (grant no. N N204 247340) is acknowledged. O.M. acknowledges the financial support from the project Interdisciplinary PhD Studies "Molecular sciences for medicine" (co-financed by the European Social Fund within the Human Capital Operational Programme).

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Anticancer Au(III) complexes: synthesis and biological characterization

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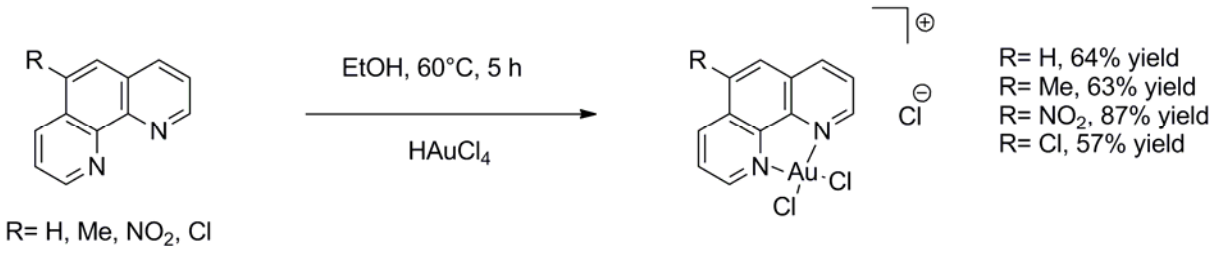
In the last two decades research on the medicinal chemistry of metal-based drug has made remarkable progresses with particular achievements in cancer chemotherapy. In fact, since the discovery of the antitumor activity of cisplatin (*cis*-$[PtCl_2(NH_3)_2]$ [1] a great number of non-platinum metal compounds have been developed with promising anticancer properties.[2]

Recently, gold coordination compounds have been taken into consideration as potential anticancer agents due to their availability with increased stability, and relevant anti-proliferative activities.[3] Indeed, gold compounds constitute a family of very promising experimental agents for cancer treatment as several gold(I) and gold(III) complexes were shown to manifest outstanding anti-proliferative properties *in vitro,* and some of them performed remarkably well even in tumour models *in vivo*. Notably, the peculiar chemical properties of the gold centre impart innovative pharmacological profiles to gold-based drugs most likely in relation to a mechanism of action rather distinct from cisplatin, for which DNA is thought to be the major target after formation of hydrolysed species.[4]

Here, we report on the synthesis of gold (III) complexes with bidentate N-donor phenanthroline ligands (Scheme 1) or tridentate terpyridine ligand. The compounds have been also screened for their cytotoxic properties on cancer cells and as zinc-finger proteins inhibitors. The results are discussed in relation to the compounds, possible mechanism of pharmacological action.



Schemes 1: General synthetic routes for the synthesis of the phenanthroline gold(III) complexes.

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Structure, cytotoxic activity and DNA binding of Pd(II) complexes bearing N'-methyl-1-thiocarbamoyl-3,5-dimethylpyrazole

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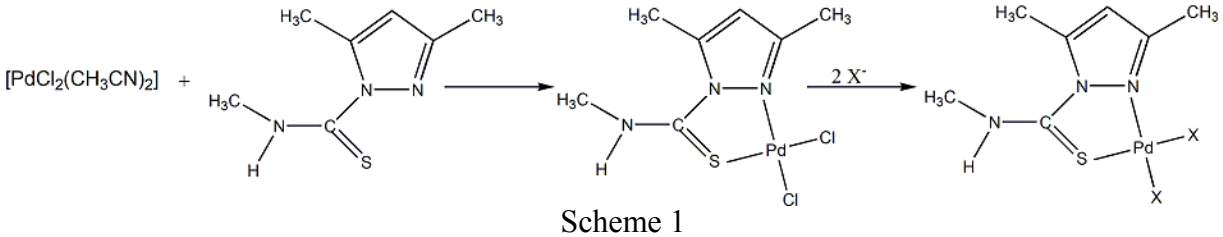
Much attention has been paid to Pd(II) compounds containing *N,S*-chelating 1-thiocarbamoylpyrazolyl ligands due to their promising antitumor activity. In particular, compounds of general formulae [PdX_2(tdmPz)] {X = Cl, Br, I, SCN; tdmPz = 3,5-dimethyl-1-thiocarbamoylpyrazole} showed interesting IC_{50} values in the range 20–30 μM towards some murine mammary adenocarcinoma cell lines [2]. Despite the intensive work in this field, studies involving the interaction of these *N,S*-chelated Pd(II) derivatives with potential pharmacological targets, such as DNA, remain scarce in literature. In the framework of our current research on the coordination and biological chemistry of Pd(II) based compounds, we describe herein the antitumor evaluation and some DNA binding studies on compounds of the type [PdX_2(tmdmPz)] {X = Cl (**1**), Br (**2**), I (**3**), SCN (**4**); tmdmPz = N´-methyl-3,5-dimethyl-1-thiocarbamoylpyrazole}.

Compound **1** is prepared by the displacement of CH_3CN ligands from [$PdCl_2(CH_3CN)_2$] by the tmdmPz (Scheme 1). Compounds **2**–**4** were readily obtained by metathetical reactions of the [$PdCl_2$(tmdmPz)] with salts of the appropriate anions.



Scheme 1

The formation of the *N,S*-chelated products was strongly supported by IR spectroscopic data. Coordination of the pyrazole ring nitrogen to Pd(II) is further suggested by the shift of the νCN_{ring} band (at 1595 cm^{-1}) to higher frequency by 15–25 cm^{-1} upon complexation. The coordination via the thione sulfur atom was suggested by the shift of *ca.* 30 cm^{-1} to lower frequency and decrease of intensity of the νC=S absorption at 800 cm^{-1} (free ligand). Although the overall pattern of the ^{1}H-NMR spectra of the complexes resembled very closely to that of the free ligand, all the signals have been shifted, except those from –NH(CH_3) group. The elemental analysis results are in accordance with the proposed structures. Anal. Obt. (calcd.) for (**1**): % C = 24.47 (24.26), % H = 3.26 (3.20), % N = 11.95 (12.12); (**2**): % C = 20.58 (19.31), % H = 2.61 (2.55), % N = 10.24 (9.65); (**3**): % C = 14.91 (15.88), % H =

2.09 (1.72), % N = 7.31 (7.94); (**4**): % C = 27.78 (27.59), % H = 3.10 (2.83), % N = 17.35 (17.87).

The ability of the complexes to interact with double stranded CT-DNA *in vitro* was verified by UV-Vis spectroscopy. The kinetics of binding was verified by ethanol precipitation method. The content of palladium in the samples was measured by Flameless Atomic Absorption Spectroscopy. The tested complexes were present at the DNA samples after 24 hours of incubation, at 37 ºC, in the dark and following 24 hours of exhausting dialysis in 10 mM $NaClO_4$ solution. However, about 30% of palladium content was again determined in the supernatants after precipitation of the dialysed samples indicating that at least 30% of the content is not covalently bound to DNA.

Cytotoxicity of complexes **1** and **4** was evaluated in human ovarian carcinoma cell lines A2780 and A2780cisR (the latter is resistant to cisplatin), and also in non-carcinoma CHO-K1 (Chinese hamster ovary cells) by colorimetric MTT assay. Cytotoxic effects were expressed as IC_{50}. The results are shown in Table 1:

Table. IC_{50} Mean Values (μM) obtained for palladium complexes (A, D) and cisplatin

compound	A2780	A2780cisR	RF[a]	CHO-K1	TI[b]
1	1.95 ± 0.05	1.7 ± 0.4	0.9	2.3	1.2
4	8.36 ± 0.56	12.1 ± 2.1	1.4	5	0.6
cisplatin	3.1 ± 0.7	15.0 ± 1.0	4.8	14.6 ± 1.4	4.7

[a] RF – Resistance factor, defined as IC_{50} (resistant)/IC_{50} (sensitive).

[b] TI – Therapeutic Index was calculated as a ratio of the IC_{50} normal cells (CHO-K1), to the IC_{50} cancer cells (A2780).

Complex **1** showed good cytotoxic activity towards both ovarian carcinoma cell lines, with IC_{50} values of 1.95 and 1.7 μM for A2780 and A2780cisR cells, respectively. Those values showed to be lower than the IC_{50} values observed for cisplatin towards the same cell lines. Conversely, compound **4** was considerably less active than **1** and cisplatin for A2780 and A2780cisR cells. By the calculations from IC_{50} data, the Resistance Factor of **1** was also lower than the one found for cisplatin (0.9 and 4.8, respectively). However, complexes **1** and **4** were also very active towards non-carcinoma cells CHO-K1, presenting an IC_{50} value of 2.3 and 5 μM, respectively. The Therapeutic Indexes of **1** and **4** were significantly inferior to that found for cisplatin.

In conclusion, this work showed the preparation, antitumor evaluation and some DNA binding experiments involving *N,S*-chelated Pd(II) compounds containing N′-methyl-3,5-dimethyl-1-thiocarbamoylpyrazole. Considering the obtained results, the present study might represent a starting point for development of new active Pd(II) compounds which could overcome cisplatin resistance.

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New copper (I/II) complexes: synthesis, crystal structure and cytotoxic properties

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Coordination compounds have an important role in biochemical/medicinal applications. Their versatility is associated with the possibility of selecting the stereo-electronic properties of the metal centre, by changing the ligand type, the oxidation state and the electronic configuration [1,2].

Cancer is one of the main problems of the modern societies and one of the primary targets of medicinal chemistry. In the last decades, after the great success of *cis*-$[PtCl_2(NH_3)_2]$, *cis*-Pt, as an antitumor agent, the interest in the use of transition metal complexes in medicine has grown rapidly [3]. In particular, the search for new compounds that could overcome cell resistance and toxicity problems associated with 1st and 2nd generation platinum complexes led to an intensive research of new complexes with other metal centres [4-6], such as gold, palladium, ruthenium, rhodium, iridium, molybdenum, iron and copper, with potentially better antitumoral properties.

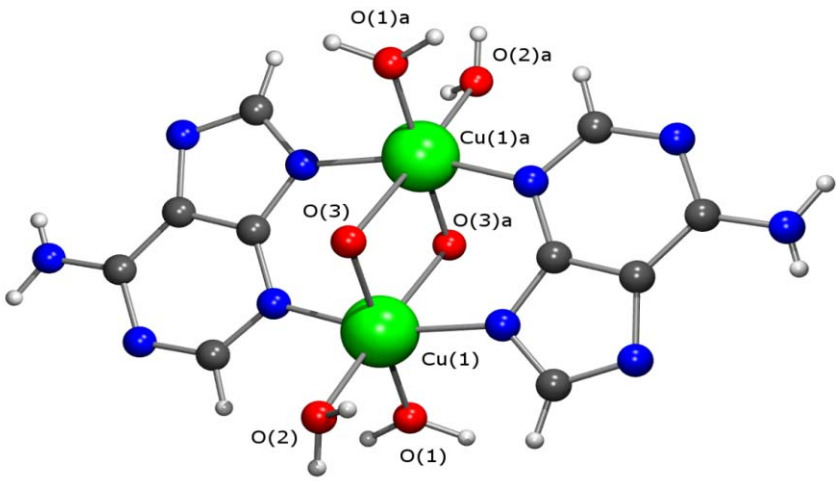

Figure 1: The X-ray structure and atom numbering scheme for complex prepared with adenine.

In this work we synthesized and characterized four new copper(I/II) complexes, coordinated with polypyridyl ligands (biimidazole (bis-Im), 2,2-bypiridine (bpy), 1,10-phenantroline (phen)), and a DNA base (adenine). The new copper complexes have been prepared using two distinct approaches: 1) the standard procedure - that is, synthesis under reflux, and 2) by hydrothermal synthesis. For all the complexes crystals suitable for single crystal X-ray analysis were obtained and their structure were determined (Figure 1). The cytotoxic properties of the referred complexes were also evaluated, using a standard MTT assay against human cell lines, in order to test their capacity for antitumoral applications.

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Vanadium and copper schiff base complexes: evaluation of the interaction with HSA and DNA and its cytoxicity

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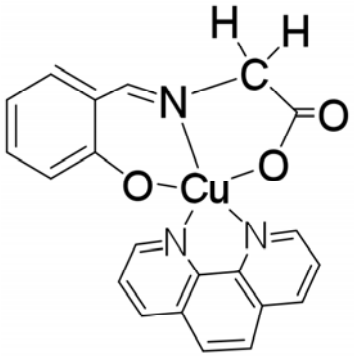
Cancer is still a leading cause of death. Metal-based compounds containing metal ions such as vanadium and copper have been reported with promising chemotherapeutic potential, and which have different mechanisms of action from those of the Platinum based drugs.

We present the evaluation of the interaction of a series of $[Cu^{II}(SB)(NN)]$ and $[V^{IV}O(SB)(NN)]$ complexes [where SB are Schiff bases derived from the reaction of salicylaldehyde and amino acids and NN are 2,2'-bipyridine (bipy) and 1-10-phenanthroline (phen) derivatives] with Human Serum Albumin (HSA) and Calf Thymus DNA. The cytotoxic activity of the complexes against different human cancer cell lines is evaluated and compared.



The interaction of the $[Cu^{II}(SB)(NN)]$ compounds with human serum albumin (HSA) was studied by circular dichroism, EPR and fluorescence spectroscopy. The complexes bind HSA without decomposing, forming $[Cu^{II}(SB)(NN)]_n$-HSA species, n= 1-3, and no evidence was found for Cu^{II}-HSA species, *e.g.* Cu bound to the ATCUN site. The fluorescence emission of the Trp214 residue (both static and dynamic quenching occurs) is strongly affected by the binding of the Cu-compounds. The spectroscopic data of the $[Cu^{II}(SB)(NN)]_n$-HSA species formed is only very slightly affected by addition of Zn^{II}, indicating that the complexes do not bind at the MBS site of HSA. The binding constants for the mixed species $[Cu^{II}(SB)(NN)]_n$-HSA formed are determined and the type of binding is discussed.

Figure 1 includes CD spectra of HSA loaded with $CuCl_2$ and [Cu(Sal-Gly)(phen)]. The binding of Cu^{2+} or [Cu(Sal-Gly)(phen)] to HSA is fast and the CD spectra do not change with time at least up to *ca.* 48 h. The two systems show very different CD spectra in the visible range, indicating that [Cu(Sal-Gly)(phen)] does not hydrolyze and probably binds to HSA maintaining its integrity.

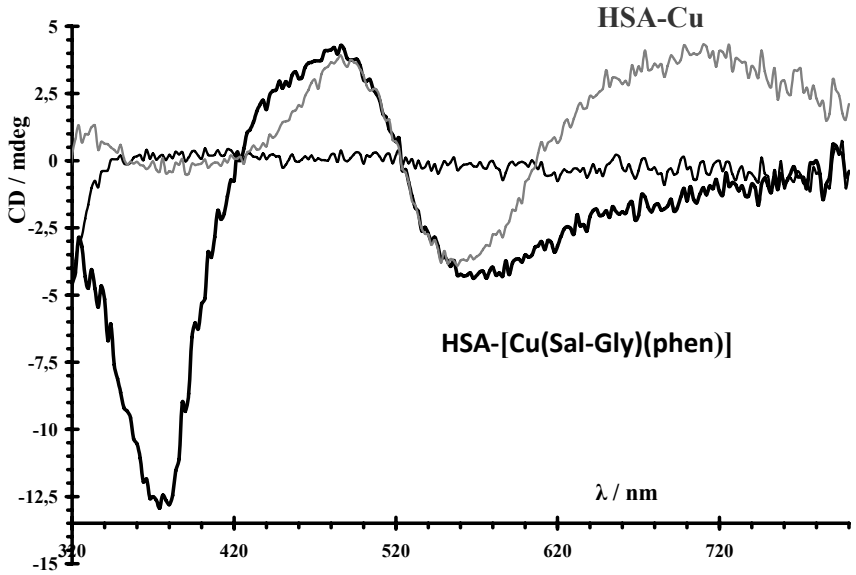


Figure 1. CD spectra of 150 μM HSA loaded with $CuCl_2$ and Cu(Sal-Gly)(phen) in individual samples (2 mole equivalents each), after 24 h of incubation. The measurements were carried out in 5% EtOH PBS buffer (pH=7.4) with a 2 cm optical path cell.

The interaction of $[Cu^{II}(SB)(NN)]$ and $[V^{IV}O(SB)(NN)]$ complexes with Calf Thymus DNA was also studied by CD and UV-Vis spectroscopy (with indication of intercalation of the complex and loss of helicity), as well as with plasmid DNA by gel electrophoresis and atomic force spectroscopy.

The cytotoxic studies showed that globally the Cu^{II}-complexes are much more cytotoxic than the corresponding $V^{IV}O$-compounds. Additionally, the phen containing complexes were found to be much more cytotoxic than those containing bipy, the IC_{50} values being *ca.* one order of magnitude better than the reference drug cisplatinum.

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Interaction between monomers of a double-tailed surfactant derived of the $Ru(bpy)_3^{2+}$ complex, $[Ru(bpy)_2\{bpy(C_{11}H_{23})_2\}]^{2+}$, and different receptors: cyclodextrin and DNA

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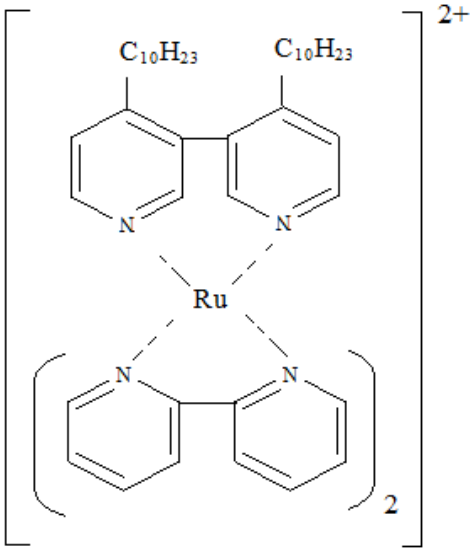
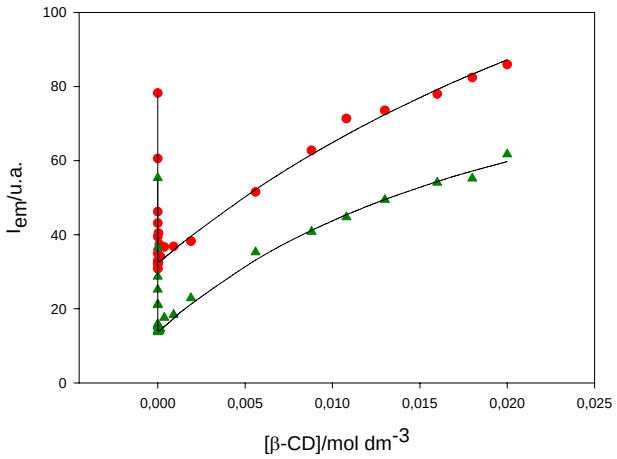
A double-tailed surfactant derived of the $[Ru(bpy)_3]^{2+}$ complex, $[Ru(bpy)_2\{bpy(C_{11}H_{23})_2\}]^{2+}$, has been synthesized. The interaction of this surfactant with different receptors (α-, β- and γ-cyclodextrin and DNA) has been studied. The surfactant forms micellar aggregates from a determined concentration. The addition of cyclodextrin to the solution increases the surfactant's concentration necessary to construct these aggregates. This behaviour confirms the formation of adducts surfactant/CD. Results show the existence of two different types of adducts between the surfactant's monomers and the different cyclodextrins studied. On the other hand, the interaction of the same surfactant with a receptor in which no inclusion happens, DNA, has also been studied. In this case the presence of the surfactant provokes a conformational change in the structure of the DNA due to electrostatic and hydrophobic interactions among the monomers and the polynucleotide. It is demonstrated that the use of several techniques is desirable to obtain reliable and accurate results.





Studies of hydrolytic DNA cleavage activity of $V^{IV}O(acac)_2$

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Studies of synthetic metallonucleases are of great interest and importance: from the most dramatic use as artificial restriction enzymes to great utility as conformational probes and deeper knowledge of the precise function of metal ions in natural nucleases.

When studying artificial nucleases, the mechanism of DNA cleavage is very much of interest. The cleavage reactions generally proceed via two major pathways: (1) oxidative cleavage of DNA involving the sugar and/or guanine base or (2) hydrolytic pathway involving the phosphate group. The latter one is particularly interesting since naturally occurring fission of the nucleic acids by endonucleases is of hydrolytic mode. The vast majority of reported studies on metallonucleases have shown that the predominant mechanism is oxidative cleavage.

Our research has been focused on studying of $V^{IV}O(acac)_2$ and several derivatives as metallonucleases. A very efficient nuclease activity of these complexes has been observed with a special emphasis on the nature of the pH buffer, underlying the remarkable activity in phosphate media in comparison with the "Good" buffers (MOPS, HEPES, Tris or Mes) [1]. This difference in activities has been explained by a scavenging effect of these organic buffers on •OH radicals. The fluorescent studies of $V^{IV}O(acac)_2$ with terephthalate, which in the reaction with •OH radicals gives a single fluorescent product – HTPA, confirmed the formation of •OH radicals which can explain the high cleavage activity of these compounds.

A purely oxidative mechanism would nevertheless not explain completely the nuclease activity of these complexes. Oxidative cleavage requires the presence of an activating agent such as dissolved oxygen. The observed nuclease activity of $V^{IV}O(acac)2$ derivatives is in fact much higher when measured under air, but it is still observed under inert atmosphere. It was hypothesised that in fact a mixed mechanism would take place, and that these complexes will also promote hydrolytic cleavage of DNA.

To confirm this hypothesis, ^{1}H and ^{51}V NMR measurements of $VO(acac)_2$ with DNA model substrates – NPP and BNPP – were carried out [2]. Obtained results have shown signs of hydrolytic cleavage of the phosphodiester but did not confirm the hypothesis because while plasmid DNA is linearized by $V^{IV}O(acac)_2$ following digestion for 1 h at 37 °C, the first sign of hydrolytic cleavage appeared only after 24 h at 50 °C. The results of ^{51}V NMR showed that the species responsible for the hydrolytic cleavage of DNA-model substrates is probably monovanadate. The nature of the buffer medium affects the extent of cleavage significantly.

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Coralyne induces triplex-to-duplex and duplex-to-triplex transitions in ds-RNA according to a temperature controlled cycle

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Over the last few years, non-canonical nucleic acids structures have aroused a great deal of interest due to their involvement in biological processes [1]. In particular, triplex structures have been given paramount importance in therapies based on antigene and antisense strategies [2].

Recently, it has been demonstrated that the fluorescent dye Coralyne, Figure 1, chloride (8-methyl-2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride), favours the formation of the poly(A)•2poly(U) triplex from the poly(A)•poly(U) duplex under suitable temperature and dye-to-polymer (C_D/C_P) conditions [3].

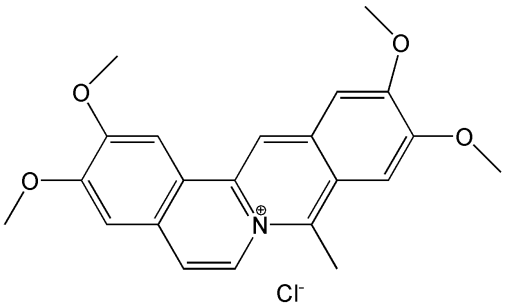

Figure 1.

It has been shown that RNA in the poly(A)•poly(U) form diproportionates at 25 ºC in the presence of Coralyne according to reaction (1), provided that the duplex (AU) is present in excess, i.e., in a [dye]/[polymer] ratio (C_D/C_P) less than 0.8.

$$\text{AUD} + \text{AU} \rightleftharpoons \text{UAUD} + \text{A} \qquad (1)$$

Moreover, melting experiments have shown that, for $C_D/C_P > 0.8$, AUD also disproportionates to triplex and single strands provided that the temperature is raised up to about 40 ºC. In this case, the process is represented by reaction (2):

$$2\ \text{AUD} \rightleftharpoons \text{UAUD} + \text{AD} \qquad (2)$$

In this work, spectrophotometric, calorimetric and kinetic analyses of the poly(A)•2poly(U)/Coralyne system have been carried out, that lend further insights into the Coralyne ability to bring about dramatic changes in the RNA structure. The sets of data

gathered agree to convey that Coralyne also is able to induce the triplex-to-duplex conversion at room temperature, provided that $C_D/C_P > 1$. The results as a whole show that, under excess of dye, the RNA/Coralyne system undergoes a cycle controlled by two key temperatures. At T_2, the duplex disproportionates to triplex, whereas at T_1 ($T_2 > T_1$) the triplex converts to duplex. A cycle operated by a change of the C_D/C_P ratio can also be devised: at low C_D/C_P ratio, the duplex disproportionates to triplex whereas, for $C_D/C_P > 1$, the triplex converts to duplex.

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Synthesis of new ruthenium arene complex, DNA binding properties and in vitro cytotoxicity

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Since the discovery of the anticancer properties of cisplatin in the 1960s by Rosenberg, numerous complexes of platinum (II) are clinically used to this purpose, however, this use is often limited by the high side effects. One future approach has centered around ruthenium complexes because some of them have shown promising anticancer activity and his side effects are minor [1].

First of all, a new imine ligand, L, has been synthesized in order to coordinate to the ruthenium by a condensation reaction between 3-aminoquinoline and 2-pyridinecarboxaldehyde. Later the ruthenium(II) complex, [RuCl(p-cim)L]Cl, has been synthesized from the reaction between $[RuCl_2(p\text{-cimeno})]_2$ and the imine to give a monocationic complex [RuCl(p-cim)(L)]Cl, showed in the figure 1 [1, 2]. The complex has been characterized by NMR spectroscopy, Mass Spectrometry, Elemental Analysis and IR spectroscopy.

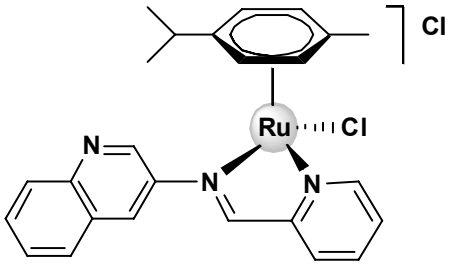

Figure 1. [RuCl(p-cimeno)(κ^2-N,N-L)]Cl, referred to in the text as Ru -Cl.

A stability study of the complex has been carried out. This compound undergoes hydrolyses in water. The hydrolyses decreases in as long as the concentration of sodium chloride is increased, being practically suppressed to ionic strength I = 0.2M. These processes were observed by measures of UV-VIS and of NMR. When the ionic strength is I = 0.2M the Ru-Cl complex is the only species present, whereas in absence of NaCl both the Ru-Cl and the $Ru\text{-}OH_2$ complexes coexist in solution [3, 4].

The results achieved by a number of techniques, namely Ultraviolet–Visible Spectroscopy, Fluorescence Spectroscopy, Circular Dichroism and Viscosity, at different ionic strengths and the absence of interaction at I = 0.2 M (NaCl) revealed that the active derivative is the aqua-complex. The interaction increased when the ionic strength decreased obtaining the highest binding affinity at I = 2.5 mM (NaCaC). The binding constant value, the lack

changes in the DNA contour length and the induced circular dichroism bands let us to conclude that this ruthenium complex interact with CT-DNA by groove-binding [3, 4].

In addition, the in vitro cytotoxicity of this drug has been determined in the human ovarian cancer cell line A2780 by the MTT cell proliferation assay with 96 hours of exposure time. A slightly positive response was observed being the IC50 value of 194 μM.

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The $Ni^{2+}$and Zn^{2+} competition in coordination to unstructured fragment of *Helicobacter's pylori* HypA

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H. pylori is a human pathogen bacteria which cause 90% of duodelnal ulcers and some types of gastric cancers. *H. pylori* produces an assortment of factors in order to adapt to the extremely adverse environment of the stomach [1]. One of them is single H_2-utilizing, membrane-bound hydrogenase enzyme which generates energy for *H.pylori*. HypA, a nickel accessory protein is required for the incorporation of nickel into the hydrogenase large subunit in *H. pylori* cell. It binds a zinc ion in it's structural site – an unstructured loop with two conserved CXXC motifs and nickel ions cannot displace zinc from its binding site [2]. Zinc probably has a structural role in this protein [3]. Our recent findings showed, that Ni^{2+} prefers thiol binding sites over N or O donors [4], with some exceptions (coordination of Ni^{2+} to the Cys-Cys motif) [5]. In this work we try to understand how Zn^{2+} binds to Ac-ELECKDCSHVFKPNALDYGVCEKCHS-NH_2 fragment of HypA protein and why Ni^{2+}, a metal with quite a high affinity towards thiolic sites, doesn't compete with zinc in the binding to this motif. Potentiometric titrations, mass spectrometry, NMR, UV-Vis and CD spectroscopy were used to compare the coordination modes of both metal complexes and to discuss about their thermodynamic stabilities.

Acknowledgments: This work was supported by the Polish State Committee for Scientific Research (N N204 146537).

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Hemoglobin-based copolymers with potential as blood substitutes: increased molecular weight, reduced prooxidant reactivity

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Hemoglobin (Hb) derivatization for blood substitute purposes typically involves multi-step processes, often with a redox reagent such as borohydride (when polymerizing with glutaraldehyde) or periodate – which incurs autooxidation and subsequent side-effects in biological tests [1,2]. Disuccinimidyl suberate (DSS) is a homobifunctional N hydroxysuccinimide ester (NHS-ester) allowing for protein crosslinking agent without toxic side-products and forming peptide bonds with the lysine residues in one single step [3]. Here, we report that Hb polymers were obtained DSS, making this the first report of a single-step polymerization for blood substitutes. The increase in autooxidation rate incurred by this polymerization is completely reversed when BSA is co-polymerized with Hb. In fact, co-polymerization of Hb with BSA appears to be beneficial for alleviating prooxidant effects, regardless of the polymerizing agent employed [4].

Key words: hemoglobin, disuccinimidyl suberate (DSS), blood substitute, oxidative stress

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[15]aneN$_4$S as a potential agent for treatment of cadmium intoxications

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Cadmium (Cd) is one of the most toxic metals. Human exposure to Cd may occur via different routes, including food, cigarette smoking, and occupational scenarios. Efforts to use chelating agents as therapeutic drugs to counteract the toxic effects of metals started in the 1940´s and since then this area has increased considerably. However, until now, none of the chelating agents available in clinic for such intoxications can be considered satisfactory since they present several drawbacks [1]. Searching for more efficient and less toxic chelating agents encouraged us to investigate the possible use of macrocyclic compounds in chelation therapy [2]. In a previous work we have demonstrated the efficacy of a pyridine containing pentaaza macrocycle in protecting human breast cells from Cd(II) cytotoxicty [3].

In this context, the aim of this work was to develop a 15-membered thia-tetraaza macrocycle - [15]aneN$_4$S, as a novel Cd(II) chelator (Fig. 1). Based on a multidisciplinary approach, we report the synthesis, characterization and thermodynamic studies of this compound. To evaluate its metal binding ability towards Cd(II), the stability constants with this metal ion and with some biological essential metal ions were determined. Moreover, we have evaluated the cytoprotective effects of [15]aneN$_4$S against Cd(II) toxicity, in human epithelial mammary cells.

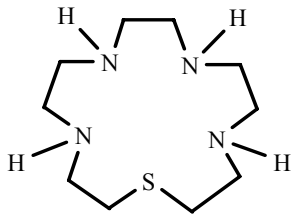

Fig.1 Macrocycle [15]aneN$_4$S.

The synthesis of [15]aneN$_4$S was performed using the high dilution technique which involved the previous esterification of thiodiglycolic acid to its methylic ester, followed by the reaction of the new fragment with triethylenetetraamine. After cyclization, [15]aneN$_4$S was prepared by the reduction of the cyclic diamide with a large excess of diborane in refluxing tetrahydrofuran. The compound was obtained upon purification using chromatographic and recrystallization techniques. The characterization was performed mainly by 1D and 2D NMR spectroscopy.

The acid-base behaviour of [15]aneN$_4$S and the stability constants of their complexes with Ca^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+} were determined by potentiometry using the HYPERQUAD program [4]. The ^{1}H NMR titration of the ligand allowed to understand the protonation sequence and determination of the protonation constants in D_2O, using the HypNMR program [5]. [15]aneN$_4$S presents high values for the two first protonation constants. The third and fourth constants are much lower due to the stronger electrostatic repulsions as they correspond to protonation of N-atoms at short distances from already protonated ones.

Mononuclear species ML, MHL and MLOH complexes were found for the metal ions understudy.

The biological effects of [15]aneN$_4$S were evaluated in MCF10A cells, a human cell line representative of normal-like mammary tissue. There is increasing data supporting an accumulation of Cd(II) in the mammary gland, justifying the usefulness of mammary epithelial cells as an adequate model to study Cd(II) injury and to evaluate the efficacy of novel protective strategies to overcome Cd(II) toxicity. We firstly assessed the cytotoxicity profile of [15]aneN$_4$S, using the MTT assay. This macrocycle, at concentrations of 25, 50 and 100 μM, decreased cell viability to values of ~70% of control cultures (24 h incubation). This moderate level of toxicity can be ascribed to the chelation of metal ions essential to cellular functions. The exposure of MCF10A cells to Cd(II) (75 μM, 24 h) led to a decrease in cell viability to 15%. The macrocycle [15]aneN$_4$S was shown to be very efficient in counteracting this toxicity ($p \leq 0.001$; Fig. 2).

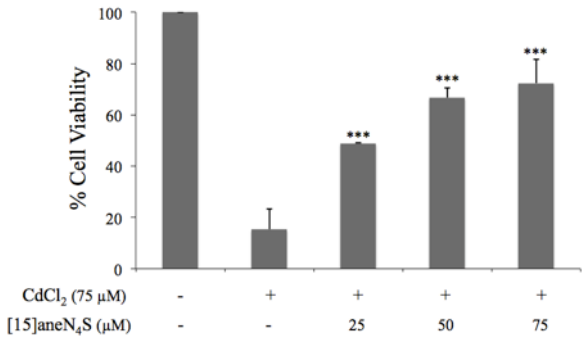

Fig. 2 - Effect of [15]aneN$_4$S on the viability of Cd(II)-treated cells (24 h, MTT assay, ***$p \leq 0.001$).

Overall, these results suggest that [15]aneN$_4$S is an effective protective agent for Cd(II)-induced cytotoxicity in human mammary cells and should be further studied towards a therapeutic application.

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Cytotoxicity of Salinomycin complexes with Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions on leukemia tumor models

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Salinomycinic acid ($C_{42}H_{70}O_{11}$, SalH) is a monocarboxylic polyether ionophorous antibiotic applied as a coccidiostat. Recently, it has been demonstrated that salinomycin effectively kills both cancer stem cells and apoptosis resistant cancer cell [1], selectively targets "CD133+" cell subpopulation and inhibits the malignant traits in colorectal cancer lines [2]. It has been reported that salinomycin elevates the effect of doxorubicin and etoposide in cancer treatment by increasing DNA damage and reducing p21 protein [3]. It has been also suggested that salinomycin may provide a promising approach for lung cancer chemotherapy [4]. In very recent studies it has been demonstrated that this polyether ionophorous antibiotic sensitizers radiation treated cancer cell by inducing G2 arrest [5]. The toxicity of the salinomycin however limits the clinical studies on its potential application as an antitumor drug. The aim of this study was to synthesize metal complexes of salinomycin with improved biological activity. Four novel complexes of salinomycin with Co(II), Ni(II), Cu(II) and Zn(II) were synthesized. The data from the spectroscopic studies have revealed that the novel compounds are of a composition $[M(Sal)_2(H_2O)_2].nH_2O$ (n = 0, 2). The cytotoxic activity of compounds SalH, SalNa, the four novel complexes and the corresponding metal(II) salts was investigated in a panel of three human tumor cell lines after 72 h continuous exposure using MTT test. The coordination compounds of Salinomycin proved to be exceptionally active cytotoxic agents against human leukemic cell lines with nanomolar IC_{50} values. Although some variability in the responsiveness of the different cell lines was detected, the coordination compounds were generally superior cytotoxic agents compared to Salinomycinic acid and sodium Salinomycin.

Acknowledgements: The financial support by *Bulgarian National Foundation for Scientific Research* (Grant № DO-02-84/2008) is acknowledged.

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Ability of Salinomycin and its metal complexes to decrease viability and proliferation of human tumor / non-tumor cell lines

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Salinomycin is a natural polyether ionophorous antibiotic with coccidiostatic and antibacterial properties. It is able to coordinate with alkali metal ions and to transfer them through cell membranes disturbing metal homeostasis and leading to cell death. Recently it was found that Salinomycin is a potential antitumor agent treating breast cancer stem cells. On the other hand we have already reported that this antibiotic binds divalent metal ions to form new complexes with improved antibacterial properties and higher cytotoxicity against leukemia cell lines in comparison to the non-coordinated ligand.

In the present study we report the ability of Salinomycin metal complexes to decrease the viability and proliferation of cultured human permanent cell lines established from the cancers of the breast (MCF-7), uterine cervix (HeLa) and liver (HepG2). The cytotoxicity assays were performed using thiazolyl blue tetrazolium test (MTT); the compounds studied were applied at concentration of 25 μM as solutions in DMSO (0.05%). The cells treated with DMSO served as controls. Generally, the metal complexes studied were found to express stronger cytostatic and cytotoxic properties as compared to Salinomycin (Table 1). The non-tumor cell line of embryonic origin (Lep3) was used for comparative purposes.

Table 1. Viability (%) of treated cell lines (concentration of compounds = 25 μM; DMSO – 0.05%; MTT test, 72 h treatment)

Compound	Lep3	HeLa	MCF-7	HepG2	RST
SalH	12.0 ± 0.3	42.4 ± 1.6	0	0	0.4 ± 0.0
SalNa	13.6 ± 0.4	66.0 ± 6.4	21.8 ± 0.6	1.2 ± 0.0	8.3 ± 0.4
SalK	4.7 ± 0.3	17.4 ± 1.5	5.8 ± 0.1	1.0 ± 0.0	2.4 ± 0.1
SalNi	13.9 ± 1.5	65.3 ± 1.0	4.6 ± 0.0	0	1.2 ± 0.0
SalMn	47.4 ± 1.1	3.9 ± 0.5	0	13.5 ± 0.3	0
SalCo	15.8 ± 0.7	12.6 ± 1.0	0.13 ± 0.0	0.3 ± 0.0	0
SalZn	1.4 ± 0.1	21.5 ± 1.4	10.1 ± 0.2	0.4 ± 0.0	4.0 ± 0.2
SalCu	0	5.4 ± 0.1	0	0	0

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Promising, highly cytotoxic ruthenium-based complexes with bulky triazolopyrimidine ligand: synthesis, structural characterization and antiproliferative activity *in vitro*

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In the development of novel non-platinum metal anticancer drugs with improved properties, ruthenium compounds occupy a prominent position, especially after the introduction of two Ru(III) coordination compounds, [imH]*trans*-[$RuCl_4$(dmso-S)(im)] (NAMI-A); im – imidazole and [indH]*trans*-[$RuCl_4(ind)_2$] (KP1019); ind – indazole, in clinical trials. These two complexes display an activity that is markedly different from that of cisplatin and the other established platinum anticancer chemotherapeutics [1, 2].

Following this research line in the design of compounds with antitumor activity, we have focused on syntheses of novel ruthenium(III) complexes with triazolopyrimidine derivatives. Our previous studies on dichloro platinum(II) compounds with triazolopyrimidines demonstrated that the *in vitro* cytotoxicity of platinum(II) depends on the nature of the heterocyclic ligand [3, 4]. Obtained results suggest that the presence of a bulky ligand (tertbutyl group in heterocyclic ring) might be a major factor in the cytotoxicity of this class of compounds.

Taking into account mentioned fact, in the search for new chemotherapeutic antitumour agents two ruthenium(III) complexes of the type *trans*-[$RuCl_3(dbtp)_2(H_2O)$] **(1)** and *mer*-[$RuCl_3(dbtp)_3]\cdot 2C_3H_6O$ **(2)**, where dbtp is 5,7-ditertbutyl-1,2,4-triazolo[1,5-*a*]pyrimidine, have been synthesized and characterized by IR, MS, UV-Vis, X-ray, magnetic and EPR studies.

Crystal structures of *trans*-[$RuCl_3(dbtp)_2(H_2O)$] (Fig. 1A) and *mer*-[$RuCl_3(dbtp)_3]\cdot 2C_3H_6O$ (Fig. 1B) indicate the octahedral geometry with small distortion due to appearance in coordination sphere bulky ligands. The heterocycle ligand coordinate to ruthenium(III) ion in a monodentate manner through the nitrogen atom in position 3. For **(1)** the triazolopirymidine ligands are in *trans* position and Ru-N(heterocycle) distances are in range 2.074-2.075 Å, whereas the Ru-Cl bond distances being 2.117-2.329Å. Introducing in coordination sphere bulky ligand in the place of water molecule **(2)** resulted in elongation Ru-N(heterocycle) distances (2.085-2.094 Å) and Ru-Cl distances (2.352-2.372 Å).

Cytotoxic *in vitro* studies against two human tumour cell lines (A549 - non-small cell lung carcinoma, T47D - breast carcinoma) and one mice fibroblasts Balb/3t3 were also been evaluated. The results (IC_{50} in the range 0.2948-2.4040 μM) indicate that the *trans*-[$RuCl_3(dbtp)_2(H_2O)$] is almost 35-times more active against T47D, 17-times against Balb3T3 and 5-times against A549 than cisplatin. Additionally, significant antitumor activity against all tumor cells (IC_{50} in the range 0.0594-1.1312 μM) has been exhibited for **(2)**.

The *mer*-$[RuCl_3(dbtp)_3]\cdot 2C_3H_6O$ presents fantastic cytotoxic parameters: 172 times more active against T47D, 28 times more active against Balb3T3 and 10 times against A549 than clinically used cisplatin, cause that this compound is strongly recommended for further *in vivo* studies. In addition, the parameters clearly confirm that presence of bulky heterocycle ligand (dbtp) has a direct influence on the cytotoxicity of ruthenium(III) complexes.

For novel Ru(III) complexes reduction potential based on cyclic voltammetry was also measured and the influence of bulky ligands in Ru(III) coordination sphere on reduction potential value will be discussed.

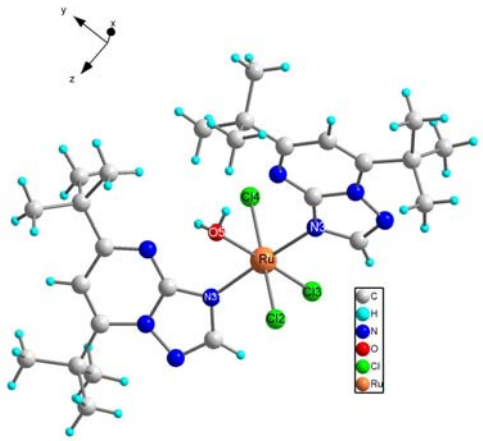
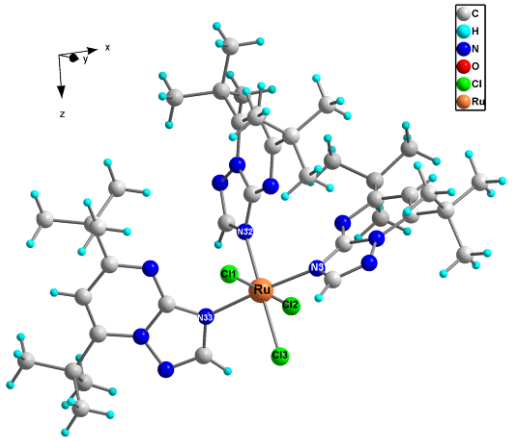
A	**B**
	
Crystal system: orthorhombic **Space group: P2(1)2(1)2(1)**	**Crystal system: monoclicnic** **Space group: P2(1)/c**

Fig.1. *Crystal structure of trans-$[RuCl_3(dbtp)_2(H_2O)]$(A) and mer-$[RuCl_3(dbtp)_3]\cdot 2C_3H_6O$ (B). The acetone molecules of complex are omitted for clarity.*

Acknowledgement

Financial support from National Science Centre (NCN); Grant No DEC-2011/01/N/ST5/02535.

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Hexafluoroglutarate platinum(II) coordination compound with 5,7-ditertbutyl-1,2,4-triazolo[1,5-a]pyrimidine. Structural characterisation and significant *in vitro* cytotoxicity

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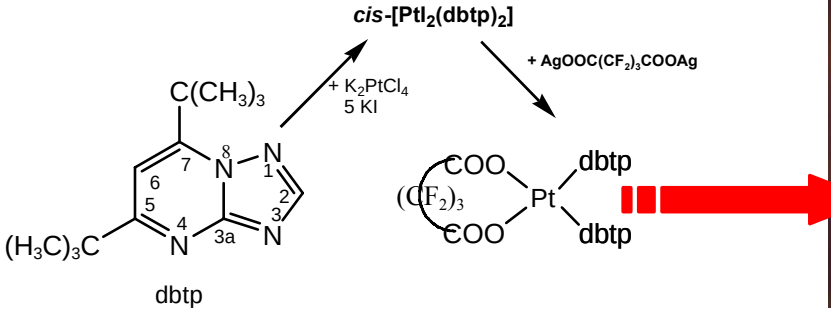
Cisplatin is one of the most commonly used anticancer drugs in the treatment of testicular, ovarian, bladder and head and neck cancer. Despite the great success of treating certain kinds of cancer there are several side-effects. Those clinical inconveniences in the cisplatin chemotherapy prompted to design new platinum compounds to afford novel drugs with improved pharmacological properties and higher antitumor activity [1,2].

Our previously studies based on the dichloro platinum complexes with 1,2,4-triazolo [1,5-*a*]pyrimidine ligands demonstrated that the nature of the alkyl group substituent in heterocyclic ligands directly influence on cytotoxicity. The lowest values of IC_{50} parameters are demonstrated by *cis*-$[PtCl_2(dbtp)_2]$ (6.16, 1.50 μM) (Fig. 2), signify that the presence of a bulky ligand (tertbutyl group in heterocyclic ring) might be a major factor in obtained a good cytostatic. As a continuation of these studies, herein we report results concerning the preparation and structural characterisation of heksafluoroglutarate platinum(II) compound with dbtp (Scheme 1).



Scheme 1. Synthetic pathways leading to the preparation of $[Pt(C_5F_6O_4)(dbtp)_2]$

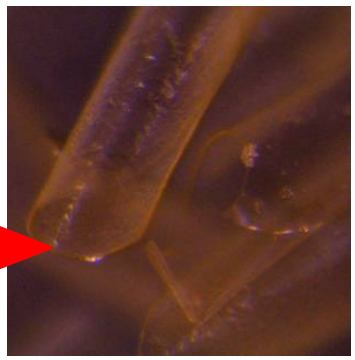


Fig. 1. Unusual tubes structure of $[Pt(C_5F_6O_4)(dbtp)_2]$

The new platinum(II) coordination compound has been characterized by IR and NMR (^1H, ^{13}C, ^{15}N, ^{19}F, ^{195}Pt). ^1H NMR spectrum exhibit singlet at 9.02 ppm from H(2) and 7.39 ppm from H(6). Both signals are deshielding due to coordination of heterocycle ligand (dbtp) to platinum ion. This effect being more expressed for H(2) (0.39 ppm) than H(6) (0.09 ppm). The coordination shifts clearly indicate monodentate coordination of heterocycle ligand via N(3) atom. Chelatation of dicarboxylate anion was confirmed by the infrared spectrum. The value of $\Delta\upsilon_{(COO)}$ ($\upsilon_{as(COO)}$- $\upsilon_{s(COO)}$) for $[Pt(C_5F_6O_4)(dbtp)_2]$ was larger than parameter Δ for hexafluoroglutarate sodium salt.

The antiproliferative activity *in vitro* against two human cell lines A549, T47D and one mice fibroplasts Balb/3t3 show that new complex have 4 or 13-times less values of IC_{50} (1.31,

0.634, 3.19 µM, respectively) than cisplatin (14.43, 7.96, 11.94 µM, respectively). In contrast to hexafluoroglutarate compound, its chloro analogue demonstrated 1 or 10-times lower potencies on the same panel of human tumor cells [3]. On the other hand, $[Pt(C_5F_6O_4)(dmtp)_2]$ was inactive against A549 and T47D, which confirm that prencence of bulky tertbutyl groups has a significant influence on cytotoxic parameters of platinum(II) coordination compounds [4].

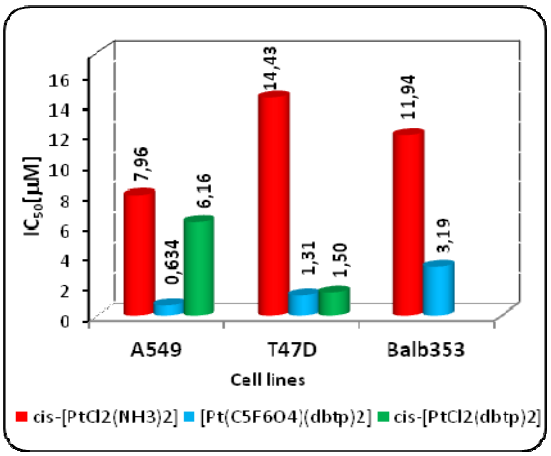


Fig. 2. In vitro cytotoxicity of some platinum(II) coordination compounds

Acknowledgement

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Synthesis, structure and physicochemical properties of Ru(III/II) and Au(III/I) phosphine complexes with pyrazole-based ligands

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The serious side effects of chemotherapeutics such as cisplatin and its derivatives[1] are the principal motivation behind the search for new compounds with better selectivity, fewer side effects and lack of resistance against primary and secondary tumours. Only a few compounds with potential anticancer properties have been found effective in clinical trials. New solutions are therefore being sought among metal complexes like Ru(III)/(II), Au(III)/(I). The interest in ruthenium complexes as potential prodrugs emerges from their features: ligand exchange rate; numerous physiologically available oxidation states; ruthenium's ability to mimic the binding of iron to biological molecules like transferrin or albumin; the octahedral coordination sphere of ruthenium ions; the successful phase I clinical trials of two ruthenium complexes (NAMI-A [2], KP1019 [3]). Gold(III/I) complexes have long been used to treat rheumatoid arthritis. Now, the focus is on the cytotoxic effects of gold(III)/(I) complexes, which readily combine with ligands containing nitrogen, sulphur or phosphorus, rendering gold salts non-toxic.

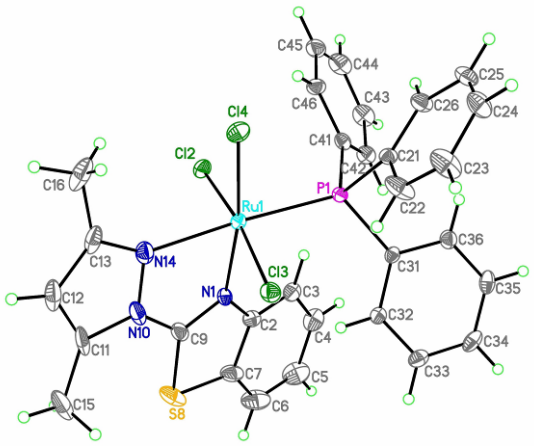

Fig.1 Complex of mer-$RuCl_3(PPh_3)L$, where L – 2-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3-benzothiazole

In our works we have focused on study of of Ru(III/II) and Au(III)/(I) complexes containing one or two types of ligands (except chloride ion) in their coordination sphere: organophosphate and/or N,S-; N,N-donor pyrazole ligands. Pyrazole ligands are interesting because of their cytotoxic effects and their ability to increase the water solubility of these complexes [4].

We have received complexes with formula $RuCl_3(PPh_3)(L)$ (fac and mer (Fig. 1) isomers), $RuCl_2(PPh_3)_2(L)$, $RuCl_3L(OH_2)$ and $AuCl(PR_3)$, $AuCl_3L$, $AuCl(PPh_3)L$ (where L =

N,S-; N,N-donor pyrazole ligands, R = 1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane, 5-(Di-tert-butylphosphino)-1′, 3′, 5′-triphenyl-1′H-[1,4′]bipyrazole, 1-[2-[Bis(tert-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole)).

The structural, spectroscopic properties of the resulting complexes have been characterized using X-ray, elemental composition and spectroscopic methods (FT-IR, ^{1}H, ^{13}C, ^{31}P NMR). Moreover redox properties of all obtained compounds have been identified by cyclic voltammetry. Our studies exhibited that ruthenium(III) and (II) complexes are pseudooctaedral and Au(III) complexes are tetracoordinated in the usual square-planar geometry, whereas the gold(I) exhibit a characteristic P-Au-Cl linear structure.

The cytotoxicity of all compounds has been determined by the MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. In these screening studies all compounds were tested for their cytotoxic properties in K562 (leukemia), HeLa (cervix carcinoma) and normal (HUVEC) cells. As the control (100 % viability in the MTT assay) cells treated with DMSO (1%) were used.

Acknowledgments

The authors wish to acknowledge the Collegium Medicum Nicolaus Copernicus University, Faculty of Pharmacy for financial support grants no 411 and 24/2010.

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Cytotoxicity of vanadocene complexes substituted in cyclopentadienyl rings

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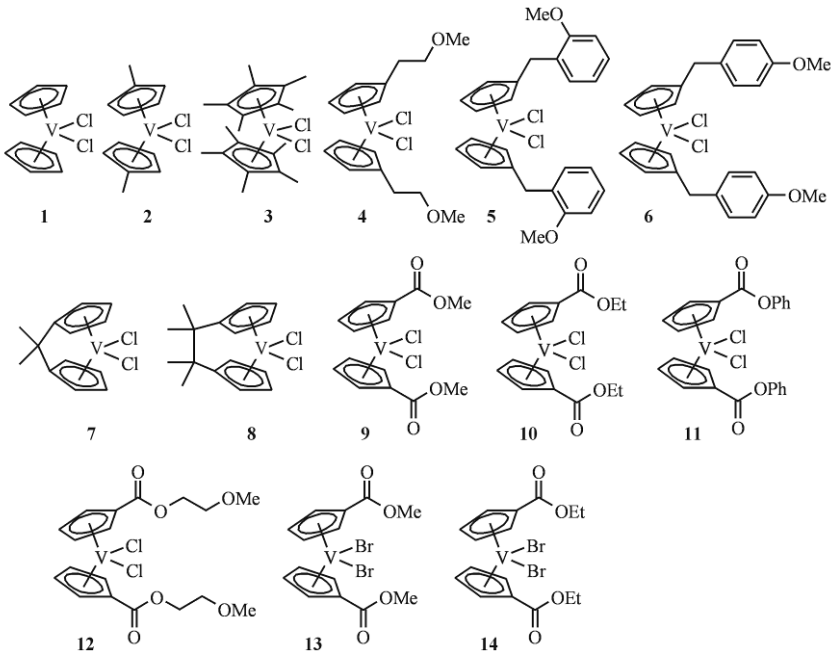
Metallocene complexes (Cp_2MX_2; M = Ti, V, Nb or Mo; X = halide) are studied for their biological activity and catalytic properties. Cytostatic properties of metallocene complexes were discovered by Köpf and Köpf-Maier in 1970s [1]. Further investigation has shown that substitution in the cyclopentadienyl rings can improve their cytostatic properties [2]. The aim of our study is to describe the effect of the substitution in the cyclopentadienyl ring on the activity of vanadocene complexes.



Scheme: Vanadocene complexes under study.

This study includes a series of compounds with alkyl substituents, with substituents containing function groups and with cyclopentadienyl rings connected with *ansa* bridge (see Scheme). Vanadocene complexes were synthesized by reaction of appropriate substituted cyclopentadienide with $VCl_3 \cdot 3THF$ or $V(acac)_3$. This reaction gives monochloride complexes (Cp'_2VCl) those react with PCl_3 to give dichloride complexes (Cp'_2VCl_2). The dibromide

analogues were prepared by reaction dichloride complexes with BBr_3. All prepared compounds were characterized by EPR and infrared spectroscopy. Structures of $(CH_3OCH_2CH_2C_5H_4)_2VCl_2$ (**4**), (o-$CH_3OC_6H_4CH_2C_5H_4)_2VCl_2$ (**5**), $(CH_3)_2C(C_5H_4)_2VCl_2$ (**7**), $(C_5H_4COOC_6H_5)_2VCl_2$ (**11**) and $(C_5H_4COOCH_3)_2VBr_2$ (**13**) were determined by single crystal X-ray diffraction analysis.

Cytotoxic effect of the vanadocene compounds was evaluated on human T-lymphocytic leukemia cells MOLT-4. It was found that vanadocene dichloride (**1**) has IC_{50} value 70 μmol/l. Higher cytotoxicity was observed in case of methoxybenzyl substituted compounds **5** (IC_{50} = 33 μmol/l) and **6** (IC_{50} = 14 μmol/l). The *ansa*-vanadocene compounds **7** and **8** show similar activity as unsubstituted analogue **1**. The alkyl, methoxyethyl and ester-substituted compounds are less active or inactive.

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Organoruthenium binuclear thiosemicarbazone complexes as potential anti-tumor agents

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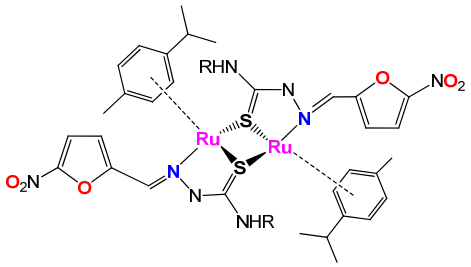
Cancer is the second largest cause of death in developed countries, and according to the World Health Organization predictions the number of worldwide deaths from cancer is projected to rise to over 13.1 million people in 2030 [1]. Statistically, two in every five people born today will be diagnosed with cancer at some stage during their lifetime [1].

The discovery of cisplatin's antitumor activity was a landmark in the field of chemotherapy [2]. To date Pt(II) compounds (Cisplatin, carboplatin and oxaliplatin) still integrate cancer chemotherapy, despite their limited spectra of action, high toxicity and incidence of resistance to treatment, which severely limit their clinical value [3]. The need to overcome these drawbacks and to expand the range of action of metallodrugs has powered the research in the pursuit for alternative and efficient therapies.

Ruthenium complexes have been among the most widely studied non-platinum metallodrug candidates, and hold great potential as alternatives in cancer treatment, affording different mechanisms of action, a different spectrum of activity and the potential to overcome platinum-resistance, as well as lower toxicity [4].

Ru(II) organometallic complexes combining the [Ru(*p*-cym)] moiety (*p*-cym = *para*-cymene) with bioactive nitrofuran thiosemicarbazone ligands were screened for their *in vitro* activity as anti-tumor agents. These compounds are dimeric structures of general formula $[Ru_2(p\text{-cym})_2(L)_2]X_2$, where X = Cl or PF_6, *p*-cym = *para*-cymene and L = thiosemicarbazone ligand derived from 5-nitrofuraldehyde [5].



Both complexes and ligands L were screened for their cytotoxicity against different human cancer cell lines. While the $[Ru_2(p\text{-cym})_2Cl_4]$ precursor was inactive, the thiosemicarbazone-phenyl derivative exhibited an IC_{50} value close to that of cisplatin against human ovarian adenocarcinoma (A2780 cell line). Further, this complex was 3- and 10-fold more active against MCF7 (breast) and the more resistant PC3 (prostate with metastatic potential) human cancer cells (respectively) than the reference metallodrug in clinical use.

As an approach to the pharmacokinetics of these complexes, the interaction with human serum albumin (HSA) for two of them was assessed by spectroscopic techniques (Circular Dichroism, UV-visible absorption and both steady-state and time-resolved Fluorescence). Both complexes bind to HSA with moderate strength and quite fast, an induced CD signal beind observed for short incubation times. For the phenyl derivative, CD and fluorescence spectroscopy results indicate a strong and specific interaction of the complex with HSA, probably involving two different binding sites (the first one located at a distance of ~2.5 nm of Trp214, and the other within the van der Waals radius of Trp214).

The effect of serum proteins on the cytotoxic activity of the most active compound in the human ovarian cancer cell line (A2780) was also addressed.

Overall our results suggest that these Ru-complexes can be transported in the blood stream by albumin, and exhibit quite interesting potential as prospective anti-tumor agents.

Acknowledgements:

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Iron (II) complex that switches from a diamagnetic to a paramagnetic state upon chemical stimulus: an approach towards responsive MRI probes

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One of the challenges in MRI is to develop so called "intelligent probes" able to monitor biological functions or chemical processes in vivo.
We have previously identified two structurally close iron (II) complexes **1** and **2** that are respectively in a low-spin and a high-spin state in aqueous media. The low-spin, diamagnetic complex (LS, **1**) does not modify the MRI signal (« off ») while the high-spin paramagnetic complex (HS, **2**) generates contrast in MRI (« ON »)[1, 2] (cf. figure below).

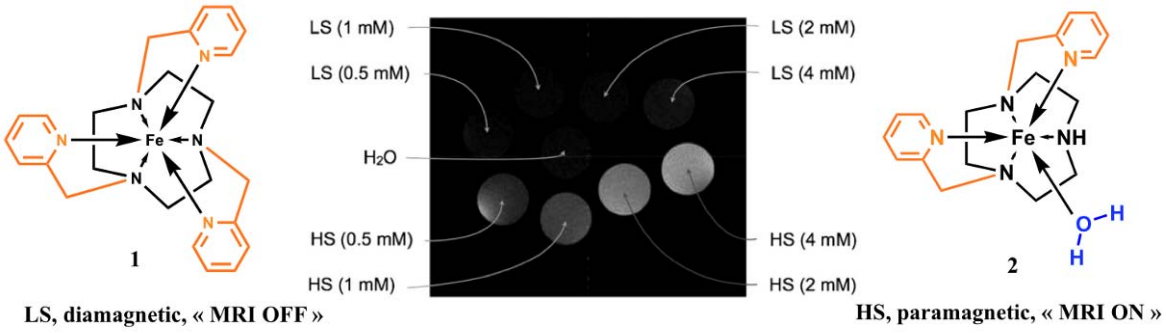
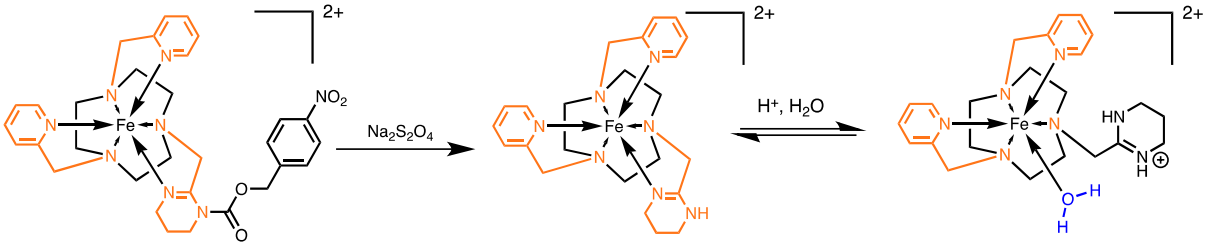


Figure : T1-weighted MR images of tubes containing [Fe(tptacn)]- $[BF4]_2$ (**1**, LS), and $[Fe(dptacn)][BF4]_2$ (**2**, HS), at a series of concentrations (4.0, 2.0, 1.0, 0.5 mM). Reference: tube containing pure water.

Those results led us to work on the design of MRI probes that can switch from the « off » to the « ON » mode upon chemical or biological stimuli by passing from a N6 to a N5O1 coordination pattern.[3] We will present herein our recent results with a probe responsive to a chemical stimulus, the principle being based on the competition between protonation and coordination to the metal center of an amidine moiety (cf. scheme below).[4]



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NO2A-*N*-(α-benzamido)propionate chelators: new leads for stable, fast labelling, targeted agents for ^{68}Ga(III) PET?

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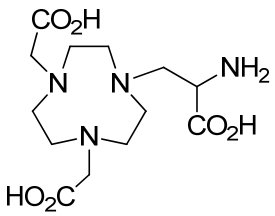
The potential benefits to medicine from ^{68}Ga(III)-based positron emission tomography (PET) is driving the development of chelators and metal complexes that can undergo a wide range of chemical modifications [1]. The Gallium isotope ^{68}Ga(III) is an excellent positron emitter: 89% positron branching accompanied by low photon emission (1077 keV, 3.22 %) [2]. ^{68}Ga(III) half-life, 68 min, is sufficient for the production and application of tracers while minimizing exposure of patients to radiation [3]. Unlike ^{18}F or ^{11}C radiotracers, ^{68}Ga(III) cannot be covalently bound to targeting vectors. Instead, ^{68}Ga(III) must be complexed with chelating agents, either before or after conjugation to targeting vectors. The labelling can be performed immediately before diagnostic examinations, minimizing the loss of activity. Gallium complexes with NOTA and its derivatives, display octahedral coordination, high thermodynamic stability, fast labelling at room temperature and similar stability in plasma and *in vivo* [3].

In this work, we describe synthetic methodologies for the preparation of a new NOTA-type ligand, NO2A-*N*-(α-amino)propionate (**L_1**) and for a model amide conjugate, NO2A-*N*-(α-benzoylamido)propionate (**L_2**) [4, 5].



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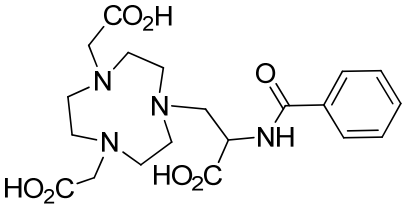

2

The stability of the complexes Ga(**L_1**) and Ga(**L_2**) was evaluated by ^{71}Ga NMR. Radio labelling kinetics with ^{67}Ga(III) was evaluated and optimized and stability studies (transchelation) of the ^{67}Ga complexes were performed. Serum stability and biodistribuition experiments were performed in rats using ^{67}Ga(III) labelled complexes. Preliminary results indicate that amide conjugates of type **L_2** are interesting leads for developing stable, fast labelling, targeted agents for ^{68}Ga(III) PET.

Aknowledgements:

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Synthesis, *in vitro* and *in vivo* characterization of new chelator DO3AAHA and its derivate DO3AAHA$_{PEG750}$

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Over the past years, a wide number of chelators have been synthetized in order to complex a diversity of metal ions useful in medical imaging. DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), is an adequate chelator for Gd(III) and Ga(III) due to the high kinetic and thermodynamic stabilities of the metal complexes [for MRI (magnetic resonance imaging) and PET (positron emission tomography) respectively] [1, 2].

In this work, the DOTA-based chelator DO3AAHA (1,4,7,10-tetraazacyclododecane-1-(6-amino)hexanoic-4,7,10-triacetic acid – Figure 1a) was synthesized and characterized. DO3AAHA acts as a bifunctional chelator due to the pendant free amino group and this group can be easily conjugated to biomolecules such as peptides or anti-bodies [3]. The Gd(III) and Ga(III) complexes of these conjugates preserve the kinetic and thermodynamic stabilities in relation to those of the analogous DOTA chelates.

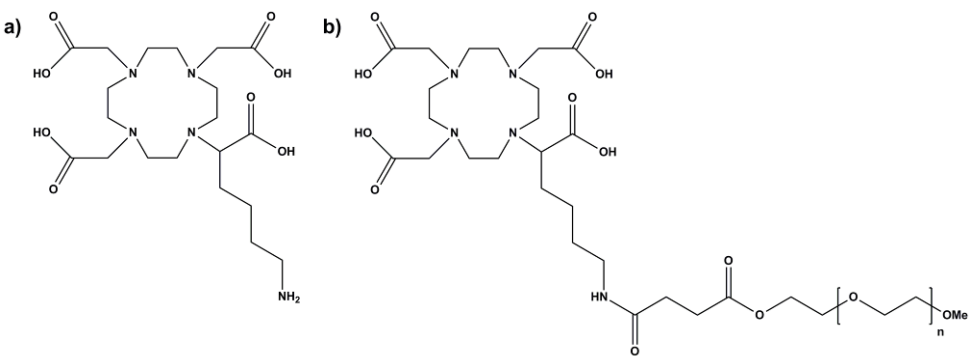

Figure 1 - Structure of a) DO3AAHA and b) DO3AAHA$_{PEG750}$.

In our first attempt to demonstrate the versatility and the advantages of DO3AAHA as a bifunctional chelator, it was attached to an activated PEG (polyethylene glycol) with Mw = 750, which afforded DO3AAHA$_{PEG750}$ (1,4,7,10-tetraazacyclododecane-1-(6-amino(PEG750))hexanoic-4,7,10-triacetic acid – Figure 1b). Adding PEG units to chelating frameworks is known to improve the pharmacokinetic properties of the resulting chelates [4].

The relaxivity (r_1 and r_2) of the Gd(III) chelates of both ligands was measured at 20 MHz at 25 and 37 °C, and it was observed similar values to DOTA [1]. The dependence of $1/T_1$ on the temperature and pH was also studied. The kinetic stability of $[Gd(DO3AAHA)]^-$ was confirmed performing a competition experiment with Zn^{2+}.

The biodistribution and blood clearance studies of the ^{67}Ga-labeled chelates were investigated in Wistar rats, showing that both agents have different *in vivo* behavior.

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Estradiol based indium complexes towards the estrogen receptor

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Cancer is a leading cause of death worldwide. The increasing knowledge of the cellular, molecular and genetic background of tumours has led to the identification of several biomarkers which have been considered as potential targets for *in vivo* molecular imaging and therapeutic purposes [1]. The estrogen receptor (ER), a ligand-inducible transcription factor that belongs to the nuclear receptor super family, is a good candidate for the oriented targeting of cancer cells since it is over-expressed in malignant cells of different etiology. Moreover ER status can predict the disease prognosis or response to hormonal therapy [2]. For these reasons the search for novel ligands to specifically target ER in tumours is a very demanding task.

Radioligands based on gamma- and positron emitting estradiol derivatives have been developed to visualize ER in cancer, however few of them have reached the clinical stage [3]. Although most of the emphasis has been focused on their imaging potential, the simultaneous emission of Auger electrons by radionuclides, as Indium-111 (^{111}In), can offer the possibility for targeted radionuclide therapy application due to their ability to induce DNA damage and cell death when the decay occurs on the nuclear compartment of tumor cells [4]. Therefore one promising approach to radionuclide therapy of ER+ tumors is the use of estradiol derivatives labelled with ^{111}In.

The most frequently applied method of linking a metal ion to a biomolecule is by means of a bifunctional chelating agent, usually a polyamino polycarboxylic ligand that efficiently coordinates the radiometal. Among the chelating agents, the cyclic 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) has been widely utilized since it forms complexes with very high thermodynamic stability and kinetic inertness [5]. However the acyclic ligand diethylenetriaminepentaacetic acid (DTPA) is also a common chelator to coordinate ^{111}In that provides very stable complexes [6].

In this work we describe the synthesis and characterization of a new estradiol derivative substituted at the 16-α position with a DTPA-like chelating ligand through a four-carbon spacer **(I),** as well as the corresponding indium complex. The properties of these compounds and their comparison with the analogous estradiol derivatives based on DOTA (**II**), previously prepared by us, will be also described herein.

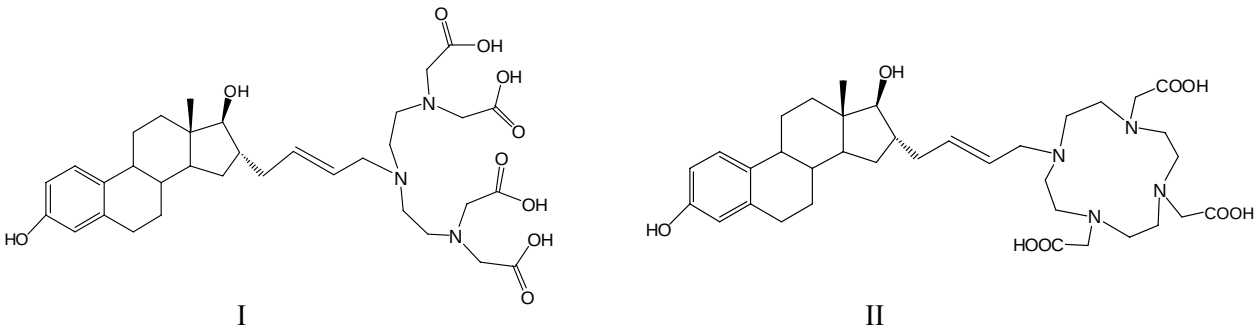

Fig.1 Estradiol derivatives with the chelating agents DTPA (I) and DOTA (II).

Acknowledgements: This work was supported by project PTDC/QUI-QUI/111891/2009.

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Structure-activity relationship studies for flavonol-derived Ru^{II}(arene) anticancer complexes

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Ru^{II}(arene) complexes are considered as promising anticancer agents, capable of overcoming major drawbacks of currently used chemotherapeutics.[1] By linking flavonols to Ru^{II}(arene) moieties (Figure 1), we have developed compounds with high *in vitro* anticancer activity, showing structure-activity relationships with regard to the position and type of substitution of the flavonol ligand, the arene and the leaving group. The compounds are capable of forming covalent bonds to DNA and show inhibition of topoisomerase IIα *in vitro*, which correlates well to the inhibition of cell growth.[2]

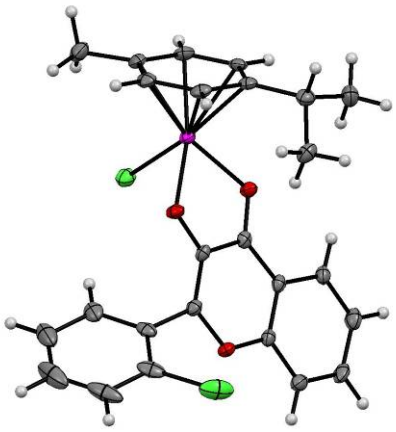

Figure 1

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Mono- and dinuclear platinum(IV) compounds containing an ethylene glycol moiety: synthesis, characterization and cytotoxicity

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Three platinum(II) compounds (cis-, carbo- and oxaliplatin) are the only metal-based drugs in worldwide clinical application against a plenitude of cancer types. Platinum(IV) compounds are well-recognized to act as prodrugs and through activation by reduction they release an active platinum(II) species. As platinum(IV) complexes are kinetically more inert, they show a cytotoxic profile, that can reduce the major drawbacks of platinum(II) drugs, like poor bioavailability, intrinsic or acquired resistance and toxic side effects.[1, 2]

Herein, we report on mono- and dinuclear platinum(IV) compounds that were synthesized in an unsymmetric manner, to yield two different axial ligands, obtained by oxidation with hydrogen peroxide in an appropriate alcohol [3] or by sterical blocking of one hydroxido group.[4] The coupling of platinum(IV) compounds to an ethylene glycol moiety increases the bioavailability. All novel complexes were characterized in detail by elemental analysis, ESI-MS, multinuclear NMR spectroscopy, RP-HPLC and X-ray crystallography. The cytotoxic activity of these metal complexes was investigated *in vitro* in three human cancer cell lines, CH1 (ovarian carcinoma), A549 (non-small-cell lung carcinoma) and SW480 (colon adenocarcinoma), featuring IC_{50} values down to the low micromolar range.

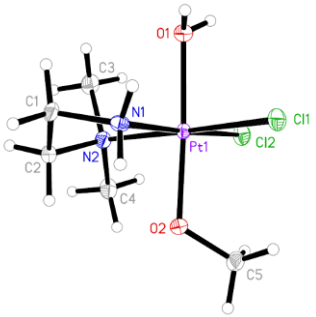

Figure 1: An asymmetric platinum(IV) compound containing an axial aqua and a methoxido group (counter ion TFA omitted).

Acknowledgements

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Tri- and tetraaza macrocyclic complexes of ^{43}Sc, ^{44}Sc and ^{47}Sc radionuclides as precursors of PET diagnosis and therapeutic radiopharmaceuticals

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Three isotopes of scandium ^{43}Sc, ^{44}Sc and ^{47}Sc are perspective radionuclides for application in nuclear medicine for diagnostic imaging and for radionuclide therapy. ^{47}Sc decays with the half-life of 3.35 days and maximum β^- energy of 600 keV and could be an alternative to carrier added ^{177}Lu radionuclide for targeted radionuclide therapy. The others scandium radionuclides, ^{44}Sc ($t_{1/2}$ = 3.92h) and ^{43}Sc ($t_{1/2}$ = 3.89h) are an ideal β^+-emitters in PET diagnosis. They can be used as an alternative to ^{68}Ga, because ^{43}Sc and ^{44}Sc have longer half-life and form stable radiobioconjugates with a structure similar to ^{90}Y and ^{177}Lu, that is important in planning radionuclide therapy.

For complexation of scandium radionuclides macrocyclic ligands having cavity size similar to Sc^{3+} ionic radius were selected: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), 1,4,7-triazacyclononane-1,4,7 triacetic acid (NOTA), 1,4,7-triazacyclodecane-1,4,7 triacetic acid and 1,4,7-triazacycloundecane triacetic acid, and analogs of NOTA with 10, 11 and 12 atoms of the carbon in the ring. Our results have shown that from the macrocyclic ligands studied DOTA is most efficient for binding scandium radionuclides ^{43}Sc, ^{44}Sc and ^{47}Sc to biomolecules. The determined stability constant of Sc-DOTA complex logK=27.0 is comparable with stability constants for Y^{3+} and heaviest lanthanides, but is higher than those for In^{3+} and Ga^{3+}.

The formation of the Sc-NOTA complex is faster than for Sc-DOTA complex. After 10 minutes the equilibrium for Sc-NOTA was reached, while for Sc-DOTA 30 minutes is needed for attaining equilibrium.

Sc-DOTA and Sc-NOTA complexes exhibit high stability in human serum at 37^0C. After 120 hours of incubation in the serum more than 97% of Sc-DOTA remains in solution. In 0.01M PBS buffer Sc-DOTA is stable, but in the case of Sc-NOTA, Sc-10 ane, Sc-11ane and Sc-12 ane complexes phosphates exchange ligands in first coordination sphere.

The ^{13}C NMR studies have shown that Sc-DOTA like Lu-DOTA forms in solution complexes with eight coordination geometry.

The obtained ^{43}Sc, ^{44}Sc and ^{47}Sc radionuclides were used for labeling the DOTATATE bioconjugate. Various concentration of DOTATATE were investigated in order to evaluate usability of the obtained Sc for labeling biomolecules. The results are presented in Table 1.

Table 1 - Efficiency of labeling the DOTATATE bioconjugate with ^{43}Sc, ^{44}Sc and ^{47}Sc radionuclides.

^{43}Sc (2 MBq)		^{44}Sc (3 MBq)		^{47}Sc (1 MBq)	
Amount of DOTATE (nmol)	Yield of labelling [%]	Amount of DOTATE [nmol]	Yield of labelling [%]	Amount of DOTATE [nmol]	Yield of labelling [%]
-	-	10	98.2	22.5	79.4
15	99.2	25	99.5	36	96.2
25	98.9	38	98.3	58.5	97.3

The high yield of labelling DOTATATE with ^{43}Sc, ^{44}Sc and ^{47}Sc was achieved. In the case of ^{44}Sc and ^{43}Sc the labeling yield exceeded 98% for all amounts of the bioconjugate.

The lipophilicity of obtained Sc-DOTATATE conjugates are nearly identical to that of Lu-DOTATATE, which suggests similar receptor affinity of both radioconjugates, while ^{68}Ga is more hydrophilic.

In conclusion, the ^{43}Sc and ^{44}Sc radionuclides can be used instead of ^{68}Ga in PET diagnosis. ^{43}Sc and ^{44}Sc have better nuclear properties, a longer half-life and form stable radiobioconjugates with a structure similar to that of ^{90}Y and ^{177}Lu, which is important when planning radionuclide therapy. Moreover, being a low energy and carrier free β^- emitter, ^{47}Sc appears to be an alternative to the carrier-containing ^{177}Lu radionuclide for targeted radionuclide therapy.

New studies of novel active platinum iodido complexes

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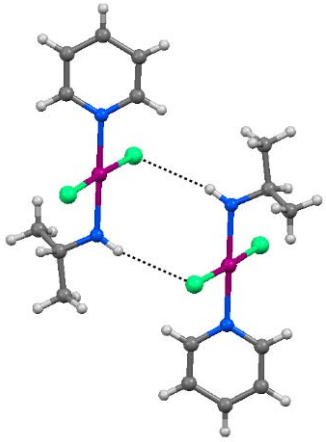
Antitumor metalodrugs research is moving towards the developing of novel drugs which can overcome their actual side effects and the acquired resistance. Our laboratory is one of the main contributor to the *trans* platinum complexes research, and is special interested in the understanding of the mechanism of action of drugs based in platinum complexes [1]. We have studied many aspects of active platinum complexes with aliphatic amines in *trans* configuration [2]. One of the latest discoveries was the impact of the leaving group in the reactivity and citotoxicity of the iodido complexes [3,4].



In this presentation we will show our latest results achieved with the synthesis of novel iodido complexes of the general formulae *trans*-[PtI_2(amine)(amine´)] where amine' is aliphatic amines and/or planar amines. Their cytotoxicity values have been also evaluated in a broad panel of cell lines. Moreover, we will include some previous results from the interaction studies with biomolecules, and we will also analyze those results with some examples of the dichlorido complexes synthesized previously by our group of research.

Acknowledgment: financial support is acknowledged to the Spanish Ministry MICINN (SAF-2009-09431 and Acción integrada PRI-AIBPT-2011-0980) and COST CM1105.

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Cytotoxicity and plasmid DNA cleavage of three vanadyl(IV) complexes containing the oxodiacetate ligand on a human osteosarcoma cell line in culture

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Strong chelating ligands are important because they offer the opportunity of trapping different metal species [1]. In living systems different metals are acquired, transported and stored mostly by low-molecular weight compounds involving multidentate oxygen donors from carboxylate, hydroxamate and catecholate ligands [1, 2]. Among the family of multidentate oxygen donor species, oda= oxodiacetate, $O(CH_2COO^-)_2$, stands as a versatile complexing agent. Oda holds an OOO donor set and can complex metal ions by forming chelate rings. On the other hand, vanadium is a transition element broadly distributed in nature in trace amounts [3]. Concerning animals and human beings, vanadium compounds, once absorbed, are retained mainly in bones [4]. Besides, it has been reported that vanadium derivatives are potentially useful drugs from a pharmacological point of view. In fact, they display potential therapeutic applications as insulin mimics, antineoplastic drugs [5-6] and osteogenic effects have also been reported [7, 8]. In particular, we are very interested in the antitumoral actions of alternative non-platinum compounds such as vanadium derivatives to provide a broad source of compounds worthy to be tested for alternative cancer treatments in a near future. Some vanadium compounds have shown deleterious effects on tumoral cell proliferation and differentiation as well as on cellular morphology [9]. This antitumoral action seems to be mediated through different mechanisms such as the generation of oxidative stress [10] as well as their interaction with DNA [6] which supports at least in part the antiproliferative effects of vanadium compounds.

In this work we report the biological effects of three interesting complexes of vanadyl(IV) cation with oda **$VO(oda)(H_2O)_2$,** oda and ophen = *o*-phenanthroline **$[VO(oda)(ophen)]\cdot 1.5H_2O$,** and oda and 2,2´-bipyridine **$[VO(oda)(bipy)].2H_2O$**, on the tumoral osteoblastic cell line; MG-63 (osteosarcoma derived from human bone). The effects on cell proliferation (crystal violet bioassay), cytotoxicity investigation through the determination of the effects on mitochondrial activity (MTT bioassay) and lysosomal activity (neutral red uptake) as well as on cell morphology (Giemsa staining and light microscopy), were investigated. Besides, we studied the mechanisms involved in the cyto- and genotoxicity (oxidative stress and DNA cleavage). **$[VO(oda)(ophen)]\cdot 1.5H_2O$** caused an inhibitory effect

on cell proliferation in the range of 50-100 μM with a stronger effect than [**VO(oda)(bipy)].2H$_2$O** and **VO(oda)(H$_2$O)$_2$** (ca 40%, 70%, 80% of survival, respectively). Moreover, they altered the lysosomal and mitochondria metabolisms with similar results to those of the proliferation assay ($p< 0.001$).

Morphological studies showed important transformations and a decrease in the number of cells in a dose response manner. Besides, **[VO(oda)(ophen)]·1.5H$_2$O** and **VO(oda)(H$_2$O)$_2$** interacted with plasmidic DNA (pA1) causing single and double strand cleavage with a stronger effect by **[VO(oda)(ophen)]·1.5H$_2$O** than **VO(oda)(H$_2$O)$_2$**. Currently, the cleavage effect of [**VO(oda)(bipy)]·2H$_2$O** is under investigation. Besides, **[VO(oda)(ophen)]·1.5H$_2$O** increased the level of Reactive Oxigen Species (ROS) over 300% the basal unlike the low level observed in **VO(oda)(H$_2$O)$_2$** and [**VO(oda)(bipy)] 2H$_2$O** ($p<0.001$).

Altogether, these results suggest that the complex **[VO(oda)(ophen)]·1.5H$_2$O** is a better candidate to be further evaluated for alternative therapeutics in cancer treatment.

In this context it is also interesting to mention that some other oxovanadium(IV) complexes containing *o*-phenanthroline or substituted *o*-phenanthrolines as ligands show interesting antitumoral activity *in vitro* and *in vivo* [11].

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Pyrazolyl-diamine Pt(II) complexes bearing DNA-intercalating moieties: Synthesis, characterization and *in vitro* evaluation

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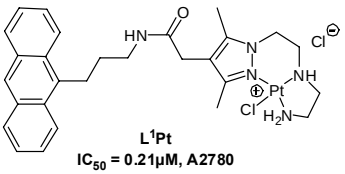
Cisplatin has a central role in cancer chemotherapy being a platinum-based anticancer drug with antitumor activity widely used. [1,2] Although cisplatin can induce apoptosis selectively in cancer cells through binding to DNA, the drug undergoes many non-selective reactions. Furthermore, the drug is rapidly distributed throughout the whole body upon administration, interacting with both healthy and cancerous tissue. [3] As a consequence, the treatment is limited by side effects. [1] Fight against toxicity and drug resistance led to the development of new and selective anti-tumoral platinum compounds. The incorporation of a functional group into the platinum complex that will interact or intercalate with DNA may increase the rate and extent of localisation of the platinum in the vicinity of its target, DNA, thereby decreasing the number of side reactions. [4,5]

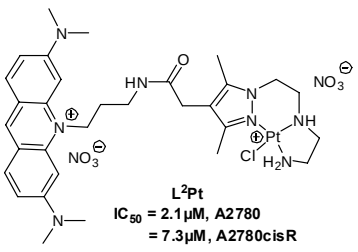
Previously, our group reported a small series of Pt(II) complexes with bidentate (pz*N) and tridentate (pz*NN) pyrazolylalkylamine chelators.[6] In the particular case of monochlorido Pt(II) complexes with tridentate pyrazolyl-diamine (pz*NN) ligands, DNA interaction studies showed that these complexes form monofunctional adducts and, consistently, they are less active than cisplatin on the ovarian carcinoma A2780 cell line. Nevertheless, their activity in the cisplatin-resistant A2780cisR cell line is significantly retained and, therefore, they presented a lower resistance factor when compared to cisplatin.[6]

These finding led us to extend the studies to related pyrazolyl-diamine Pt(II) complexes functionalized with planar and aromatic DNA-intercalating groups. In this way, we expected to obtain compounds displaying an enhanced cytotoxicity due to synergistic effects between platination and intercalation of DNA.



L[1]Pt
IC_{50} = 0.21μM, A2780
= 0.63μM, A2780cisR

In this communication, we will report on the synthesis, characterization an in vitro evaluation of new $[Pt(pz*NN)Cl]^{n+}$ complexes anchored by pyrazolyl-diamine ligands bearing anthracenyl (**L[1]Pt**) or acridine orange (AO) groups (**L[2]Pt**) for DNA intercalation. The *in vitro* evaluation of these new complexes comprised the following



L[2]Pt
IC_{50} = 2.1μM, A2780
= 7.3μM, A2780cisR

studies: i) cytotoxicity against cisplatin-sensitive and cisplatin-resistant human ovarian cancer cell lines (A2780 and A2780cisR, respectively); ii) interaction with supercoiled DNA by checking their ability to modify the electrophoretic mobility of the covalently closed circular (ccc) and open circular (oc) forms of ϕX174 plasmid DNA; iii) cell and nuclear uptake by measurement of the Pt content using the ICP-MS technique. For the AO-containing Pt(II) complex, its cellular uptake in the A2780 cell line was also followed by fluorescence microscopy, taking advantage of the fluorescence emission characteristics of the AO unit.

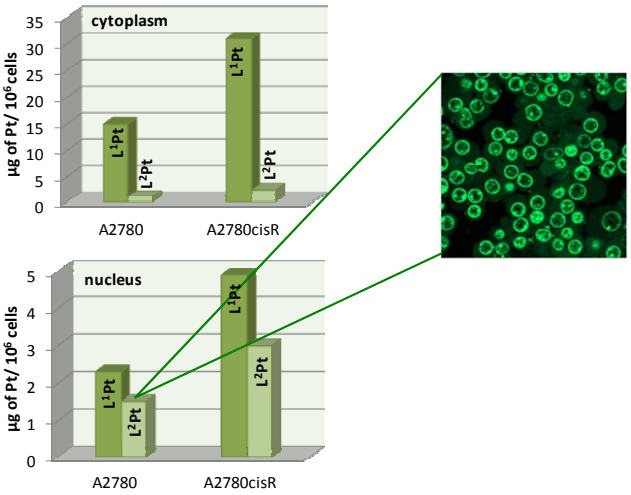


Figure 1– Cell and nuclear uptake of **L^1Pt** and **L^2Pt** in the A2780 and A2780 cisR cancer cell lines after 3h of incubation, with an insert of the confocal fluorescence microscopy images of A2780 cells upon exposure to **L^2Pt**.

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Copper(II) complexes of histidine containing peptides as models of the Cu,Zn-SOD enzyme

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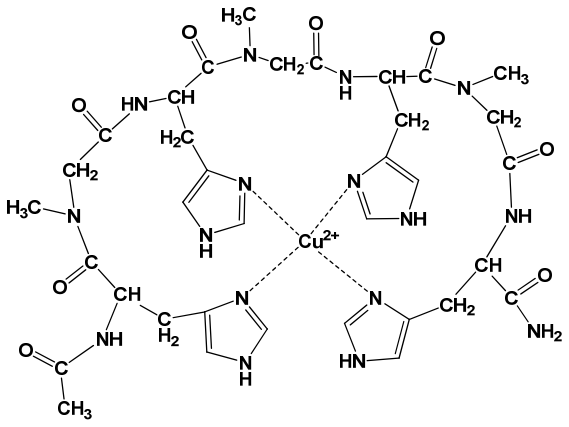
Histidine imidazole nitrogens are frequent side chain donor groups in proteins and play important roles in the binding of transition metal ions. Several proteins and enzymes are known in which the metal ion is coordinated to the protein through these donor atoms. This fact is well-demonstrated by different metalloenzymes (e.g. superoxide-dismutase (SOD)) and other proteins including prions, amyloid-β-peptides, histones and SPARC.

Our work is focusing on mimicking the Cu,Zn-superoxide dismutase enzyme. This enzyme catalyzes the disproportionation of superoxide to hydrogen peroxide and dioxygen so it reduces the risk of oxidative stress by removing the highly reactive oxygen species. To mimic the active site of Cu,Zn-SOD enzyme several histidine containing peptides were synthesized and their coordination ability was investigated. Among the ligands there were two, three and four histidine containing peptides with the general formulae: Ac-His-Xaa-Xaa-His-NH_2, Ac-His-Xaa-His-Yaa-His-NH_2 and Ac-$(His\text{-}Sar)_n$-His-NH_2 where Xaa and Yaa can be Gly, Ala, or Val and n=1, 2, 3. These peptides containing varying numbers of histidine in different positions in the peptide chain were studied by pH potentiometry [1-3], cyclic voltammetry [4] and spectrophotometry.

The equilibrium studies of the copper(II) complexes of these peptides showed that the presence of several histidyl residues in the molecules provides a high possibility for the formation of macrochelates (ML) *via* the binding of imidazole-N donor atoms (Scheme 1). The increase in the number of histidyl residues results in enhanced stability of the complexes and these species are present predominantly under slightly acidic or neutral pH conditions (pH 5-7). [2] These complexes can be seen as structural models of the copper(II) binding site of the Cu,Zn-SOD enzyme.



Scheme 1: The structure of $[CuL]^{2+}$ complex of Ac-$(His\text{-}Sar)_3$-His-NH_2 peptide

To support this view we studied the redox properties and the SOD activity of those complexes in which the metal ion is bound through imidazole-N donoratoms. The redox potential values were studied by cyclic voltammetry using a three electrode assembly [4] and the SOD activity was determined by the indirect nitroblue tetrazolium method.

The redox potential values of those complexes in which the copper(II) ion is bound exclusively through imidazole-N atoms fall into the positive redox potential range that characterizes the SOD enzyme. The SOD activity of these complexes is similar to the previously published SOD model compounds. Thus the cyclic voltammetric measurements and the SOD activity assay in agreement with the equilibrium studies showed that those complexes can be capable of decomposing the superoxide radical anion in which the metal ion is coordinated exclusively through imidazole nitrogen atoms.

Acknowledgements:

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Targeting the breakpoint in Duchenne Muscular Dystrophy

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The process of DNA targeting within the cell - induced by specifically positioned double stranded cleavage of DNA near the mutated sequence - can be applied for gene therapy of monogenic diseases, such as DMD. For this purpose highly specific artificial nucleases have to be developed. The present zinc-finger nucleases exert a minor cytotoxicity, which must be avoided in therapeutic applications [1]. The HNH motif - a conserved ββα-metal-binding structure [2] - comprises the active centre of numerous nucleases. Since it functions under positive allosteric control, it may serve as a catalytic centre of new type of zinc-finger nucleases.

We developed a method for approaching the mutation sequence in the largest human gene, responsible for DMD. A zinc finger protein was designed using semiempirical method to target the determined DNA sequence in a DMD patient. It was tested for specific binding in in vitro experiments. Furthermore, the conditions of the function of HNH motif from Colicin E7 were investigated in order to apply it for a possible active centre of a specific artificial nuclease. The results show the possible direction of the development of the new artificial nucleases for gene therapy of monogenic diseases.

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Molybdenum substituted rubredoxin from *Desulfovibrio* gigas

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Rubredoxin (Rd) is a small (~6 kDa), single iron protein with four cysteinyl thiolate groups coordinating the metal in a tetrahedral geometry.

In several *Desulfovibrio* species, rubredoxin is involved in electron donation to superoxide reductase [1] and rubredoxin-oxygen oxidoreductase [2], as part of the oxygen detoxification pathway [1, 3].

The plasticity, the simple active center and a low molecular mass makes this protein a good target for metalloprotein design and synthesis of metal substituted derivatives. The replacement of native metal ion is often perform to investigate the structure of a metalloprotein and several spectroscopic techniques are used to study metal binding sites in proteins [4].

Rubredoxin is a significant model that can mimic the sulphur tetracoordinated metals in some biological systems. The native iron in *Desulfovibrio* species rubredoxins were effectively replaced by other metals like nickel, cobalt and zinc, but never substituted with a tetrahedral sulphur coordination metal.

In this work a recombinant rubredoxin from *Desulfovibrio* gigas was overexpressed, in large scale, in *E.coli*. The soluble cellular extract was purified in two steps consisting of an anionic exchange chromatography and a size-exclusion chromatography. The native iron atom present in the active centre was successfully removed by precipitation with trichloroacetic acid. The apo-rubredoxin was Mo reconstituted adding amonium tetrathiomolybdate (TTM). The influence of the TTM:protein ratio, incorporation time and pH for molybdenum reconstituted rubredoxin was investigated. UV-visible spectroscopy was used for protein characterization and extinction coefficient determination (ε_{310}= 7000 $M^{-1}cm^{-1}$, ε_{453}= 2400 M^{-1} cm^{-1}). The molybdenum content in the incorporation conditions was also determined by ICP-AES spectroscopy. The protein showed to incorporate one molybdenum atom per monomer of protein. EPR spectroscopies are currently been performed to get insights on the type of Mo cluster formed.

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Elucidation of probable responses to molybdate stress in *Desulfovibrio alaskensis* by proteome analysis

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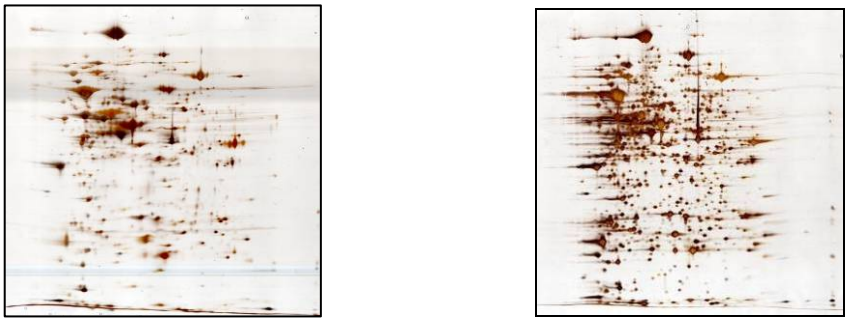
Metals play many important structural and functional activities in cell metabolism as they serve as essential cofactors for a variety of enzymatic reactions. However, when present in high levels, they can become toxic for the cell. In the present study we investigated the effect of high molybdate (Mo) concentrations on *Desulfovibrio alaskensis* G20 (*Da*G20) cells at a proteomic level. Growth studies were carried out to determine the molybdate concentration yielding 70% cell growth inhibition. Two-dimensional gel electrophoresis of both soluble and membrane fractions of the Mo stressed cells were compared with the respective fractions from nonstressed (normal) cells (Figure 1). The identity of proteins, up- or down-regulated was assessed by MALDI-TOF mass spectrometry.



Cells grown in media with 100µM Mo **Cells grown in media without Mo**

Fig.1. 2D Gel maps of soluble fractions of *D alaskensis* cells grown in 100µM molybdenum and without molybdenum Postgate C media

Our results show that the proteins affected by the stress conditions are mainly involved in processes related to energy metabolism, amino acid, purines and pyrimidine biosynthesis, stress response and transport proteins. By discussing the probable roles played by the identified proteins, we attempted to have a deeper understanding on the impact of high Mo levels in the environment on sulphate reducing bacteria.

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Interaction of polytopic aza-scorpiand receptors with nucleotides and nucleic acids

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Over the past few decades, small molecules that bind to DNA have shown significant promise as diagnostic probes, reactive agents and therapeutics. However, despite the large number of cellular roles that RNA plays in biological processes, this macromolecule has been considered only recently an attractive target for therapeutic intervention.[1]

Several dominant non-covalent binding modes of small molecules to double stranded DNA/RNA are already well described (intercalation, minor or major groove binding or external electrostatic binding).[2] However, combination of several binding modes within one molecule as well as incorporation of steric and structural features controlling three-dimensional recognition drew much attention in the last two decades. [3]

We present here a study of the interaction of two polytopic phenanthroline/pyridine tail-tied aza-scorpiands with calf thymus DNA and synthetic polynucleotides by mean of fluorescence titrations, melting point curves and molecular dynamic analysis. In order to evaluate their ability to complex with DNA/RNA components, interaction of receptors with nucleotides has been followed by pH-metric titrations, ^{1}H and ^{31}P NMR techniques and molecular dynamic analysis. Finally, compounds have been tested for their potential antiproliferative effect on a panel of 4 human cell lines which were derived from 3 cancer types.

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